RESTRICTED POLICY DOCUMENT

Chief Medical Officer's Working Group Report on CFS / ME

Matters of continuing concern submitted by the 25% ME Group for the Severely Affected 9 March 2001

Introduction

This response is made on behalf of the 25% ME Group which represents those most severely affected by ME. ME is characterised by the cardinal feature of post-exertional muscle fatiguability and as such, it is distinct from CFS as defined by both the 1991 (Oxford) criteria and the 1994 (CDC) criteria, both of which concentrate on fatigue or tiredness rather than on muscle fatiguability related to exertion. There is clear evidence that patients with ME have very obvious and very significant clinical signs, yet these patients are virtually ignored in the current climate of focusing on the much broader category of undifferentiated CFS. Those with severe ME are at the end of the spectrum on two counts: ME is at the end of the CFS spectrum and additionally, those who are severely affected are at the end of the ME spectrum itself.

Whilst there is no doubt that a substantial number of people fall into the category of severe ME, there is another very large cohort who, whilst fulfilling to some extent the Ramsay definition of ME published by the UK ME Association in November 1981, nevertheless do not fulfill the criteria for the 25% ME Group, which represents ME sufferers who are virtually house or bed-bound.

There has been no official attempt to identify or quantify such severely ill patients, but there are databases in existence: apart from that of the 25% Group, there is also the database of CHROME (Case History Research on ME) and there is one maintained by the ME Association Singles Group, of which members of the CMO's Working Group will doubtless already be aware. The symptom patterns and the obvious degree of disablement are unmistakable.

It is on behalf of those who are very severely ill that this submission is made. It does not set out to be a recital of the history of previous epidemics of ME; its only objective is to obtain official recognition of the plight of those who do not fit the current case definition of CFS, so that such patients will no longer be excluded from future commissioning perspectives and service provision / delivery as at present.

Whilst constrained by the expediently narrow terms if its remit, nevertheless the CMO's Working Group has a unique opportunity to redress the consequences of poor science which have prevailed in the field since 1988 and to bring to an end the reign of moral neglect of ME, whether as a subset of CFS or as a nosological entity.

The problem

Following circulation of the CMO's Working Group draft report on CFS/ME version 6 dated 20 February 2001[1] (chapters 1- 3 only), a single overriding factor causes concern.

That factor is the rejection of the need for rigorous scientific evaluation of the issue of subgroups within the encompassing term "chronic fatigue syndrome" or CFS, notably the refusal to acknowledge the clinical difference between ME and other forms of CFS, a difference which many believe has important implications for management and treatment outcomes.

After the enforced recapitulation by the UK Government over the BSE issue, together with mounting international evidence that medical advisers to the UK Ministry of Defence are likely to be in error over their denial of the existence of Gulf War syndrome, it is necessary to be ever mindful of the fact that the most well-known UK adviser on GWS who says that there is no such condition as GWS [2] is the same person who is advising the CMO's Working Group on CFS / ME. That same medical adviser was widely perceived to be the one who was most associated with the 1996 Report of the Joint Royal Colleges on CFS. [3] He is notorious for his well-publicised opinion that there is no such condition as ME and for claiming those who think they suffer from it have simply a *belief* that they have a condition called ME. [4] [5] In the light of such past experience, it would be unfortunate if the forthcoming CMO's report on CFS / ME were to be shown to be as flawed and as biased as the 1996 Report on CFS, which was heavily criticised. [6] [7]

Crucial to the understanding of the complexity of the problem is the question of case definition and related nomenclature. Whilst there is clear evidence that ME is not synonymous with other chronic fatigue states which come under the umbrella of CFS, it is the case that many US studies of "CFS" (also known as chronic fatigue and immune dysfunction syndrome or CFIDS) use more stringently defined populations *(see the quotation from Professor Friedberg on page 16 below)* and are thus likely to be referring to those with ME or "core" CFS. An important consideration is that most of the UK psychiatric studies of "CFS" are often referring to other fatigue states in which the primary symptom is tiredness or "fatigue". This is widely accepted as being the result of

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[1] CMO's Working Group Draft 6 Restricted Policy Document, 20 February 2001

[2] Is there a Gulf War syndrome? Khalida Ismail, Anthony David, Simon Wessely et al *Lancet 1999:353:179-182*

[3] Chronic Fatigue Syndrome: report of a joint working group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. October 1996 / CR54. (RCP Publications Unit)

[4] Microbes, Mental illness, the Media and ME: The Construction of Disease. Simon Wessely. 9th Eliot Slater Memorial Lecture, 12 May 1994

[5] Psychiatry in the allergy clinic: the nature and management of patients with non-allergic symptoms. LM Howard S Wessely. *Clinical and Experimental Allergy 1995:25:503-514*

[6] The Royal Colleges' Report on Chronic Fatigue Syndrome: Insidiously Biased and Potentially Harmful. TE Hedrick. *CFIDS Chronicle 1997:10:1:8-13*

[7] Conference: Fatigue 2000. The National ME Centre in conjunction with The Essex Neurosciences Unit. 23-25 April 1999. Presentations by Professor LJ Findley and by Dr Derek Pheby

the 1991 (Oxford) CFS case definition having broadened the criteria to include psychiatric disorder in which "fatigue" is a predominant symptom. A case definition of CFS which does not require post-exterional muscle fatiguability is hardly capable of excluding the ubiquitous fatigue from which all mankind will suffer from time to time: this broadened case definition has created a conglomerate group under one label (CFS) which has allowed some physicians to conclude that CFS is a primary psychiatric disorder.

By case definition, those with ME or "core" CFS are excluded from the majority of UK psychiatric studies (see below).

Notwithstanding the efforts of one particular adviser to the CMO's Working Group to get ME reclassified from neurological to psychiatric in the WHO International Classification of Diseases, [8] the ICD still classifies ME as neurological (ICD 10 G.93.3) and classifies fatigue syndromes as psychiatric (ICD 10 F.48).

Indisputably, the case definitions are different: by those case definitions, patients designated as having CFS have **no physical signs at all**, whereas ME cannot be diagnosed in the absence of reproducible (mostly neurological) objective signs.

The Oxford (1991) case definition for CFS specifically states, ***"There are NO clinical signs characteristic of the condition"***.

The CDC (1994) case definition for CFS specifically states ***"We dropped ALL physical signs from our inclusion criteria"***.

Where do patients with ME or "core" CFS (i.e. those with observable physical signs of neuromuscular-immuno-endocrine-vascular disorder) fit into the current CFS case definition?

It is simply not the case (as stated in chapter 3, page 17 of the draft) that for *"some patients with established disease, any name that was previously applied will have become incorporated into their belief systems".* It is a matter of recognition that the name "ME" is known to represent a particular constellation of serious symptoms.

By seeking to equate one specific syndrome with another syndrome which does not have the same features, the CMO's WG may be doing a grave disservice to medical science: it is scientifically unacceptable that one name should refer to two different case definitions, each of which having different symptom profiles.

[8] Chronic Fatigue, ME and ICD 10. David A; Wessely S. *Lancet 1993:342:1247-1248*

What is ME?

ME has been documented in the medical literature from 1934. The Wallis definition of ME (not CFS) was in 1957. [9] Sir Donald Acheson's (a former UK Chief Medical Officer) major review of ME was in 1959. [10] The Royal Society of Medicine held a symposium on ME on 7 April 1978, from which ME was accepted as a distinct entity. The symposium proceedings were published in The Postgraduate Medical Journal in November that same year. [11] The Ramsay case description was published in 1981. [12] The forthcoming WG report cannot make all this disappear from the annals of medical history by ignoring it.

ME is a multi-system disorder associated with enteroviruses [13] related to the poliomyelitis virus. ME used to be known as "atypical poliomyelitis". There are acknowledged similarities and overlaps between ME (as distinct from CFS) and the post-polio syndrome (PPS), particularly concerning the nature and source of the pathophysiology, including virological evidence that enteroviruses persist in the human central nervous system. Specifically, the mechanism of the incapacitating exhaustion is identical in the two conditions (ie. in ME and PPS). Crucially, a distinction is made between ME and CFS. [14]

In ME, the most striking feature is extreme post-exertional muscle fatiguability, which is quite distinct from "fatigue", together with extreme malaise. It commonly starts with diarrhoea, together with a persistent headache and / or vertigo (dizziness is a particularly striking and chronic feature), with a stiff neck and back, together with generalised muscle pain. It affects not only the central nervous system but the autonomic and peripheral nervous systems as well. Sympathetic nervous system dysfunction is integral to ME / "core" CFS pathology. [15] There may be significant and permanent damage to skeletal or cardiac muscle as well as to other end-organs including the liver, pancreas, endocrine

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[9] An investigation into an unusual disease in epidemic and sporadic form in general practice in Cumberland in 1955 and subsequent years. Wallis AL. *University of Edinburgh Doctoral Thesis 1957*

[10] The Clinical Syndrome Variously Called Benign Myalgic Encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia. ED Acheson. *Am J Med 1959:569-595*

[11] Epidemic Neuromyasthenia 1934-1977: current approaches. Ed: WH Lyle and RN Chamberlain. *Postgraduate Medical Journal 1978:54:637:705-774 Pub: Blackwell Scientific Publications, Oxford*

[12] Myalgic Encephalomyelitis: A Baffling Syndrome with a Tragic Aftermath. A.Melvin Ramsay pub: The ME Association, November 1981

[13] Review by JF Mowbray, Emeritus Professor of Immunopathology, Imperial College School of Medicine,London: Myalgic Encephalomyelitis / Chronic Fatigue Syndrome and Enteroviral - Mediated Organ Pathology. John Richardson. *The Haworth Press Inc.New York, March 2001*

[14] The Post-Polio Syndrome: Advances in the Pathogenesis and Treatment. Proceedings of the First International Scientific Conference on the Post-Polio Syndrome. Ed: Dalakas MC, Bartfeld H & Kurland LT. *Annals of the New York Academy of Science 1995:753:1-409*

[15] Sympathetic Dysfunction Demonstrated by Isometric Hand-grip Response in Chronic Fatigue Syndrome. JN Baraniuk et al. Presented at the AACFS Conference, Seattle, Jan 2001 # 126

glands and lymphoid tissues, [16] with evidence of dysfunction in the brain stem. Injury to the brain stem results in disturbance of the production of cortisol (required for stress control) via damage to the hypothalamus and to the pituitary and adrenal glands. The late effects include not only muscle but joint pain; many patients can walk only very short distances and require a wheelchair. There is difficulty with breathing, with sudden attacks of breathlessness, problems with swallowing and voice production, thermodysregulation with sweating and shivering, and low blood pressure. There is difficulty with simple tasks such as climbing stairs and dressing, and with short-term memory.[17] Cognitive impairment includes difficulty with memory sequencing, processing speed, word searching, spatial organisation and calculation. Uncharacteristic emotional labilty is prevalent. There are usually chronic problems with diarrhoea and frequency of micturition, including nocturia. Vascular headaches are common and recurring. [18] Patients have to be cautious about drugs, especially those acting on the central nervous system i.e. anaesthetics, as there is an increased occurrence of adverse reaction. [19]

ME is a potentially severe, chronic and disabling disorder from which complete recovery is unlikely. Cycles of severe relapse are common, together with characteristic evolution of further symptoms over time. Death occurs almost entirely from end-organ damage, mainly from cardiac or pancreatic failure, but suicide is not uncommon and is related to the current climate of disbelief and rejection of welfare support. [20]

Despite claims from some quarters to the contrary, in ME there ***is*** evidence of inflammation of the central nervous system (CNS); that is what helps to differentiate ME from other forms of CFS. There are many references in the medical literature to inflammation of the CNS in ME and in "core" CFS [21] [22] [23] [24] [25] but such CNS inflammation is not found in all variants of CFS. It is incorrect to deny the existence of CNS inflammation in at least some forms of CFS (i.e. in ME), even though such inflammation is by no means universal in all forms of CFS. In some cases of ME there is

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[16] Myalgic Encephalomyelitis / Chronic Fatigue Syndrome and Enteroviral-Mediated Organ Pathology. John Richardson. *The Haworth Press Inc. New York, March 2001*

[17] Myalgic Encephalomyelitis – Then and Now. AM Ramsay EG Dowsett. In: The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome. Ed: BM Hyde, J Goldstein, P Levine. Pub: The Nightingale Research Foundation, Ottawa, 1992

[18] Cardiac and Cardiovascular Aspects of Myalgic Encephalomyelitis. BM Hyde A Jain. *ibid*

[19] Allergy and the chronic fatigue syndrome. Stephen E Straus et al *J All Clin Immunol 1988:81:791-795*

[20] The Epidemiology of Myalgic Encephalomyelitis (ME) in the UK. Evidence submitted to the All Party Parliamentary Group of Members of Parliament. EG Dowsett J Richardson. 23 Nov 1999

[21] A clinical description of a disease resembling poliomyelitis seen in Adelaide. Pellew RAA. *Med J Aust 1955:42:480-482*

[22] A chronic illness characterized by fatigue, neurologic and immunologic disorders. D.Buchwald, PR Cheney, DL Peterson, DA Ablashi, RC Gallo, AL Komaroff et al. *Annals of Internal Medicine 1992:116:103-113*

[23] Detection of intracranial abnormalities in patients with chronic fatigue syndrome. RE Schwartz et al. *Am J Roentgenology 1994:162:935-941*

[24] A 56 year old woman with CFS. AL Komaroff. *JAMA 1997: 278:14:1179-1184*

[25] Encephalomyelitis resembling benign myalgic encephalomyelitis. SGB Innes. *Lancet 1970: 969-971*

evidence of oligoclonal bands in the cerebrospinal fluid. [26] [27] It is accepted by the most experienced ME clinicians that some degree of encephalitis has occurred both in patients with ME and in those with post-polio syndrome: the areas chiefly affected include the upper spinal motor and sensory nerve roots and the spinal nerve networks traversing the adjacent brain stem (which is *always* damaged). [28] In nearly every patient there are signs of disease of the central nervous system. [29] Recent research continues to support neurological involvement. [30] [31] [32] [33] [34]

In the UK, patients with neurological signs and symptoms are usually the sickest and as such they are excluded from studies of "CFS", so the results of studies from which such patients are excluded are not representative of the true situation.

Physical signs found in ME

In cases of severe ME there are definite physical signs indicative of physical illness and not abnormal illness behaviour. Some of these signs are often present in less severely affected cases but are dismissed or trivialised in order to comply with the definition of CFS. Not all patients have all signs, but throughout the ME literature, the following are common in the sickest patients. Observable signs include nystagmus; sluggish visual accommodation; abnormality of vestibular function with a positive Romberg test; abnormal tandem or augmented tandem stance; abnormal gait; hand tremor; incoordination; cogwheel movement of the leg on testing; muscular twitching or fasciculation; hyper-reflexia without clonus; facial vasculoid rash; vascular demarcation which can cross dermatomes with evidence of Raynaud's syndrome and / or vasculitis; [35] mouth ulcers; [36] [37]

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[26] Neuromuscular Abnormalities in Patients with Chronic Fatigue Syndrome. Carolyn L.Warner,Reid R.Heffner, D Cookfair. In: The Clinical & Scientific Basis of ME / CFS. Ed: BM.Hyde, J Goldstein, P Levine. Pub. The Nightingale Research Foundation,Ottawa 1992

[27] The Differential Diagnosis between Multiple Sclerosis and Chronic Fatigue Postviral Syndrome. Charles M.Poser. *ibid*

[28] Polio Encephalitis and the Brain Generator Model of Post-Viral Fatigue. Bruno RL et al *Journal of Chronic Fatigue Syndrome. 1996:2: (2,3):5-27*

[29] A new clinical entity? Editorial: *Lancet 26 May 1956*

[30] Schwartz RM, Komaroff AL et al. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. *AmJ Roentgenol 1994:162: (4):35-41*

[31] McGarry F, Gow J and Behan PO. Enterovirus in the chronic fatigue syndrome. *Ann Intern Med 1994:120:972-973*

[32] Brainstem perfusion is impaired in patients with chronic fatigue syndrome. Costa DC, Tannock C and Brostoff J. Q J Med 1995:88:767-773

[33] Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. Tirelli U et al. *Am J Med 1998:105: (3A): 54S - 58S*

[34] Neurological dysfunction in chronic fatigue syndrome. Chaudhuri, A and Behan PO. *JCFS 2000:6: (3-4):51-68*

[35] The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome *pp. 42, 62, 70, 73, 87, 89, 91, 268, 376, 427-430.* Ed: BM Hyde, J Goldstein, P Levine. Pub: The Nightingale Research Foundation, Ottawa 1992

[36] Outbreak at The Royal Free. ED Acheson. *Lancet 20 August 1955:304-305*

[37] M.E. Post-Viral Fatigue Syndrome. Dr Anne Macintyre. Unwin Hyman 1989

hair loss; [38] [39] [40] a labile blood pressure; flattened or even inverted T-waves on 24 hour Holter monitoring [41] (a standard 12 lead ECG is usually normal); orthostatic tachycardia; shortness of breath (patients show significant reduction in all lung function parameters tested); [42] abnormal glucose tolerance curves, liver involvement [43] [44] [45] [46] (an enlarged liver is usually not looked for, so missed) and destruction of fingerprints: (atrophy of fingerprints is due to perilymphocytic vasculitis and vacuolisation of fibroblasts [47]).

From conversations which members of the Key Group have had with other Key Group members (especially those members in the discipline of psychiatry), it is abundantly clear that they are unfamiliar with the signs and symptoms of ME as distinct from other chronic fatigue states (which some equate with chronic fatigue), and that there is still a wide gap in their comprehension of the differences between subgroups.

What is CFS?

The term "CFS" did not come into existence until 1988. As a basis for sound scientific research, it has been a disaster. "CFS" is not a single diagnostic entity: it has become a heterogeneous and non-specific label embracing many different medical and psychiatric conditions in which tiredness and fatigue are prominent. The first (1988 Holmes et al) definition of CFS concentrated on "fatigue" persisting for at least six months, with a sore throat and tender lymph glands in the neck, together with cognitive impairment. It excluded the cardinal features of ME, which had been documented for decades (a specific form of post-exertional muscle fatiguability, extreme fluctuation and variability of symptoms, and chronicity). Ten years earlier in 1978, the UK Royal Society of Medicine had accepted that ME was a distinct nosological entity. [48] In 1988 the eighteen strong panel of medical scientists and clinicians charged with formulating a new case definition and new name could not agree: two of the most clinically experienced members refused to sign the final document and withdrew from the panel because the proposed definition

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[38] Chronic Fatigue and Immune Dysfunction Syndrome: a Patient Guide. CFIDS Assn. 1989
[39] The Disease of a Thousand Names. DS Bell. Pollard Publications, New York 1991
[40] How do I diagnose a patient with CFS? J.Goldstein. In: The Clinical and Scientific Basis of ME/CFS Ed: BM Hyde, J Goldstein, P Levine. Pub: The Nightingale Research Foundation, Ottawa, 1992
[41] Cardiac involvement in patients with CFS as documented with Holter monitor and biopsy data AM Lerner et al *Infectious Diseases in Clinical Practice 1997:6:327-333*
[42] Lung function test findings in patients with chronic fatigue syndrome, De Lorenzo et al. *Australia & New Zealand Journal of Medicine. 1996:26:4:563-564*
[43] Icelandic Disease (benign myalgic encephalomyelitis or Royal Free Disease). AM Ramsay EG Dowsett et al. *BMJ May 1977:1350*
[44] Chronic Fatigue Syndrome in Northern Nevada.SA Daugherty et al *Rev Inf Dis 1991:13:S3944*
[45] Chronic Fatigue Syndrome and Depression: Biological Differentiation and Treatment CM Jorge, PJ Goodnick. *Psychiatric Annals 1997:27:5:365-386*
[46] Symptoms patterns in long-duration chronic fatigue syndrome. F.Friedberg et al *J Psychosom Res 2000:48:59-68*
[47] Presentation by Dr Paul Cheney. Chronic Fatigue Syndrome National Consensus Conference. Sydney, Australia, 1995
[48] Epidemic neuromyasthenia 1934-1977: current approaches. Ed: WH Lyle & RN Chamberlain. *Postgraduate Medical Journal 1978 (November):54: 637:705-774*

and new name were too different from the ME with which they were so familiar. [49] Those two members were Dr Alexis Shelokov (USA) and Dr Gordon Parish (UK).

Notwithstanding the position of the Royal Society of Medicine, the case definition of CFS comprehensively ignores the overt features of neurological disease seen in ME (ME is often confused with multiple sclerosis [50]). It also ignores the evidence that ME (including "core" CFS which probably equates with ME) has features of autoimmune disorder
(e.g. lupus [51] [52]) and features of allergy and multiple chemical sensitivity (MCS), [53] [54] [55] [56] [57] [58] which is now officially recognised in the International Classification of Diseases, *ref: ICD 10: SGBV:3.1:code T78.4: Chemical Sensitivity Syndrome, Multiple.* Data presented at the American Association for Chronic Fatigue Syndrome (AACFS) Fifth International Research and Clinical Conference in Seattle in January 2001 showed that MCS was present in 42.6% of CFS patients compared with 3.8% of controls. [59] The immune abnormalities follow a recognisable, consistent and reproducible pattern, with clear evidence of an immune activation state, but this is not reflected in the current case definition, hence the worldwide support for a name change. Currently, the favoured choice (proposed and supported by immunologist Professor Nancy Klimas of the University of Miami) is for NIEDS or Neuro-Immune-Endocrine Dysfunction Syndrome.

It may well be the case that ME is one of the currently recognised conditions which are characterised by chronic fatigue, but ME is different in clinical presentation from other chronic fatigue syndromes. The evidence speaks for itself. Other postviral fatigue states are clinically in contrast to the three cardinal features of ME.[60] Other fatigue states which may follow flu, measles, chickenpox, herpes or mononucleosis lack not only the clinical but also the laboratory features of ME. [61]

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[49] Osler's Web. Inside the labyrinth of the Chronic Fatigue Syndrome Epidemic. Hillary Johnson. Crown Publishers Inc. New York ,1996

[50] The Differential Diagnosis between Multiple Sclerosis and Chronic Fatigue Postviral Syndrome. Charles M Poser. In: The Clinical and Scientific Basis of ME / CFS. Ed: Byron M Hyde, Jay Goldstein & Paul Levine. Pub: The Nightingale Research Foundation, Ottawa,1992

[51] as reference 47

[52] A Multi-centre study of autoimmunity in CFS. K Sugiura, D Buchwald, A Komaroff, E Tan et al AACFS, Seattle, January 2001 # 037

[53] Correlation between allergy and persistent Epstein Barr virus infections in chronic-active EBV infected patients. George B Olsen, James F Jones et al *J All Clin Immunol 1986:78:308-314*

[54] The Myalgic Encephalomyelitis Syndrome. JC Murdoch. *Family Practice 1988:5:4:302-306. Pub: Oxford University Press*

[55] Allergy and the chronic fatigue syndrome. Stephen E Straus, Janet Dale et al *J All Clin Immunol 1988:81:791-795*

[56] History of the chronic fatigue syndrome. Stephen E Straus. *Rev Inf Dis 1991:13:1:S2-S7*

[57] Epidemiology of Chronic Fatigue Syndrome. Paul Levine. *Clin Inf Dis 1994:18:1:S57-S60*

[58] Comparison of patients with chronic fatigue syndrome,fibromyalgia and multiple chemical sensitivities. D Buchwald, D Garrity. *Arch Intern Med 1994:154:2049-2053*

[59] Multiple Chemical Sensitivity in CFS. JN Baraniuk et al. AACFS Seattle, Jan 2001 # 124

[60] Myalgic encephalomyelitis or what? AM Ramsay. *Lancet 1988:100*

[61] ibid: *101*

The current case definition of CFS unequivocally states that those with CFS have no physical signs, but those with ME always do have physical signs. The overriding difficulty is that some clinicians in some medical disciplines apparently fail to see them or have no desire to look for them.

It is not the case (as stated in chapter 3 on page 20 of the draft) that some CFS / ME patients *"seem"* to have neuro-muscular symptoms. Patients with ME do have such symptoms. The non-psychiatric medical literature is explicit about such symptoms. In ME, those symptoms do not, as stated in chapter 3 of draft 6 of the CMO's report, "*reflect deconditioning (or) social isolation consequent on agoraphobia".* It is not disputed that some patients with on-going fatigue due to psychiatric disorder may have symptoms of deconditioning but those patients represent a different category of fatigue syndrome from the one which is formally classified as ME. Those severely affected by ME are indeed socially isolated, but such social isolation is not due to agoraphobia and it is necessary to make an accurate distinction before applying a presumptive label which unjustifiably stigmatises.

Where is the evidence that there is a need for careful subgrouping within "CFS"?

There is now an unmistakable recognition that sound research has strengthened the need for consideration of subgroups. [62] [63] [64] [65] [66] [67] [68] [69]

A recent Editorial in the Journal of Chronic Fatigue Syndrome [70] makes the point that *"the sorting of patients into subpopulations….is helping in the design and interpretation of clinical trials for therapeutic interventions aimed at particular disease manifestations".*

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[62] A Subgroup Analysis of Cognitive Behavioural Treatment Studies. Fred Friedberg. *JCFS 1999:5:3-4:149-159*

[63] Estimating rates of chronic fatigue syndrome from a community-based sample: a pilot study. Jason LA et al. *Am J Community Psychol 1995:23(4):557-568*

[64] Politics, Science and the Emergence of a New Disease. The case of Chronic Fatigue Syndrome. Jason LA et al. *Am Psychol 1997:52:9:973-983*

[65] Chronic fatigue syndrome, Fibromyalgia and Multiple Chemical Sensitivities in a community-based sample of chronic fatigue syndrome - like symptoms. Jason LA et al. *Psychsom Med 2000:62(5):655-663*

[66] Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. John DeLuca, Benjamin H Natelson et al. *J Neurol Sciences 1999:171:3-7*

[67] Fatigue 2000 Conference Proceedings. The National ME Centre in conjunction with The Essex Neurosciences Unit. 23-25 April 1999

[68] Severe and very severe patients with chronic fatigue syndrome: perceived outcome following an inpatient programme. DL Cox LJ Findley. *JCFS 2000:7(3):33-47*

[69] Symptom patterns in long-duration chronic fatigue syndrome. Fred Friedberg et al. J *Psychsom Res 2000:48:59-68*

[70] Editoral. Roberto Patarca-Montero. *JCFS 2000:7(4):1*

The 1994 CDC criteria for CFS (whilst referring only to CFS) themselves recommend that researchers use stratification techniques to identify subgroups of patients. [71]

One clear message which emerged from the National Institutes of Health (NIH) State of the Science Conference on CFS held on 23-24 October 2000 in Arlington, Vancouver was that CFS is heterogeneous and researchers ***must*** subgroup patients by features including chronicity, immunology and neuroendocrinology. [72] Conference participants included
Dr David Bell, Professor Dedra Buchwald and Professor Nancy Klimas, all world-renowned experts on CFS.

Roberto Patarca-Montero, Assistant Professor of Medicine and Director of the Laboratory of Clinical Immunology, University of Miami School of Medicine (as well as Editor of The Journal of Chronic Fatigue Syndrome) emphasises the importance of subsets of patients in his paper "Directions in Immunotherapy". [73]

Experienced researchers and clinicians presented evidence at the Fifth International AACFS Conference held in Seattle, 27-29 January 2001 about the need for subgrouping. Some examples include the following:

--- Professor Leonard Jason from De Paul University, Chicago, concluded that *"Subtype differences detected may account for some of the inconsistencies in findings across prior studies that have grouped CFS patients into one category. Subtyping patients according to more homogeneous groups may result in more consistent findings which can then be used to more appropriately and sensitively treat the wide range of illness experience reported by different types of individuals with CFS"* [74]

--- Professor De Meirleir from Brussels compared immunological profiles in three different subgroups of CFS patients; he found significant differences between the groups. [75]

--- Dr Pascale de Becker from Brussels presented evidence that there is a need to assess the homogeneity of a large CFS population in order to establish those symptoms which can improve differentiation of CFS patients. [76]

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[71] The Chronic Fatigue Syndrome: A Comprehensive Approach to its Definition and Study. Keiji Kukuda, Michael C Sharpe, Simon Wessely et al. *Ann Int Med 1994:121:12:953-9*
[72] Conference calls for Serious Research. T.Lupton. *CFIDS Chronicle 2001:14:1:12-13*
[73] Directions in Immunotherapy. Roberto Patarca-Montero. *The CFS Research Review 2001:2:1*
[74] Subtyping patients with Chronic Fatigue Syndrome in a Community Based Sample. Leonard A Jason et al. Presented at AACFS, January 2001 # 011
[75] Cytokine Levels in CFS Patients with a Different Immunological Profile. Kenny De Meirleir et al. Presented at AACFS, January 2001 # 017
[76] A Definition Based Analysis of Symptoms in a Large Cohort of Patients with Chronic Fatigue Syndrome. Pascale De Becker et al. Presented at AACFS January 2001 # 019

--- Dr Paul Levine from Washington demonstrated that factor analysis is an important tool for separating subgroups of CFS; he showed that it should be utilised in future attempts to develop case definitions for CFS to identify discrete patient groups, which may have different pathogeneses and responses to treatment. [77]

--- Dr Katherine Rowe from Australia presented evidence showing that at least three distinct subgroups can be identified within the CFS syndrome. [78]
--- A large international multicentre study of autoimmunity was presented by E.Tan (with, amongst others, participants from The Scripps Research Institute, La Jolla, California; the University of Washington; Harvard Medical School, Boston; State University of New York and George Washington University,Washington DC.
Of interest is that another participant was Simon Wessely from Kings College, London). This large study reflected the heterogeneity from one CFS centre to another; it emphasised the importance of subcategorising CFS studies. [79]

In the light of current awareness of the overriding need for consideration of subgroups within CFS (including that which has emerged from Seattle), there is concern that if some of the content of chapter 3 of the present draft is incorporated into the final version, then the UK CMO's Report may be immediately dismissed and be held in derision by well-informed clinicians and patients alike.

The various views of the WG on the need for subgroups

In February 1999 a member of the CMO's Key Group (Dr Derek Pheby of The Unit of Applied Epidemiology, Frenchay Campus, Bristol) produced a discussion document [80] for the Working Group to consider. In that document, the author is unequivocal about the need for attention to be given to the existence of subgroups and he quotes from the Report of the UK National Task Force on CFS / PVFS / ME. [81] The Task Force Report states unequivocally that ***"Although both the terms "CFS" and "ME" have a range of applications, they do not represent the same populations".***

It is a matter of record that those who favour a psychiatric aetiology (and who wish to eradicate the classification and even the existence of ME [82]) were unhappy about the Report from the Task Force; indeed, the Report itself acknowledges this, stating *" People who gave us their much-valued help are not necessarily in agreement with the opinions expressed".* Being known to be in disagreement with the Report from the National Task

[77] Use of Factor Analysis in Detecting Subgroups (of CFS patients). Paul H Levine et al Presented at AACFS January 2001 # 052
[78] Symptoms Patterns of CFS in Adolescents. Katherine Rowe et al. AACFS Jan 2001 # 064
[79] A multicenter study of autoimmunity in CFS. K.Sugiura, D Buchwald, A Komaroff, P Levine, S Wessely, EM Tan et al. Presented at AACFS 2001 # 037
[80] Discussion Document: an overview of the recent research literature. Dr Derek Pheby.Feb 1999
[81] Report from The National Task Force on Chronic Fatigue Syndrome, Postviral Fatigue Syndrome, Myalgic Encephalomyelitis. Westcare, Bristol 1994
[82] Eradicating ME. Report of a lecture given by Simon Wessely on 15 April 1992 at Belfast Castle,Belfast. Pfizer / Invicta Pharmaceuticals 1992: 4-5

Force (which did not have a psychiatric bias), the proponents of the psychiatric view responded to the Task Force Report by producing their own report (that of the Joint Royal Colleges' mentioned above, in the Preface to which it confirms that the authors of the Joint Royal Colleges' Report are not in agreement with all the findings of the National Task Force report).

In his discussion document for the CMO's Working Group, Dr Pheby explicitly states (emphasis added):

" The National Task Force recommended that five main sets of issues should be addressed, i.e. ***Clarify the difference between the various chronic fatigue syndromes…*** *areas where in the view of the Task Force research needed to be encouraged included:* ***clear definition of the various chronic fatigue syndromes****"*

" CFS is a ***spectrum*** *of disease"* [i.e. not a disease entity in itself (quoting Levine) [83] who is emphatic that *"It is clear that CFS is not a single entity"]*

"Variations in prognosis may be attributable once again to the heterogeneity of the condition, ***with different subgroups having different prognoses"***

"The heterogeneity of CFS has made it very difficult to interpret research results from different studies which may have been conducted in very dissimilar populations"

"If progress is to be made, it is necessary to consider…the possible existence of subgroups within the population of patients with CFS / ME"

"The increasing knowledge of pathological processes occurring in CFS / ME has led to a belief that it should be possible to define subgroups on the basis of biomarkers and thus to draw a distinction between CFS and ME"

"It has been argued by many that not only can ME be differentiated from CFS by biological markers, but that its clinical features also differ"

Under "Priority Areas for Research", the author concludes *"Certain areas for research have been identified as being important in enabling the Working Group to achieve its objectives. These include…systematic reviews to consider* ***subgroups****"*

On 24th August 2000 Helen Wiggins of the NHS Executive (who co-compiled chapters 1 and 2 of version 6) e-mailed a correspondent as follows:

" I would also like to assure you that the CFS/ME Working Group is aware that treatment that works for one person does not necessarily work for another. Hence the

[83] Epidemiologic advances in chronic fatigue syndrome. Levine PH. *Journal of Psychiatric Research 1997:31:1:7-18*

fact that the team undertaking the Systematic Review will look at evidence that subgroups of patients respond differently to treatment".

On 18th August 2000 Professor Pinching wrote to Mrs Anne Crocker of Okehampton as follows:

".... there is no doubt in my mind that the CMO's Group is well aware of the heterogeneity of CFS/ME....obviously "one size" will not fit all....I hope very much that the final product will adequately address these issues".
In an e-mail to a correspondent dated 11th December 2000 Professor Pinching wrote:

" I am all too well aware of the fact that current treatment options are unsatisfactory and that there is a significant group of patients where our current very limited armamentarium is either ineffective or worse".

On 11th January 2001 he e-mailed a correspondent as follows:

" It may be that we can define subgroups that are useful and I would have no problem with the concept (I have done this on other disease entities (when) subgrouping has also been helpful), recognising that a broad spectrum of related things can be seen as a useful grouping...."

The apparent change of mind by the authors of chapter 3 of the draft regarding the need for subgroups

Chapter 3 was compiled by Dr Derek Pheby, Professor Anthony Pinching and Dr Tim Chambers. From what had earlier been made known of the WG's intentions (examples of which are set out above), many people were hopeful that the matter of subgroups would be addressed, especially given their importance in relation to the implications for treatment outcomes.

Seemingly this is not to be.

To the consternation of a very considerable number people (not only in the UK but via the internet to a worldwide readership), a paper on CFS recently appeared in Prescribers' Journal [84] (published by the Department of Health for the benefit of all UK GPs). It was authored solely by Professor Pinching whilst he currently holds the position of Deputy Chair of the CMO's Key Group and as such, it caused an outcry. It was deemed to be a forerunner of the CMO's Report on the basis that even when wearing two hats, the same wearer could not credibly hold substantially divergent views. The article was seen as illustrating very clearly the extent of the problem of differentiation between the specific and the generic and just how easy it is for the unwary (or those who are following a pre-determined agenda) to "lump together" ME with other fatigue states.

[84] Chronic fatigue syndrome. Anthony J Pinching. *Prescribers' Journal 2000:40:2:99-106*

In the article, Professor Pinching states (emphasis added):

> *" CFS …is a clearer appreciation of a pattern of symptoms previously characterised in many different ways"*
>
> *" **over investigation can be harmful** and counterproductive to the management of these patients…**causing them to seek abnormal test results to validate their illness"***
>
> *" patients may need guidance about claims…. from other practitioners"*
>
> *" (patients) …avoid activity, fearing relapse, but then develop symptoms of deconditioning…or **excessive awareness of physiological changes"***
>
> *" cognitive behavioural therapy…can substantially optimise rehabilitation"*
>
> *" Complementary therapists…sometimes reinforce unhelpful illness beliefs"*
>
> *" **The essence of treatment is activity management and graded rehabilitation**".*

The author does not even mention ME or the key manifestations of it and he expressly states that the fatigue found in CFS is *"not related to ongoing exertion"*. In ME, there is always **post-exertional muscle fatigue**, without which the diagnosis of ME is unsustainable.

Further, on 2nd December 2000 Professor Pinching produced his own personal draft for the CMO's Report.[85] In it he states that CFS has been the preferred medical term for this disorder, or group of disorders, in recent years; that "myalgic" is inappropriate to the significant proportion of those who have no muscle pain, and that "encephalomyeltitis" (meaning inflammation of the brain and spinal cord) is evidently incorrect in implying a pathophsyiological process for which there is no evidence *(sic)*.

In version 6, chapter 3 on page 18 of the draft, it states:

> *"we do not see that it is either practicable or appropriate to use the term ME to define a subgroup within CFS, or even distinct from it……there is currently no clear evidence from the literature formally to differentiate ME from CFS on grounds of either pathophysiology or response to treatment"*
>
> *" **The Working Group suggests for the meantime that the terms CFS and ME are used synonymously** as the composite CFS/ME for the purposes of this report".*

On page 20 of chapter 3 of the draft, it states:

[85] CMO's CFS/ME Key Group: Draft for discussion, prepared by Prof AJ Pinching. 2.xii.00

> "*For the meantime, it seems appropriate to regard CFS / ME as a single, albeit diverse, clinical entity……..on present evidence (subdividing categories of CFS) may be considered a matter of semantics and personal philosophy rather than a matter of established fact".*

Good science surely requires attention to detail and not the broad-brush approach, however politically expedient or financially attractive such an approach might be.

To the acute dismay of those who represent the subset of patients who <u>*do*</u> have evidence of CNS disturbance (including inflammation), this latest draft of the CMO's Report seems to ignore Dr Pheby's carefully prepared and accurate document and instead to accept Professor Pinching's personal view -- a view which echoes that of the psychiatric lobby as expressed in the Report of the Joint Royal Colleges (as did his article and choice of references in Prescribers' Journal referred to above). As already mentioned, this draft (version 6, chapter 3) states categorically:

> ***" We do not see that it is either practicable or appropriate to use the term ME to define a subgroup within CFS, or even distinct from it".***

Can this really be called "evidence-based medicine"?

In the final Report, clinicians' view of the impact of the illness will need to reflect both patients' clinical reality and the established laboratory abnormalities found in the various subgroups, not just the prevailing misconceptions so widely promoted by a group of UK psychiatrists. Those misconceptions are:

1. a psychological rehabilitation programme is the treatment of choice for those with ME / CFS

2. any differences between subgroups (or between ME and CFS) are of no clinical significance

3. brain imaging and / or laboratory abnormalities found in ME / CFS are merely inconsequential epiphenomena.

It is likely that the three misconceptions above all derive from one event. That event was a meeting held at Green College, Oxford in 1990 and it resulted in the 1991 Oxford criteria for CFS; it was convened by three psychiatrists and chaired by a fourth (Professor Anthony Clare). Clare informed attendees that the only reason for calling the meeting was to deal with "*a group of patients with a cluster of symptoms who get a lot of publicity".*[86] It is Professor Clare who, together with psychiatrists Simon Wessely and Michael Sharpe, is to be one of the three keynote speakers as experts on CFS at the forthcoming World Congress of Neurology organised by Professor Hughes of Guy's

[86] Consensus on research into fatigue syndrome. *BMJ 1990:300:382*

Hospital in London on 18th June 2001: a complaint of lack of balance has been lodged with the organisers which is understood to be receiving attention.

Implications for treatment if the CMO's final report continues to assert that there is no need for subgrouping.

In the pursuit of both medical science and medical practice it is necessary to be as specific as possible. Nowhere is this more true than in relation to the various categories of "CFS". Not only is a broad brush approach potentially harmful (particularly the use of CBT involving aerobic graded exercise regimes) to those with mitochondrial damage, [87] the claimed success with the approach of just one group of UK psychiatrists and their colleagues has not been replicated elsewhere. Fred Friedberg, Clinical Professor in the Department of Psychiatry at the State University of New York makes the point that

"Several studies of graded activity-oriented cognitive behavioural treatment for CFS, all conducted in England, have reported dramatic improvements in functioning and subsequent reductions in symptomatology. On the other hand, cognitive behavioural interventions conducted in Australia and the United States have not found significant improvements in functioning or CFS symptoms. Furthermore, descriptive studies of CFS patients in England, the US and Australia suggest that the CFS population studies in England show substantial similarities to depression, somatization or phobia patients, while the US and Australian research samples have been clearly distinguished from depression patients and more closely resemble fatiguing neurological illnesses". [88]

Such disparate findings are likely to be the result of different authors studying different subgroups of CFS. It would reflect badly if the CMO's WG report failed to understand the importance of this concept.

With this in mind, a few examples of the findings presented at Seattle (AACFS Conference, January 2001) are set out below. To imagine that one treatment modality (especially the psychological approach of cognitive behaviour therapy with or without a programme of graded exercise) could apply to all cases of "CFS" would indeed be inappropriate or worse, a fact which Professor Pinching appeared to appreciate in his e-mail of 11 December 2000 mentioned above.

Some findings presented at the AACFS Conference, Seattle, January 2001

It is perhaps worth reiterating that the American term "CFS" reflects patients who are likely to have ME / "core" CFS rather than psychiatric disorder as facilitated by the

[87] International Congress of Bioenergetic Medicine. Dr Paul Cheney. Orlando, Florida, 5-7 February 1999

[88] A Subgroup Analysis of Cognitive Behavioural Treatment Studies. Fred Friedberg. *JCFS:1999:5:3-4:149-159.* Also published as Chronic Fatigue Syndrome: Advances in Epidemiological, Clinical and Basic Science Research. Ed: Roberto Patarca-Montero. Pub: The Haworth Press Inc. New York 1999

current CFS case definition: this situation is one which requires immediate international input to end what is obviously a most confusing and unsatisfactory situation for all involved.

In his keynote address, Professor Komaroff reminded physicians that with CFS, just because something is not yet written does not mean that it is not true.

Brain studies / Neurology

Different neurobiological profiles are found in CFS patients compared with healthy controls. Using assays which measured hormones and cytokines with a potential for affecting the central nervous system (cortisol, prolactin, oestrogen, progesteron, CRP, neopterin, TNFalpha, TGFbeta, DHEA-s), significant differences were found in CFS patients compared with controls. [89]

Both baseline heart rate and plasma epinephrine were increased in CFS patients, suggesting an activated sympathoadrenal state. [90]

Sympathetic nervous system dysfunction is integral to CFS pathology. [91]

A wealth of studies (about 85%) confirm autonomic nervous system (ANS) dysfunction in up to 90% of CFS patients, with resulting effects on many vital functions (blood pressure, pulse rate, breathing and body temperature). Professor Komaroff said that there is substantial evidence that both the sympathetic and parasympathetic nervous systems are abnormal in CFS.

CFS patients showed reduced activation of medial/basal frontal regions but a greater activation of dorsolateral frontal and temporal lobes than controls. This MRI study showed unique features of cognitive impairment, demonstrating that more areas of brain activity were used in task solving than in controls (ie. CFS patients are working harder than controls to solve the same problem and use more brain areas than controls). [92]

A quantitative volumetric study suggests that some CFS patients show a lateral ventricular enlargement, which may be associated with white matter loss in the frontal as well as the parietal lobes. [93]

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[89] Neuroendocrinological Profiles in Patients with CFS. B Evengard et al. AACFS # 001

[90] Orthostatic intolerance and sympathoadrenergic reactivity in chronic fatigue syndrome. PMMB Soetekouw et al AACFS # 085

[91] Sympathetic Dysfunction Demonstrated by Isometric Hand-grip Response in Chronic Fatigue Syndrome. JN Baraniuk et al. AACFS # 126

[92] Brain correlates of cognitive effort in chronic fatigue syndrome and healthy control subjects. Mahurin RK, Buchwald DS et al AACFS # 088

[93] Chronic Fatigue Syndrome: Quantitative Assessment of Cerebral Volumes. Gudrun Lange, Benjamin Natelson et al. AACFS # 045

Psychopathology

CFS patients do not display the same improvement with treatment as seen in depressed patients. Little overall change is seen in CFS patients on either physical or mental scores after antidepressant treatment. [94]

Expectancy effects do not account for heightened pain sensitivity. [95]

Findings from one of the largest well-studied patient groups in the world which used a factor analysis (done by computer, which eliminates all bias by the researcher) suggests that psychiatric disorder is not a core aspect of CFS and that this is a strong argument against CFS being a psychosomatic or "functional somatic" disorder. [96]

Whilst significant neuropsychological impairment was found in CFS patients, no subject performed in the range suggesting lack of effort or feigned impairment. [97]

The often-proposed hypothesis that CFS is a form of somatisation disorder was tested. It is apparent that there is no relationship between the number of medically unexplained symptoms and psychiatric diagnosis. CFS has no relation to somatisation disorder [98]

Visual processing disabilities

Investigation of the biological basis of visual processing disability in CFS showed that alteration in visual processing response is associated with evidence of altered connective tissue turnover. [99]

Biochemistry

Symptom expression is associated with changes in serum lipid levels. Significant changes in glucose, amino acid and inflammatory mediating fatty acids may be involved in symptom expression. Increases in levels of polyunsaturated fatty acids had the highest correlation with both fatigue and muscle pain scores. [100]

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[94] A comparison of treatment outcome in CFS and in major depression. SN Schwartz, R Jones. AACFS # 106

[95] Increased pain sensitivity in fibromyalgia/CFS. RH Gracely, DJ Clauw et al. AACFS # 141

[96] A factor analysis study of syptoms in 1573 patients with chronic fatigue syndrome. P De Becker, N McGregor, K De Meirleir. AACFS # 020

[97] Malingering in chronic fatigue sydrome: a neuropsychological investigation. Lana Tiersky Benjamin Natelson et al AACFS # 102

[98] The relationship between medically unexplained somatic symptoms and psychopathology in chronic fatigue syndrome. Daniel Cukor, Lana Tiersky, Benjamin Natelson. AACFS # 028

[99] Scotopic vision alterations in chronic fatigue syndrome. NR McGregor, RH Dunstan et al AACFS # 057

[100] Analysis of serum lipid changes associated with self-reported fatigue, muscle pain and the different chronic fatigue syndrome factor analysis symptoms clusters. McGregor NR, Dunstan RH, De Meirleir K et al. AACFS # 059

Objective examination of skeletal muscle tissue in CFS patients (biopsy of the vastus lateralis muscle) showed that activity of all skeletal muscle anti-oxidative enzymes were significantly increased in CFS patients compared with controls. Lipid analysis showed fatty acid modifications in patients but not in controls. Fluorsecence polariztion showed a significant decrease of membrane rigidity with a consequent increase in membrane fluidity.
There is evidence of a dengenerative process of the muscle tissue in CFS patients, as typically occurs in mitochondrial myopathies. This may contribute to muscle fatiguability and it supports an organic origin for CFS. [101]

Virology

CFS patients with active HHV6 infection (viraemia) have activation of coagulation and are hypercoaguable. Since HHV6 is known to infect endothelial cells, there may be a resultant endothelial cell dysfunction triggering the coagulation system. [102]

Genetic abnormalities

Recent studies have demonstrated circulating plasma RNA in Gulf War Syndrome patients. A study was therefore conducted to determine the presence or absence of RNA in CFS patients and to determine if the amplified sequences of RNA were similar to or different from those found in GWS. All chronic illnesses studied (including GWS, CFS, AIDS and multiple myeloma) show prominent RNA not observed in normal controls. Prominent RNA bands so far sequenced show homology with human genes which are noted for their tendency for gene rearrangement under severe physiologic stress. The most amplified sequences appear to be disease specific. [103]

Dr N.Afari, Associate Director of the University of Washington CFS Research Centre said that genetic abnormalities may team up with environmental influences to produce CFS. Environmental influences which worldwide researchers are investigating include the frequent pairing of CFS with food and chemical sensitivities. [104]

Microbiology

The dysregulation of the important anti-viral 2-5 RNase L pathway in CFS is a potential biomarker for the disorder. The RNase L pathway is a series of enzymatic reactions which go on inside white blood cells when they perceive themselves to be challenged by viruses and possibly also by some toxic exposure. Elevated levels of RNase L are associated with reduced maximal oxygen consumption (VO_2max) and exercise duration in patients with CFS. Both abnormal RNase L activity and low oxygen consumption were observed in

[101] Oxidative Damage in Chronic Fatigue Syndrome. D Racciatti et al. AACFS # 150
[102] Hypercoaguable state associated with active Human Herpes Virus 6 (HHV6) viraemia in patients with CFS. JH Brwer, D Berg. AACFS # 098
[103] RNAs in the plasma of patients with chronic fatigue syndrome: a novel mechanism for chronic illness expression with both treatment and diagnostic implications. PR Cheney, HB Urnovitz AACFS # 074
[104] Dr N Afari . Reporting on AACFS Conference. Judith Blake. Seattle Times 26 January 2001

most patients with CFS. These findings demonstrate that patients' extremely low tolerance for physical activity is likely to be linked to abnormal oxidative metabolism, perhaps resulting from defective interferon responses. [105]

Much of the Belgian work focused on the abnormal enzyme pathways found in CFS. In healthy people, the enzyme breaks down viral RNA and destroys the infected cell. The 37 KDa (kiloDalton) low molecular weight (LMW) RNase L fragment found in CFS patients is produced by calpain (an apoptotic enzyme) cleavage, and the whole process affects the calcium and potassium channel mechanisms. The channelopathy will lead to low body potassium. Instead of the normal size 80KDa enzyme, those with CFS show only a
37 KDa size enzyme. Testing the ratio of the 37KDa and 80KDa enzymes has revealed that a high ratio is associated with more severe clinical symptoms. The 37KDa RNaseL is associated with incomplete cell death (which means that the cell constituents cannot be recycled for use by other cells). [106]

Patients suffering from CFS present many symptoms, including pain, which are likely to reflect dysregulation in cellular ion transport. Fragments released by a pathological protein cleavage result in dysregulation of sodium channels, which play a major role in the generation of pain and hyperalgesia in peripheral neurons, with a resultant shift in the pain sensitivity threshold as well as (if occuring in epithelial cells) to drenching sweats. An improper function of the sulfonylurea receptor (SUR1) could lead to an extreme loss of cellular potassium. Improper function of ATP binding cassette (ABC) transporters leads to serious neurological dysfunctions. Common symptoms of CFS could be due to a malfunction of various ABC transporters. [107]

Immunology

Increased apoptosis (programmed cell death) in peripheral blood mononuclear cells (PBMC) of patients with CFS has been suggested to contribute to the symptomatology. RNase L activation has been directly linked to the induction of apoptosis. This study showed that the activation of RNase L in the PBMC of CFS patients upregulates apoptotic activity in these cells. This suggests that the peturbed apoptotic process may play a role in the altered immunologic functions in CFS. [108]

A large number of CFS patients have an abnormal immunological profile which can result in the production of immunologic mediators such as interferon, interleukin and

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[105] Comparison of maximal oxygen consumption and RNase-L enzyme in patients with chronic fatigue syndrome. CR Snell et al. AACFS # 026

[106] The low molecular weight ribonuclease L present in peripheral blood mononuclear cells of CFS patients is formed by proteolytic cleavage of the native enzyme. P.Englebienne, RJ Suhadolnik et al. AACFS # 065

[107] The interaction of RNase L ankyrin domain with ABC transporters might explain pain and many of the physiological disorders of CFS. P Englebienne, K De Meirleir et al. AACFS # 069

[108] Apoptotic dysfunction consecutive to RNase L cleavage is likely to be central to the maintenance of chronic fatigue syndrome. P.Engelbienne, K De Meirleir et al. AACFS # 068

other cytokines. The upregulation of the 2-5A Synthetase /Rnase L pathway shown in CFS patients indicates an activated immune state. According to their immunologic profile, CFS patients were divided into three groups. The results show that the presence of an increased amount of LMW RNase L correlates with higher levels of interferon gamma. [109]

Autoimmunity in CFS was reviewed. Low titres of antinuclear antibodies have been found in CFS patients. A major multi-centre study looked at the presence of autoantibodies to a cellular protein expressed primarily in neuronal cells (MAP2). Initial studies with immunohistochemistry showed a high percentage of CFS sera reactive to centrosomes. Preliminary evidence shows that other proteins beside MAP2 might also be target antigens in CFS autoimmunity. Of interest is the high frequency of reactors in lupus and rheumatoid arthritis compared with CFS patients. [110]

The intracellular content of the Natural Killer (NK) cell is perforin, a cell lytic protein common in many cells of the immune system which correlates with the cytolytic potential of the cell. In CFS, this chemical is reduced in NK cells. This finding substantiates claims of an NK associated defect in CFS and suggest a molecular basis for the reduced cytotoxicity (immune system killer cell function). This defect may not be NK specific but may encompass the cytotoxic T cell subset as well. Mice which were genetically engineered to have low or absent levels of perforin showed the same immune abnormalities as CFS. Other abnormalities found include activated lymphocytes in various subsets, elevated levels of immunoglobulins (IgG in particular) and increased levels of immune molecules called pro-inflammatory cytokines. Also found was a reduced activity of delayed hypersensitivity. [111]

Overlapping symptomatologies between CFS and Gulf War Syndrome have been observed by different investigators. It was therefore of great importance to verify whether various immunologic abnormalities found in CFS are also found in GWS. Overall differences between the two groups were not significant. The results indicate that, as in the case of CFS, Gulf War veterans are suffering from neuroimmunological disorder. Importantly, it was shown that basic laboratory testing is not sufficient for these groups of patient: advanced immunological tests including immune function and antibodies to the neurological system are needed. [112]

This needs to be compared with the recommendations in the Joint Royal Colleges' Report on CFS, which specifically state that no investigations should be performed to confirm the diagnosis *(page 45)* and that immunological abnormalities should not

[109] Cytokine levels in patients with a different immunological profile. Kenny De Meirleir et al AACFS # 017

[110] A multi-centre study of autoimmunity in CFS. K Sugiura, D Buchwald, A Komaroff, E Tan et al AACFS # 037

[111] Flow cytometric measurements of perforin and natural killer cell activity. Kevin Maher, Nancy Klimas, Mary Ann Fletcher. AACFS # 047

[112] Immunological studies on the blood of patients with Gulf War Syndrome. A.Vojdani. AACFS # 076

"*deflect the clinician from the biopsychosocial approach….and should not focus attention….towards a search for an 'organic' cause*" *(page 13).* It may also be salutary to reflect on the opinion expressed by Professor Pinching in his article on CFS in Prescribers' Journal ie. that *"over-investigation can (cause patients) to seek abnormal test results to validate their illness"* .

Conclusion

The practice of medicine ought not to be a pitched battle between patients and their clinicians. Such an unsatisfactory situation may have arisen because for the most part, patients with severe ME / "core" CFS are far better informed than their doctors about their condition. Sufferers know that the disorder is much more than "chronic fatigue" and that not only are many doctors failing to offer support but instead are denigrating them and dismissing or trivialising other symptoms with which patients present. There is considerable anecdotal evidence that many GPs refuse home visits for ME / "core" CFS patients however sick they are, and there is an alarming tendency for such patients to be summarily removed from a GP's list. One patient was informed by the GP that he had no time for people who only *thought* they were ill. Sadly, as far as ME / CFS patients are concerned, it still seems to be true that the *"average doctor will see they are neurotic and he will often be disgusted with them".*[113] Why should this be?

The notion that ME / CFS is a single entity affecting mostly females with a dysfunctional belief which is amenable to psychotherapy must surely now be dispelled.

There is increasing understanding that a variety of viruses may play a part in the aetiology and symptomatology of the composite "CFS" [114] and it is suggested that there might be various pathways into the final common pathway of neurobiologic dysregulation. [115]

The current draft (version 6) states in chapter 3 on page 13 that *"It is not clear whether it is more common now than previously".* This ignores the evidence from UNUM (one of the largest disability insurers in the United States). In April 1994, UNUM reported that in the five years from 1989 - 1993, mens' disability claims for CFS increased 360%, whilst women' claims for CFS increased 557%. **No other disease category surpassed these rates of increase.** In order of insurance costs, CFS / ME came second in the list of the five most expensive chronic conditions, being three places above AIDS. At the AACFS

[113] Chronic fatigue and myalgia syndromes. Simon Wessely. In: Psychological Disorders in General Medical Settings. Ed: N.Sartorius et al Pub: Hogrefe and Huber 1990

[114] Human Herpes Viruses and Chronic Fatigue Syndrome. Hay J and Jenkins FJ. In: Chronic Fatigue Syndrome. Ed: Stephen E Straus. Pub: Marcel Dekker Inc. New York 1994

[115] Understanding Chronic Fatigue Syndrome: An Empirical Guide to Assessment and Treatment. Friedberg F and Jason L. Pub: American Psychological Association, Washington 1998

Conference in Seattle (January 2001), Dr N.Afari, Associate Director of the University of Washington's CFS Research Centre, stated that the disorder appeared to be increasing. [116] Whether it is increasing or not, patients require and deserve at least the same level of medical and social support as is provided for other serious and chronic conditions.

It is to be hoped that the final version of the CMO's Working Group report on CFS / ME will address the need for subgroups and that it will recommend a concerted effort to unravel this particularly perplexing and complex disorder which can and does have a devastating and far reaching effect on the lives of so many people.

[116] Judith Blake, Seattle Times, 26th January 2001