Immunological, neuroendocrine and neurological evidence (including evidence of CNS inflammation) documented in ME/CFS that NICE chose to ignore in the production of its Clinical Guideline 53

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Executive Summary

"*ME is not a new disorder; there are many reports in the medical literature spanning at least 70 years and in April 1978 the Royal Society of Medicine accepted ME as a distinct entity. It is a serious and complex disorder which can affect virtually every major system in the body, with neurological, immunological, cardiovascular, respiratory, hormonal, gastrointestinal and musculo-skeletal manifestations*" (M Hooper; "The Mental Health Movement: The Persecution of Patients?" December 2003 pp 17-18 http://www.meactionuk.org.uk/SELECT_CTTEE_FINAL_VERSION.htm).

In the light of the above it is simply remarkable that the Guideline Development Group (GDG) which produced the NICE Clinical Guideline CG53 on Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) chose to ignore decades of medical and scientific literature, literature that includes an evidence-base of over 4,000 biomedical publications regarding the disorder that they set out to consider.

Whilst it is true that ME/CFS is a serious multi-system organic disorder affecting virtually all the organs and systems in the body, this document looks in particular at the abnormalities found in three specific areas: the immune system, the neuroendocrine system, and central nervous system. For each of these three areas illustrations of research findings are given, all of which provide evidence of biomedical abnormalities found in patients with ME/CFS, and all of which the GDG chose to ignore. In addition, the document starts by briefly considering the issue that the term "CFS/ME" as used by NICE was in fact misleading.

Some of the key points in the document are summarised as follows:

(i) The term "CFS/ME" used by NICE was misleading

- The Wessely School's modus operandi of combining all states of unexplained fatigue into one heterogeneous label ("CFS/ME") has had detrimental consequences for patients, as noted as long ago as 1994
- By ignoring the existing evidence-base for ME/CFS, the GDG was able to ignore the documented biomarkers that separate ME/CFS from "CFS/ME" and was therefore expediently able to recommend only behavioural interventions.
- NICE has essentially reduced "CFS/ME" to chronic tiredness and just one other symptom.

(ii) Illustrations of immunological dysfunction in ME/CFS from the published literature that NICE disregarded

- "Our investigations suggest that this syndrome is characterised by objective laboratory abnormalities (and) immune dysfunction appears to be a hallmark of the disease process"
- "In a normal population, 20% of lymphocytes are active at any given time. 'In (ME)CFS, up to 80% of the cells are working'. These lymphocytes and cytokines are so up-regulated that they cannot be driven any harder. It is as if they have been pushed as far as they can go and the immune system is completely exhausted"
- "Our observations strongly suggest that a large population of (ME)CFS patients have immunologic disorders and that their symptoms could be explained by a chronic immune activation state (and) that (ME)CFS represents a type of autoimmune disease in which a chronically activated immune system reacts against the host"

- "The exacerbation of symptoms after exercise differentiates (ME)CFS from several other fatigue-associated disorders. Research data point to an abnormal response to exercise in patients with (ME)CFS compared to healthy sedentary controls, and to an increasing amount of evidence pointing to severe intracellular immune dysregulation in (ME)CFS patients"
- "The data presented in this report are consistent with the presence of an underlying, detectable abnormality in immune cell behaviour of many ME/CFS patients, consistent with an activated inflammatory process, or a toxic state".

(iii) **Illustrations of neuroendocrine dysfunction in ME/CFS from the published literature that NICE disregarded**

- "There is an increasing volume of evidence to support the view that patients with (ME)CFS have unique endocrinology patterns. The cardinal findings include attenuated ACTH responses to CRH and low 24-hour urinary cortisol. These are compatible with a mild central adrenal insufficiency"
- "Our group has established that impaired activation of the HPA axis is an essential neuroendocrine feature of (ME)CFS"
- "The right and left adrenal gland bodies were reduced by over 50% in the (ME)CFS subjects, indicative of significant adrenal atrophy in a group of (ME)CFS with abnormal endocrine parameters"
- "We compared cortisol response in the (ME)CFS subjects with the response in control subjects and in those with secondary adrenal insufficiency. We have shown that cortisol increment at 15 and 30 minutes is significantly lower in the (ME)CFS group than in controls. However, there was no difference between the (ME)CFS group and those with secondary adrenal insufficiency in any of the parameters. Consequently, reduced adrenal responsiveness to ACTH exists in (ME)CFS".

(iv) **Illustrations of neurological dysfunction in ME/CFS from the published literature that NICE disregarded**

- "Some people think that (ME)CFS can look like MS and there are clinical features that are overlapping. The most specific neurologic symptom is dysequilibrium. These patients have a balance disturbance and on certain simple neurologic tests they fall over. On more sophisticated neurologic tests of vestibular function they are often grossly abnormal. Nearly every patient had something abnormal within the central nervous system (CNS), and also neuromuscular problems. Over half of (ME)CFS patients will typically show lesions within the central nervous system"
- "The symptoms of (ME)CFS have long been viewed as a neurologic pattern, as indicated by other names for the condition such as myalgic encephalomyelitis (and) atypical poliomyelitis. Neurologic involvement is beginning to be confirmed by documentation of abnormalities in cerebral perfusion, hypothalamic function, and neurotransmitter regulation. A link is being forged between the symptom pattern and objective evidence of CNS dysfunction. The view that (ME)CFS is a primary emotional illness has been undermined by research findings"
- "A complete neurological examination should be an integral part of the diagnostic assessment of illnesses described as CFS"
- "Our data suggest that (ME)CFS may involve a primary neurological abnormality. (ME)CFS patients also show dysfunction in complex auditory processing that is of the same magnitude as that found in patients with multiple sclerosis. Other data show that patients with ME/CFS had significantly lower brain stem perfusion ratios than either healthy or depressed controls"
- "(ME)CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. Physical activity-induced EEG signal changes may serve as physiological markers for more objective diagnosis of (ME)CFS".

Immunological, neuroendocrine and neurological evidence (including evidence of CNS inflammation) documented in ME/CFS that NICE chose to ignore in the production of its Clinical Guideline 53

Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a complex multi-system biomedical disorder, hence there is considerable overlap of multi-system symptomatology. This document should therefore be read in conjunction with the four preceding documents already submitted: (1) "*Evidence that the Guideline Development Group that produced the NICE Guideline on CFS/ME (CG53) failed to fulfil its remit, particularly in relation to the danger of graded exercise therapy*" (7th July 2008); (2) "*Background information and illustrations of evidence that CBT cannot improve ME/CFS which NICE disregarded*" (25th July 2008); (3) "*Evidence of cardiovascular problems in ME/CFS that NICE disregarded*" (4th August 2008) and (4) "*Medication and ME?"* (27th August 2008), which provides evidence of mitochondrial (muscle) dysfunction that has been demonstrated in ME/CFS that NICE also disregarded.

This present document provides illustrations of evidence concerning immunological, neuroendocrine and neurological dysfunction that has been documented in ME/CFS, all of which the Guideline Development Group (GDG) that produced the NICE Guideline CG53 ignored (J Inf 2007:55:6:567-571), thus enabling the GDG to recommend that only the pre-ordained intervention (behavioural modification and incremental aerobic exercise) be delivered throughout the nation to people with "CFS/ME".

By ignoring the existing evidence-base for ME/CFS, the GDG was able to ignore the documented biomarkers that separate ME/CFS from "CFS/ME" (a term coined by Wessely School psychiatrists – who claim to specialise in "CFS/ME" -- to denote somatoform disorder, which includes all states of unexplained "tiredness") and was therefore expediently able to recommend only behavioural interventions.

The Guideline, however, is a **Clinical Guideline**, and part of its remit was to aid diagnosis, but the GDG failed to identify or define the disorder to which its Guideline purports to relate.

Instead, the GDG intentionally combined all states of "medically unexplained chronic fatigue" within the heterogeneous label "CFS/ME" which was in direct defiance of the many international calls for sub-grouping (see below).

It was, however, in accordance with the ethos of the Wessely School, which is that amalgamating "fatiguing illnesses" will clarify the pathophysiology of "fatigue".

Referring to the CDC Fukuda 1994 case definition of "CFS" (in the production of which Michael Sharpe and Simon Wessely were involved), Michael Sharpe et al state: "*The exclusion of persons (with psychiatric disorders) would substantially hinder efforts to clarify the role that psychiatric disorders have in fatiguing illnesses"* (Ann Intern Med 1994:121:12:953-959).

The Wessely School's modus operandi of combining all states of unexplained fatigue into one heterogeneous label ("CFS/ME") has had detrimental consequences for patients, as noted as long ago as 1994 in the National Task Force Report on CFS/ME/PVFS produced by the charity Westcare (now subsumed into Action for ME) that was supported by the Department of Health, and as noted by many international researchers (see below).

This amalgamation of "fatigue states" also pertained in the Chief Medical Officer's (CMO) Working Group's Report of January 2002, which was dismissive of the need for sub-grouping: "*This question may be considered a matter of semantics and personal philosophy"* (Annex 4:3, written by Professor Anthony Pinching, Lead Adviser on "CFS" to the Department of Health, who was responsible for setting up the "CFS" Centres in the UK).

That NICE has indeed adopted the Wessely School paradigm (i.e. the psychosocial / behavioural model of "CFS/ME") has been confirmed.

The influence of Wessely's team on the NICE Guideline on "CFS/ME" featured in the 2007 R&D (Research & Development) annual reports by NHS organisations in England (Department of Health), in which the South London and Maudsley NHS Trust stated in section 2A ("Examples of impact on health and social care"): ***"We begin by summarising key achievements and follow with six examples that illustrate the impact of our research. The examples that follow have been selected to illustrate the breadth of our portfolio of research and evidence-based practice"***. The section on "Chronic Fatigue Syndrome" boasts: "*In October 2006, NHS Plus published "Occupational Aspects of the Management of Chronic Fatigue Syndrome: a National Guideline". It was accompanied by two additional leaflets, one for Health Care professionals and one for employers. This report was heavily influenced by research carried out at our Chronic Fatigue* (sic) *Unit.* ***The NICE CFS/ME guideline also includes priority recommendations to which our research, led by Trudie Chalder and colleagues, has contributed: 'When the adult or child's main goal is to return to normal activities, then the therapies of first choice should be CBT or GET because there is good evidence of benefit for this condition in mild to moderately affected adults and some evidence in mild to moderately affected children'****. As a result of our research we have developed our chronic fatigue syndrome service to include treatment at home. In addition we now offer telephone treatment routinely after demonstrating its effectiveness".*

There could be no clearer confirmation of the impact of the Wessely School's beliefs about "CFS/ME" on the NICE Guideline, which recommends only mind-altering therapies in conjunction with incremental aerobic exercise.

<u>The term "CFS/ME" used by NICE is misleading</u>

It was in September 2003 that a Working Group including ME/CFS experts Professor Nancy Klimas and Professor Leonard Jason advised the US Department of Health and Human Services of the unsuitability and inadequacy of the term "CFS". Their submission stated:

"The vast majority of patients and physicians believe that the name CFS too narrowly focuses upon a single, poorly-defined symptom (fatigue) and promotes misunderstanding of the illness"

"Patients feel the name CFS has substantially contributed to the disparaging manner in which they are perceived and treated by physicians, family, and the general public (and) that this misunderstanding has directly and negatively impacted the quality of medical care and support they are able to obtain "

"We recommend a new name (under which) subgroups of patients can be more accurately stratified according to variations in illness presentation, pathophysiology (and) results of diagnostic testing"

"Foundation for our recommendation was guided by several important principles. First, the name must not imply that the aetiology is clearly understood. Second, it must reflect common symptoms reported by most patients. Third, our recommendation must be supported by data published in the peer-reviewed literature"

"The number of symptoms reported by patients is very large. However, most of the commonly reported symptoms are associated with (or may be indicative of dysfunction of) the neurologic, neuroendocrine and / or immunologic systems"

"(We) recommend a new term called neuroendocrineimmune dysfunction syndrome (NDS). The recommendations are based on (1) the profile and frequency of the commonly reported symptoms and (2) the published evidence (that) supports an aberration or dysfunction of the neurologic, neuroendocrine, and immunologic systems".

The Working Group attached a list of the published evidence in support of their recommendation, pointing out that: **"*The following scientific publications provide a sound basis (for the term NDS) that reflects common symptoms. The articles were selected because they have withstood scientific scrutiny and***

represent critical findings. While other publications are available, the chosen articles are widely respected, cited and (are) representative of current understanding of the science".

The full submission and the listed articles (separated into categories of Neurologic System -- sub-divided into autonomic nervous system, neuroendocrine system and neurocognitive problems -- and Immune System) are available at http://www.iacfsme.org/Portals/0/pdf/namechange_document_submitted.pdf

In stark contrast, NICE has essentially reduced "CFS/ME" to chronic tiredness and just one other symptom (Full Guideline, p 165)**. In doing so, NICE has ignored the existing evidence-base of over 4,000 biomedical publications on the disorder.**

Further, NICE claims to have been guided by the 2002 Report of a Working Group to the Chief Medical Officer, whose membership was heavily over-represented by the Wessely School. Not only does that Report recommend GET and CBT (*"The majority of the Working Group agreed that graded exercise therapy can benefit many outpatients with CFS/ME"* [page 47] and *"The majority of the Working Group accepts that CBT can improve functioning in many patients with CFS/ME"* [page 49]), it was strongly criticised because it advises clinicians (page 40) that the specialist investigations (ie. immunological assays and nuclear medicine imaging) which are delivering hard evidence of organic pathology in ME/CFS are neither necessary nor appropriate for these patients. That was a matter for concern at the time, and remains a matter of concern, since the NICE Guideline adopts the same stance.

It is also a matter for concern that NICE has recommended only behavioural interventions for such a clearly complex and serious biomedical disorder when there is substantial evidence of immunological, endocrine and neuroendocrine dysfunction in ME/CFS, with persistence of illness.

At the ME Research UK international conference held at the University of Cambridge on 6th May 2008, Nancy Klimas, Professor of Medicine at the University of Miami and Director of the (ME)CFS Research Centre reviewed some of this evidence.

Although the Cambridge conference post-dated the publication of the NICE Guideline (on 22nd August 2007), much of the reviewed evidence pre-dated publication and was available to the GDG, yet it was comprehensively ignored.

Professor Klimas noted that chronic immune activation has long been thought to be a component of ME/CFS, with T-lymphocytes being chronically activated – indeed CD8 cells in ME/CFS patients typically demonstrate an increase in activation markers (CD38; HLA-DR) and a reduction in CD8 suppressor cells. Furthermore, there is evidence that the homeostasis between the cell-mediated (T-helper, or Th1) immune response and the humoral (Th2) immune response is disrupted in ME/CFS, and there is evidence of increased pro-inflammatory cytokine expression (TNFα; IL1 and IL6).

Professor Klimas reviewed the evidence for viral persistence and reactivation (eg. enterovirus, HHV6 and EBV) and discussed the evidence for endocrine dysfunction, particularly reduced cortisol. She noted that autonomic dysfunction has been measured as neurally-mediated hypotension, orthostatic hypotension, parasympathetic dysfunction and sympathetic over-activation.

She also spoke about gene expression microarray data having become a highly productive tool for understanding ME/CFS research, noting studies that included the differential expression of 35 genes for T-cell activation, neuronal and mitochondrial regulatory abnormalities, and that pre- and post-exercise challenge gene studies have indicated differences in genes that regulate ion transport and intracellular functions.

Dr Jo Nijs from the Vrije University, Brussels, examined the accumulating evidence of intracellular immune dysfunction in ME/CFS and concluded that proteolytic cleavage of the native RNase-L is characteristic of dysregulation of intracellular immunity in people with ME/CFS, and that there is increasing evidence for up-regulation of various aspects of the 2-5A synthetase / RNase-L pathway (an important anti-viral pathway) and for immune cell apoptosis in ME/CFS. Notably, the dysregulation and

up-regulation of the 2-5A synthetase / RNase-L pathway in ME/CFS are not just epiphenomena: there is hard evidence supporting their clinical importance. Nijs explained that decreased natural killer (NK) cell function, the presence of infections and intracellular immune dysfunctions are all inter-related components of ME/CFS pathophysiology.

Professor Julia Newton from the University of Newcastle (UK) spoke of her work on autonomic dysfunction in ME/CFS and its effects on respiration, bladder and bowel function, and on cardiovascular function such as maintenance of heart rate and blood pressure. Autonomic dysfunction is a frequent finding in people with ME/CFS. Her research group has shown that 89% of ME/CFS patients experience symptoms on standing (orthostatic intolerance) and her studies examining haemodynamic responses to standing have shown that ME/CFS patients have Positional Orthostatic Tachycardia Syndrome, and that cardiovascular parameters correlate with increasing fatigue.

(The above summary is taken from the Report on the Cambridge conference "New Horizons 2008" by Dr Neil Abbot of MERUK, to whom grateful acknowledgement is made: a set of 4 DVDs of the whole conference is available for £5 from MERUK: telephone: 01738-451234; email: meruk@pkavs.org.uk; website: www.meresearch.org.uk).

The scientific evidence in this summary alone renders incomprehensible the failure of the GDG to heed the serious biomedical abnormalities that have been demonstrated in ME/CFS.

The ignoring of the existing evidence-base on ME/CFS would seem to make the GDG's recommendation for behavioural modification as the single management approach for "CFS/ME" (which they stipulate includes the WHO ICD-10 classified neurological disorder ME) tantamount to serious professional negligence, especially given that the NICE Guideline ignores the many international calls for more specialist laboratory investigations and actually proscribes such testing.

Further, the Guideline does not recommend biomedical research into these key areas as a matter of priority. Quoting the Gibson Report of November 2006, it does briefly refer to the need for research into the "*biological basis of CFS/ME*" (page 169) but then changes this to the "*encouragement of further appropriate research to identify causative factors*" (page 187).

As far as the Wessely School psychiatrists are concerned (who were advisers to NICE and who are renowned for their intransigent belief that ME does not exist and that what they term "CFS/ME" is an aberrant illness belief), "*appropriate research to identify causative factors*" is centred on their own (unproven) psychosocial model, not on essential biomedical research.

As far as State-sponsored research is concerned, the Medical Research Council (MRC) categorises "CFS/ME" as a mental disorder and it is a matter of record that Wessely School psychiatrists control the purse strings in relation to "CFS/ME" funding, so perhaps it is not surprising that the MRC has a track record of rejecting funding for biomedical research into ME/CFS, despite paying lip-service in 2003 by announcing its 'research strategy for CFS/ME'. There is undisputed evidence of psychiatric bias on the part of the MRC, because approximately 91% of the MRC's total grant-spend on ME/CFS in five years has gone on psychiatric trials of behavioural interventions (CBT/GET), with the MRC stating: "*CBT will be based on the illness model of fear avoidance (and) GET will be based on the illness model of deconditioning and exercise avoidance"* (Dr Neil Abbot; "Breakthrough", Autumn 2008: 8-9; MERUK).

In contrast, the MRC is known to have turned down no less than 33 biomedical and pathophysiological research projects on ME/CFS. It is unlikely that these 33 applications were all so badly written that they could be rejected, since some were from established researchers with a sound track record. It is held by many that the MRC has a case to answer over the non-funding of biomedical research into ME/CFS.

By recommending only mind-altering therapies combined with incremental aerobic exercise, the NICE Guideline is perpetuating this psychiatric bias.

Despite the many calls for appropriate immunological investigations in the following illustrations, the Guideline firmly rejects the need for such investigations.

It is perhaps significant that in the 1996 Joint Royal Colleges Report on "CFS" that was orchestrated by the Wessely School psychiatrists, Simon Wessely, Peter White et al specifically advised Government bodies against immunological investigations:

- "***The Royal Colleges have stressed that approaches to these patients should not be based on simple biomedical models"*** (page 2)

- ***"Since the case definition has been revised*** (i.e. by Wessely School psychiatrists themselves) ***it is no longer necessary to exclude those with common psychiatric disorders"*** (page 8)

- ***"The possibility that abnormalities of immune function play a role in the pathogenesis of CFS has attracted considerable attention. Some use the results of immunological tests as evidence for a so-called 'organic' component in CFS. Such abnormalities should not deflect the clinician from the (psychosocial) approach and should not focus attention towards a search for an 'organic' cause"*** (page 13)

- ***"No investigations should be performed to confirm the diagnosis"*** (page 45) (CFS: Report of a Joint Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. Royal College of Physicians, CR54, October 1996).

Illustrations of immunological dysfunction in ME/CFS from the published literature that NICE disregarded in the production of its Clinical Guideline 53 (illustrations of neuroendocrine and neurological dysfunction follow this section on immunological dysfunction)

1987

Irving Salit, Associate Professor of Medicine and Microbiology at the University of Toronto and Head of the Division of Infectious Diseases at Toronto General Hospital, noted: "*Findings include mild immunodeficiency, slightly low complement, anti-DNA antibodies and elevated synthetase, which is an interferon-associated enzyme commonly increased in infections.* ***This illness is of major importance because it is so prevalent and because it has such devastating consequences: afflicted patients are frequently unable to work or carry on with usual social activities.*** *We have found that a wide variety of infections may precipitate this illness (including Coxsackie B and mycoplasma). Some patients have mild elevations of IgM or IgG (and) low levels of anti-nuclear antibody. Patients tend to tolerate medications very poorly and many have a history of drug allergies. Most patients do not improve on anti-depressants and are usually exquisitely sensitive to the side effects. It is important for the physician to understand their suffering. There are enough abnormalities of organic disease to suggest that (it) is not purely a psychological ailment"* (Clin Ecol 1987/8:V:3:103-107).

1987

US clinicians and researchers who became world leaders in ME/CFS (including Paul Cheney, Daniel Peterson and Anthony Komaroff) noted: "*These studies demonstrated that a majority of patients with (ME)CFS have low numbers of $NKH1^{+}T3^{-}$ lymphocytes, a population that represents the great majority of NK cells in normal individuals. (ME)CFS patients had normal numbers of $NKH1^{+}T3^{+}$ lymphocytes, a population that represents a relatively small fraction of NK cells in normal individuals. When tested for cytotoxicty against a variety of different target cells, patients with (ME)CFS consistently demonstrated low levels of killing. In humans, studies suggest a correlation between low NK activity and serious viral infections in immunocompromised hosts.* ***We have carried out extensive phenotypic and functional***

characterisation of NK cells in patients with this syndrome (and have) found that the majority had abnormally low numbers of NKH1$^+$ cells. *Further characterisation of such cellular subset abnormalities and the resulting alteration in quantitative and qualitative NK cytotoxic function will hopefully improve our understanding of the immunopathogenesis of this illness"* (M Caliguri et al. The Journal of Immunology 1987:139:10: 3306-3313).

1988

"*We report patients (who) had a specific deficiency of IgG1 subclass. The finding of IgG1 subclass deficiency in these patients is novel, as lone deficiency of this subclass is rare and affected patients appear to have common variable hypogammaglobulinaemia. Further scrutiny of cases (of ME/CFS) may reveal a range of subtle immunological abnormalities"* (Robert Read, Gavin Spickett et al. Lancet, January 30 1988:241-242).

1989

"(ME)CFS has been associated with abnormal T cell function. These patients have diminished phytohaemagglutinin-induced lymphocyte transformation and decreased synthesis of interleukin. We studied the display of CD3, CD5, CD2, CD4, CD8 and Leu-M3-defined antigen in peripheral blood mononuclear cells in (ME)CFS who fulfilled the (1988 Holmes et al) criteria. Patients had reduced expression of CD3. These data indicate that in (ME)CFS, some patients have T lymphocytes (CD2- and CD5- positive cells) without immunoreactive CD3" (ML Subira et al. The Journal of Infectious Disease 1989:160:1:165-166).

1989

"Disordered immunity may be central to the pathogenesis of (ME)CFS. Reduced IgG levels were common (56% of patients), with the levels of serum IgG3 and IgG1 subclasses particularly affected. The finding of significantly increased numbers of peripheral blood mononuclear cells that express Class-II histocompatibility antigens (HLA-DR) in our patients implies immunological activation of these cells. ***Once activated, these cells may continue to produce cytokines which may mediate the symptoms of (ME)CFS****"* (AR Lloyd et al. The Medical Journal of Australia 1989:151:122-124).

1989

"Our investigations suggest that this syndrome is characterised by objective laboratory abnormalities (and) immune dysfunction appears to be a hallmark of the disease process*. The best marker appears to be lowered NK activity"* (NL Eby, S Grufferman et al. In: Natural Killer Cells and Host Defense. 5th International NK Cell Workshop, Hilton Head, SC. Ed: Ades EW, Lopez C. Basel, Karger 1989:141-145).

1990

"In order to characterise in a comprehensive manner the status of laboratory markers associated with cellular immune function in patients with this syndrome, patients with clinically defined (ME)CFS were studied. ***All the subjects were found to have multiple abnormalities in these markers****.* ***The pattern of immune marker abnormalities observed was compatible with a chronic viral reactivation syndrome. A substantial difference in the distribution of lymphocyte subsets of patients with (ME)CFS was found when compared with normal controls.*** *Lymphocyte proliferation after PHA and PWM stimulation was significantly decreased in patients (by 47% and 67% respectively) compared with normal controls. Depression of cell-mediated immunity was noted in our study population, with over 80% of patients having values below the normal mean. The present report confirms that a qualitative defect is present in these*

patients' NK cells (which) might represent cellular exhaustion as a consequence of persistent viral stimulus. Results from the present study indicate that there is an elevation in activated T cells. ***A strikingly similar elevation in CD2$^+$ CDw26$^+$ cells has been reported in patients with multiple sclerosis.*** *In summary, the results of the present study suggest that (ME)CFS is a form of acquired immunodeficiency. This deficiency of cellular immune function was present in all the subjects we studied"* (Nancy G Klimas et al. Journal of Clinical Microbiology 1990:28:6:1403-1410).

1990

"*(A) subnormal number of CD8 lymphocytes, a raised serum IgE level and a positive VP1 antigen are sufficiently frequent to suggest that they should become part of the routine screening of such patients.* ***In the present ME study, patients show a 40% incidence of both clinical and laboratory evidence of atopy.*** *It has been shown that T cell deficiency, particularly of the suppressor subset, can predispose to atopy without a genetic family history.* ***We have undertaken extensive T cell subset measurements in normal subjects subjected to psychological stress and would point out in none of these did we see CD8 levels as low as in some 40% of our ME patients****"* (JR Hobbs, JA Mowbray et al. Protides of Biological Fluids 1990:36:391-398).

1991

"*Compared with controls, (ME)CFS patients showed an increase in CD38 and HLA-DR expression.* ***These data point to a high probability (90%) of having active (ME)CFS if an individual has two or more of the CD8 cell subset alterations. Laboratory findings among (ME)CFS patients have shown low level autoantibodies, which may reflect an underlying autoimmune disorder****. A persistent hyperimmune response of the remaining CD8 cells might lead to an outpouring of cellular products and cytokines (eg. interferon, tumour necrosis factor, interleukin-1) that are characteristically associated with myalgia, fatigue, (and) neurological signs and symptoms associated with acute viral infections.* ***Unless the immune system is brought back into balance, this chronic activation affects the individual further and might eventually lead to other clinical illnesses****"* (Alan L Landay et al. Lancet 1991:338:707-712).

1991

In "Review of laboratory findings for patients with chronic fatigue syndrome" **Buchwald and Komaroff et al listed the following (yet NICE claims there are no abnormal laboratory findings**): "*Various abnormalities revealed by laboratory studies have been reported in adults with (ME)CFS. Those most consistently reported include depressed natural killer cell function and reduced numbers of natural killer cells; low levels of circulating immune complexes; low levels of several autoantibodies, particularly antinuclear and antithyroid antibodies; altered levels of immunoglobulins (and) abnormalities in number and function of lymphocytes"* (Reviews of Infectious Diseases 1991:13 (Suppl 1): S12- S28).

1992

A major study looking at neurological, immunological and virological aspects in 259 (ME)CFS patients found that neurological symptoms, MRI findings and lymphocyte phenotyping studies suggest that patients ***"may have been experiencing a chronic, immunologically mediated inflammatory process of the central nervous system"*** and that "***Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with oedema or demyelination in 78% of patients****. We think that this is probably a heterogeneous illness that can be triggered by different environmental factors (including stress, toxins and infectious agents), all of which can lead to immune dysfunction and the consequent reactivation of latent viruses"* (D Buchwald, Paul Cheney, Daniel Peterson, Robert C Gallo, Anthony Komaroff et al. Ann Int Med 1992:116:2:103-113).

1993

At the 1993 Los Angeles Conference on (ME)CFS, evidence was presented by Professor Nancy Klimas from the University of Miami that she and her team have been able to accurately predict 88% of (ME)CFS patients with a mathematical model of immunological parameters. This model combines levels of activated T cells and CD4 inducers of cytotoxic T cells with NK cell count and function: "*In a normal population, 20% of lymphocytes are active at any given time. 'In (ME)CFS, up to 80% of the cells are working'.* ***These lymphocytes and cytokines are so up-regulated that they cannot be driven any harder. It is as if they have been pushed as far as they can go and the immune system is completely exhausted"*** (CFIDS Chronicle: Summer 1993).

1993

"Using the immunophenotypic data presented, we were able to demonstrate that almost 50% of (ME)CFS patients, especially those with severe symptoms, showed signs of $CD8^+$ cell activation and an abnormal suppressor / cytotoxic $CD8^+$ cell ratio. ***Our observations strongly suggest that a large population of (ME)CFS patients have immunologic disorders and that their symptoms could be explained by a chronic immune activation state (and) that (ME)CFS represents a type of autoimmune disease in which a chronically activated immune system reacts against the host****. The 3:1 female/male ratio would not be unexpected: autoimmune syndromes are more common in women.* ***Because of the autoreactive nature of this condition, it might also lead to other immune disorders, such as well-recognised autoimmune diseases and multiple sclerosis"*** (Jay A Levy et al. Contemp Issues Infec Dis 1993:10:127-146).

According to Dr Elizabeth Dowsett, former President of the ME Association, at least 13% of ME/CFS patients are indistinguishable from patients with multiple sclerosis (personal communication).

1994

"The chronic fatigue immune dysfunction syndrome (CFIDS) is a major subgroup of the chronic fatigue syndrome (CFS). We and other investigators have reported a strong association between immune dysfunction and a serological viral activation pattern among patients in this group. This finding appeared similar to that for a variety of conditions, such as chronic active hepatitis and systemic lupus erythematosus*, in which a definite association between a particular HLA-DR/DQ haplotype and increased disease frequency has been reported.* ***We thus elected to examine a cohort of patients with CFIDS, with use of HLA-DR/DQ typing****.* ***A significant association between CFIDS and the presence of HLA-DQ3 was noted****. The association with HLA-DQ3 could represent an additive effect for patients who also have HLA-DR4 and/or HLA-DR5. (Our) results are intriguing. DQ3 was significantly more prevalent in patients than controls. It is possible that DR4 and DR5 are also associated with an increased risk of developing CFIDS.* ***These findings strongly suggest that further evaluation of persons with CFIDS, including an investigation of an HLA Class I linkage dysequilibrium, are warranted****. The data presented herein suggest that CFIDS, together with a variety of immune-mediated diseases, may share similar sequences of pathogenic mechanisms (and) in a subpopulation (of CFIDS), a genetic predisposition may be triggered immunologically by any number of potential stimuli,* ***resulting in a state of chronic immune dysequilibrium****. This model could easily explain findings with regard to viral infection (and) allergies"* (RH Keller, N Klimas et al. Clin Inf Dis 1994:18: (Suppl 1): S154-156).

1994

"These data suggest a correlation between low levels of NK cell activity and severity of CFIDS. Compromised or absent natural immunity is associated with acute and chronic viral infections such as AIDS, CFIDS and various immunodeficiency syndromes*. Stratification of patients with CFIDS into distinct groups according to the severity or duration of physical abnormalities might allow identification of*

laboratory abnormalities that are associated with severity. ***The fact that NK cell activity decreases with increased severity and duration of certain clinical variables suggests that measurement of NK cell function could be useful for stratification of patients and possibly for monitoring therapy for and / or the progression of CFIDS****"* (EA Ojo-Amaize et al. Clin Inf Dis 1994:18: (Suppl 1):S157-159).

1994

"The immune system is a readily accessible, sensitive indicator of environmental or internal changes, and studies conducted by different groups over the past few years have provided valuable evidence for changes in immune status among individuals with (ME)CFS. To gain insight into the nosology and aetiology of (ME)CFS, we assessed patterns of soluble immune mediator expression at the protein and mRNA levels in individuals with (ME)CFS. ***The data presented in this report are consistent with previous evidence of immune dysregulation among patients with (ME)CFS and point to a dysregulation of TNF*** *(tumour necrosis factor)* ***expression as a distinctive feature of this condition****. Imbalances in TNF and associated changes in levels of other cytokines may underlie many of the characteristic features of (ME)CFS.* ***In addition, TNF-α can have deleterious effects on the central nervous system****"* (Roberto Patarca, Nancy G Klimas et al. Clin Inf Dis 1994:18: (Suppl 1):S147-153).

Tumour necrosis factor is a cytokine involved in systemic inflammation. Its primary role is in the regulation of immune cells. Increased TNF causes apoptosis, inflammation and tumorigenesis.

1994

"The up-regulated 2-5A pathway in (ME)CFS is consistent with an activated immune state and a role for persistent viral infection in the pathogenesis of (ME)CFS. The object of this study was to measure key parameters of the 2-5A synthetase/RNase-L antiviral pathway in order to evaluate possible viral involvement in (ME)CFS. The data presented suggest that 2-5A synthetase/RNase L pathway is an important biochemical indicator of the anti-viral state in (ME)CFS. ***Evidence that this pathway is activated in (ME)CFS was identified in this subset of severely disabled individuals as related to virological and immunologic status. This pathway phenotype could result from chronic over-stimulation due to chronic viral reactivation****"* (RJ Suhadolnik et al. Clin Inf Dis 1994:18(Suppl 1):S96-S104).

1994

"In the study of a complex illness such as (ME)CFS, the most important aspect is case definition*. Patients whose symptoms are primarily related to upper respiratory tract infections may have different precipitating agents and pathogenesis than those with predominantly gastrointestinal disturbances. It has been noted for a number of years that a history of allergies appears to be an important risk factor for (ME)CFS.* ***In addition to a history of allergy, other factors, such as exposure to chemicals, were noted to be possible triggers****.* ***The spectrum of illnesses associated with a dysregulated immune system now must include (ME)CFS****"* (Paul H Levine. Clin Inf Dis 1994:18(Suppl 1):S57-S60).

1995

"One rationale for the immunological approach stems from the experience accumulated with similar syndromes such as autoimmune and environmentally-triggered diseases. (ME)CFS may be associated with certain HLA Class II antigens, as are some forms of environmental disease. These observations underscore the distinction between (ME)CFS and psychiatric maladies. Viruses are frequently reactivated in association with immune system dysregulation in (ME)CFS and may contribute to symptomatology*"* (Roberto Patarca. JCFS 1995:vol I:3/4:195-202).

1996

An important paper from Konstantinov and Tan et al demonstrated the occurrence of autoantibodies to a conserved intracellular protein (lamin B1), **which provides laboratory evidence for an autoimmune component in ME/CFS**. The authors found that 52% of patients with ME/CFS develop autoantibodies to components of the nuclear envelope (NE), mainly nuclear lamins, suggesting that in addition to the other documented disturbances of the immune system, **humoral autoimmunity against polypeptides of the NE is a prominent immune derangement in ME/CFS.** 67% of ME/CFS patients were positive for NE reactivity compared with 10% of normal controls. **Autoantibodies to NE proteins are relatively infrequent and most fall into the category of an unusual connective tissue disease characterised by brain or skin vasculitis.** The authors concluded that **such activation "*could be the result of various triggering agents, such as infections or environmental toxins. Future work should be directed at a better understanding of the autoimmune response of (ME)CFS patients to other NE antigens*"** (K Konstantinov et al. J Clin Invest 1996:98:8:1888-1896).

1996

In 1996, Hilgers and Frank developed a score for severity of ME/CFS to correlate with parameters of immune activation. This was effected by a 30-point criteria score, basic laboratory programmes and immunological profiles in 505 patients. In addition, tests of the complement system, immune activation markers, hormones and viral / bacterial intracellular serology were evaluated. Seventeen significant symptoms not currently in the CDC case definition were added, these being respiratory infections, palpitations, dizziness, dyspepsia, dryness of mouth / eyes, allergies, nausea, paresthesia, loss of hair, skin alterations, dyscoordination *(sic)*, chest pain, personality changes, eczema, general infections, twitches and urogenital infections. A significant correlation between the criteria score and immunological parameters could be evaluated in 472 of the 505 patients. **The data confirm that a reduced or unstable immune control or delayed immune reaction to persisting viruses or bacterial intracellular pathogens, possibly triggered by common infections or other environmental factors, can lead to a chronic neuroimmune activation state and autoimmune disorders** (JCFS 1996:2: (4):35-47).

1997

"The level of bioactive transforming growth factor β was measured in serum from patients with (ME)CFS and compared with normal controls, patients with major depression, patients with systemic lupus erythematosus and patients with multiple sclerosis. ***Patients with (ME)CFS had significantly higher levels of bioactive TGFβ than the healthy controls, patients with major depression, patients with systemic lupus erythematosus and patients with multiple sclerosis. Of greatest relevance to (ME)CFS are the effects of TGF β on cells of the immune and central nervous systems. There is accumulating evidence that TGFβ may play a role in autoimmune and inflammatory diseases"*** (AL Bennet, AL Komaroff et al. J Clin Virol 1997:17:2:160-166)

1997

"(ME)CFS is associated with dysregulation of both humoral and cellular immunity, including mitogen response, reactivation of viruses, abnormal cytokine production, diminished natural killer (NK) cell function, and changes in intermediary metabolites*. The biochemical and immunologic data presented here identified a subgroup of individuals with (ME)CFS with an RNase L enzyme dysfunction that is more profound than previously observed (and) is consistent with the possibility that the absence of the 80-kDa and 40-kDa RNase L and presence of the LMW RNase L correlate with the severity of (ME)CFS clinical presentation"* (Robert Suhadolnik, Daniel Peterson, Paul Cheney et al. Journal of Interferon and Cytokine Research 1997:17:377-385).

Professor Suhadolnik explained in lay terms the significance of this paper (reported by Patti Schmidt in CFIDS Chronicle, Summer 1997, page 17): "*He has found a particular place in the immune system, the 2-5 RNase L antiviral pathway, where something is wrong. 'The whole antiviral pathway heats up out of control' explained Suhadolnik.* ***'You're really sick physiologically. Your body just keeps going and going like the Energiser bunny, making ATP and breaking it down. No wonder you're tired'****. He's found a novel protein in CFIDS patients in that viral pathway. 'In most cases, the human body is able to resist infection thanks to a cascade of biochemical events triggered by the body's immune system. If these antiviral defence pathways are functioning correctly, the spread of the virus is prevented'. Suhadolnick believes that (ME)CFS patients' bodies are responding to a central nervous system virus that interferes with their viral pathways' ability to fight off infection ".*

1997

A highly-respected paper by Vojdani and Lapp et al stressed the importance of cell apoptosis (and the pivotal role of protein kinase RNA in this) in ME/CFS: "***A prominent feature of (ME)CFS is a disordred immune system.*** *Recent evidence indicates that induction of apoptosis might be mediated in a dysregulated immune system by the up-regulation of growth inhibitory cytokines. The purpose of this study was to evaluate the apoptotic cell population, interferon-* α *and the IFN-induced protein kinase RNA (PKR) gene transcripts in the peripheral blood lymphocytes of (ME)CFS individuals, as compared to healthy controls.* ***One of the distinguishing manifestations of (ME)CFS is abnormal immune function, characterised by a decreased NK cell-mediated cytotoxic activity, reduced mitogenic response to lymphocytes, altered cytokine production, elevated titres of antibodies to a number of viruses, and abnormal production of interferon (IFN).*** *The induction of apoptosis through immune defence mechanisms is an important mechanism for elimination of cancer cells as well as virus-infected cells. In the present study, the up-regulation of IFN-*α *and the IFN-induced PRK in (ME)CFS individuals is accompanied by the induction of apoptosis. In addition, dysregulation of cell cycle progression is associated with the induction of apoptosis in (ME)CFS individuals.* ***Quantitative analysis of apoptotic cell population in (ME)CFS individuals has shown a statistically significant increase compared to healthy controls. The population of apoptotic cells in 76% of (ME)CFS individuals was well above the apoptotic cell population in the control cells.*** *Activation of PKR can result in induction of apoptosis. This activation of the PRK pathway could result from (a) dysregulated immune system or chronic viral infection"* (A Vojdani et al. Journal of Internal Medicine 1997:242:465-478).

1998

"The increased expression of Class II antigens and the reduced expression of the costimulantory receptor CD28 lend further support to the concept of immunoactivation of T-lymphocytes in (ME)CFS and may be consistent with a viral aetiopathogenesis in the illness. ***We report, for the first time, increased expression of the apoptosis repressor protein bcl-2 (and) we demonstrated changes in different immunological parameters, each of which correlated with particular aspects of disease symptomatology (and) measures of disease severity"*** (IS Hassan, WRC Weir et al. Clin Immunol & Immunopathol 1998:87:1:60-67).

1999

*"****It is of great importance to develop biomarker(s) for differentiation between viral induced (ME)CFS (without sensitivity to chemicals) versus chemically-induced (ME)CFS.*** *Since interferon induced proteins 2-5A Synthetase and Protein Kinase RNA (PKR) have been implicated in the viral induction of (ME)CFS, the objective of this study was to utilise 205A and PKR activity for differentiation between (ME)CFS induced by either viruses or chemicals. A clear induction of 2-5A and PKR was observed when MDBK cells were exposed to HHV6, MTBE, and benzene.* ***We conclude that 2-5A and PKR are not only biomarkers for viral induction, but biomarkers to other stressors that include (chemicals)"*** (Vojdani A, Lapp CW. Immunopharmacol Immunotoxicol 1999:21(2):175-202).

1999

An article from researchers at the Institute of Immunology in Moscow discussed immunity impairment as a result of neurohormonal disorders and noted that at the base of (ME)CFS lie disturbances of the central nervous system, the endocrine system and the immune system: ***"It was found back in 1987/8 that there is an increase in the level of HLA DR and IL-2 receptors and an increase in the ratio CD4/CD8 in patients suffering from this syndrome"*** (Artsimovich NG et al. Russ J Immunol 1999:4(4):343-345).

It is notable that Russian researchers were aware of these cardinal biomarkers of ME/CFS as long ago as 1999, but that eight years later, the NICE Guideline Development Group (who are acclaimed by NICE as "experts" in the disorder) still were apparently ignorant of these diagnostic biomarkers.

2000

"The purpose of the present study was to investigate the relationship between immunologic status and physical symptoms in (ME)CFS. ***(Results) revealed significant associations between a number of immunologic measures and severity of illness. Specifically, elevations of T-helper/inducer cells, activated T cells, activated cytotoxic/suppressor T cells, and CD4/CD8 ratio were associated with greater severity of several symptoms. Furthermore, reductions in T-suppressor/cytotoxic cells also appeared related to greater severity of some (ME)CFS-related physical symptoms and illness burden****"* (SE Cruess, Nancy Klimas et al. JCFS 2000:7(1):39-52).

2000

"Blood and lymph nodes samples were obtained from patients with (ME)CFS. While a greater proportion of T lymphocytes from both lymph nodes and peripheral blood of (ME)CFS patients are immunologically naïve, the proportions of lymphocytes with a memory phenotype predominate in lymph nodes and peripheral blood of (ME)CFS patients. ***(ME)CFS has been proposed to be a disease of autoimmune aetiology and in this respect it is interesting to note that decreased proportions of CD45RA+T (naïve) cells are also seen in the peripheral blood of patients with autoimmune diseases****"* (Mary Ann Fletcher, Nancy Klimas et al. JCFS 2000:7(3):65-75).

2000

A major and detailed Review of the immunology of (ME)CFS was published by internationally-renowned immunologists Professors Robert Patarca and Nancy Klimas, together with the distinguished long-time ME/CFS research immunologist Mary Ann Fletcher. It contains 212 references. It is clear that people with (ME)CFS have two basic problems with immune function: (1) immune activation and (2) poor cellular function. These findings have a waxing and waning temporal pattern consistent with episodic immune dysfunction. The interplay of these factors can account for the perpetuation of (ME)CFS with remission / exacerbation cycles. The Review considers the evidence of immune cell phenotypic distributions; immune cell function; cytokines and other soluble immune mediators; immunoglobulins; autoantibodies; circulating immune complexes; Type I to Type II cytokine shift and the relationship between stressors, cytokines and symptoms. The data summarised indicate that (ME)CFS is associated with immune abnormalities that can account for the physiopathological symptomatology, and **recommends that future research should further elucidate the cellular basis for immune dysfunction in (ME)CFS and its implications** (JCFS 2000:6(3/4):69-107).

2001

In "Detection of immunologically significant factors for (ME)CFS using Neural-Network Classifiers", authors Hanson, Gause and Natelson were able to demonstrate what had previously been hypothesis: "*Of*

significant interest was the fact that, of all the cytokines evaluated, the only one to be in the final model was IL-4 (which) suggests a shift to a Type II cytokine pattern. Such a shift has been hypothesised, but until now convincing evidence was lacking" (Clin Diagn Lab Immunol 2001:8(3)658-662).

2002

"The present review examines the cytokine response to acute exercise stress. The magnitude of this response bears a relationship to the intensity of effort but many environmental factors also modulate cytokine release. ***The main source of exercised-induced IL-6 production appears to be the exercising muscle. Cytokine concentrations are increased in (ME)CFS. Exercise-induced modulations in cytokine secretion may contribute to allergies (and) bronchospasm****"* (Shepherd RJ. Crit Rev Immunol 2002:22(3):165-182).

2003

A study was carried out by Belgian researchers to determine whether bronchial hyper-responsiveness (BHR) in patients with (ME)CFS is caused by immune system abnormalities. Measurements included pulmonary function testing, histamine bronchoprovocation test, immunophenotyping and ribonuclease (RNase) latent determination. There were 137 (ME)CFS participants. *"****Seventy three of the 137 patients presented with bronchial hyper-responsiveness. The group of patients in whom BHR was present differed most significantly from the control group, with eight differences in the immunophenotype profile in the cell count analysis, and seven differences in the percentage distribution profile. We observed a significant increase in cytotoxic T-cell count and in the percentage of BHR+ patients. Immunophenotyping of our sample confirmed earlier reports on chronic immune activation in patients with (ME)CFS compared to healthy controls, (with) BHR+ patients having more evidence of immune activation***" (Nijs J, De Meirleir K, McGregor N et al. Chest 2003:123(4):998-1007).

2003

Japanese researchers focused on immunological abnormalities against neurotransmitter receptors in (ME)CFS using a sensitive radioligand assay. They examined serum autoantibodies to recombitant human muscarinic cholinergic receptor 1 (CHRM1) and other receptors in patients with (ME)CFS and the results were compared with those in patients with autoimmune disease and with healthy controls. The mean anti-CHRM1 antibody index was significantly higher in patients with (ME)CFS and with autoimmune disease than in controls. **Anti-nuclear antibodies were found in 56.7% of patients with (ME)CFS. The patients with positive autoantibodies to CHRM1 had a significantly higher score of 'feeling muscle weakness' than negative patients among (ME)CFS patients. The authors conclude: "*** ***Autoantibodies to CHRM1 were detected in a large number of (ME)CFS patients and were related to (ME)CFS symptoms****.* *Our findings suggest that subgroups of (ME)CFS are associated with autoimmune abnormalities of CHRM1"* (Tanaka S, Kuratsune H et al. Int J Mol Med 2003:12(2):225-230).

2003

Looking at complement activation in (ME)CFS in the light of the need to identify biological markers in (ME)CFS, US researchers used an exercise challenge to induce symptoms of (ME)CFS and to identify a marker that correlated with those symptoms. "***Exercise challenge induced significant increases of the complement split product C4a at six hours after exercise only in the (ME)CFS group****"* (Sorensen B et al. J All Clin Immunol 2003:112(2):397-403).

2003

"(ME)CFS is an increasing medical phenomenon leading to high levels of chronic morbidity*. The aim of this study was to screen for changes in gene expression in the lymphocytes of (ME)CFS patients. In a small but well-characterised population of (ME)CFS patients, differential display has been used to clone and sequence genetic markers that are over-expressed in the mononuclear cells of (ME)CFS patients.* ***Many researchers have recognised that current methods of diagnosis lead to the selection of a heterogeneous sample, and these data support that view.*** *It is encouraging that the wide 'spread' of data seen in (ME)CFS patients is not seen in the control samples.* ***The data presented here add weight to the idea that (ME)CFS is a disease characterised by over-expression of genes, some of which are known to be associated with immune system activation.*** *Identifying the triggering events for the induction of these genes will increase our understanding of this disease.* ***Some interesting possibilities include viral infection, neuroendocrine disturbances, and allergen exposure. A link with allergy may be particularly pertinent since approximately 80% of (ME)CFS patients are atopic. Some of the genes identified in this study may therefore be linked with the increase in allergic effects seen in (ME)CFS****"* (R Powell, S Holgate et al. Clin Exp Allergy 2003:33:1450-1456).

2003

In an Invited Review, Patrick Englebienne from the Department of Nuclear Medicine, Vrije University, Brussels, explained in simple terms the significance of RNase L: *"RNase L (2-5-oligoadenylate-dependent ribonuclease L) is central to the innate cellular defence mechanism induced by Type I interferons during intracellular infection. In the absence of infection, the protein remains dormant. Recent evidence indicates, however, that the protein is activated in the absence of infection and may play a role in cell differentiation (and) immune activation.* ***A de-regulation of this pathway has been documented in immune cells of (ME)CFS patients. This protein escapes the normal regulation (resulting in) a cascade of unwanted cellular events.*** *Recent data indicate that the RNase L system role is not limited to the cell defence mechanism against intracellular infection but extends to the complete innate and adaptive immune systems, including NK and T-cell proliferation and activation, as well as to cell differentiation and proliferation.* ***The presence of unregulated active RNase L fragments in immune cells may lead to deleterious effects which are inherent to the cellular targets of the protein (because) an unregulated destruction of rRNA and of mitochondrial RNA leads to cell apoptosis. Should the RNase L de-regulation exist in muscle cells, it would necessarily restrain normal muscular development and hence activity (and) muscular weakness is a common feature of (ME)CFS****"* (JCFS 2003:11(2):97-109).

2004

"The exacerbation of symptoms after exercise differentiates (ME)CFS from several other fatigue-associated disorders. Research data point to an abnormal response to exercise in patients with (ME)CFS compared to healthy sedentary controls, and to an increasing amount of evidence pointing to severe intracellular immune dysregulation in (ME)CFS patients. The dysregulation of the 2-5A synthetase/RNase L pathway may be related to a chanelopathy, capable of initiating both intracellular hypomagnesaemia in skeletal muscles and transient hypoglycaemia. This might explain muscle weakness and the reduction of maximal oxygen uptake, as typically seen in (ME)CFS patients. The activation of the protein kinase R enzyme, a characteristic feature in at least a subset of (ME)CFS patients, might account for the observed excessive nitric oxide (NO) production in patients with (ME)CFS. Elevated NO is known to induce vasodilation, which may cause and enhance post-exercise hypotension" (J Nijs, K De Meirleir, N McGregor, P Englebienne et al. Med Hypotheses 2004:62(5):759-765).

2004

"Immunological aberration (in ME/CFS) may be associated with an expanding group of neuropeptides and inappropriate immunological memory. Vasoactive neuropeptides act as hormones, neurotransmitters, immune modulators and neurotrophes. They are immunogenic and known to be associated with a range of autoimmune conditions. They are widely distributed in the body, particularly in the central, autonomic and peripheral nervous systems and have been identified in the gut, adrenal gland, reproductive organs, vasculature, blood cells and other tissues. They have a vital role in maintaining vascular flow in organs and are potent immune regulators with primary anti-inflammatory activity. They have a significant role in protection of the nervous system (from) toxic assault. *This paper provides a biologically plausible mechanism for the development of (ME)CFS based on loss of immunological tolerance to the vasoactive neuropeptides following infection or significant physical exercise. Such an occurrence would have predictably serious consequences resulting from the compromised function of the key roles these substances perform"* (Staines DR. Med Hypotheses 2004:62(5):646-652).

2004

"Patients (with ME/CFS) are more likely to have objective abnormalities of the immune system than control subjects. We measured the frequency of certain HLA antigens (and) restricted our analysis to Class II molecules, as these appear to be more specific predictors of susceptibility to immunologically-based disorders. ***The frequency of the HLA-DQ1 antigen was increased in patients compared to controls. This association between (ME)CFS and the HLA-DQ1 antigen translates into a relative risk of 3.2"*** (RS Schacterle, Anthony L Komaroff et al. JCFS 2004:11(4):33-42).

2004

"(ME)CFS is a serious health concern (and) studies have suggested an involvement of the immune system. ***A Symposium was organised in October 2001 to explore the association between immune dysfunction and (ME)CFS, with special emphasis on the interactions between immune dysfunction and abnormalities noted in the neuroendocrine and autonomic nervous systems of individuals with (ME)CFS.*** *This paper represents the consensus of the panel of experts who participated in this meeting (which was co-sponsored by the US Centres for Disease Control and the National Institutes of Health).* ***Data suggest that persons with (ME)CFS manifest changes in immune responses that fall outside normative ranges. It has become clear that (ME)CFS cannot be understood based on single measurements of immune, endocrine, cardiovascular or autonomic nervous system dysfunction. The panel encourages a new emphasis on multidisciplinary research into (ME)CFS.*** *The panel recommends the implementation of longitudinal studies that include the following key elements: well-characterised cases and controls; assays designed to measure immune function: (a) natural killer cell activity; (b) percentage of peripheral blood lymphocytes expressing activation markers; (c) pro-inflammatory cytokines and soluble receptors; (d) Th-1 and Th-2 responses; (e) activity of the 2-5A synthetase pathway, and (f) serum immunoglobulin levels; selected measures of autonomic nervous system and neuroendocrine functioning; functional magnetic resonance imaging studies; studies to demonstrate the presence or absence of viral/microbial genetic material***. ***The use of interdisciplinary, multi-site (including international) longitudinal studies to explore links between the variations noted in (ME)CFS patients' immune, neuroendocrine, and cardiovascular systems is critical. Three primary methodological barriers impair the investigations of (ME)CFS: poor study design, the heterogeneity of the CFS population, and the lack of standardised laboratory procedures. The quality of previous CFS research (is hampered by) multiple differences in methods of subject recruitment and classification (and) clinical definitions applied and outcome measures used. It is our obligation to overcome the methodological barriers outlined above"*** (Gerrity TR et al. Neuroimmunomodulation 2004:11(6):351-357).

It is to be noted that the term "multidisciplinary research" used by non-psychiatrists means what it says, whereas when the same term is used by Wessely School psychiatrists and UK Government agencies, it means the involvement of psychiatrists.

It is also to be noted that UK Government agencies (including the CMO, the MRC and NICE) all specifically advise against the recommendations above that are designated by US experts as being of "critical" importance, and proscribe the use of immunological assays and nuclear medicine imaging for patients with ME/CFS in the UK.

2004

"Many patients with (ME)CFS have symptoms that are consistent with an underlying viral or toxic illness. *Because increased neutrophil apoptosis occurs in patients with infection, this study examined whether this phenomenon also occurs in patients with (ME)CFS.* ***Patients with (ME)CFS had higher numbers of apoptotic neutrophils, lower numbers of viable neutrophils, and increased expression of the death receptor, tumour necrosis factor receptor-1 on their neutrophils than did healthy controls. These findings provide new evidence that patients with (ME)CFS have an underlying detectable abnormality in their immune cells"*** (Kennedy G et al. J Clin Pathol 2004:57(8):891-893).

Commenting on this paper, Dr Neil Abbot, Director of Operations at ME Research UK, noted: "*The new paper by Dr Gwen Kennedy (MERGE Research Fellow) and colleagues reports evidence of increased neutrophil apoptosis (programmed cell death) in ME/CFS patients. Neutrophils represent 50-60% of the total circulating white blood cells and are fundamental to the functioning of an intact immune system.* ***The data presented in this report are consistent with the presence of an underlying, detectable abnormality in immune cell behaviour of many ME/CFS patients, consistent with an activated inflammatory process, or a toxic state"*** (Co-Cure RES MED 30th July 2004).

2005

"Arguments exist as to the cause of (ME)CFS. Some think that it is an example of symptom amplification indicative of psychogenic illness, while our group thinks that some (ME)CFS patients may have brain dysfunction. We did spinal taps (lumbar puncture) on (ME)CFS patients. ***We found that significantly more (ME)CFS patients had elevations either in protein levels or numbers of cells than healthy controls and (some) patients had protein levels and cell numbers that were higher than laboratory norms. In addition, of the 11 cytokines detectable in spinal fluid, (some) were lower in patients than in controls (and some) were higher in patients. The results support two hypotheses: that some (ME)CFS patients have a neurological abnormality and that immune dysregulation within the central nervous system may be involved in this process.*** *A recent study showing elevations of IL-8 and IL-10 levels during chemotherapy-induced symptoms resembling some of those seen in (ME)CFS provides additional evidence for this hypothesis"* (Benjamin H Natelson et al. Clin Diagn Lab Immunol 2005:12(1):52-55).

2005

An article in The Scientist pointed out the need to measure cytokines in diverse disorders: "*The immune system is often likened to the military. The body's army has weapons such as antibodies and complement, and soldiers such as macrophages and natural killer cells. The immune system sports an impressive communications infrastructure in the form of intracellular protein messengers called cytokines and the cellular receptors that recognise them. The cytokine family consists of such soluble growth factors as the interleukins, interferons, and tumour necrosis factor, among others.* ***Their measurement has become an integral part of both clinical diagnostics and biomedical research"*** (JP Roberts. The Scientist 2005:19:3:30).

It again needs to be noted that the NICE Clinical Guideline 53 proscribes such measurements (as did the MRC's "CFS/ME Research Advisory Group Research Strategy" Report of 1st May 2003, as did the CMO's Report of 2002, and as did the Joint Royal Colleges Report of 1996).

2005

"Hyperactivation of an unwanted cellular cascade by the immune-related protein RNase L has been linked to reduced exercise capacity in persons with (ME)CFS. This investigation compares exercise capabilities of (ME)CFS patients with deregulation of the RNase L pathway and CFS patients with normal regulation. The results implicate abnormal immune activity in the pathology of exercise intolerance in (ME)CFS and are consistent with a channelopathy involving oxidative stress and nitric-oxide toxicity" (Snell CR et al. In Vivo 2005:19(2):387-390).

2005

*"**Diminished NK cell cytotoxicity is a frequently reported finding (in ME/CFS**). However, the molecular basis of this defect has not been described. Perforin is a protein found within intracellular granules of NK and cytotoxic T cells. **Quantitative fluorescence flow cytometry was used to the intracellular perforin content in (ME)CFS subjects and healthy controls. A significant reduction in the NK cell associated perforin levels in samples from (ME)CFS patients compared to healthy controls was observed. There was also an indication of a reduced perforin level within the cytotoxic T cells of (ME)CFS subjects, providing the first evidence (of) a T cell associated cytotoxic deficit in (ME)CFS. Because perforin is important in immune surveillance and homeostatis of the immune system, its deficiency may prove to be an important factor in the pathogenesis of (ME)CFS and its analysis may prove useful as a biomarker in the study of (ME)CFS"*** (Maher KJ, Klimas NG, Fletcher MA. Clin Exp Immunol 2005:142(3):505-511).

2005

"Previous research has shown that patients with (ME)CFS present with an abnormal exercise response and exacerbations of symptoms after physical activity. The highly heterogeneous nature of the CFS population and the lack of uniformity in both diagnostic criteria and exercise testing protocols preclude pooling of data. Still, we conclude that at least a subgroup of CFS patients present with an abnormal response to exercise. Importantly, the exacerbation of symptoms after exercise is seen only in the (ME)CFS population and not in fatigue-associated disorders such as depression**. Earlier (studies) revealed that in (ME)CFS patients, irrational fear of movement is not related to exercise performance. **The aim of this study was to examine the interactions between several intracellular immune variables and exercise performance in (ME)CFS. These data add to the body of literature showing impairment of intracellular immunity in patients with (ME)CFS. The results provide evidence for an association between intracellular immune dysregulation and exercise performance in patients with (ME)CFS" (J Nijs, N McGregor, K De Meirleir et al. Medicine & Science in Sports & Exercise 2005:Exercise Immunology in CFS:1647-1654).

2005

*"The hypothesis of the present study is that the appearance of cell-specific autoimmune antibodies may define subsets of (ME)CFS. **(ME)CFS is clinically similar to several autoimmune disorders that can be diagnosed and characterised by autoantibody profiles**. For this reason, we conducted an exhaustive evaluation of 11 ubiquitous nuclear and cellular autoantigens in addition to two neuronal specific antigens. Very few studies have evaluated the presence of autoantibodies in people with (ME)CFS. The findings of this study hint that evaluation of certain autoantibodies may give clues to on-going pathology in subsets of (ME)CFS subjects. **Among (ME)CFS subjects, those who had been sick longer had higher rates of autoantibodies"*** (S Vernon et al. Journal of Autoimmune Diseases May 25th, 2005:2:5).

2006

*"**The diagnostic criteria of CFS define a heterogeneous population composed of several subgroups. This study was designed to examine NK cell activity as a potential subgroup biomarker. The results (provide) evidence in support of using NK cell activity as an immunological subgroup marker in (ME)CFS. Improved treatment options will only come with better understanding of the syndrome's underlying pathophysiology The present study specifically investigated the existence of an immunological subgroup of CFS patients.** Reduced NK cell activity may contribute to enhanced cytokine production. **Given the role that NK cells play in targeting virally infected cells, a clinically significant reduction in NK cell activity may lead to activation of latent viruses and new viral infections. (ME)CFS is a misunderstood condition. Research in the last two decades has produced little advancement in the understanding of the pathophysiology of (ME)CFS. Unfortunately, this lack of progress seems to have further contributed to the belief among some members of the medical community that (ME)CFS is not an actual organic condition"*** (Scott D Siegel, Mary Ann Fletcher, Nancy Klimas et al. J Psychosom Res 2006:60:6:559-566).

2006

"(ME)CFS is a poorly defined medical condition which involves inflammatory and immune activation. The Type I interferon antiviral pathway has been repeatedly shown to be activated in the most afflicted patients. An abnormal truncated form of ribonuclease L (37-kDa RNase L) is also found in (ME)CFS patients and this protein has been proposed as a biological marker for (ME)CFS. The levels of this abnormal protein have been significantly correlated to the extent of inflammatory symptoms displayed by (ME)CFS patients. (Our) results suggest that chronic inflammation due to excess nitric oxide plays a role in (ME)CFS and that the normal resolution of the inflammatory process is impaired" (M Fremont, K De Meirleir et al. JCFS 2006:13(4):17-28).

2007 (April) (the NICE Guideline was published on 22nd August 2007)

"For decades, (ME)CFS patients were – and still are – dismissed as lazybones or hypochondriacs. Many medical doctors and insurance companies still assert that (ME)CFS is a mental condition. The mainstream treatment for (ME)CFS is CBT, which means that patients with (ME)CFS are being treated as having a mental illness with 'treatments' that do not treat any underlying cause. Doctors who treat (ME)CFS patients as suffering from an organic disorder and scientists who examine the biological causes of (ME) are often considered quacks by their colleagues (and) insurance companies, which are sometimes even officially supported by governments in their attempts to eliminate the scientific view that (ME)CFS is an organic disorder. The official acceptance of the latter obviously would mean that the national health care systems are obliged to financially support those patients who are now considered hypochondriacs and, therefore, may easily be suspended from the national health care systems. There is, however, evidence that (ME)CFS is a severe immune disorder with inflammatory reactions and increased oxidative stress. Maes et al show that patients with (ME)CFS show very high levels of nuclear factor kappa beta in their immune cells. NFkβ is the major mechanism which regulates inflammation and oxidative stress. Thus, the increased production of NFkβ in the white blood cells of patients with (ME)CFS is the cause of the inflammation and oxidative stress (seen) in (ME)CFS" (Maes et al. Neuroendocrinology Letters, 2007. http://www.michaelmaes.com/).

Evidence has continued to mount since the publication of the NICE Clinical Guideline, for example:

2007

*"Recent research has evaluated genetic signatures, described biologic subgroups, and suggested potential targeted treatments. **Acute viral infection studies found that initial infection severity was the single best predictor of persistent fatigue**. Studies of immune dysfunction (have) extended observations of natural*

killer cytotoxic cell dysfunction of the cytotoxic T cell through quanitative evaluation of intracellular perforins and granzymes. Other research has focused on a subgroup of patients with reactivated viral infection. ***Our expanded understanding of the genomics of (ME)CFS has reinforced the evidence that the illness is rooted in a biologic pathogenesis that involves cellular dysfunction and interactions between the physiologic stress response and inflammation. A large body of evidence links (ME)CFS to a persistent viral infection. (ME)CFS patients exhibited a distinct immune profile compared with fatigued and non-fatigued individuals. These patients displayed increased anti-inflammatory cytokines. Investigators noted the tropism with brain and muscle and suggested that the neuroinflammation seen in neuroimaging studies of a subgroup of CFS patients may result from enteroviral infection.*** (Note that the NICE Guideline proscribes neuroimaging studies in the UK). ***The clinical implications are consistent with an immune system that may allow viral reactivation and raises a concern for tumour surveillance as well. The preponderance of available research confirms that immune dysregulation is a primary characteristic of (ME)CFS. These advances should result in targeted therapies that impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation"*** (Nancy G Klimas et al. Current Rheumatology Reports 2007:9:6:482-487).

Illustrations of neuroendocrine dysfunction in ME/CFS from the published literature that NICE disregarded in the production of its Clinical Guideline 53 (for reasons of space, this is only a small sample)

1991

"Several lines of evidence suggest that the various components of the hypothalamic-pituitary-adrenal (HPA) axis merit further study in these patients. Debilitating fatigue, an abrupt onset precipitated by a stressor, feverishness, arthralgias, myalgias, adenopathy, postexertional fatigue, exacerbation of allergic responses are all characteristic of glucocorticoid insufficiency. ***Compared to controls, patients with (ME)CFS showed a significant reduction in basal total plasma cortisol (and) a proportionately higher response to the amount of ACTH released during stimulation with oCRH. We suggest that the hyper-responsiveness of the adrenal cortex to ACTH in patients with (ME)CFS reflects a secondary adrenal insufficiency in which adrenal receptors have become hyper-responsive to inadequate levels of ACTH. In the light of the post-infectious presentation of (ME)CFS in the majority of patients, it should be noted that viral infections can alter neurotransmitter and / or neuroendocrine regulation"*** (Mark A Demitrack et al. Journal of Clinical Endocrinology and Metabolism 1991:73:6:1224-1234).

1992

"The syndrome of (ME)CFS has a lengthy history in the medical literature. The clinical presentation, with evidence of persistent immune stimulation, lends support to the idea that (ME)CFS represents a clinical entity with potential biological specificity. ***We showed that patients with (ME)CFS demonstrate a significant hypocortisolism****"* (Mark A Demtrack et al. Biol Psychiatry 1992:32:1065-1077).

1993

"Patients with (ME)CFS lose muscle protein synthetic potential, but not muscle bulk. These perturbations may contribute to the feature of muscle weakness associated with persistent viral infection in the muscles themselves. 80% of patients had serological indications of current or on-going VP1 positive enterovirus infection*. There has to be persistent enterovirus infection to produce the response; it does not rely on the body's development of antibody.* ***Furthermore, skeletal muscle RNA was significantly reduced. This reflects a reduced capacity to synthesise proteins. Our results imply that there is a subgroup of patients with (ME)CFS in which symptoms of skeletal muscle weakness may be related to proximal myopathy. Direct evidence has been obtained for a subcellular metabolic defect in the muscle***

per se. These studies indicate that up to 80% of patients with (ME)CFS have identifiable mitochondrial abnormalities" (VR Preedy TJ Peters et al. J Clin Pathol 1993:46:722-726).

1993

"The baseline AVP values were significantly lower in patients with (ME)CFS when compared to healthy controls. The mean total body potassium (TBK) was 9% lower than predicted*. This study also showed that some patients with (ME)CFS appear to have an increased total body water content when compared with healthy controls. Abnormalities of water metabolism in patients with (ME)CFS have previously been reported.* ***This interference with hypothalamic function may be due to the presence of persistent virus, most likely enterovirus. In such a chronic infection, Oldstone has shown that the agent may persist in cells without producing any evidence of damage but effecting a profound disturbance of hormones and neurotransmitters****"* (AMO Bakheit et al. Acta Neurol Scand 1993:87:234-238).

1994

"One of the characteristic complaints of patients with (ME)CFS is the skeletal muscle-related symptom. We show that patients had a deficiency of serum acylcarnitine. This deficiency might induce an energy deficit and/or abnormality of the intramitochondrial condition in the skeletal muscle, resulting in general fatigue, myalgia, muscle weakness and postexertional malaise in patients with (ME)CFS. The measurement of acylcarnitine would be a useful tool for the diagnosis and assessment of (ME)CFS" (H Kuratsune et al. Clin Inf Dis 1994:18: (Suppl 1):S62-S67).

Note that in the UK, this measurement is proscribed by NICE.

1995

"The role of steroids in growth hormone production was determined in patients with (ME)CFS. There were abnormal responses of growth hormone production to administered steroids in patients with (ME)CFS. These data suggest an abnormality in the glucocorticoid receptor bearing neurones that control growth hormone responses in affected patients. These data clearly pointed to an abnormality in neuroendocrine control. Another condition that bears striking similarities to (ME)CFS is post-polio syndrome*"* (T Majeed et al. Journal of the Irish Colleges of Physicians and Surgeons 1995:24:1:20-24).

1996

In a study examining abnormality of adrenal function, Japanese researchers found that *"****these abnormalities are quite different from those found in patients with mental or physical diseases reported previously****"* (Yamaguti K et al. JCFS 1995:2:2/3:124-125).

1996

"In reviewing stress-response systems, it is important to keep in mind that activity of stress-response systems is determined by genetic and environmental factors. ***In (ME)CFS we have demonstrated a significant increase in plasma levels of the serotonin metabolite 5-hydroxyindoleacetic acid. Patients with a longer duration of disease do tend to have more severe basal abnormalities in cortisol levels***" (LJ Crofford et al. Rheum Dis Clin N Am 1996:22:2:267-284).

1996

"There is an increasing volume of evidence to support the view that patients with (ME)CFS have unique endocrinology patterns. The cardinal findings include attenuated ACTH responses to CRH and low 24-hour urinary cortisol. These are compatible with a mild central adrenal insufficiency. It is well-documented that infectious diseases are often accompanied by various forms of neuroendocrine disturbances with acute viral infections activating the HPA axis. An increase in peripheral turnover of 5-HT may explain the heightened allergic responsiveness as well as the musculoskeletal pain seen in (ME)CFS" (LV Scott TG Dinan. JCFS 1996:2:4:49-59).

1997

"It is notable that the pattern of alteration in the stress response suggests a sustained inactivation of central nervous system components of this system. ***It has not escaped the view of clinical authors that (ME)CFS and its historical antecedents shares many of the characteristics with endocrine disease states (in which there is) functional interdependence of the endocrine system and the nervous system****. It is only recently that clinical researchers have clearly documented that neuroendocrine disturbances are evident in patients with (ME)CFS (which) have brought into view a broader understanding of the variety of physiologic accompaniments of this condition. (ME)CFS appears to wax and wane with periods of increased stress.* ***Results of this work provide confirmatory support for an impairment (of) the HPA axis (and) is consistent with the view that adrenocortical function is impaired****"* (MA Demitrack. J psychiat Res 1997:31:1:69-82).

1998

"Our group has established that impaired activation of the HPA axis is an essential neuroendocrine feature of (ME)CFS. *It is now recognised that (ME)CFS leads to significant physical and psychological debility in a large segment of the population. We have suggested that the findings of reduced adrenal glucocorticoid function in (ME)CFS are most consistent with a central nervous system defect in the activation of this axis.* ***(We found) a basal hypocortisolism. On its own, this observation is a striking finding. These observations provide an important clue to the development of more effective treatment for this disabling condition****"* (MA Demitrack, LJ Crofford. Ann N.Y. Accad Sci 1998:840:684-697).

1999

"The right and left adrenal gland bodies were reduced by over 50% in the (ME)CFS subjects, indicative of significant adrenal atrophy in a group of (ME)CFS with abnormal endocrine parameters*"* (Scott LV et al. Psychoneuroendocrinology 1999:24:7:759-768).

2000

*"****Baseline adrenaline levels were significantly higher in (ME)CFS patients. We conclude that (ME)CFS is accompanied by a resistance of the immune system to regulation by the neuroendocrine system. Based on these data, we suggest (ME)CFS should be viewed as a disease of deficient neuroendocrine-immune communication****"* (Kavelaars A et al. J Clin Endocrinol Metab 2000:85:2:692-696).

2001

"In the investigation of (ME)CFS, fine needle aspiration (FNA) cytology has been tested in addition to conventional biochemical thyroid function tests. Of 219 patients, 40% were diagnosed with definite

cytological lymphocytic thyroiditis. ***We strongly advocate FNA cytologic assessment of the thyroid in patients with (ME)CFS****"* (B Wikland et al. Lancet 2001:357:956-957).

In a subsequent letter, Wikland stated: "*In a letter published in The Lancet (24th March 2001) we report on fine needle aspiration cytology of the thyroid in (ME)CFS. No less than 40% of our patients showed definite autoimmune thyroiditis. Less than half of these patients fulfilled conventional biochemical criteria of hypothyoidism.* ***In our opinion, this aspect merits wider recognition****"* (Bo Wikland. eBMJ 9 January 2002).

2001

"One of the most consistent findings in (ME)CFS is a decrease in Th1-mediated immune responses. (ME)CFS patients have been shown to display a disturbed HPA axis and have low levels of cortisol. We speculate that in these patients IL-10 and IL-12 are differently affected by glucocorticoids. ***The present study shows that, in particular, IL-10 secretion (and its sensitivity to GC) differs from that in healthy controls****"* (J Visser et al. Journal of Neuroimmunology 2001:119:2:343-349).

2003

"Endocrinologists were not included in the working groups that prepared two recent reports on (ME)CFS, despite its clinical overlap with Addison's disease, which is a classic endocrine disease. The failure to include at least one endocrinologist in those panels may explain why in their reports there is not a single word about the 42 clinical features that (ME)CFS shares with Addison's disease*. The failure of both the English and Australian reports to mention other important endocrine abnormalities of (ME)CFS represents a serious omission. Cognitive behaviour therapy may have benefited depressed subjects (but) not patients with (ME)CFS.* ***(ME)CFS and Addison's disease also share reduced cardiac dimensions, increased heart rate, postural hypotension, orthostatic tachycardia, dizziness upon standing, dehydration, anorexia, nausea (and) diarrhoea. Moreover (they) also share leucocytosis, lymphocytosis, elevations of transaminase values, enhanced TSH secretion, respiratory muscle dysfunction, reduction in exercise capacity and increased sensitivity to chemical exposures****. Reason suggests that the clinical overlap of (ME)CFS with Addison's disease reflects the endocrine and adrenal abnormalities found in (both disorders) and omitted unjustifiably in both the English and Australian reports, namely hypocortisolism, impaired adrenal cortical function, reduced adrenal gland size, antibodies against the adrenal gland, and impaired production of DHEA.* ***Richard Horton, editor of The Lancet, has recently written*** *(JAMA 2002:287:2843-2847)****: 'Failure to recognise the critical footprint of primary research weakens the validity of guidelines and distorts clinical knowledge****' "* (R Baschetti. Eur J Clin Invest 2003:33:1029-1031).

Baschetti was referring to the 2002 UK Report of the CMO's Working Group and the Australian Report in the Medical Journal of Australia 2002:176:S17-S56. There was no endocrinologist on the NICE Guideline Development Group which produced the NICE Guideline in August 2007.

2003

"Patients with (ME)CFS typically present a normal thyroid function. From (our) observations, we raise the hypothesis that molecular mechanisms could explain the development of a clinical hypothyroid state in the presence of a normal thyroid function. Whilst biochemically euthyroid, (ME)CFS patients are clinically hypothyroid. Signal transduction mechanisms could account for a peripheral T3 resistance syndrome leading to a clinically hypothyroid but biochemically euthyroid state, as observed in diseases characterised by dysregulations in the antiviral pathway or during the therapeutic use of INF α / β" (P Englebienne et al. Med Hypotheses 2003:60:2:175-180).

2003

The following article is in Serbian and comes from the Institute of Endocrinology, Belgrade; no author is listed:

"Similarities between the signs and symptoms of (ME)CFS and adrenal insufficiency prompted the research of the HPA axis derangement in the pathogenesis of (ME)CFS. ***We compared cortisol response in the (ME)CFS subjects with the response in control subjects and in those with secondary adrenal insufficiency. We have shown that cortisol increment at 15 and 30 minutes is significantly lower in the (ME)CFS group than in controls. However, there was no difference between the (ME)CFS group and those with secondary adrenal insufficiency in any of the parameters. Consequently, reduced adrenal responsiveness to ACTH exists in (ME)CFS****"* (Srp Arh Celok Lek 2003:131:9-10:370374).

It should be noted that Wessely School psychiatrists have carried out several endocrinological studies on "CFS" patients and have had varying results, possibly because of their chosen case definition. Despite the compelling evidence of international researchers, the Wessely School psychiatrists found no evidence of endocrine abnormality in some of their studies, whilst in others they did find evidence of such abnormalities. Overall, these Wessely School researchers concluded that even though a distinct abnormality was found (low cortisol), it was likely to be "*an epiphenomenon caused by the behavioural changes typical of CFS*" (GJ Rubin, M Hotopf, A Cleare et al. Psychosom Med 2005:67:3:490-499).

Following the publication of the NICE Guideline, Wessely School psychiatrists have continued to publish studies on "CFS", the results of which do not accord with existing biomedical science, for example: *"It has been argued that perceived functional incapacity might be a primary characteristic of CFS. (Our) sample consisted of 73 patients with a diagnosis of CFS according to the Oxford criteria randomly selected from clinics in the Departments of Immunology and Psychiatry at St Bartholomew's Hospital, London. The findings suggest that perceived functional incapacity is a primary characteristic of CFS"* (Priebe S et al. Psychopathology 2008:41(6):339-345).

To refer to "*perceived incapacity*" in these patients is not only offensive to patients but is also an insult to the many clinicians and researchers who have uncovered the reality of the incapacity through the scientific process (in which psychiatry plays no part).

Illustrations of neurological dysfunction in ME/CFS from the published literature that NICE disregarded in the production of its Clinical Guideline (for reasons of space, this is a limited sample)

Evidence of inflammation in the central nervous system:

Despite denials by Wessely School psychiatrists, there is evidence of **inflammation of the central nervous system** in ME/CFS.

Just a few illustrations of published evidence of inflammation of the central nervous system that NICE chose to disregard include: Pellew RAA (Med J Aust:1955:42:480-482); Innes SGB (Lancet:1970:969-971); Buchwald, Cheney, Peterson D, Komaroff, Gallo et al (Ann Int Med: 1992:116:103-113): Schwartz RE et al (Am J Roentgenology:1994:162:935-941); Komaroff AL (JAMA:1997:278:14:1179-1184). There are other more recent papers such as Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P et al. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. Am J Med 1998:105:54S–58S; Chaudhuri A, Behan PO. In vivo magnetic resonance spectroscopy in chronic fatigue syndrome. Prostaglandins, Leukotrienes and Essential Fatty Acids 71 (2004) 181–183; Yamamoto S et al. Reduction of serotonin transporters of patients with chronic fatigue syndrome. NeuroReport 2004:15:2571-2574.

Evidence of neurological dysfunction:

1962

ME/CFS was included by the distinguished neurologist Lord Brain in his textbook "Diseases of the Nervous System", Oxford University Press, sixth edition: pp355 " *(ME) is the term applied to a disorder which has been recognised in many parts of the world. Its features are the severity of the symptoms in relation to the slightness of the physical signs. A characteristic feature of the muscular weakness is the intermittency of power of muscular contraction. Changes which are believed to be characteristic have been found on electromyography. A striking feature is the tendency for relapses to occur during the months, and in some cases even years, after the infection".*

1990

Extract from a Press Conference by Professor Paul Cheney held in San Francisco in September 1990 and reported in CFIDS Chronicle, September 1990:

"***I believe this is a disease that affects the central nervous system (CNS) and I'll show you some slides to help convince you of that. We are going to (look at) what evidence there is for neurologic disease in these patients****. This is a study done by Dr Carolyn Warner from the Dent Neurologic Institute in Buffalo, New York, which specialises in multiple sclerosis.* ***Some people think that (ME)CFS can look like MS and there are clinical features that are overlapping. The most specific neurologic symptom is dysequilibrium. These patients have a balance disturbance and on certain simple neurologic tests they fall over. On more sophisticated neurologic tests of vestibular function they are often grossly abnormal. Nearly every patient had something abnormal within the central nervous system, and also neuromuscular problems, or muscle itself.*** *These patients are cognitively impaired and you can prove it by formalised psychometric tests.* ***Other evidence of CNS involvement can be demonstrated by tests looking directly at the CNS.*** *These are slices of brain created by using magnetic resonance imaging.* ***These inflammatory and/or demyelinating plaques can be seen in the white matter, in the cerebellum and white matter tracts throughout the high cerebral convexities and in the frontal lobes. Over half of (ME)CFS patients will typically show lesions within the central nervous system.*** *Professor Ismael Mena, chairman of the Department of Nuclear Medicine at Harbourview UCLA Medical Centre, found that there were defects in perfusion of temporal lobes primarily. He looked at regional cerebral blood flow and found that in (ME)CFS patients compared to controls, there was a diminishment of cerebral blood flow in the right temporal lobe that was significant.* ***In other words, blood flow to the right temporal lobe was impaired in these patients. The temporal lobe seems to get really hit by this disease. I want to point out that 71% of patients with (ME)CFS are abnormal by this technique****".*

It is again noted that in the UK, NICE proscribes nuclear imaging scans.

1991

"Patients with (ME)CFS often complain of dysequilibrium. Data suggests that their symptoms of dysequilibrium can be substantiated with quantitative laboratory testing. The abnormalities are more suggestive of CNS deficits than of peripheral vestibular deficits*"* (JMR Furman. Rev Inf Dis 1991:13: (Suppl 1):S109-111).

1994

In a CME (continuing medical education) credit article, Dr David Bell, an internationally-acclaimed paediatrician specialising in ME/CFS, wrote in Postgraduate Medicine: "***Findings now point to CNS involvement****: Recent research has yielded remarkable data (and has) provided a steady current of scientific*

additions to our understanding of (ME)CFS". Reviewing the immunological abnormalities (and noting that the patients who were the most disabled had the highest levels of interleukin-1), Bell pointed out that a consistent pattern of immune dysfunction is emerging, which helps to characterise and define the illness. He noted the elevated levels of cytokines, particularly those that affect neuronal tissue. He reviewed the evidence for retroviral markers, the pituitary and hypothalamic abnormalities, and the neuroendocrine abnormalities. He reviewed the cerebral perfusion abnormalities and highlighted the importance of elevated serum ACE levels seen in ME/CFS: ***"Another addition to the bewildering array of laboratory abnormalities found in patients with (ME)CFS is an increased serum concentration of angiotensin-converting enzyme (ACE). This is a marker not only for sarcoidosis but also for diseases involving the blood vessels. This finding is of importance because of the clinical similarities between (ME)CFS and sarcoidosis.*** *Shared symptoms include fatigue, neurologic dysfunction and arthalgia.* ***In patients with an elevated ACE level, attention to the lymph nodes and eyes is called for".*** Bell concluded: ***"The symptoms of (ME)CFS have long been viewed as a neurologic pattern, as indicated by other names for the condition such as myalgic encephalomyelitis (and) atypical poliomyelitis. Neurologic involvement is beginning to be confirmed by documentation of abnormalities in cerebral perfusion, hypothalamic function, and neurotransmitter regulation. A link is being forged between the symptoms pattern and objective evidence of CNS dysfunction.*** *A majority, and perhaps all, of the symptoms of (ME)CFS may be neurologic in origin.* ***The view that (ME)CFS is a primary emotional illness has been undermined by research findings"*** (David S Bell. Postgraduate Medicine 1994:96:6:73-81).

1994

"Because a complete neurological examination is not emphasised as part of the diagnostic workup, it is possible that less obvious neurological findings may be overlooked. Careful evaluation of neurological features may be one approach to distinguishing subtypes. *The neurological symptoms and signs were neuropsychological changes, cutaneous sensory changes, paresis, abnormal muscle movements, abnormal muscle tone, deep tendon reflex changes, cranial nerve signs, posterior column signs, ataxia, and vasomotor instability.* ***Activity or exercise was a precipitant or exacerbation or relapse. Many of the neurological signs and symptoms were not reported on. A complete neurological examination should be an integral part of the diagnostic assessment of illnesses described as CFS"*** (NC Briggs, Paul Levine. Clin Inf Dis 1994:18: (Suppl 1):S32 –S42).

1995

To assess the clinical impression that patients with (ME)CFS do not walk normally, the gait kinematics of patients with (ME)CFS were studied. Results showed that (ME)CFS patients were significantly slower at running speed than the controls. Further analysis revealed that patients with (ME)CFS took smaller steps than the controls. "***The data indicate that (ME)CFS patients have gait abnormalities when compared to sedentary controls. These could be due to balance problems, muscle weakness, or central nervous system dysfunction"*** (Boda WL, Natelson BH et al. Journal of the Neurological Sciences 1995:156-161).

1996

"A growing literature exists suggesting that a component of (ME)CFS may include abnormalities in cardiovascular control. *Vagal power, a measure of cardiac parasympathetic activity, was computed.* ***In an earlier study, we showed that patients with (ME)CFS had significantly less vagal power than healthy controls during controlled breathing. Our findings suggest that vagal dysregulation may be an additional symptom of (ME)CFS. Moreover, they suggest the presence of a biological link between fatigue and the autonomic nervous system. The (ME)CFS group had less vagal power than the controls at every stage (and also) during the first stage of recovery. These results indicate that vagal power responses in patients with (ME)CFS are different from healthy controls. A common complaint in (ME)CFS is that patients are unable to exert themselves for prolonged periods due to a lack of energy. Our findings might explain this. It is possible that reduced vagal power might interfere with the normal recovery process that***

follows bouts of exertion. This interference might exacerbate fatigue immediately or for several days following exertion, a common complaint in (ME)CFS. Decreases in vagal power have been identified in several medical conditions, including congestive heart failure. Our data suggest that (ME)CFS may involve a primary neurological abnormality. (ME)CFS patients also show dysfunction in complex auditory processing that is of the same magnitude as that found in patients with multiple sclerosis. Other data show that patients with ME/CFS *(sic)* ***had significantly lower brain stem perfusion ratios than either healthy or depressed controls"*** (DL Cordero, BH Natelson et al. Clinical Autonomic Research 1996:6:329-333).

1997

"The aim of this study was to investigate the role of the autonomic nervous system in (ME)CFS. Autonomic signs and symptoms have appeared frequently in reports of CFS, also called myalgic encephalomyelitis*. The three criteria used to determine autonomic symptoms eligibility were (1) dizziness upon standing and rapid heart beat; (2) dizziness upon standing and either nausea, diarrhoea, constipation and night sweats and (3) rapid heart beat and either nausea, diarrhoea, constipation or night sweats.* ***Recent reports have documented neurocardiogenic syncope in patients, again suggesting autonomic dysfunction in (ME)CFS. Several autonomic function test results were significantly different in the (ME)CFS group when compared to controls. Our study found that neither depression nor anxiety correlated with any of the measures of autonomic dysfunction. Deconditioning alone did not explain these autonomic abnormalities. 89% of patients in this study reported that the onset of fatigue was preceded by (an infectious illness), a history typical of patients with (ME)CFS. Our results provide evidence for an association between an autonomic neuropathy and (ME)CFS. An exercise programme, alone and in combination, cannot now be generally recommended for patients with (ME)CFS"*** (R Freeman, AL Komaroff. Am J Med 1997:102:357-364).

1998

"Spatial and temporal parameters of gait were collected from (ME)CFS patients by using instrumentation of movement analysis. ***Interestingly, abnormalities were present from the beginning of the gait, which indicates that they are unlikely to be caused by the rapidly increasing fatigue. This strengthens the hypothesis of a direct involvement of the central nervous system in the onset of the disease****"* (R Saggini et al. Journal of the Neurological Sciences 1998:154:18-25).

1998

"A substantial body of clinical evidence now supports an association between various forms of hypotension and (ME)CFS. Features that exacerbated (patients') fatigue included physical exertion, a hot shower, prolonged standing (such as waiting in line at the grocery store) and a warm environment. Importantly, all (ME)CFS patients but none of the controls developed orthostatic symptoms (during testing), suggesting that orthostatic intolerance may be a defining feature of the illness. Virtually all (ME)CFS patients have their symptoms provoked by the simple process of assuming an upright posture. There is a high prevalence of allergic disease among those with (ME)CFS *(and) one would expect to find a mechanism by which allergic disease increases the activation of the NMH reflex pathway. Undem et al have shown that both viral infection and allergic reactions to food antigens enhance the excitability of mechanically sensitive vagal afferents in the airway (which provides a link between these clinical situations).* ***Investigations into the high prevalence of neurally mediated hypotension and other forms of autonomic dysfunction among those with (ME)CFS should improve our understanding of this disorder****"* (Peter C Rowe and Hugh Calkins. Am J Med 1998:105:3A:15S-21S).

1999

"The fatigue in (ME)CFS is similar to that found in disorders of the central nervous system such as multiple sclerosis, Parkinson's disease and multiple system atrophy*. It is now clear that (ME)CFS patients differ from patients with major depression in their symptoms (and) biologic markers such as steroid metabolism. We propose dysfunctional ion channels in the cell membranes as the key abnormality in (ME)CFS which may also be responsible for the altered neuroendocrine functions reported in this condition. Associated symptoms that are common in (ME)CFS include paroxysmal attacks of angina-like chest pain (Syndrome X), nocturnal attacks of sweating and palpitations, irritable bowel syndrome, vertigo or dysequilibrium, photophobia (and) daily migraine-like headaches. Autonomic dysfunction in (ME)CFS is well-recognised.* ***One of the most characteristic features of the illness is the fluctuation in symptoms which can be induced by physical and/or mental stress****. Acquired ion channel abnormalities in myocardium could explain the pathogenesis of Syndrome X. Acquired mutations of a similar nature may form the basis of the cardiac dysfunction seen in Syndrome X and (ME)CFS. The role of abnormal ionophores governing both Syndrome X and (ME)CFS assume importance in the light of the fact that a highly significant proportion of (ME)CFS patients have cardiomyopathy. (ME)CFS is an episodic neurological disorder with a basic mechanism of disease involving abnormal ion channel functions"* (Abhijit Chaudhuri et al. Hum Psychopharmacol Clin Exp 1999:14:7-17).

2000

In 2000, the CFIDS Association of America produced a 24 page document entitled "**Neurological Findings in (ME)CFS: A Survey of the Research"** containing 175 references. It is available from the CFIDS Association of America, email: info@cfids.org

2001

A quantitative assessment of cerebral ventricular volumes in (ME)CFS patients found that volumes were larger than in the control groups. "*The results of this study provide further evidence of pathophysiological changes in the brains of participants with (ME)CFS"* (Lange G, Natelson BH et al. Appl Neuropsychol 2001:8(1):23-30).

2003

Research at the Salk Institute, La Jolla, California, identified a gene that may link certain pesticides and chemical weaponry to a number of neurological disorders. The finding, published in the 17 March online version of Nature Genetics, was the first to demonstrate a clear genetic link between neurological disorders and exposure to organophosphate (OP) chemicals. OPs include household pesticides as well as the nerve gas sarin. The research showed that OPs inhibit the activity of a gene called neuropathy target esterase (NTE). Some of the neurological problems echoed many of the symptoms of Gulf War Syndrome.

This is important because the Proceedings of The National Academy of Science (PNAS) published evidence that NTE is inhibited by several OP pesticides, chemical warfare agents, lubricants and plasticisers, leading to OP-induced delayed neuropathy in more than 30,000 human cases (PNAS 2003:100:13:7983-7987). It is highly significant in ME/CFS, because gene expression research has demonstrated 16 genes as having an expression profile associated with (ME)CFS. These genes can be grouped according to immune, neuronal and mitochondrial functions. A neuronal component was identified that is associated with central nervous system hypomyelination, and the researchers specifically noted the association of organophosphates and chemical warfare agents: *"A neuronal component is suggested by up-regulation of NTE. NTE is a target for organophosphates and chemical warfare agents, both of which may precipitate (ME)CFS"* (N Kaushik, ST Holgate, JR Kerr et al. J Clin Pathol 2005:58:826-832). Stephen Holgate is MRC Clinical Professor of Immunopharmacology at the University of Southampton and this is top-rank research, not mere hypothesis.

2004

"The purpose of this study was to determine whether brain activity of (ME)CFS patients during voluntary motor actions differs from that of healthy controls. *Fifty-eight channels of surface EEG were recorded simultaneously from the scalp. Major findings include (1) Motor performance of the (ME)CFS patients was poorer than the controls (2) Relative power of EEG theta frequency band during performance of tasks was significantly greater in (ME)CFS than in the control group (3) The amplitude of MRCP (motor activity-related cortical potential) negative potential for tasks was higher in (ME)CFS than the control group.* ***These results clearly show that (ME)CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. Physical activity-induced EEG signal changes may serve as physiological markers for more objective diagnosis of (ME)CFS***" (Siemionow V et al. Clin Neurophysiol 2004:115(10:2372-2381).

It is worth noting once again that such investigations for these patients in the UK are proscribed by NICE.

2004

In 2004, The Lancet published a Review entitled "**Fatigue in neurological disorders**" by Abhijit Chaudhuri et al (Lancet 2004:363:978-988). It included (ME)CFS as a neurological disease and it contained 94 references.

2005

In a study looking at gray matter volume reduction in (ME)CFS, researchers found significant reductions in global gray matter volume in (ME)CFS patients compared with matched controls: "*Moreover, the decline in gray matter volume was linked to the reduction in physical activity, a core aspect of (ME)CFS. These findings suggest that the central nervous system plays a key role in the pathophysiology of (ME)CFS and point to an objective and quantitative tool for clinical diagnosis of this disabling disorder"* (FP de Langea et al. NeuroImage 2005:26:3:777-781).

The persistence of the Wessely School's ignoring of the biomedical evidence

Following the publication of the NICE Guideline, the Wessely School's determination to promote their own model and to force the implementation of the Guideline's recommendations continues unabated.

In July 2008, the same Systematic Review team at the Centre for Reviews and Dissemination at York which produced the alleged "evidence-base" upon which the GDG relied to support its behavioural interventions for "CFS/ME" (the advisers to the team being members of the Wessely School) published another Systematic Review, this time of alleged risk factors for the development of "CFS/ME".

This latest Systematic Review was funded by NICE. The authors state: "*The work forms part of the independent (sic) synthesis of research evidence to support the development of these guidelines".*

The authors specifically acknowledge the input of members of the CG53 Clinical Guideline GDG, and they acknowledge assistance from *"two anonymous reviewers".*

Of the 27 references cited, no less than 16 are from the Wessely School.

Unsurprisingly therefore, the conclusion states: "*Significantly associated with the development of CFS/ME in the final predictive model were being female, presence of anxiety disorder, mood disorder, emotional instability, sick certification after viral illness, no sport in spare time at 10 years old, visits to GP"* and it mentions "*psychological characteristics*".

The authors concede that: "*Not all studies seem to have excluded CFS/ME defining factors for the prediction of CFS/ME, which makes the studies difficult to compare"* (Risk factors for chronic fatigue syndrome / myalgic encephalomyelitis: A systematic coping review of multiple predictor studies. Hempel S, Chambers D, Bagnall A-M, Forbes C. Psychological Medicine July 2008:37(7):915-926).

It is disturbing that no attention seems to have been paid by the Systematic Review team or its advisers to the existing scientific evidence: "***We found that the best predictor for (ME)CFS was the intensity of the initial infectious disease. There were no other factors, psychological or biological, that held up under thorough analysis****"* (Dr Williams Reeves, Chief of Chronic Viral Diseases Branch, Centres for Disease Control, USA: November 2006: http://www.cdc.gov/od/media/transcripts/t061103.htm?id=36410 and ***"The syndrome was predicted largely by the severity of the acute illness rather than by demographic or psychological factors"*** (I Hickie et al. BMJ 2006:333:575).

It is curious indeed that the Wessely School repeatedly asserts the need for "evidence-based medicine" in "CFS/ME", yet pays no heed to it.

Conclusion

Throughout these illustrations there have been repeated calls for further investigation of patients with (ME)CFS.

The fact that in the UK, the NICE Guideline proscribes such investigations and recommends only mind-altering interventions that are designed to disabuse patients of the notion that they are physically sick, together with incremental aerobic exercise, might be construed as State-sponsored abuse of extremely sick people.