

PROCEEDINGS OF THE
COMPLEMENTARY MEDICINE
IN
CHRONIC FATIGUE SYNDROME
NATIONAL CONSENSUS CONFERENCE
&
CHRONIC FATIGUE SYNDROME
RESOURCE DOCUMENTS

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EDITOR

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Extract from Proceedings
Presentations of Dr Paul Cheney

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THE CHENEY PAPERS

This document represents the presentations given by Dr Paul Cheney, keynote speaker at the Complementary Medicine in CFS National Consensus Conference held at the Convention Centre, Darling Harbour, Sydney Australia on the weekend of February 19 and 20, 1995.

The Conference was presented by the Australian Comprehensive Medicine Association (ACMA) and the Institute of Functional Medicine, and was attended by one hundred and fifty medical scientists and medical practitioners from around Australia. These included university researchers, consultant physicians, and general practitioners. Over thirty presentations were made during the two days, covering all aspects of Chronic Fatigue Syndrome, from preliminary research findings through to the results of intervention outcome studies.

Following the Conference, Dr Cheney returned to Australia in August, 1995, to provide a three day intensive workshop for practitioners treating mainly Chronic Fatigue Syndrome patients. The workshop provided in depth understanding of the causes of CFS, and the biological processes involved. A diagnostic program has evolved from the workshop, allowing for better categorisation and management of CFS sufferers. The doctors at the workshop have adopted this as a common diagnostic standard, and will be implementing the therapeutic practices which have proven benefit in this disease. The names and contact numbers of the practitioners attending the Cheney Clinic Protocols Workshop are available by phoning the Institute of Functional Medicine (1 800 650 806), or by contacting the Australian Comprehensive Medicine Association (+61 2 968-4422).

The full proceedings, including the consensus statement, are available from:

**Institute of Functional Medicine, 1 Bradley Ave, Milsons Point, NSW 2061 Australia
or by phoning 1 800 650 806 (within Australia); or by fax on +61 2 9959-5071**

The cost of the proceedings is \$A90 (plus postage and packaging), and comprises 200 pages of conference transcripts and summaries, as well as approximately 200 pages of articles, references, resources and information on CFS for physicians, patients, carers and the interested public.

The Australian Comprehensive Medicine Association is a medical organisation representing medical practitioners who provide additional skills, drawn from the various fields of Complementary Medicine and Alternative Medicine, in their medical practices. Its mission is to promote and foster safe and effective Complementary Medical practice within a framework of Total Health Care. ACMA is involved in setting uniform and high educational and practice standards within Complementary Medicine, and to initiating and supporting quality education and research in the field. This will result in improved practice standards, and better outcomes for those who wish to look at complementary practices for optimising their health or managing their illnesses.

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*The history of medicine is a story of
amazing foolishness and amazing intelligence*

Jerome Tarshis

Where We've Been and Where We're Headed

A historical and clinical perspective on CFS
as a guide for future directions.

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Abstract

In recent years it has become ever more apparent that a difficulty to diagnose but clinically recognisable disorder characterised by unexplained debilitating fatigue and other systems exists in large numbers in communities across the developed world. Recent studies using defined case definitions ¹, for 'Chronic Fatigue Syndrome' have revealed that community prevalence rates range from 40 ² to 267 ³ cases per 100,000. Much larger prevalences can be seen in certain medical professions (680 cases per 100,000 nurses) ⁴ or primary care setting (1,000 cases per 100,000 visits) ⁵.

There is also a sense that the numbers of such patients may be increasing. In April 1994, one of the largest disability insurers in the United States, UNUM Corp of Portland, Maine, reported that in the five years from 1989 through 1993, men's disability claims for CFS increased 360%; women's claims increased 557%. No other disease category surpassed these rates of increase. We will present evidence that there may have been a sharp rise in the case production rate of CFS beginning in the late 1970s and peaking in 1987 followed by a slow decline since that time.

In our view, the clinical coherence of these patients surpasses the sometimes differing clinical description of similar fatiguing illness reported over the past several centuries, both sporadic ^{6,7,8} and epidemic ^{9,10,11}. We will present evidence of this clinical coherence in a case-control study of physical findings. It is likely that the syndrome we call chronic fatigue syndrome is both very old and also very new. What is old is the pathophysiology of post-infectious or post-stressor syndrome which results in a self-maintaining cycle of dysfunction with the most important locus of injury within the central nervous system. While there are many ways to get sick, there are only a few ways to feel sick, and fewer ways still to remain sick. On the other hand, the coherence of these patients and the rather remarkable rise and fall in case production which is fixed in time suggests the distinct possibility that a novel agent or process exists.

There are therefore two challenges before us; one is to elucidate the common pathophysiology of long term fatiguing illness of variable aetiologies or triggers and the other is the remarkable challenge of reducing some and possibly most cases of CFS to a single aetiology evident since the late 1970s

References

1. [Holmes, GP., Kaplan, JE., Gantz, NM., Komaroff, AL., Schonberger, LB., Straus, SE., Jones, JF., Dubois, RE., Cunningham - Rundles, C., Pahwa, S. Tosato, G., Zegans, LS., Purtilo, DT., Brown, N., Schooley, RT. and Brus, I. "Chronic Fatigue Syndrome, a Working Case Definition." *Annals of Internal Medicine* \(1988\):108, 387-389](#)
 2. [Lloyd, AR. et al "Prevalence of chronic fatigue syndrome in an Australian population." *Med J Aust.* \(1990\): 153,522-528.](#)
 3. [Buchwald, D. et al "Prevalence of chronic fatigue and chronic fatigue syndrome in a large community based HMO." AACFs Research Conference presentation : Ft. Lauderdale, FL., October \(1994\):pg 9.](#)
 4. [Jason, L.: Pilot study results reported in *The CFIDS Chronicle.*, Winter \(1995\): Vol 8 No 1: pg 6.](#)
 5. [Bates, DW. et al. \(Prevalence of chronic fatigue and chronic fatigue syndrome in a primary care practice." *Arch Int. Med.* \(1993\): 153,2759-2765.](#)
 6. [Manningham, R. "The symptoms, nature, causes and cure of the febricula, or little fever: commonly called the nervous fever or hysteric fever, the fever on the spirits, vapous, hypo or spleen." 2nd Edition. London: J Robinson 1750:52 -3.](#)
 7. [Beard, G. "Neurasthenia, or nervous exhaustion." *Boston Medical and Surgical Journal.* 1896: 3 \(new series\):217-220.](#)
 8. [Da Costa, JM. "On irritable heart, a clinical study on a form of functional cardiac disorder and its consequence." *Am. J. Med. Sci.* 1871; 121, 17-52.](#)
 9. [Poskanzer, DC., Henderson, DA., et al. "Epidemic neuromyasthenia: Outbreak in Punta Gorda Florida." *NEJM* \(1957\) :257, 356-364](#)
 10. [Gilliam, AG. "Epidemiological study of an epidemic, diagnosed as poliomyetis, occuring among the personnel of the Los Angeles County Hospital during the summer of 1934" *Public Health Bulliten* No. 240, April \(1938\).](#)
 11. [Sigurdsson, B., Sigurjonsson, J., Sigurdsson, JH., Thorkelsson, J., and Gudmundsson, K. "A disease epidemic in Iceland simulating poliomyelitis." *American Journal of Hygiene.*\(1950\): 52,222-38.](#)
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Where We've Been & Where We're Headed

Dr Paul Cheney

Summary of major points from transcript of talk

There is an appropriate quote from the philosopher, William James.

When a thing was new, people said 'It's not true'.

Later when the truth became obvious, people said 'It's not important'.

And when its importance could not be denied, people said 'Anyway, it's not new.'

Chronic Fatigue Syndrome has features of autoimmune disorders (eg lupus), features of allergy and Multiple Chemical Sensitivities (MCS), features of neurological disease (like MS), and features of psychiatric disease. The syndrome shares many features of infectious disorders (like HIV), and features of tempero-limbic encephalopathies. The disorder does not fit the definitions of other diseases, and probably is a distinct entity.

CDC Case Definition

The Centre for Disease Control has recently revised the case definition of CFS in the Annals of Internal medicine (Dec 15, 1994;121:953-959 - see appendix). The definition now includes a separate diagnostic category for prolonged fatigue which does not meet the necessary criteria for CFS. This is termed Idiopathic Chronic Fatigue (ICF).

Diagnostic criteria for CFS (from Annals article, see Appendix)

The critical issues in the proposed diagnostic criteria is that prolonged, unexplained fatigue must have been present for more than 6 months, and four or more of the seven symptoms listed must have been present for at least six months following the onset of the fatigue. In addition, certain factors must be excluded, including:

- any active medical disease which can cause fatigue
- obesity, with a BMI more than 45
- alcohol or substance abuse

There is a major problem with the case definition in my opinion, and that is that five of the eight symptoms relate to pain. So a patient without pain cannot, by definition, fulfil the diagnostic criteria for CFS. This seems to me incorrect.

As well, the diagnostic criteria do not include symptoms of environmental sensitivities and balance problems, which I believe are common in CFS.

The case definition does define certain data which should be collected, and testing required to exclude other illness. These include:

- Thorough history related especially to the time of onset of the fatigue
- Mental status examination
- Thorough physical examination
- Pathology testing, namely: complete blood count;leukocyte differential; erythrocyte sedimentation rate (ESR); serum alanine aminotransferase;total protein; albumin; globulin; alkaline phosphatase; calcium; phosphorous; glucose; blood urea nitrogen; electrolytes; creatinine; thyroid-stimulating hormone (TSH); and urinalysis

The case definition goes on to describe the information required in addition, termed

“essential subgrouping variables”. The majority are questionnaires, and include:

- Psychological inventories for excluding psychiatric disorders
- Questionnaires to assess the severity of fatigue
- Duration of fatigue
- Assessment of current level of function, using the Medical Outcome Study Short Form 36, and the Sickness Impact Profile

In summary, conforming to the requirements of the case definition is an ONEROUS task, and not likely to be able to be performed in clinical practice.

Is CFS a New Disease?

The disease seems to have been around for some time, under various names. CFS, or something like CFS, has been variously termed:

- Neuromyasthenia in 1869 by Beard
- Myalgic encephalomyelitis (ME) in the 1950s in the UK
- Chronic Epstein-Barr Virus (CEBV) in the 1980s by Strauss & Jones
- Post infectious (fatigue) syndromes
- Low Natural Killer syndrome in Japan

There have been many published studies of epidemics over past 100 years. However, original articles from 1700s and after show one striking issue - that the syndrome described often results in death. This is not what we see today, and it makes me wonder if we really are talking about the same illness.

Hallmarks of CFS

There are certain hallmarks of the illness we currently term CFS. These include:

- Abrupt onset in previously healthy adult
- Post exertional fatigue
- Alcohol intolerance
- Headaches described as “pressure” more than “pain” nineteen times out of twenty
- Medication and environmental sensitivities
- Balance complaints, including dizziness, are striking
- Unusual cognitive processes - usually not present at the start of the illness, but progressing to become the major symptom complex over time. These include difficulty with memory sequencing, processing speed, word searching, spatial organisation and calculation. These are often the primary reason for disability, and almost invariably are among the top 3 complaints in any CFS patient.
- Age distribution is mainly in the 30s, with the peak at age 38. Age 25-50 is the “modal range”. There appear to be few children and elderly.

Physical Findings

The signs of CFS are usually not considered, but can include the following abnormalities on formal testing:

- Low grade fever in 38%
- Low blood pressure (especially neurally mediated hypotension)
- Abnormal oropharynx with “crimson crescents” on soft palate
- Lymphodynia, or tender lymph nodes (they are not usually swollen)

- Hyperreflexia without clonus
- Positive Romberg, tandem stance, and augmented tandem stance. Most CFS patients fall over in these tests.
- Trouble with subtraction (serial sevens, etc)
- Destruction of fingerprints in 10%. Fingerprint atrophy is due to a perilymphocytic vasculitis and vacuolisation of fibroblasts.
- Facial vasculoid rashes
- Tenderness in left posterior cervical nodes, more prominent on the left due to thoracic duct inlet on the left. Immune activation causes increased lymphatic flow, and congestion where the thoracic duct joins the left jugular. Tenderness present in 90% of patients.

We performed a study looking at CFS and signs and symptoms. Controls were selected by Random Digit Dialling method.

Cases	Control	Sign
80%	20%	Hyperreflexia without clonus
80%	20%	Crimson crescent in oropharynx
44%	16%	Loss of fingerprints
32%	0%	Fever > 99.2° F
88%	0%	Tender posterior cervical nodes
92%	0%	Supraclavicular tenderness
84%	4%	Rhomberg mild positive
92%	4%	Augmented Tandem Stance positive

Prevalence

Prevalence and incidence have been reported over a very broad range, depending greatly on the selection criteria & the type of study undertaken. The following shows the “range” of the data.

Author/Institution (country)	Reported Incidence/Prevalence	Type of study/criteria
CDC (USA)	10 cases/100,000 of pop/yr	(referral by doctors)
Lloyd (Australia)	40 cases/100,000 of pop/yr	(referral by doctors)
Bates (Boston)	300 cases/100,000 visits	(on old CDC definition)
Harvard Primary Care Clinic	1,000 cases/100,000 visits	(on Australian definition)
Buckwald (Seattle)	267 cases/100,000 visits	(on old CDC definition)
Jason (Chicago)	200 cases/100,000 visits	(on old CDC definition)
• Jason (Chicago) (<i>est</i>)	600 cases/100,000 visits (<i>est</i>)	(on new CDC definition)

It is also noted that CFS has the highest rate of increase in claims among insurers over the past five years of any illness.

Note that the community- based studies do not suggest significant sex ratio differences. The preponderance of women among CFS cases presenting to doctors may well be an artifact, and due to factors related to doctor visits.

*We must turn to nature itself, to the observations of the body
in health and disease, to learn the truth.*

Hippocrates (c. 460 BC – 377 BC)

Proposed Pathophysiologic Mechanisms of Chronic Fatigue Syndrome

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Abstract

Conceptualising this complex disorder is a first step in the process of understanding and successfully treating Chronic Fatigue Syndrome (CFS)

Chronic fatigue syndrome represents a chronic, debilitating and prolonged illness characterized by numerous symptoms but most especially fatigue, cognitive dysfunction and pain. Frequent but subtle physical findings support laboratory evidence ^{1,2,3} involving excessive alpha-interferon production ⁴ and functional brain scan evidence ^{5,6,7} of central nervous system injury which is likely metabolic and possibly due to alpha-interferon itself. Immune activation with excess lymph production may produce peripheral pain ⁸ in certain tissues which is then amplified centrally by injury to key central nervous system structures ⁹ and mediated by opioid receptor linked alpha-interferon induced neurotoxicity ¹⁰, Fatigue itself may ultimately have cellular basis at a level of mitochondrial dysfunction ^{11,12,13}. Organ systems may be differentially affected and within organ systems there may be a mosaic of affected and unaffected cells, the sum of which defines the degree of organ dysfunction immune activation and its effects on the CNS may set up a vicious cycle which is independent of an initial triggering agent or event which may no longer be present. It is also possible that a persistent causative agent(s) exists and plays an active role in the maintenance of this pathophysiology. The exact nature of this putative agent remains unknown but the clinical presentation and the presence of high levels of alpha-interferon or its sub-cellular effects ¹⁴ favours a viral etiology.

References

1. Kilmas, N., Salvato, F., Morgan, R. and Fletcher, M. "Immunologic Abnormalities in Chronic Fatigue Syndrome." *J. of Clinical Microbiology*. (1990): 28,1403-1410.
2. Lloyd, AR., Wakefield, D., Boughton, CR., Dwyer, JM., "Immunologic Abnormalities in The Chronic Fatigue Syndrome." *Medical Journal of Australia* (1989): 151(3), 122-124.
3. Landay, AL., Jessop, C., Lennette, ET., & Levy, JA. "Chronic Fatigue Syndrome : Clinical Condition Associated with Immune Activation" *The Lancet* (1991): Vol. 338, No. 8769.
4. Suhaldonik, RJ., Reichenbach, NL., Hitzges, P., Sobol, RW., Peterson, DL., Henry, B., Ablashi, D., Muueller, WEG., Schroeder, HC., Carter, WA., and Strayer, DR., "Up-regulation of the 2-5 A RNaseL Pathway associated with Chronic Fatigue Syndrome." *Clin. Inf. Dis.* (1994): Vol. 18, Suppl. 1 : S96 - 104.
5. Schwartz, RB., Komaroff, AL., Garada, BM., Gleit, M., Dolittle, TH., Bates, DW., Vasile, Rg., Holman, BL. "SPECT Imaging of the Brain: Comparison of Findings in patients with Chronic Fatigue Syndrome, AIDS Dementia Complex, and Major Unipolar Depression." *American Journal of Radiology*. (1994): 162, 943-951.
6. Buchwald, D., Cheney, PR., Peterson, DL., Henry, B., Wormsley, SB., Geiger, A., Abalashi, DV., Salahuddin, Z., Saxinger, C., Biddle, R., Kikines, R., Jolesz, FA., Folks, T., Balachandran, N., Peter, Jb., Gallo, RC., and Komaroff, AL., " A Chronic Illness Characterised by Fatigue, Neurologic and Immunologic Disorders, and Active Human Herpesvirus - 6" *Annals of Internal Medicine* (1992): Vol. 116 (2): 103-113.
7. Cheney, PR., & Gallen, C. "CFS; A Clinical Perspective on the use of MEG and EEG brain mapping" *The Third Annal Conference - Chronic Fatigue Syndrome and the Brain.*, Bel-Air, California, April (1992)
8. Straus, SE., Fritz, S., Dale, JK., Gould, B., Stober, W. "Lymphocyte phenotype and function in the chronic fatigue syndrome" *J. Clin. Immunol.* (1993): 13(1), 30-40.
9. Demitrck, Mark A., Dale, Janet K., Straus, Stephen E., Laue, Louisa., Listwak, Sam J., Kruesi, Markus JP., Chrousos, George P., and Gold, Philip W. " Evidence for Impaired Activation of the Hypothalamic - pituitary - adrenal Axis in Patients With Chronic Fatigue Syndrome." *J. Clin. Endocrinology and Metabolism* (1991): vol. 73, No. 4.
10. Saphier, D., Welch, JE., CHuluyan, HE., "Alpha- Interferon Inhibits Adrenocortical Secretion via u-opioid Receptors in the Rat.", *European Journal Of Pharmacology*. (1993): 236, 183-191.
11. Cheney, PR., Lapp, CW., Davidson, M., Naegele, C., " Bicycle Ergometry with Gas Analysis and Neuroendocrine Responses to Exercise in Chronic Fatigue Syndrome." *4th Annual Conference of Medical Neurobiology of Chronic Fatigue Syndrome and Fibromyalgia*, Los Angeles, CA., May (1993)
12. Kuratsune, H., Yamaguti, K., Takashi, S., and Kitani, T., "Acylcarnitine Deficiency in Chronic Fatigue Syndrome." *Clin. Inf. Dis.* (1994) Vol. 18, Suppl. 1: S62-67.
13. Eisinger, J.,MD., Plantamura, A.,MD., and Ayavou, T.,MD., " Glycolysis Abnormalities in Fibromyalgia." *Journal of The American College of Nutrition*. Vol. 13, No.2 (1994): 144-148.
14. Suhadolnik, RJ., Reichenbach, NL., Hitzges, P., Adelson, ME., Peterson, DI., Cheney, PR., Salvato, P., Thompson, C., Loveless, M., Muller, WG., Schroder, HC., Strayer, DR., and Carter, WA., "Changes in the 2-5A Synthetase/RNase L Antiviral Pathway in a Controlled Clinical Trial with Poly(1)-Poly(C12U) in Chronic Fatigue Syndrome." *In Vivo* 8 (1994): 599-604.

Proposed Pathophysiological Mechanism of CFS

Dr Paul Cheney

From Notes & References kindly provided by Dr Cheney

Chronic Fatigue Syndrome (CFS) , also known as Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS), represents an emerging clinical disorder of unknown cause marked by chronic disability and multiple, somatic complaints. Although typically a chronic illness without remission, cycles of severe relapses are common as well as a characteristic evolution of symptoms over time.

In its classic form, CFIDS begins abruptly with a mono-like or flu-like illness and then rapidly evolves into a severe and debilitating fatigue state with a dramatic loss of functional capacity. Over time there are increasingly severe neurocognitive problems which often become the primary reasons for disability. Different patients have different symptoms, but the general pattern or constellation of symptoms, their evolution and the major symptoms are remarkably coherent when patients are viewed as a group and over time.

The top three complaints which form the basis for the clinical coherence of the syndrome are;

debilitating fatigue, characteristic cognitive complaints, and pain.

The view that these patients usually turn out to have other more definable disorders, while the true for fatigue in general¹, is certainly not the case for meeting the CDC case definition for CFS ².

Among the most common symptoms are:

low grade fever or subnormal temperatures	dizziness or balance problems
myalgias (esp axial skeletal muscles)	migrating sensory dysesthesias
deep bone pain in the extremities	sensitivity to heat, cold, light, sound, chemicals
arthralgias	decreased alcohol tolerance
pressure headaches	food and drug intolerance
sleep disorders	visual disturbances
enlarged and/or painful lymph nodes	disabling cognitive impairments
night sweats	acneform, herpetiform, morbilliform skin eruptions
recurring upper respiratory tract infections (<i>sinus, pharynx, & bronchi</i>)	an assortment of respiratory, cardiac, gastrointestinal and genitourinary complaints.
new onset of worsening of allergies	

1 Sates, PW, Schitt W, Buchwald, D et al, " Prevalence Of Fatigue And Chronic Syndrome In A Primary Care Practice." Arch Inter Med. 1993; 153:2795-65

2 Holmes GP, Kaplan JE, Gantz NM Komaroff AL. et. al. "Chronic fatigue Syndrome: A Working case Definition", Ann Intern Med 1988, 109:387-389

Among the most common physical findings in CFS are palpable, slightly enlarged, discolored shaped (as opposed to shotty or spherical) and tender posterior cervical chain lymph nodes, which are almost always left predominant and extend into the supraclavicular node area. This left-sided predominance and lymphatic channel tenderness extending into the medial supraclavicular node area strongly suggests increased lymph production and clinically supports the published reports of immune activation in CFIDS^{3 4 5} (see 1 in diagram).

Lymphatic fluid carries the protein messages, or cytokines, released by antigen-processing cells. In an immune activation state, lymphatic fluid flow increases. An acceleration of lymph production would cause fluid retention and tissue edema, which is common pathways of the lymphatic system, such as the left supraclavicular area. Anatomically, over 90 percent of lymph flows back into the blood stream just below the left collarbone: 10 percent or less to the right. Therefore, with increased flow, congestion will occur prominently within node chains closest to the juncture; hence... left-sided dominance of lymph node tenderness in the supraclavicular area.

Common physical exam findings

- a higher than normal incidence (greater than 80 percent of patients versus 20 percent of controls) of hyper-reflexia; and
- abnormalities of vestibular function with the inability to maintain the Romberg, tandem stance, or augmented tandem stance positions (seen in over 90% of patients vs. no controls)

These abnormalities clinically support the evidence of central nervous system (CNS) injury observed on functional and structural brain scans^{6 7 8 9}, and suggested by neuropsychometric testing (see 4 in diagram)¹⁰, the link between immune activation and CNS injury may be in the intense activation of alpha interferon induced 2'-5' A antiviral

3 Kilmas n; Savata F; Morgan R; Fletcher M; "Immunologic Abnormalities in the Chronic fatigue Syndrome" J Clinical Microbiol 1990;28:1403-101

4 Lloyd AR; Wakefield D; Broughton CR; Dwyer JM; " Immunological Abnormalities in the Chronic fatigue Syndrome" Med J Australia 1989; 151 (3); 122-124

5 Landay AL; Jessop C, Lennette ET; Levy JA; "Chronic fatigue Syndrome: Clinical condition Associated With Immune Activation" Lancet 1991; 338(8769); 707-712

6 Mena, I., "Findings in Regional cerebral Blood Flow by means of Brain SPECT in CFS and Late Life Depression", Fourth Annual Conference – Medical Neurobiology of CFS and Fibromyalgia, Bel-Air, CA; May 1993

7 Buchwald, D., Cheney, PR, Peterson, DL, et al "A Chronic Illness Characterised by Fatigue, Neurologic and Immunologic Disorders and Active Human Herpesvirus-6", Ann Intern Med, 1992;116(2):103-113

8 Cheney PR, Gallen C, Preston, M, "CFS:A Clinical perspective on the Use of MEG and EEG Brain-Mapping", The Third Annual Conference - Chronic Fatigue Syndrome and the Brain, Bel-Air, CA, April 24-26, 1992.

9 Schwartz et al "SPECT Imaging of the Brain: Comparison of Findings in Patients with Chronic Fatigue Syndrome, AIDS Dementia Complex, and Major Unipolar Depression", American Journal of Radiology, 162; April, 1994

10 Daugherty, SA, Henry BE, Patterson DL, Swans RL, Bastien S, Thomas RS, "Chronic Fatigue Syndrome in Northern Nevada", Rev. Infect. Dis., 1991; 13(1);539-544

pathway seen in the great majority of CFIDS patients (*see 2 in diagram*)¹¹. Alpha interferon is known to induce neurotoxic injury to limbic structures and serotonergic pathways via opioid receptors (*see 5 in diagram*)¹² agonist/ antagonist.

Deleterious effects on CRH (corticotrophin releasing hormone) the TRH (thyrotropin releasing hormone) production in the hypothalamus (a key limbic structure) are known to exist in CFS patients (*see 6,7 in the diagram*)^{13 14}. The CRH deficiencies could then set up a positive feedback loops (*see 6 in the diagram*) which maintains immune activation and thus creates a vicious cycle.

Recent studies on CFS patients have also demonstrated evidence of a metabolic disorder involving cellular energy production (*see 3 in the diagram*). Studies at UCLA and elsewhere have demonstrated reduced oxygen consumption at maximal exercise consistent with defect in mitochondrial function^{15 16}. Additional indicators of defects in trans-membrane mitochondrial transport mechanisms have been reported in CFS¹⁷ and CFS-related disorders¹⁸.

Finally, most patients with CFS show evidence of abnormalities in citric acid cycle intermediated on overnight urine using gas chromatography technology. Taken together this evidence supports a defect in cellular energy production at the level of the mitochondria. We may ultimately view this defect in cellular energy production as cellular basis of fatigue in Chronic Fatigue Syndrome, as well as the basis in related and unrelated disorders.

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- 11 Suhaldonick RJ, Reichenbach NL, Hitzges Pet al, "Up-Regulation of the 2'-5' RNase-L Pathway Associated with Chronic Fatigue Syndrome" Clin. Inf. Dis. Vol 18, Supp 1, PpS96-S104, Jan 1994
 - 12 Saphler D, Welch JE, Chuluyan HE, "Alpha Interferon Inhibits Adrenocortical Secretion via μ Opioid Receptors in the Rat", European J. Pharmacology, 1993; 236:183-191
 - 13 Demitrack MA, Dale JK, Straus SE, et al, "Evidence for Impaired Activation of the Hypothalamic-Pituitary-Adrenal Axis in Patients with Chronic Fatigue Syndrome", J Clin. Endocrine Metabol., 1991; 73(4)
 - 14 Neeck G, Riedel W, "Thyroid Function in Patients with Fibromyalgia Syndrome", J. Rheumatol., 1992; 19(7)
 - 15 Daly J, "The Ventilatory Response to Exercise in CFS", The Third Annual Conference - Chronic Fatigue Syndrome and the Brain, Bel-Air, CA, April 24-26, 1992.
 - 16 Cheney PR, Lapp CW, Davidson M, Naegele C, "Bicycle Ergometry with Gas Analysis and Neuroendocrine Responses to Exercise in Chronic Fatigue Syndrome", Fourth Annual Conference - Medical Neurobiology of CFS and Fibromyalgia, Bel-Air, CA; May 1993
 - 17 Kuratsune H, Yamaguti K, Takahashi M et al, "Acylcarnitine Deficiency in Chronic Fatigue Syndrome", Clin. Inf. Dis., 1994;18(1):S62-S67
 - 18 Eisinger J, Plantamura A, Ayavou T, "Glycolysis Abnormalities in Fibromyalgia", Journal of the American College of Nutrition, Vol. 13, No. 2, 144-148 (1994)

Summary

Chronic Fatigue Syndrome represents a chronic, debilitating and prolonged illness characterized by numerous symptoms but especially fatigue, cognitive dysfunction and pain. Frequent but subtle physical findings support laboratory evidence of central nervous system injury which is likely metabolic and possibly due to alpha interferon itself. Immune activation with excess lymph production may produce peripheral pain¹⁹ in certain tissues, which is then amplified centrally by injury to key central nervous system structures, and mediated by opioid receptor-linked. alpha-interferon induced neurotoxicity. Fatigue itself may ultimately have a cellular basis at the level of mitochondrial dysfunction.

Organ systems may be differentially affected, and within organ systems there may be a mosaic of affected and unaffected cells, the sum of which defines the degree of dysfunction. Immune activation and its effects on the CNS may set up a vicious cycle which is independent of an initial triggering agent or event, which may no longer be present. It is also possible that a persistent causative agent exists, and plays an active role in the maintenance of this pathophysiology. The identity of this putative agent (or agents) remains unknown, but the clinical presentation, and the presence of high levels of alpha-interferon, or its subcellular effects, favour a viral etiology.

19 Straus SE, Fritz S, Dalem JK, et al, "Lymphocyte Phenotype and Function in the Chronic Fatigue Syndrome, J. Clin. Immunol., 1993;13(1):30-40

*When a lot of remedies are suggested for a disease,
That means it can't be cured.*

Anton Chekhov (1860 – 1904)
Russian dramatist

The Diagnosis & Management of Chronic Fatigue Syndrome

*An Overview of Useful Methods in
General and Specialist Practice*

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Abstract

The diagnosis of chronic fatigue syndrome is made on clinical grounds. This method includes a careful history which details the major and minor symptoms common to this syndrome of debilitating fatigue characteristic cognitive complaints and typical pain are the striking hallmarks of the disorder. The Post exertional relapses, balance disorder, alcohol intolerance, pressure-like headaches and unrefreshing sleep add to its recognition. Physical findings of tender, left predominant lymphodinia in the supraclavicular and posterior cervical node chains and an abnormal vestibular function exam add more weight to the clinical impression. Finally, essentially normal routine blood work which nevertheless yields some clues to this disorder helps to confirm that no other defined illness is likely to explain this syndrome.

There are many other tests which can help confirm the conceptual view of this disorder as an immune activation state with neuroendocrine sequelae and a variety of metabolic problems centred on the mitochondria. Various functional tests to the liver, gut, brain autonomic nervous system and aerobic exercise potential can confirm functional impairments and support rational treatment. There are no tests, however, that can

diagnose the disorder and the tests lack specificity or their specificity for CFS is unknown when compared to other clinically similar diseases. It should be noted, however, that CFS is not unique on the issue of tests that support but do not diagnose. The diagnoses of multiple sclerosis, lupus erythematosus and mononucleosis are often supported by non-diagnostic tests. In addition, in CFS, there are some tests that support rational treatment that appears to improve symptoms. There are also tests that appear necessary to document functional impairments for successful disability application. Some of these tests will be discussed in this talk.

The traditional treatment of chronic fatigue syndrome has been largely symptomatic and driven by anecdote or one's conceptual view of the disorder. The problem with symptomatic treatment is that what makes one feel better may not be better, such as suppressing cough in pneumonia or steroid therapy in AIDS. The better approach is to conceptualize the illness so that you can target the critical link in the pathophysiology and to confirm in the individual patient whether by tests or clinical instinct and experience that they conform to your conceptual view of model. Treatment should be monitored and ideally, multi-dimensional, patient outcome assessment tools used to document functional and/or symptom improvement. In our opinion, there is no one best way to manage these patients but a broad based, comprehensive approach seems to work best. Elements should include basic nutritional support such as diet adjustments, vitamin and mineral recommendations and specially configured nutrition; lifestyle adjustment and exercise prescriptions; psychological counselling if appropriate; immune modulatory techniques; antiviral approaches in some patients; various metabolic and functional resuscitation therapies, especially liver-gut function and broad-spectrum anti-oxidant protection. Finally, the single most important therapy should be steps to address an as yet ill-defined neurotoxicity present in these patients using generic concepts such as blocking NMDA receptor mediated amplification of non-specific brain injury. The most important symptoms to address are sleep disturbance and pain. The approach to pain relief in certain very ill patients in severe pain can easily be the most challenging problem in CFS management.

The Diagnosis and Management of CFS

Paul Cheney

Summarised Transcript of Presentation

This is a talk on useful diagnostic procedures, concentrating particularly on routine blood work. Just as there are a lot of interesting, observable, and subtle abnormalities on physical exam, there are also subtle abnormalities on routine tests. There was an excellent paper recently published by Komeroff and company produced by Harvard that I'll organize my talk around, and then I'll try to fly through useful management techniques that I've found helpful and a couple of more novel approaches that I've found useful.

There are a range of tests that I have found useful, although I find myself doing (sometimes) less and less testing as I go along. I tended to do more tests years ago than I do now. A lot more attention to routine testing, certain immunologic tests, looking for a pattern of immune activation, combined with discrete defects is helpful. We are trying to look for one or two tests which seem to be the most sensitive and least expensive, to look at this pattern of immune activation and discrete defects.

Viral Activity or Re-activation

I've tended not to do as much testing in this area. It's just too much of a swamp at times. There are some interesting things coming along in terms of antigen capture assays, particularly for HHV-6, that might be most appropriate to perhaps identify a subgroup of patients that really do have significant viral replication using antigen capture techniques.

Metabolic Testing

DHEAS seem to identify at least 14% of the patients with very low, even absent DHEAS. I've found that DHEAS tends to mark a subgroup of patients that do not do well over time.

I look at the combination of T4/TSH trying to assess tertiary hypothyroidism, in which both of these are low and going down together.

Urinary free cortisol have been useful in the very ill or hospitalised patient. I've seen significant reductions in cortisol production in the seriously ill patient, sometimes requiring intervention.

One test I have found increasingly useful is the urinary organic acid analysis as a fingerprint of metabolism.

Other Useful Tests:

- Liver function assays such as benzoate and caffeine assays
- Lactulose/mannitol gut permeability assays
- Serum lipid peroxides for trying to assess ROS injury
- Essential fatty acid analysis (primarily red cell membranes) has been useful in guiding appropriately the treatment, whether you give them more omega 6 or omega 3.

- Psychological assessment (MMPI) has been useful in looking for scale elevations in 1,2,3,7 and 8 characteristic of this syndrome. If you see aberrations of the MMPI that deviate greatly from this you may think more about confounding psychological problems that don't quite map out like CFS. A hospital depression/anxiety scale I found useful. It's designed for medically ill people who have depression and anxiety as opposed to more classic scales.

Neurological Issues

Some people I assess for possible multiple sclerosis using MRIs. I do lumbar punctures on seriously ill individuals and EEGs can also be useful. These are not applied across the board and are generally limited to very ill individuals.

Neuropsychological testing is useful for documenting a disability.

Function Tests

- Exercise ergometry gas analysis has easily been the most useful single test for arguing for disability in these patient populations. It's well accepted by Social Security in the United States and is a measure of physical functioning
- Cognitive evoked computer EEG may be very useful for establishing disability. It's like neuropsychological testing, except I think it's more sensitive to the issues involved with these patients
- Tilt table testing with Isuprel drips establishing a dysautonomia and a variety of interesting treatment modalities that have been developed for this type of dysautonomia
- SPECT scanning I've used, but I insist that they do it with an MCUI type of analysis rather than just sticking it up and looking for asymmetric hyperperfusion

Routine Tests in the Chemical Panel

- LDH is, interestingly, low in a lot of the patients. Of all the liver injury tests, this one may be the most associated with function
- Uric acid and total cholesterol/HDL ratios. These can be clues to oxidant stress. In the seriously ill patient, uric acids go down under severe oxidant stress and HDL tends to go down as well
- Alkaline phosphatase may also be somewhat elevated in these patients

Complete Blood Counts (CBC)

- Atypical lymphocytes
- Leucocyte aberrancies - leucopenias and leucocytoses
- The sedimentation rate has been very useful - about 40% are low. It's not uncommon to see a 45 year old woman with this disease with a sedimentation rate of 0, yet you can see 10% with slightly elevated ESRs. If you pull out the original British literature for establishing the normal range for sedimentation rates, the normal range shifts with age, and women have higher sedimentation rates than

men, and older women have the highest sedimentation rates. By the time you get to about 30 years of age and you're female, 0 - 3 is actually outside the normal range according to the British literature

Immunologic Testing

- Low level ANAs that fluctuate positive/negative at low levels are very common.
- Various dysgammaglobulinaemias, including high IgG levels, low IgG levels and subclass deficiencies, are fairly common, and then C1Q immune complexes can be common
- Two colour flow cytometry looking at various immune activation markers. The one that we found the most sensitive is the CD3 CD26 marker for immune activation. A very interesting one has been the CD4/ CD8 ratio - in the Lake Tahoe patients we see extraordinary elevations with this ratio, well above 10, we see 10 - 12 - 14 as the value of this ratio, due both to CD8 depletion and CD4 expansion. We've also seen a subset of patients, about 15%, with low CD4 counts - below 500. We even have patients that are fairly stable in the 200-300 range
- The [Multitest CMI] skin test has been published in an Australian journal, and has been useful as a simple, cheap, functional assessment tool - a hypoergic result or anergic result should be interpreted as probably evidence of immune activation
- Serum and then cell-associated alpha interferon levels using the new ELISA kits, as opposed to the radio-immuno assays. We're getting 60% positivity on serum and on cell associated testing, 90% positivity. "Cell associated" is where the cell is disrupted by freeze-thaw or other methods, and then the alpha interferon is assayed
- IL2 receptor - very simple and can mark immune activation in the various immune function tests with respect to NK function. I've learnt that it's important to assess the NK killing per NK cell and not just the gross kill - need to normalise the ability of NK cells to kill off cancer cells in the assay
- Various mitogen stimulation tests

What Distinguishes CFS?

I will present here work published in the Archives of Internal Medicine by Bates and Kormaroff at Harvard (see Appendix). They looked at literally hundreds of chemistry panels and routine tests in CFS patients at Harvard in Boston and University of Washington in Seattle. Hundreds of cases were analyzed against quite a number of controls in both settings.

- There was atypical lymphocytosis of greater than 2% present in 8% of the patients and 1% of the normals with a p value below 0.01.
- LDH was elevated in 11% of cases, 29% of normals, and essentially what they were seeing was a shift toward lower levels of LDH in CFS patients.
- Cholesterol was elevated in 53% at the level of 200 milligrams per decilitre in CFS patients, 33% in the normals were just missing. their p values are pretty impressive. At the level of 220, 38% of cases were elevated versus 20% controls.

- Alkaline phosphatase was elevated in 18% above 89 units per litre vs 5% of normals.

So there were some subtle abnormalities in the chemistry panels that can point in the direction of this disorder. In addition the following tests showed significant differences between groups:

- Immune complexes using C1Q binding assays, were elevated in 35% of the cases and in only 2% of the controls
- Immunoglobulin G elevated about 12.5 g/litre in 25% of the cases, 4% of the controls (with a nice p value)
- ANA present at 1 in 40 or higher in 15% of the cases and none of the controls

From this it seems that simple CBC chemistry panel, immune complexes, immunoglobulin G, quantitated immunoglobulins, and ANA can display clues to the presence of this illness. The interpretation he gives in his paper for elevated IgG and immune complexes is basically immune activation state, and you could interpret that for the low level ANAs as well.

Management

In terms of treatment, I will provide a quick overview of various treatment areas:

- Modified elimination and / or rotation diets
- Activity modification is very important - limited exercise prescription that plays to their strengths and avoids their weaknesses
- Specially configured nutritional supplementation, again designed to play to the strengths
- Symptom relief - addressing sleep, pain, depression, anxiety, panic and emotional lability
- Immuno-modulation
- Assessing for treatable hormonal and neuro-endocrine issues in a subset of patients
- Consideration of anti viral agents in a subset of patients has been useful.

NUITS (New, Unusual, or Investigative Treatments)

- Hydrotherapy
- Ultraclear Maintain
- A very interesting modality used in brain-injured children - this we have not actually done, but are going to do
- Ampligen in a multi-centre trial we've used
- Neurotherapy using EEG biofeedback

What I do in the first 6 weeks

1/ Modify Their Diet.

Put them on polyphasic digestive enzymes with particular emphasis on proteolytic digestive enzymes as opposed to lipolytic can be most helpful and is very cheap therapy

The modified elimination diet is low fat and eliminates red meat, processed sugar, aspartame, optionally gluten, and optionally low fat. We tend to eliminate these in the sicker patient and allow it in the less sick if they tolerate it. We have them go on/off/on in a 3 week cycle to see if it influences symptoms, especially GI symptoms, but other

symptoms as well. We tend to restrict fruits and fruit juices to be taken with food as opposed to an empty stomach, and obviously restrict foods to which they are sensitive or allergic. A four day rotation has been optionally useful in some patients.

We put them on a soy-based branched-chain amino acid rich nutrient supplement to take advantage of a particular pathway. I think they use this compensatory pathway to block higher mitochondrial transport regions, of which several defects have now been published.

2/ Activity Limitations

Pacing, avoid overheating and no hot bathing. In a direct analogy to MS, there used to be a test for MS called the MS hot tub test - if you thought someone had MS, you put them in a jacuzzi at 104 degrees and activate their MS. Likewise with CFS patients, you put them in a jacuzzi at 104 degrees and it will activate their CFS symptoms. I think the concept is that in an immune activation state, if you raise the body temperature you activate it more.

3/ Exercise Prescription

We have reason to believe their anaerobic systems are still working okay, so we emphasize anaerobic training (primarily light weights - lifting for 30 seconds, resting for 60 seconds) about 20 minutes 3 times a week. On the other hand, aerobic training is a problem and we think there is a mitochondrial problem in these patients so if they exceed certain aerobic boundaries they'll get sick. So we have them go to their limit and not exceed it, and the limit is defined by the patients; for some it's walking around the bed, for some it's walking around the house, for others it's walking around the block and for some it's walking around the neighbourhood, but there is a limit beyond which they can't exceed or they get worse. Aerobic exercise that seems to be tolerated are walking, swimming or cycling, I think because it can be done without overheating, and they can be titrated to that limit.

4/ Supplements

- Broad spectrum multivitamin orally
- Broad spectrum antioxidant orally
- High dose B12
- High dose sublingual CoQ10
- Magnesium - if I had to pick out one thing that it is most important to concentrate on in these patients it would be magnesium, both oral and injectable. I particularly like magnesium glycinate - it has excellent bio-availability, very few side-effects, and there may be some additional advantages to using glycine as well
- Flaxseed oil as an EFA source - it has omega 3, omega 6 and omega 9 integrated in it. This can be really important in a subset of sicker patients

Drug Therapy

Klonopin is one of the most useful drugs I have ever used in this syndrome over the years, using very low doses in the daytime, and much higher doses at night.

I use Doxepin or Sinequan elixir in very low doses (1-5mg at night - 2 drops on the tongue) - for its immune modulatory effects on the histamine receptor. It also seems to synergise with Klonopin to improve sleep.

Hydrotherapy is used as an immune modulator.

Kutapressin has been useful in a subset of patients -it is both an immune modulator and it has broad spectrum anti viral effects against HHV6, probably all the known human herpes viruses and even perhaps other viruses.

Some antivirals in selected individuals who seem to have recurrent herpetiform eruptions.

Gammaglobulin - at least the IM injection in a subset of patients seems to help them if they're getting recurrent infections. I'm not sure it's as useful for the syndrome itself except in high dose IV approaches which I think are too expensive and I can't get it done in the States. I typically just use IM gammagobulin for a selected group of people who have trouble with recurrent infections of the upper respiratory tract.

Diamox LA (acetazolamide) is a very useful drug. I began to use this in Lake Tahoe when lumbar puncturing patients with incredible pressure headaches and balance disturbances. They had high opening pressures, and asking the neurologist what do I do for high opening pressure of unknown cause, he said try Diamox. We did, and it has been very useful to treat pressure-type headaches in patients with high opening pressure. It also seems to help balance problems, and over time may help some of the neuro cognitive component, as it influences brain blood flow.

The newer Specific Serotonin Reuptake Inhibitors (SSRIs) are useful for energy, emotional lability, and depression.

I've found Neurontin, Deseril and Melatonin Extendtabs all to be useful for sleep. In the study analyzing CSF fluid, the third most common thing seen was melatonin deficiency in the CNS in the CSF fluid. So sometimes adding melatonin helps.

Calcium channel blockers - particularly nifedipine, which is a centrally acting calcium channel blocker, has been helpful.

DHEA - in selected individuals that are very low - we have tried with mixed results.

We also tend to use the T3/T4 derivatives when we see evidence of hypothyroidism.

A variety of increasingly aggressive approaches to pain. And we had some patients with severe pain for a period of time, who were eventually switched back to Nubane. I have a particular interest in Nubane because it is a drug that blocks a particular type of receptor. I used this on the basis of the studies by Saffir showing interferon alpha neurotoxicity mediated through the receptor which Nubane blocks.

The MSQ is a multi dimensional assessment tool for symptomatology. The patients fill this out - the higher the number, the sicker they are. You can also look at different dimensions of their symptomatology.

Treatment of CFS

I had 10 consecutive CFS patients presenting at my clinic, and I intervened relatively conservatively, not a lot of drugs. 6 weeks after intervention the percent reduction in the initial MSQ score in one group of them was 30 - 60% lower. There was another group who got on average 8% worse, who had the exact same intervention. It's as if to say - if you get below 200 on the MSQ, I can help you, with fairly conservative intervention, yet if you score 200 or higher what I was doing to make other people better was almost guaranteed to make you worse.

Firstly we thought that this was the effect of the act of getting to the clinic, eating strange food, being talked at for 3 hours, etc for the sicker individuals. At about 9 - 20 weeks, on average, the ones getting better continued to get better and the ones getting worse continued to get worse. Treating the disease symptomatically seems to backfire in the sicker patients.

In an article in Scientific American on stroke therapy showed how brain injury of almost any kind can be amplified by the NMDA receptor (primary excitatory receptor present on most if not all neurons). This excitation of the NMDA receptor amplifies the original injury and if sufficiently amplified, will kill the cell. So you might not be able to do anything about the primary damage, but you are able to do something about the injuring amplification induced by this receptor by either inhibiting this receptor or inhibiting the downstream effects of the firing of this receptor. You can inhibit this receptor with magnesium, Klonopin and possibly other drugs that change the balance between NMDA and GABA firing. Another way to look at it is that GABA and NMDA are balancing each other out, and in a balanced form they set the threshold potential for neuronal polarisation within the normal range.

Under conditions of brain injury, of whatever kind, NMDA fires in excess over GABA which has the effect of lowering the threshold potential. The neuron now tends to fire inappropriately, scrambling information, processing in the area in which this is occurring. If NMDA is in even greater excess, you further lower the threshold potential and the neuron fires all the time. Going the other way, GABA firing over NMDA, increases the threshold potential, which if appropriate is good (if you're sleeping). If you continue to raise GABA, the neuron shuts down, it doesn't fire at all.

What we're attempting to do with these patients then, by using Klonopin and magnesium is to shift them to be reset at a different firing ratio so they process better.

The rationale for using high doses of B12 is not because the patient is deficient in the vitamin, they are deficient in an enzyme to which the vitamin is a co-enzyme. We think there is way too much attention payed to the antioxidants themselves and not nearly enough attention payed to the bioflavonoids which resuscitate the anti-oxidants. A recent article in the New England Journal of Medicine on smokers - just beta-carotene in very high doses tended to accelerate their cancer production over placebo and that acceleration was not seen when vitamin E was added. The antioxidant system is a cascade system. It's very important that at the bottom, you recycle the antioxidants, and the bioflavonoids are recyclers - and it may be dangerous to treat with high doses of an antioxidant without attention to the recycler.

The Most Important Foundations in Treating CFS

- Lifestyle adjustment •
- Diet prescription •
- Exercise prescription •
- Nutrition •

Issues Of Neurotoxicity

Magnesium and antioxidants are capable of protecting the central nervous system against the potentially neurotoxic effects of certain compounds, and are useful in the overall management for this reason.

Liver/Gut Issues

Specially configured nutrition is important. There seems to be a problem in transporting food across the mitochondrial membrane. In the case of Acyl carnitine, not only is it important in transporting fat, it's very important in transporting toxins out of the mitochondria. A defect in acyl carnitine can not only create problems in terms of energy generation, but the mitochondria can literally be poisoned. There may be a problem with pyruvate decarboxylase.

The low fat EFA supplemented modified elimination diet with organic foods, intervening with soy based which is 50% branch chain amino acids (eg vegetables). We tried to fill these patients with calories that we think they can utilize better given the particular problems of mitochondrial dysfunction. These people tend to eat empty calories in the food chain. They have nutritional utilisation blocks, mitochondrial transport blocks, enzyme deficiencies and cell homeostasis problems.

Ultraclear Maintain (Sustain in the US)

The treatment protocol was two scoops twice a day, supplemented with vitamins and supplemented with a branch chain amino acid rich product. Patients were treated for 12 weeks and assessed. In weeks 12 to 14 they were randomized, some were taken off and some left on. In weeks 14 to 20 the patients could choose - they could opt to maintain it, or opt to continue it, and we would follow their process. Nine people went on the study. Three people crashed and burned on this product within one week of taking it. Five people tended to improve over the 12 weeks and one did not. Those who were taken off in the 12 to 14 week period tended to worsen. It seems to help a subset of patients and another subset of patients seemed to deteriorate. It doesn't work in a small group of patients that tolerate it. The people who were intolerant of it were the ones with the low sulphate to creatinine ratio (ie a suggestion of glutathione deficiency).

Hydrotherapy

The concept is that the immune system is an issue of balance between suppression and activation. Immune activation typically produces a reactive suppression which is unique and precise. The idea is to use their own lymphatic fluid. We put them in a vertical floatation unit with tepid water one hour three times weekly. This procedure increases lymphatic return through the thoracic duct into the left internal jugular vein. It's like they're getting infused with their own lymphatic fluid. We have seen some absolutely

dramatic improvement in the MSQ score in some patients - on average about 23% improvement of the MSQ; with the greatest improvement of 42%. Some people did get worse with this therapy and there seemed to be a grouping with low interleukin receptors that tended to get better with therapy and a group with high IL2 receptors that tended to get worse with therapy. Hydrotherapy is bidirectional, it can down regulate the patient, but it can also upregulate him/her and make them feel worse (which may not be bad in the long term if they need to be upregulated against a threat - viral perhaps)

"Health is a state of complete physical, mental and social wellbeing, and not merely the absence of disease"

(World Health Organization 1946)