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THE GROUP ON SCIENTIFIC RESEARCH INTO MYALGIC ENCEPHALOMYELITIS

(THE GIBSON PARLIAMENTARY INQUIRY)

Illustrations of Clinical Observations and International Research Findings from 1955 to 2005 that demonstrate the organic aetiology of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome

Malcolm Hooper Eileen Marshall Margaret Williams

12th December 2005

Prepared for The Group on Scientific Research into Myalgic Encephalomyelitis (the Gibson Parliamentary Inquiry) that has been established "to assess the progress of scientific research on ME since the publication of the Chief Medical Officer's Working Group Report into CFS/ME in 2002, (and) to increase public understanding of scientific research into ME/CFS (and) to identify research and funding requirements in establishing the cause of ME/CFS".

This document is a compilation of illustrations taken from the published evidence-base of the organic aetiology of ME/CFS over the fifty years from 1955 to 2005.

To faciliate comparison it also includes Appendices of illustrations from the published works of psychiatrists who believe ME/CFS to be a behavioural disorder.

Malcolm Hooper
Emeritus Professor of Medicinal Chemistry
Department of Life Sciences
University of Sunderland
SR2 7EE, UK

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EXECUTIVE SUMMARY

- There is a large and significant published international evidence-base that ME/CFS is a legitimate medical disorder with numerous reproducible biomarkers of organic pathology, but this evidence has been consistently buried in the UK by "Wessely School" psychiatrists (so named after its leading activist Professor Simon Wessely) who have vested interests in promulgating their own hypothesis that ME is nothing but an "aberrant illness belief" that is best managed by compulsory "behavioural rehabilitation" regimes

- Wessely School psychiatrists themselves admit that their favoured therapies have limited impact on the disorder and that any modest improvement disappears after several months

- Despite this, the Medical Research Council (MRC) and the UK Government have directed substantial funding into these therapies but nil funding for biomedical research into ME/CFS

- This is a human rights travesty

- Patients with ME/CFS who are not mentally ill are forced to attend psychiatric clinics; a single attendance at a psychiatric unit constitutes a *de facto* psychiatric diagnosis in the eyes of many, including GPs, employers, insurance companies, and family members

- No credible evidence exists that ME/CFS is a mental health issue, yet Wessely School psychiatrists continue to exercise a virtual monopoly on ME/CFS research in the UK

- There is an urgent need to end the Wessely School stranglehold on ME/CFS research, as well as the promulgation of their retrograde belief that the scientific biomedical approach to disease is a *(quote)* "blind alley" that should be replaced by a "psychosocial" model of disease (in which thoughts, feelings, beliefs and behaviour in the social context are responsible for diseases), and also their potentially seriously damaging psychosocial "management" regimes that are imposed on those with ME/CFS on pain of withdrawal of State and medical insurance benefits

- The Wessely School argument that syndromes like ME/CFS cause "unnecessary expenditure of medical resources" has been criticised by a leading US researcher for its pernicious public policy implications (see *Lancet Correspondence, 11th December 1999:354, Number 9195)*

- Research funding for ME/CFS must be urgently directed towards scientific and medical disciplines other than psychiatry and the MRC must cease to reject high quality biomedical research proposals on ME/CFS (known to have been submitted)

- Many GPs and most NHS Consultants (for example, cardiologists, neurologists, chest physicians, rheumatologists, immunologists) have virtually no accurate knowledge about ME/CFS and

therefore underestimate both its seriousness and the multi-system dysfunction it causes, so patients are simply dismissed and abandoned without support

- The malign influence of Wessely School dogma extends throughout Government Departments, throughout the NHS, and even extends to the Judiciary: one High Court litigant was told that "Judges regard ME as psychological self-indulgence"; one Local Health Board will only fund treatment for ME/CFS where the prime focus is cognitive behavioural therapy and/or graded exercise therapy; a spokesman for Grampian NHS Trust is on record in 2003 (ie. more than a year after the publication of the CMO's Working Group report) as stating: "ME is not a condition we recognize or treat"

- The damage perpetrated on those with ME/CFS by Wessely School adherents cannot be quantified

- Illustrations from the international literature showing that the Wessely School hypothesis about the nature of ME/CFS is wrong begin on page **9** below

- Appendices: (provided for direct comparison of the biomedical with the psychosocial models of the disorder)

    1. Illustrations of actual quotations about patients with ME/CFS from psychiatrist Professor Simon Wessely (page **129**)

    2. Illustrations of actual quotations about patients with ME/CFS from psychiatrist Professor Michael Sharpe (page **146**)

    3. "Wessely's Wisdom? Some more open questions for Professor Wessely" (page **162**). This document asks Professor Wessely some cardinal questions about ME/CFS that he and other Wessely School adherents have consistently failed to address

    4. "Unanswered Questions: do inconsistencies matter in medicine?" (page **171**). This document looks at the irrationality of drawing conclusions across differing patient populations; at the absurdity of relying on assumptions as the basis for a compulsory management regime of behavioural modification for patients with ME/CFS; at the divergent assertions about the efficacy of cognitive behaviour therapy and at the inherent danger of applying a 'one size fits all' policy.

INTRODUCTION

This document has been compiled to acquaint Members of Parliament with the existing international evidence base on the organic nature of myalgic encephalomyelitis (ME) / Chronic Fatigue Syndrome (CFS). It should be read in conjunction with our previous submission entitled "For UK Parliamentary Inquiry into ME/CFS: Chronological List of Documents Relevant to the Inquiry" (7th November 2005).

On 28th July 2005 there was a meeting between Dr Gibson MP, Professor Malcolm Hooper and members of the Norfolk ME community, at which Dr Gibson stressed his determination to hear evidence from both sides of the medical divide (ie. from those advocating a biomedical aetiology and from those advocating a purely psychosocial aetiology), and especially from affected patients. What Dr Gibson offered at that meeting was an open-minded, comprehensive and transparent examination and evaluation of **all** the evidence, **including and especially** the failure of the insurance industry to meet legitimate claims by those with ME/CFS, the problems of those with ME/CFS in obtaining State benefits, and the lack of all support for those with ME/CFS.

We and others, including senior NHS Consultants, are concerned that Members of the Parliamentary Inquiry should understand the travesty that currently exists in the UK in relation to ME/CFS. A group of psychiatrists known to patients and researchers alike as the "Wessely School" strenuously promotes their own hypothesis that ME/CFS is a mental health disorder that is best managed by a regime of cognitive behavioural therapy (CBT) which incorporates compulsory graded exercise therapy (GET) as a form of "rehabilitation". CBT is described in the Chief Medical Officer's Working Group 2002 Report on CFS/ME as "a tool for constructively modifying attitudes and behaviour".

Emanating from the Wessely School, a spurious medical consensus has emerged, namely that the syndrome is a primary psychiatric (behavioural) disorder. There is no evidence whatever that ME/CFS is a psychiatric disorder, and even adherents of the Wessely School themselves admit that CBT/GET has limited impact on the illness.

Objective evidence that such interventions are effective in ME/CFS is lacking: in 2001 a Leading Article found there was no such evidence and questioned whether the reported improvement might actually be an illusion (*JAMA 2001:286:11:1360-1368).*

Professor Simon Wessely himself has conceded that his therapies are "not remotely curative" and are only "modestly effective" and that "these interventions are not the answer to ME/CFS" *(Trials and Tribulations: JAMA 2001:286:11).*

Professor Wessely is also on record as stating: "cognitive behaviour therapy has been shown to improve functional impairment and fatigue for up to eight months after treatment. Observed gains may be transient" (*Am J Psychiatry 2001:158:2038-2042).*

It was as long ago as 1997 that Simon Wessely made public his own knowledge about the questionable safety of such therapies: "People involved in psychotherapy should know that it has side effects and risks. There is evidence that some intensive courses do have rates of casualties" (*Guardian, 11th March 1997, page 16)*. This must surely raise legitimate doubts about the assertions of Wessely School psychiatrists that the regime they promote so assiduously for those with ME/CFS is "safe" and "acceptable to patients" when there is no such evidence (because evidence of the efficacy of CBT/GET in those with authentic ME does not exist).

Despite these contra-indications, the Medical Research Council (MRC) and the UK Government have directed millions of pounds sterling into these psychotherapy strategies, which are the **only** Government-funded provision for patients with ME/CFS. This imbalance in funding has had negative consequences for those afflicted by ME/CFS.

The evidence set out below needs to be borne in mind when considering the unproven dogma about ME/CFS that currently dominates UK Government policy, namely that "CFS/ME" is a mental health issue.

It is important to understand that the expedient term "CFS/ME" is a heterogeneous label that specficially and intentionally includes psychiatric disorders in which "fatigue" is a dominant feature and which therefore cannot be synonymous with ME/CFS, also known as Post Viral Fatigue Syndrome / PVFS, and sometimes known in the US as Chronic Fatigue and Immune Dysfunction Syndrome or CFIDS.

The view that "CFS/ME" is a mental health issue also prevails at the Medical Research Council -- see the 32 page Report of January 2005 from the MRC Neurosciences and Mental Health Board's Strategy and Portfolio Overview Group, which clearly states: "Mental health research in this instance covers CFS/ME" (*NMHB Mental Health Scoping Study Repor*t). Given that ME/CFS is internationally classified by the World Health Organisation as a neurological disorder, the MRC was questioned about its own "classification" and in a written response dated 6th December 2005 Dr Robin Buckle stated: "This classification for the Mental Health Scoping Study was pragmatic, and related to the grants associated with the activities of one section of the office, allowing for an analysis of research trends".

It is unacceptable that Wessely School psychiatrists continue to exert a virtual monopoly on ME/CFS research in the UK when the international evidence clearly does not support their hypothesis about the nature of it.

The Wessely School view of ME/CFS is not accepted by most of Wessely's medical peers in the USA, nor is it shared by all psychiatrists in the UK.

However, to the detriment of UK patients, the Wessely School hypothesis is now misguidedly believed to be scientific fact by many UK doctors, as well as by the medical insurance industry with which these psychiatrists are closely involved as medical advisers, and by the commercial company that holds the contract to carry out assessments for State benefits (formerly a French company called SEMA, then from 2002 a Franco-German conglomerate called Schlumberger SEMA and currently a massive multi-national company with headquarters in Paris called Atos Origin whose UK head office is at 4, Triton Square, Regents Place, London NW1 3HG).

We draw attention to the fact that five years ago, there was an Inquiry by the House of Commons Social Security Select Committee that resulted in a major 245 page Report ("Medical Services"; HC 183, 12th April 2000): it was condemnatory about the way the SEMA Group mishandled Social Security claims and it took evidence from at least eight sources about specific difficulties experienced by those with ME/CFS. There was a long debate in the House of Commons on the Government's response. Nothing, however, has changed since the publication of that Report: if anything, the situation has worsened considerably for many patients with ME/CFS.

We wish to place on record our concern that the Gibson Inquiry does not allow itself to be misdirected or misled into believing that post-2002 "progress" in research in ME/CFS in the UK has been significant simply by virtue of the setting up of 50 Government-funded "CFS Centres", because these Centres offer only the same psychotherapy regimes that are promoted by the Wessely School; indeed, the situation has deteriorated so dramatically that, for example, the South & East Dorset NHS Primary Care Trust actively includes 'somatisation' in its GP referral protocol for "CFS/ME" patients (somatisation is the manifestation of emotional distress through constantly changing physical symptoms).

Not only are CBT and GET regimes potentially harmful for those with ME/CFS (unknown numbers of whom may be in a form of heart failure), but they continue to ignore the existing and established evidence-base of scientific knowledge that demonstrates the organic nature of the disorder, which cannot be in sufferers' best interests, since the evidence is abundant that even moderate physical exercise is likely to induce relapse.

Should the Gibson Inquiry allow itself to be misdirected or misled, it will be seen as yet another manipulated betrayal of the ME/CFS community, particularly as the terms of reference currently make no mention of the need for effective support for both patients and their carers.

We wish to make it plain that we fully endorse the need to move forwards, but we maintain that the only way to do this is to build upon, not ignore, the existing knowledge base of biomedical research evidence.

We completely support Dr Gibson's view as set out in his Press Release of 1st December 2005: three years on from the CMO's Working Group Report, "the time is right to evaluate how much further we have come in understanding the causes of ME, establishing a programme of research on all aspects of the condition and securing adequate investment for this research".

THE EVIDENCE

This present document is lengthy because it provides some indication of how extensive is the existing biomedical evidence-base that has been so effectively buried by those who insist that the disorder is

perpetuated by the "aberrant behaviour" of both ME sufferers themselves and those medical professionals who support them in their conviction that ME is a physical, not a mental health issue.

It has been compiled because (i) we accept it is unrealistic to expect Members of Parliament on the Inquiry to visit and review the existing knowledge-base for themselves, and (ii) because we maintain that without this knowledge, their deliberations will inevitably be based on fallacious assumptions.

According to Anthony Komaroff, Professor of Medicine at Harvard and a renowned world expert on ME/CFS, there are more than 2,000 papers which demonstrate that ME/CFS is an organic, not psychiatric, disorder. The following examples are therefore merely illustrative but provide hard evidence of some of the published clinical observations as well as some of the international biomedical research findings on ME/CFS from 1955 to 2005.

Based on this evidence, it is submitted that in the light of the undisputed biomarkers of serious organic pathology, the psychiatric paradigm lacks both validity and scientific credibility, as do the numerous attempts by Wessely School adherents to re-classify ME from its current neurological classification in the World Health Organisation International Classification of Diseases to a mental (behavioural) classification.

Indeed in 1999, Leonard Jason, Professor of Psychology, DePaul University, Chicago, was outspoken, writing that it is regrettable that the disorder is portrayed in such a narrow way, and that flaws in the case definition of "CFS" have led to "inaccurate and biased characterization of ME/CFS which incorrectly favours a psychiatric view of the illness" because "the British case definition does not consider psychiatric disorders are exclusionary for (ME)CFS".

Jason pointed out that "the erroneous inclusion of people with primary psychiatric conditions in ME/CFS samples will have detrimental consequences for the interpretation of treatment efficacy findings".

He also stated that there has been an ignoring of "a large body of medical research demonstrating biological abnormalities in individuals with ME/CFS. For years, investigators have noted numerous biomedical abnormalities among ME/CFS patients, including over-activated immune systems, biochemical dysregulation in the 2-5A synthetase / RNASE L pathway, muscle abnormalities, cardiac dysfunction, abnormal EEG profiles, abnormalities in cerebral white matter, decreases in blood flow throughout the brain, and autonomic nervous system dysfunction. Unfortunately, some uninformed physicians continue to believe that (ME)CFS and other disorders like it are primarily psychiatric in nature. Some confuse (ME)CFS with neurasthenia. Biases such as these have been filtered through to the media, which portrays ME/CFS in an overly simplistic and stereotyped way (which) compromises patient-doctor relationships and medical care for patients" (see *LISTSERV home page at LISTSERV.NODAK.EDU 18th March 1999).*

We submit that the behaviour of the Wessely School in relation to ME/CFS may be considered to be perverse and may even amount to scientific misconduct because of its adverse impact on the health and well-being of sufferers.

This is because of the Wessely School's relentless dismissal for almost two decades of the international biomedical evidence that ME/CFS is an organic (not psychiatric) disorder, particularly:

(i) their repeated failure to distinguish between "chronic fatigue" and ME/CFS (even though the differences have been repeatedly brought to their attention and even though as long ago as 1990, the American Medical Association issued a specific notice emphasizing that chronic fatigue is not the same as chronic fatigue syndrome)

(ii) their demonstrable bias that has resulted in the deliberate suppression of the biomedical evidence on ME/CFS by UK medical journals

(iii) their selective manipulation of others' published papers (by claiming other authors' findings support their own view when such is not the case)

(iv) their unscrupulous determination to "eradicate" ME by asserting that it is nothing more than an "aberrant illness belief" and their tactics of denial (for referenced evidence and illustrations of such tactics of denial, see "The Mental Health Movement: Persecution of Patients" available online at http://www.meactionuk.org.uk/SELECT_CTTEE_FINAL_VERSION.htm and "Consideration of Some Issues Relating to the Published Views of Psychiatrists of the 'Wessely School' in relation to their belief about the nature, cause and treatment of ME" at http://www.meactionuk.org.uk/consideration.htm)

(v) their focusing on the single symptom of chronic "fatigue" in ME/CFS and ignoring of other significant symptoms and signs, especially cardiovascular, neurological and immunological

(vi) their deliberate dilution of the case description to include any "medically unexplained" fatigue, ie. their obfuscation of the case definition so that it specifically includes somatisation disorders (which instantly greatly increases the numbers of patients with an alleged diagnosis of "CFS/ME" who can be coerced into enrolling in the Wessely School management regime); if those with ME/CFS are physically unable to continue and have no option but to withdraw from these regimes, they immediately risk losing their State benefits and their medical insurance payments)

(vii) their advice to Government that no tests should be performed on those with ME/CFS to confirm the diagnosis (other than the most basic screening, which is universally known to be normal in ME/CFS)

(viii) their advice to Government that the reported biomedical abnormalities "should not deflect the clinician from the biopsychosocial approach and should not focus attention towards a search for an 'organic' cause" (*ref: Joint Royal Colleges' Report on CFS, CR54, 1996)*

(ix) their influence and functioning in areas of medicine in which they have no expertise: as psychiatrists, it follows that areas of complex medical science such as immunology, vascular biology and muscle pathology which underpin ME/CFS are not within their remit of expertise. In July 2005 the General Medical Council criticised and struck off Professor Sir Roy Meadow from the Medical Register for acting outside his area of expertise. The Chairman of the Disciplinary Hearing told Meadow: "Your misguided belief in the truth of your argument is both disturbing and serious. You should not have strayed into areas that were not within your remit of expertise". During the GMC hearing, Robert Seabrook QC stated that Meadow had ignored almost three decades of relevant research and that this was not simply a case of poor research or simple error: it was a calculated move that enabled him to impress his own theses on the public mind. Many in the ME community draw a parallel with Professor Wessely in relation to ME/CFS. (For a more detailed consideration, see http://www.meactionuk.org.uk/Another_Meadow.htm).

As Professor Jason stated in his letter of 12th May 2005 to the Editor of Psychology Today, ME/CFS is a "devastating" chronic disorder and he questioned why it is assumed that it is only sufferers themselves who believe it to be an organic disorder when many scientists, including himself, support such a view.

He noted that much of the published data asserting a psychiatric aetiology derives from tertiary centres where instruments to assess psychiatric symptoms have often been inappropriately selected, so one cannot conclude that ME/CFS is a psychiatric illness.

Jason further noted that although there is a group of investigators who feel it is the "misbeliefs" that the patient support groups "inadvertently re-inforce" which account for the illness, many other researchers hold the view that there are neurologic, neuroendocrine, autonomic and immunologic explanations for ME/CFS.

Jason admonished those who improperly insist that psychiatric interventions be imposed on those with ME/CFS: "To suggest that efforts to help people cope with a chronic illness is the primary and only way to cure them does a disservice to all individuals with this condition" (see *Co-Cure, 12th May 2005).*

Professor Jason is a leading American psychologist who is author of one of the largest US epidemiological studies on ME/CFS, the recipient of numerous National Institutes of Health grants and the originator of a research portfolio that is widely considered to be scientifically superior in construct to that of Professor Simon Wessely.

As John Lalor noted on 4th December 2005 in the Irish Independent: "Psychiatrist and author Thomas Szasz claimed that the misuse of psychiatry was 'linked to the political power intrinsic to the social role of the psychiatrist in totalitarian and democratic societies alike'. Szasz' concept of power and psychiatry relates directly to the present state of health services as a whole".

No-where is this more apposite than in relation to ME/CFS politics in the UK: it was at the Second World Congress on (ME)CFS held in Brussels in September 1999 that ME/CFS expert Professor Daniel Peterson from the US went on record saying that ten years ago (ie. in 1989) he believed that (ME)CFS would be resolved by science; he had since changed his mind and believed that it could only be resolved by politics.

The evidence below speaks for itself, from which the assertions of the Wessely School that ME/CFS is a behavioural disorder can readily be seen to be entirely without foundation, especially their assertions that it is perpetuated by "aberrant illness belief" and by "the misattribution of normal bodily sensations" and that patients "seek and obtain secondary gain by adopting the sick role".

Indeed, the unsubstantiated and unproven beliefs of the Wessely School about the nature of ME/CFS have already been shown to be as erroneous as the equally dogmatic assertions of their psychiatrist predecessors who in the 1940s decreed that the intention tremor that characterizes Parkinsons Disease (PD, which used to be known as the shaking palsy) was caused by an inner conflict resulting from the wish to masturbate (*Psychodynamcis in Parkinsonism. Booth G. Psychosomatic Medicine 1948:10:1-14).* It was not until the discovery of the neurotransmitters, especially dopamine, in the late 1950s that psychosocial studies on PD were replaced by biomedical research studies.

Psychiatrists have a long track record in mis-attribution of medical disorders: the literature is replete with examples of psychiatrists having claimed – with certainty – "unexplained" symptoms as psychiatric disorder: many common conditions, including diabetes (which in the 1930s was said to represent "the last stand of neurosis" caused by sexual repression), epilepsy, multiple sclerosis, pernicious anaemia, myasthenia gravis, gastric ulcer, glaucoma, asthma and Dupuytren's contracture have all been claimed as psychiatric disorders until medical research proved otherwise.

Such is the "certainty" of psychiatry, yet it is such "certainty"about ME/CFS that the present New Labour Government and its departments so enthusiastically espouse at incalculable cost to many severely sick people.

It is surely simplistic to think that UK government agencies can be so intellectually inferior to their international counterparts as to be unaware of the convincing science that supports an organic aetiology for ME/CFS, so why do these bodies continue to ignore this evidence?

The answer would seem to be a bizarre scandal of such magnitude that people who are unaffected by it regard it as risible and therefore dismiss it as fictional conspiracy.

ILLUSTRATIONS FROM THE LITERATURE

1955

Outbreak at the Royal Free ED Acheson (who later became Sir Donald Acheson, UK Chief Medical Officer)
Lancet 1955:394-395

"All outbreaks have been remarkable for the relatively long active course of the disease and for marked muscular pain and spasm. Sensory symptoms and signs are additional features".

1956

A new clinical entity? Editorial (although at the time this Editorial was anonymous, it was later conceded by Sir Donald Acheson that he had written it)
Lancet 1956 (May 26);789-790

"In spite of perplexing variations in the clinical picture from case to case it soon became clear that a new clinical entity had appeared"

"Relapses are frequent"

"Among the more characteristic features are the severe muscular pains, often accompanied by exquisite tenderness. Most commonly they affect the neck, back or limbs but there may also be Bornholm-like chest and abdominal pains"

"In nearly every patient there are symptoms or signs of disease of the central nervous system"

"Hepatitis and splenomegaly may also turn out to be part of the picture"

"The term 'benign myalgic encephalomyelitis' does describe some of the striking features by (1) symptoms and signs of damage to the brain and spinal cord; (2) protracted muscle pain with paresis and cramp; (3) emotional disturbances in convalescence; (4) normal cerebrospinal fluid; (5) involvement of the reticulo-endothelial system; (6) a protracted course with relapses in severe cases"

"We believe that its characteristics are now sufficiently clear to differentiate it from, need it be said, hysteria".

1959

The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia ED Acheson
Am J Med 1959:26:569-595

"Pain in the muscles was an almost constant feature. In severe cases it was agonizing and unresponsive even to opiates"
"Definite parasthesia occurred. Diplopia (was noted)"

"It would be manifestly erroneous to consider as hysteria the emotional instability associated with this illness. The disorder is not a manifestation of hysteria"

"Other sensory disturbances consisted of loss of memory and difficulty in concentration"

"It is concluded that the disease is recognizable in its epidemic form on clinical and epidemiological grounds and therefore may properly be considered a clinical entity".

1969

Letter to the Editor Joyce R Adamson
New England Journal of Medicine 1969:281:798

"This entity is in danger of becoming a 'wastebasket' diagnosis because of its variable signs and symptoms. Almost every conceivable neurologic sign has been described under the heading of epidemic neuromyasthenia".

1970

Encephalomyelitis resembling benign myalgic encephalomyelitis SGB Innes
Lancet 1970: (May 9):969

"Motor weakness may not be confirmed on formal testing since it appears to take the form of an incapacity for sustained muscular effort".

1977

Iceland Disease (benign myalgic encephalomyelitis or Royal Free disease) AM Ramsay, EG Dowsett et al
BMJ 1977: (May 21):1350

"Physical findings may include hepatitis"

"Objective manifestations of the disease can still be present over thirty years after the initial illness".

1978

Epidemic myalgic encephalomyelitis Editorial
BMJ 1978: (3 June):1436-1437

"The features common to every epidemic include headache, unusual muscular pains (which may be severe), lymphadenopathy and low grade fever. In a minority of cases frank neurological signs can be detected by careful clinical examination: there may be nystagmus, diplopia, myoclonus, bulbar weakness, motor weakness, increased or decreased tendon reflexes, disturbances of the sphincters and extensor plantar responses"

"Fasciculations, cranial nerve lesions and extrapyramidal signs have also been reported"

"One characteristic feature of the disease is exhaustion, any effort producing generalised fatigue. Often there (is) emotional instability and lack of concentration. The clinical outcome may take any of three courses: some patients recover completely, some follow a relapsing course and some are permanently incapacitated"

"At a symposium held recently at the Royal Society of Medicine to discuss the disease and plan research there was clear agreement that myalgic encephalomyelitis is a distinct nosological entity"

"Other terms that have been used to describe the disease were rejected as unsatisfactory for various reasons: the cardinal clinical features show that the disorder is an encephalomyelitis…indeed, the exhaustion and tiredness are similar to that described by patients with multiple sclerosis"

"From the patient's point of view the designation 'benign' is misleading, since the illness may be devastating"

"Some authors have attempted to dismiss this disease as hysterical, but the evidence now makes such a tenet unacceptable. The organic basis is clear --- from the detection of an increased urinary output of creatine, the persistent findings of abnormal lymphocytes in the peripheral blood of some patients, the presence of lymphocytes and an increased protein concentration in the cerebrospinal fluid and the neurological findings. Immunological studies showed a high incidence of serum anticomplementary activity and the presence of ill-defined aggregates on electron microscopy of acute-phase sera". *(This Editorial was fully referenced).*

1978

An outbreak of encephalomyelitis in the Royal Free Hospital Group, London, in 1955
Nigel Dean Compston
Postgraduate Medical Journal 1978:54:722-724

"It became clear early on that there was organic involvement of the central nervous system. There was objective evidence of involvement (of the CNS)"

"The most characteristic symptom was the prolonged painful muscle spasms"

"Bladder dysfunction occurred in more than 25% of all the patients"

"Objective evidence of brain stem and spinal cord involvement was observed"

"McEvedy and Beard's (psychiatric) conclusions ignore the objective findings".

1979

Clinical and biochemical findings in ten patients with benign myalgic encephalomyelitis
AM Ramsay A Rundle
Postgraduate Medical Journal 1979:55:856-857

"Ten patients were investigated for blood levels of myoglobin and various enzymes. The biochemical pattern bears a close similarity to that found in Duchenne muscular dystrophy (DMD). These findings are discussed with particular reference to the recent suggestion that the permeability of cell membranes may be impaired by changes in intracellular energy mechanisms"

"The dominant clinical features could be classified as follows: (1) abnormal muscle fatigability (with severe pain, particularly in the legs and back) (2) circulatory impairment was a feature of all cases, suggestive of hypothalamic damage and (3) impairment of memory and inability to concentrate was common in all patients"

"The duration of illness in the ten cases was 35 years, 9 years, 6 years, 3 years, 2 years, 23 years, 17 years, 2 years, 5 years and 17 years respectively. A tendency to severe relapse was a feature of (four) cases"

"If the aetiological factor in benign myalgic encephalomyelitis impairs the permeability of the muscle cell membrane as a result of changes in the intracellular energy content, this could be followed by a differential loss of intracellular proteins".

1981

Was it Benign Myalgic Encephalomyelitis? CS Goodwin
Lancet 1981:January 3: 37

"In 1969 it was suggested that ME should only be diagnosed if neurological and muscle signs were found. Parish has described the neurological signs and the symptoms of involvement of the autonomic nervous system"

"It is important that the title 'myalgic encephalomyelitis' should be restricted to patients who show some of each of the three major features of the disease: Firstly, symptoms and signs in relation to muscles, such as recurrent episodes of profound weakness and exhaustion, easy fatiguability, and marked muscle tenderness. Secondly, neurological symptoms or signs, especially affecting the eyes, or weakness of peripheral muscles, as demonstrated by the voluntary muscle test; or some loss of peripheral sensation; or involvement of the autonomic nervous system (orthostatic tachycardia, abnormal coldness of the extremities, episodes of sweating or pallor, [and] bladder disturbances). Thirdly, biochemical abnormalities, such as a raised urinary creatine, or an abnormal electrophoresis pattern with raised IgM".

1983

Sporadic myalgic encephalomyelitis in a rural practice BD Keighley EJ Bell
JRCGP June 1983:339-341

"ME (is) a distressing and often prolonged illness. Many of the patients included in the study had been dismissed by hospital clinicians with the implication that there was no organic basis for their problems. As the study progressed, a pattern to the complexity of the symptoms developed (which included) malaise, exhaustion on physical or mental effort, chest pain, palpitations, tachycardia, polyarthralgia, muscle pains, back pain, true vertigo, dizziness, tinnitus, nausea, diarrhoea, abdominal cramps, epigastric pain, headaches, paraesthesiae and dysuria"

"The group described here are patients who have had miserable illnesses. There is a large number of ill and unhappy patients in the community".

1984

Myalgic encephalomyelitis and the general pracitioner JC Murdoch
New Zealand Family Physician 1984:11:127-128

"Recent reports have shown an association with infection with the Coxsackie *(sic)* and two authoritative editorials have pointed to an entirely physical basis for the disorder"

"Most sufferers had monumental problems with work, family and personal life and with their doctors. They should be warned to expect a long illness charaterised by relapses. They should be certified as unfit for work"

"In the long-term sufferer, patients are often anxious to identify food and chemical allergies".

1984

Myalgic encephalomyelitis Cory Matthew
New Zealand Medical Journal 1984: 14th November:782

"It has been my consistent observation that activity requiring physical exercise or mental concetration exacerbates the condition"

"Many ME patients also experience food and chemical intolerances, and are often therefore unusually sensitive to the side effects of drugs".

1984

Myalgic encephalomyelitis AJ Brook-Church
ibid

"An attempt to recover normal fitness and activity levels can exacerbate the condition and bring about a relapse".

1985

Dignostic Criteria and (Laboratory) Tests for ME WR Gorringe
ANZMES, 10th October 1985

"The following features are commonly represented: atopy, history of food reactions and allergies"

"ME can be indistinguishable from multi-allergy syndrome"

"(There is) a tendency to a relapsing course"

"(In addition to the classic features), other features include (a) plethora of symptoms – usually involving multi-organ systems. The person may have a moist chest, headaches with sore muscles of the shoulders, neck and back. They may have frequency of urine or an irritable bowel. There is often oesophageal reflux with oesophageal tenderness and intermittent oesophegeal spasm. Chest pain may be intermittently prominent, and may be severe enough for hospital admission (and there may be) palpitations and a tight chest. Vision (is) often blurred, (with) stinging -- often burning -- pain behind the eyes (and) sensitivity to light. (There may be) sore joints"

"The commonest mistake doctors make is failing to take a wide enough view (with) an adequate systems review when encountering apparently unconnected complaints"

1985

Persisting Illness and Fatigue in Adults with Evidence of Epstein Barr Virus Infection
Stephen E Straus et al
Annals of Internal Medicine 1985:102:7-16

(Note that in the US, the condition was at that time thought to be associated with the Epstein Barr (glandular fever) virus and so was known as chronic EBV disease)

"By all regards, including formal evaluations, many of these patients appeared to be neurotic. However, our detailed studies have uncovered a series of subtle, yet objective, organic abnormalities in these patients"

"This disorder is not rare"

"It is of immeasurable benefit to patients with this disorder to document an organic basis for their complaints".

1985

The postviral fatigue syndrome – an analysis of the findings in 50 cases PO Behan, WMH Behan, E J Bell
Journal of Infection 1985:10:211-222

"Our data confirm the organic basis of the illness (and) suggest that it is associated with disordered regulation of the immune system and persistent viral infection"

"The illness was severe, with a high morbidity and a disastrous effect on their lives".

1985

Electrophysiological studies in the post-viral fatigue syndrome Goran A Jamal Stig Hansen
JNNP 1985:48:691-694

"The post-viral fatigue syndrome, also known as ME, has been recognised recently as a distinct neurological entity with increasing evidence of the organic nature of the disease"

"The most important findings were type II fibre predominance, subtle and scattered fibre necrosis and bizarre tubular structures and mitochondrial abnormalities"

"About 75% of the patients had definitely abnormal single fibre electromyography results. This was regarded as evidence of abnormality in the peripheral part of the motor unit"

"We conclude that we have shown clear electrophysiological evidence of an abnormality in the peripheral part of the motor end unit in patients with post-viral fatigue syndrome".

1986

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

(Note that in the 1980s (ME)CFS was known as Chronic EBV Disease)

"Eighty percent of patients demonstrate clinically significant IgE mediated allergic disease, including food and drug reactions"

"The data indicate that patients have a high association with hypersensitivity states"

"Percent positive responsiveness to allergens is consistent with the high degree of allergy observed in these patients".

1987

The postviral fatigue syndrome: a review MI Archer
JRCGP 1987:37:212-216

"Relapses are precipitated by undue physical or mental stress"

"However compelling the evidence for an hysterical basis may be, there is further, equally compelling, evidence of organic disease"

"Some patients do have frank neurological signs"

"Muscle biopsies showd necrosis and type II fibre predominance".

1987

Myalgic encephalomyelitis (ME) syndrome – an analysis of the clinical findings in 200 patients
J Campbell Murdoch
The New Zealand Family Physician 1987:14:51-54

"Two hundred patients fitting the criteria were seen between January 1985 and December 1986"

"All had other symptoms, the most common of which were irritability, lack of concentration, short-term memory problems, vertigo, visual upset, recurrent sore throat, difficulty with breathing, palpitations, abdominal distension and diarrhoea"

"On examination there were two important common findings – the presence of acute tenderness in the muscle bulk and a positive Romberg's sign, indicating vestibular upset"

"17% of patients had a positive smooth muscle antibody and a further 11% had a weakly positive SMA. 4% had anti-nuclear antibody and two patients had weakly positive thyroid autoantibody"

"This syndrome has about the same prevalence as Parkinson's disease and is more prevalent than multiple sclerosis"

"The clinical findings strongly suggest that the musculature and the central nervous system are the main sites of disorder in these patients"

"In addition, nuclear magnetic resonance revealed abnormal muscle metabolism"

"Such patients become immunocompromised. That ME patients are immunocompromised is beyond question"

"Surely the underlying message is that patients with this syndrome need not await the solving of this puzzle before they are accorded the sick role (and) in the interim, it is our duty to care for them as sick".

1987

Phenotypic and functional deficiency of natural killer cells in patients with Chronic Fatigue Syndrome
Michael Caliguri, Dedra Buchwald, Paul Cheney, Daniel Peterson, Anthony L Komaroff et al
J Immunol 1987:139:3306-3313

"These studies show that a majority of patients with (ME)CFS have low numbers of NKH1 T3- lymphocytes"

"When tested for cytotoxicity against a variety of different target cells, patients with CFS consistently demonstrated low levels of killing"

"In this study we demonstrate that a majority of patients with (ME)CFS have abnormally low numbers of NKH1+T3- cells that result in a distinct NK subset abnormality, as well as a deficiency of cytotoxicty against both standard and viral-infected targets"

"(This study) will hopefully improve our understanding of the immunopathogenesis of this illness".

1987

ME Fact Sheet
ME Action Campaign: 1987

"Drug therapy is not recommended in general, and there are some drugs, particulary anaesthetics, that can have disastrous effects".

1987

Royal Free Disease: Fatigue that's viral, not hysterical Charles Shepherd
MIMS, October 1987

"Certain factors are almost guaranteed to worsen ME. Surgery and general anaesthetics may cause relapse".

1988

Anaesthetics and ME/CFS
A Consultant Anaesthetist (Dr F.L.M of the McNeil Centre for Research in Anaesthesia, Philadelphia)
Meeting Place, Journal of the Australia and New Zealand ME Society: 1988:30:29-30

"When there may be neural involvement by a disease, spinal or epidural anaesthesia is not recommended because of the risk of worsening symptoms"

"Normally, a depolarizing muscle relaxant is used, (but) in persons with neuromuscular disease such as demyelination, which has been decribed for (ME/CFS), this drug has a known risk of causing potassium release from muscle, which can lead to cardiac arrest"

"Because of chronic muscle weakness, breathing may be impaired (and) muscle weakness increases the risk of respiratory failure"

"More care than usual is appropriate in the case of (ME/CFS)".

1988

Postviral fatigue syndrome PO Behan WMH Behan
Crit Rev Neurobiol 1988:4:2:157-178

"Any kind of muscle exercise can cause the patient to be almost incapacitated for some days afterward. In severe cases, the patient is usually confined to bed"

"Psychiatric diagnoses abound: many patients will already have been labelled as neurotic, neurasthenic, or depressed"

"What is certain is that when one reviews PFS with its clinical features and laboratory results, it becomes plain that this is an organic illness in which muscle metabolism is severely affected".

1988

Human Enteroviral Infection EG Dowsett
J Hosp Inf 1988:11:103-115

"Enteroviral syndromes range from trivial to severe and many are unrecognised or underinvestigated"

"Myalgic encephalomyelitis has been the cause of more than 50 epidemics. Serious (neurological) sequelae are common. Enteroviral infections in humans, as in animals, may be persistent"

"The main features (of ME) are prolonged fatigue following muscular exercise, an extended relapsing course which, unlike other postviral fatigue, lasts for months or years"

"An association with neurological, cardiac and other characteristic enteroviral complications (including) pancreatitis has long been recognised as part of severe generalised enteroviral infection".

1988

Postviral fatigue syndrome: persistence of enterovirus RNA in muscle and elevated creatine kinase
LC Archard, NE Bowles et al
JRSM 1988:81:325-331

"These data show that enterovirus RNA is present in skeletal muscle of some patients with postviral fatigue syndrome up to 20 years after onset of disease and suggest that persistent viral infection has an aetiological role"

"These results provide further evidence that Coxsackie B virus plays a major role in ME, either directly or by triggering immunological responses which result in abnormal muscle metabolism".

1988

Transmissible disease and psychiatry RP Yonge
JRSM 1988:81:322-325

"This was the first time that it was possible to show unequivocally that there was an organic basis for the fatigue experienced by a patient diagnosed as having postviral syndrome"

"Nuclear magnetic resonance (imaging) has shown a metabolic basis for the fatigue experienced by some patients diagnosed as suffering from postviral fatigue syndrome"

"We have shown that muscle fatigue and weakness for which there has previously been no explanation is indeed in the muscle rather than in the mind".

1988

Chronic fatigue syndromes: relationship to chronic viral infections Anthony L Komaroff
Journal of Virological Methods 1988:21:3-10

"The fatigue and associated symptoms are debilitating in all patients and can be fully disabling in some"

"There are a group of conditions which go by different names but which may share a final common pathogenic pathway. (These include) true chronic mononucelosis; another, much less frequent group have apparent severe chronic active EBV infection; another chronic, fatiguing illness is called myalgic encephalomyelitis; another illness characterized by chronic fatigue is fibromyalgia (and) finally, there are patients with what we now call chronic fatigue syndrome"

"One simple piece of evidence that these ("CFS") patients are suffering from an 'organic' illness is the sudden onset of the illness in 85% of the patients"

"A few of the individuals in our group had acute neurologic events: primary seizures (7%); acute, profound ataxia (6%); focal weakness (5%); transient blindness (4%) and unilateral parasthesias not in a dermatomal distribution"

"On past medical history, the only clearly striking finding is a high frequency of atopic or allergic illness in approximately 50%"

"On physical examination, unusual and abnormal findings are observed in up to 50% of patients, (including) hepatosplenomegaly"

"Because of the neurologic and cognitive symptoms, (some) patients have had lumbar punctures. In 45% of the patients, there was pleocytosis (*the presence of an abnormally large number of lymphocytes in the cerebrospinal fluid)*. In several patients, the lymphocytes were described as 'atypical' "

"It is the judgment of the neuropsychologists that the pattern of test performance suggests an 'organic' deficit, rather than cognitive dysfunction secondary to mood disorder".

1988

Allergy and the chronic fatigue syndrome Stephen E Straus et al
J Allergy Clin Immunol 1988:81:791-795

"Many patients report inhalant, food or drug allergies (and) this article emphasizes our assessment of one of (the syndrome's) more common manifestations, allergy"

"Allergies are a common feature of patients with the chronic fatigue syndrome"

"Attempts to avoid all the allergens further isolate the victims of 'total allergy' "

"A variety of immunologic abnormalities can be detected in patients with the chronic fatigue syndrome, abnormalities that suggest that the immune system may participate in the pathogenesis of this disease"

"It is possible that individuals with a heightened reactivity to allergens also respond more vigorously to certain infectious antigens. Inherent hyper-responsiveness would be the initiation by certain infectious

agents of a level and duration of lymphokines and interleukin release that would in themselves perpetuate the reactive symptoms of the syndrome"

"Among the features of this syndrome is a high prevalence of allergy, an allergy that appears to be substantial".

1988

The chronic fatigue syndrome (myalgic encephalomyelitis) – myth or mystery?
FHN Spracklen
South African Medical Journal 1988:74:448-452

"The frequency of this condition is demonstrated by the increasing number of ME associations being founded around the world"

"The strength of the ME lobby in the UK is illustrated by the fact that the Member of Parliament for Clydesdale, Jimmy Hood, drew attention to ME with the first reading of a Bill on 23rd February 1988 and the second reading on 15th April 1988. This was used to attract public attention and counter the suffering and injustice caused by this terrible illness"

"Hood requested an annual report on progress made in investigating the causes, effects anmd treatment of ME"

"A promise was given by the Parliamentary Under-Secretary of State for the Department of Health and Social Services, Mrs Edwina Curry, that ME was recognized under the NHS and would be treated correctly in all NHS hospitals"

"The difficulty in understanding (ME)CFS is that one is probably dealing with several different entities, all of which can result in the Ramsay triad of (i) muscle fatiguability, where even after a minor degree of physical effort, three or more days may elapse before muscle power is restored; (ii) an extraordinary variability or fluctuation of symptoms even over 24 hours; and (iii) an alarming chroncity"

"In Mowbray's opinion, 62% of cases are due to persistent infection with enteroviruses, especially when muscle fatigue occurs only on exertion"

"Mowbray stresses that pericraditis is found in 10% of patients"

"Reflecting British thinking, Dowsett has stated that the evidence for persistent enteroviral infection is so strong that the use of the term CFS as opposed to ME is to be deplored"

"There is no question that fatigue is worsened by exercise"

"It seems unlikely that the neuropsychiatric symptoms described in this syndrome are causative"

"Attempts to invoke concepts like mass hysteria (and) psychosomatic illness seem unwarranted"

"Two-thirds of patients report respiratory or gastro-intestinal symptoms"

"While the onset in 20% of cases may be insidious, the remainder follow acute vertigo, Bornholm's disease, pericarditis, herpangina, thyroiditis, parotitis, viral meningitis or acute visual disturbances"

"Electron microscopy has shown increased mitochondria and 'bizarre tubular structures' "

"Periods of physical stress should be avoided"

"Since exertion and physiotherapy are known to aggravate symptoms, rest is probably the most important treatment".

1989

The Chronic Fatigue Syndrome Anthony L Komaroff, Stephen E Straus, Nelson M Gantz, James F Jones
Ann Int Med 1989:110:5:407

"We agree that primary psychiatric disease is common in patients with fatigue and that only an occasional patient seeking medical care for chronic fatigue has a well-recognised organic illness"

"We believe there is another disorder, the chronic fatigue syndrome, that is likely to be an organic disorder"

"A critical question has not been addressed: are patients fatigued because they have a primary mood disorder, or has a mood disorder developed as a secondary component of a chronic organic illness?"

"We are concerned about the interpretation of data: many of the instruments base the diagnosis of psychiatric disease on the presence of symptoms that could well reflect an underlying organic illness"

"It would be inappropriate to conclude that patients with chronic fatigue had only a primary psychiatric disorder".

1989

Statement to the (USA) House Appropriations Subcommittee, 25th April 1989
James F Jones, National Jewish Center for Immunology, Denver
CFIDS Chronicle: Spring 1989:28-30

"For the patients, there is no question that the illness exists. For the physicians who see these patients, the similarities among them allow ready identification of a distinct clinical illness. For those who scoff at this concept, one can only query as to what happened to their curiosity and their ability to listen to patients".

1989

Natural Killer Cell Activity in the Chronc Fatigue- Immune Dysfunction Syndrome
Nancy Eby, Seymour Grufferman et al
In: Natural Killer Cells and Host Defense. Ed: Ades EW and Lopez C. 5th International Natural Killer Cell Workshop. Pub: Karger, Basel, 1989:141-145

"Our investigations suggets that (ME)CFS is characterized by objective laboratory abnormalities and that the currently used names for the syndrome are inappropriate. A more appopriate name for this syndrome would be chronic fatigue-immune dysfunction syndrome (CFIDS), since immune dysfunction appears to be the hallmark of the disease process".

1989

Progress towards an answer to Chronic Fatigue: an interview with 'USA Today', 13th April 1989
Stephen E Straus, National Institutes for Allergy and Infectious Diseases
CFIDS Chronicle: Spring 1989:77-78

"Many of the immunological and physical features of ME/CFS cannot be explained by mental illness".

1989

Chronic Fatigue Syndrome wreaks havoc with victims' lives
John Esdale, Rheumatologist, Montreal General Hospital.
CFIDS Chronicle: Spring 1989:79

"It is a real organic problem and people who have it don't need the additional stress of hearing doctors tell them they are crazy".

1989

CFIDS in Children David S Bell, Instructor in Paediatrics, Harvard Medical School
CFIDS Chronicle: Spring 1989:34-37

"The most obvious factor is of course the severity of CFIDS".

1989

Chronic Fatigue Syndrome Gerald H Ross et al
Canadian Medical Association Journal 1989:140:361

"We have found that many people with this clinical picture have concomitant food and chemical sensitivities"

"We were therefore greatly surprised to learn from Dr Holland (*ibid: 706)* that 'it would be non-therapeutic to offer such a patient empathy' and that we must not condone a belief in a 'non-existent disease' "

"These statements are difficult to reconcile with the immunologic abnormalities, disorders of muscle metabolism and abnormal results of muscle biopsies found in such patients".

1989

Chronic Fatigue Syndrome Gerald H Ross, William Rea et al
Canadian Medical Association Journal 1989:141:11-12

"Being unable to find physical diagnoses for (ME)CFS does not necessarily mean that psychologic illness is the cause. It may simply be that our understanding of the factors precipitating the illness is far from complete"

"Medical history teaches us that once physical causes for 'psychologic' symptoms are discovered, the condition moves as if by magic from the psychiatic to the medical realm"

"It is our experience that a substantial percentage of (ME)CFS cases may arise or be worsened by adverse reactions to components of the environment, such as food, inhalants and chemicals".

1989

Presentation at the American Academy of Neurology Conference, April 1989
Carolyn L Warner
(also in Neurology, March 1989:39:3:Suppl 1:420)

"The abnormalities we found provide evidence for central nervous system and neuromuscular involvement".

1989

Chronic Fatigue J Cuozzo
JAMA 1989:261:5:697

"The disabling weakness and exhaustion a patient with ME/CFS experiences is so profound that 'fatigue' is probably an insult".

1989

Immunological abnormalities in the chronic fatigue syndrome Andrew R Lloyd, Denis Wakeford, Clement R Broughton and John M Dwyer
Med J Australia 1989:151:122-124

"A concurrent immunological disturbance is likely to be associated with the persistence of viral antigen"

"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"

"These cell-surface antigens may have been induced by interferons or other cytokines. Once activated, these cells may continue to produce the cytokines which may mediate the symptoms of CFS".

1989

Myalgic encephalomyelitis: postviral fatigue syndrome and the heart Norman Grist
BMJ 1989:299:1219

"Similar immunological and metabolic disturbances in myalgic encephalomyelitis may also result from chronic infection, usually with enteroviruses, providing the organic basis of the postviral fatigue syndrome"

"This condition is characterised by severe fatiguability and recuperation through rest. The myocardium, however, cannot rest --- except terminally".

1989

Postviral fatigue syndrome DO Ho-Yen
British Journal of Hospital Medicine 1989:42:250

"I believe that postviral fatigue syndrome is a distinct entity with a precise definition. In only a few patients is there confusion with psychiatric illness"

"As I understand the article *(referring to an article by Wessely),* graded exercise has been suggested but has **not** 'led to improvement in patients'. This article's suggestion of exercise until symptoms cease is the reason why a patient may be hospitalised".

1989

Neuropsychological Deficits in Chronic Fatigue Syndrome Sheila Bastien
Paper presented at the International Conference 'Epstein-Barr Virus: The First 25 Years", Oxford University, UK, April 1989; also published in CFIDS Chronicle, Summer / Autumn 1989: 24-26

"A population of (ME)CFS patients was tested neuropsychologically over a period of three years. The age range was 16 to 65. All patients had multiple physical symptom complaints that are typical of this condition"

"(Patients) reported problems with memory, concentration, sequencing, spatial relations, calculation, word-finding, comprehension, visual discrimination, and motor ability"

"Many of these individuals were observed to have significant motor and balance problems"

"Verbal memory was 68% below the mean T score on the immediate condition and 68% below the mean T score on the delayed condition"

"The pattern of focal and lateralised impairments in these patients is consistent with an atypical organic brain syndrome".

1989

Chronic Fatigue and Immune Dysfunction Syndrome: A Patient Guide
CFIDS Association, Charlotte, North Carolina, 1989

In addition to the commonly known symptoms such as profound fatigue, low grade fever, sore throat, painful lymph nodes, muscle weakness, myalgia, sleep disturbance, headaches, migratory arthralgia, photophobia, transient visual scotoma, forgetfulness, confusion and cognitive difficulties, the following form part of the clinical picture: "spacial disorientation, blurring of vision, sensitivity to light, eye pain, frequent (spectacle) prescription changes, emotional lability, chills and night sweats, shortness of breath, dizziness and balance problems, sensitivity to heat and cold, irregular heartbeat, abdominal pain, dirrahoea, numbness of face or extremities, burning in hands or feet, hearing sensitivity, menstrual problems, hypersensitivity of the skin, chest pain, rashes, allergies and sensitivities to odours and chemicals, weight changes without changes in diet, feeling 'in a fog', fainting, muscle twitching, seizures, and hair loss".

1990

Chronic Fatigue Syndrome and the Psychiatrist Susan E Abbey Paul E Garfinkel
Can J Psychiatry 1990:35:625-632

"The number of patients having (ME)CFS has increased. Research has demonstrated that cognitive (and) affective symptoms are prominent (and) psychiatrists are being asked to participate in the assessment and management of patients with this syndrome"

"Two patterns of illness have been recognized: relapsing and remitting, and continuous"

"It is not yet certain whether psychoneurosis can fully explain some of the physical and immunological aberrations noted in such patients"

"All of the findings regarding psychopathology are descriptive and do not allow for conclusions about the direction of the relationship --- ie. whether the psychopathology is secondary to (ME)CFS) or is the cause of (it)"

"Findings related to psychopathology may be artifactual"

"The pathophysiology of fatigue attributable to psychiatric disease remains unclear (and) it is premature to make aetiological assumptions".

1990

Clinical and General Research Findings in CFIDS Paul Cheney
Press Conference, San Francisco, September 1990, reported in CFIDS Chronicle, September 1990: 7-8

"I believe this is a disease that affects the central nervous system and I'll show you some slides to help convince you of that. We are going to explore what evidence there is for neurologic disease."

"This is a study done by Dr Carolyn Warner from the Dent Neurologic Institutue in Buffalo, New York, which specializes in multiple sclerosis. Some people think that (ME)CFS can look like MS and there are clinical features that are overlapping"

"I think this study is important because this is an MS specialist looking at (ME)CFS and seeing they are not MS, and then looking at them neurologically"

"Here are a number of symptoms. You can see that the great majority of these (ME)CFS cases have neurologic symptoms"

"The most specific neurologic symptoms that I find in (ME)CFS is dysequilibrium"

"These patients have a balance disturbance and on certain simple neurologic tests they fall over"

"On more sophisticated tests of vestibular fuinction they are often grossly abnormal"

"Nearly every patient had something abnormal within the central nervous system"

"Our evidence of central nervous system involvement can be demonstrated by tests looking directly at the CNS"

"These inflammatory and/or demyelinating plaques can be seen in the white matter, in the cerebellum and white matter tracks throughout the high cerebral convexities and in the frontal lobes"

"These lesions are not specific, they could be inflammation, they could be demyelination, there could be an element of destruction. What it says is that there is something going on in the brain".

1990

The diagnosis of postviral syndrome DJD Perrins
JRSM 1990:83:413

"The clinical pattern of myalgic encephalomyelitis has much in common with multiple sclerosis".

1990

The chronic fatigue syndrome: a return to common sense AM Denman
Postgraduate Medical Journal 1990:66:499-501

"It is salutary to reflect how many sufferers from infectious mononucleosis (glandular fever) may in the past have been maligned for their allegedly 'functional' illness before appropriate laboratory tests became available. Similar considerations apply to chronic fatigue following enteroviral infection, particularly by Coxsackie B virus"

"In some patients, muscle pain and easy fatiguability may be so prominent as to suggest a separate diagnostic category 'myalgic encephalomyelitis'. This is also a point of practical importance if a form of the syndrome existed in which active physical rehabilitation were contra-indicated"

"Progress will only be achieved if the different categories of chronic fatigue are dissected with scientific objectivity and therapeutic reason".

1990

Patient management of the postviral fatigue syndrome DO Ho-Yen
JRCGP 1990:40:37-39

"The subgroup of patients with immunological abnormalities may have a prolonged illness"

"It has been suggested that a new approach to the treatment of patients with postviral fatigue syndrome would be the adoption of a cognitive behavioural model (Wessely S, David A, Butler S, Chalder T: Management of chronic (postviral) fatigue syndrome. *JRCGP 1989:39:26-29*). Those who are chronically ill have recognised the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness".

1990

Objective measurement of personality variables in epidemic neuromyasthenis patients
A. Sricklin et al
South African Medical Journal 1990:77:31-34

"Too often only one aspect of the illness is treated, with little attention to other symptoms".

1990

The psychiatric status of patients with the chronic fatigue syndrome Ian Hickie et al
Br J Psychiat 1990:156:534-540

"We conclude that psychological disturbance is likely to be a consequence of rather than an antecedent risk factor to the syndrome. Our results suggest that patients are no more psychologically disturbed before the onset of their illness than members of the general population"

"There is no evidence from our well-defined sample to support the hypothesis that CFS is a somatic presentation of an underlying psychological disorder. In particular, there is no evidence that CFS is a variant or expression of a depressive disorder".

1990

Myalgic encephalomyelitis: an alternative theory CWM Wilson
JRSM 1990:83:481-483

"In his discussion paper on myalgic encephalomyelitis (April 1989 JRSM), Wessely suggested that a new term should be used to describe the observed symptoms. In his definition of CFS, he did not refer to any of the somatic symptoms which are always present"

"Evidence of biochemical and neurological changes have been reported in the brain. These symptoms are resistant to tranquillisers and antidepressant therapy in ME. Indeed, patients are often allergically sensitive to these drugs"

"The identification of viral antibodies in the tissues confirms the existence of a previous viral challenge".

1990

CD8 Deficiency in patients with muscle fatigue following suspected enteroviral infection (myalgia encephalitica) JR Hobbs, JA Mowbray, JE Monro et al
In: Protides of the Biological Fluids 1990:36:391-398

"Postviral states have been shown to be associated with acquired (secondary) T-cell deficiencies, particularly with CD8 dysfunction, and even immune paresis"

"It is also clear that the acquisition of T-cell deficiency, particularly the CD8 subset, can itself impair immune regulation and predispose to atopy not previously experienced by the patient"

"It is known that psychological disturbance can influence immunity. We, ourselves, have undertaken extensive T-cell subset measurements in normal subjects subjected to psychological stress, and would point out that in none of these did we see CD8 levels as low as in some 40% of our ME patients"

"It seems unlikely that the severe CD8 deficiency found could be due to psychological disturbance".

1990

Immunologic Abnormalities in Chronic Fatigue Syndrome Nancy Klimas et al (Nancy Klimas is Professor of Medicine, University of Miami School of Medicine; she is also Director of Immunology, Director of AIDS research and Director of the Allergy Clinic at Miami)
J Clin Microbiol 1990:28:6:1403-1410

"(ME)CFS is a clinical state of some complexity. In order to characterize in a comprehensive manner the status of laboratory markers associated with cellular dysfunction in patients with this syndrome, 30 patients were studied"

"All the subjects were found to have multiple abnormalities in these markers"

"The most consistent immunological abnormality detected was low natural killer (NK) cell cytotoxicity"

Lymphocyte phenotypic marker analysis of peripheral blood lymphocytes showed that there were significant differences between patients with (ME)CFS and controls"

"The pattern of immune marker abnormalities observed was compatible with a chronic viral reactivation syndrome"

"Depression of cell-mediated immunity was noted in our study population, with over 80% of patients having values below the normal mean"

"The values obtained were closely similar to those we observed in a group of human immunodeficiency virus type I-seropositive (HIV) intravenous drug users"

"Result 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"

"Functionally, the CD45RA+ CD4 cells, also termed Tinf, for inflammatory CD4 cells, can transfer delayed-type hypersensitivity"

"Selective depletion of CD4+ CD45RA+ cells was noted during the active phases of multiple sclerosis, but not in patients in remission or with inactive multiple sclerosis or other neurological diseases. Deficiencies quantitatively similar to those observed in patients with (ME)CFS were also reported in patients with other autoimmune diseases"

"The results of the present study suggest that (ME)CFS is a form of acquired immunodeficiency".

1990

Persistence of enteroviral RNA in chronic fatigue syndrome is associated with the abnormal production of equal amounts of positive and negative strands of enteroviral RNA L Cunningham NE Bowles RJM Lane V Dubowitz LC Archard
J Gen Virol 1990:71:1399-1402

"This suggests that enteroviral persistence in muscle is due to a defect in control of viral RNA synthesis"

"These data are the first demonstration of persistence of defective virus in clinical samples from patients with (ME)CFS".

1990

Myalgic encephalomyelitis --- a persistent enteroviral infection? EG Dowsett AM Ramsay et al
Postgraduate Medical Journal 1990:66:526-530

"Myalgic encephalomyelitis is a common disability but frequently misinterpreted"

"This illness is distinguished from a variety of other post-viral states by a unique clinical and epidemiological pattern of characteristic enteroviral infection"

"Advice to avoid over-exertion is mandatory"

"In our opinion, two major errors are responsible for the present confusion surrounding the case definition, aetiology and diagnosis of ME. First, there has been a failure to distinguish the syndrome from postviral debility following Epstein Barr mononucleosis, influenza and other common fevers. Second, there has been a failure to recognise the unique epidemiological pattern of ME".

1990

Aerobic work capacity in patients with chronic fatigue syndrome MS Riley DR McClusky et al
BMJ:1990:301:953-956

"Patients with the chronic fatigue syndrome have reduced aerobic work capacity compared with normal subjects"

"We found that patients with the chronic fatigue syndrome have a lower exercise tolerance than either normal subjects or patients with the irritable bowel syndrome. The main reason for the impaired exercise performance seems not to be diminished motivation"

"Previous studies have shown biochemical and structural abnormalities of muscle in patients with the chronic fatigue syndrome"

"Patients with (ME)CFS invariably indicated an aspiration to return to (their) previous level of activity".

1991

Immunological Markers in ME/CFS Presentation at the AACFS Research Conference, November 1990. Professor Nancy Klimas
(reported in CFIDS Chronicle: Spring 1991:47-50)

"The most compelling finding was that the NK (natural killer) cell cytotoxicity in (ME)CFS was as low as we have ever seen in any disease. This is very significant data. (ME)CFS patients represent the lowest cytotoxicty of all populations, including HIV AIDS, we have ever studied".

1991

The Disease of a Thousand Names David S Bell
Pollard Publications, New York, 1991

In addition to the standard symptoms such as exhaustion, headache, malaise, short term memory loss, muscle pain and abdominal pain, included in his list of 50 commonly presented symptoms in ME/CFS are

the following: double vision, balance disturbance, dizziness, palpitations, shortness of breath, easy bruising, swelling of extremities and eyelids, incontinence, and hair loss".

1991

Chronic fatigue syndrome and depression Ian Hickie et al
Lancet 1991: (April 13):337

"Kendell seeks to draw together similarities between (ME)CFS and depression but ignores important differences. Patients with typical depression are characterised by clinical features such as anhedonia, weight loss, suicidal ideation, psychomotor retardation or agitation that are notably absent in (ME)CFS"

"Patients with (ME)CFS lack many essential characteristics of patients with primary depression; their symptoms more closely resemble those seen with depression complicating primary medical disorders".

1991

Chronic fatigue syndrome: clinical condition associated with immune activation
Alan L Landay, Carol Jessop, Evelyne Lennette, Jay A Levy
Lancet 1991: (21 September):338:707-712

"Despite (the) clinical findings, some physicians question whether there is such a syndrome"

"Immunological disorders such as those seen in viral infections have been described in (ME)CFS – eg. decreased function of NK cells and macrophages, reduced mitogenic response of lymphocytes, B-cell subset changes, and activation of CD8 cells"

"These findings further support the notion that (ME)CFS involves immune disorders due most likely to an infectious agent"

"Depression developed in many patents after two years of illness"

"We found that patients could be placed into three groups according to their symptoms. Group A consisted of patients whose illness was so severe that they had less than 25% of their normal daily activity and also had multiple symptoms; group B had reduced physical activity and group C initially had many symptoms but had substantially improved"

"Three cell surface markers gave noteworthy results. 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"

"Evaluation of CD8 cell subsets in control subjects with a diagnosis of depression showed no significant differences compared with healthy controls"

"Laboratory findings have shown low level autoantibodies which may reflect an underlying autoimmune disease"

"When all (ME)CFS patients were considered, we found a state of immune activation specifically among the CD8 lymphocyte population. Moreover, the suppressor subset of CD8 (CD11b) was reduced in many patients, significantly so in patients with multiple symptoms and severe incapacitating illness (group A)"

"Our findings suggest that the CD8 CD11b population is reduced, and the CD38 and HLA-DR markers remain persistently raised"

"The immune disorder in CFS does not seem to reflect depression".

1991

Mitochondrial abnormalities in the post-viral fatigue syndrome WMH Behan et al
Acta Neuropathol 1991:83:61-65

"The findings described here provide the first evidence that PFS may be due to a mitochondrial disorder precipitated by a virus infection"

"The pleomorphism of the mitochondria in the patients' muscle biopsies was in clear contrast to the findings in the normal control biopsies"

"Diffuse or focal atrophy of type II fibres has been reported, and this does indicate muscle damage and not just muscle disuse".

1991

Evidence for Impaired Activation of the Hypothalamic Pituitary Adrenal Axis in Patients with Chronic Fatigue Syndrome Mark A Demitrack, Stephen E Straus et al
J Clin Endocrinology & Metabolism 1991:73:1224-1234

"Several lines of evidence suggest that the various components of the hypothalamic pituitary adrenal axis (the HPA axis) merit further study in these patients, for instance, debilitating fatigue, and abrupt onset precipitated by a stressor, arthralgias, myalgias, post-exertional fatigue, exacerbation of allergic responses and disturbances of mood and sleep are all characteristic of glucocorticoid insufficiency"

"A deficiency of CRH (cortico-releasing hormone) could theoretically contribute to the lethargy and fatigue that are the cardinal symptoms of (ME)CFS"

"Identification of psychological illness by standard diagnostic criteria includes many symptoms that are an inherent part of the definition of (ME)CFS"

1991

Biopsychosocial aspects of Chronic Fatigue Syndrome JDL Yeomans SP Conway
J Inf 1991:23:263-269

"(ME)CFS is associated with physical, psychological and social distress. The illness cannot be defined using just one of these dimensions. Such a unilateral approach has resulted in unnecessary controversy over the nature of the 'real' core of (ME)CFS"

"Psychiatric case definition is central to a psychiatrist's work and deserves careful attention in discussions of (ME)CFS with medical colleagues"

"It was hoped (that our present study) would avoid selection biases favouring the presence of psychiatric illness as might occur with selection by specialised fatigue clinics"

"A single item on the HAD depression scale refers to 'feeling slowed down'. Not surprisingly, this was cited by all patients. When this single item was removed from analysis, no patient retained a rating of depression. This emphasised the importance of possible false positive diagnosis of depression on the basis of somatic symptoms"

"Wessely and Powell (JNNP 1989:52:940-948) found the total psychiatric morbidity in (ME)CFS was 72% ---other studies have found it to be 21%. (Our) study finds a variable prevalence depending on the criteria used. This emphasised the ease with which psychiatric rating scales may lead to false positive diagnoses in patients with physical symptoms"

"It is possible that studies of (ME)CFS have had a tendency to over-estimate the prevalence of depression"

"The absence of (biological markers) has been interpreted as support for a psychogenic aetiology for (ME)CFS. It is important to diagnose such syndromes correctly, and (our) study suggests that questionnaires alone may over-emphasise psychiatric syndromes"

"It is unnecessary and indeed unproductive to force patients into unsuitable diagnostic categories as a condition of treatment".

1991

Postviral fatigue: current neurobiological perspective PGE Kennedy
In: Postviral Fatigue Syndrome. British Medical Bulletin 1991:47:4:809-814 Ed: PO Behan, DP Goldberg and JF Mowbray pub: Churchill Livingstone

"It is clear that there is now a widespread consensus that postviral fatigue syndrome (PVFS) is a definite disease entity. Recent intense research has made it no longer acceptable to dismiss PVFS as non-organic"

"Molecular viral studies have proved to be extremely useful. They have confirmed the likely important role of enteroviral infections, particularly with Coxsackie B virus"

"The PVFS has now come of age as a definite organic entity".

1991

The management of Post Viral fatigue Syndrome in General Practice David G Smith
ibid:265-279

"In the absence of any coherent move in Britain to develop criteria for the disease, the medical profession has had to fall back on the American Working Case definition of chronic fatigue syndrome, Holmes et al 1988, although this is not synonymous with ME".

1991

Assessment and Diagnosis of ME in the Psychiatric Clinic Rachel Jenkins
ibid 241-246

"Once one is familiar with the concept of post-viral fatigue syndrome, such patients are in practice not too difficult to differentiate from those with true psychiatric illnesses such as depressive illnesses, anxiety, hypochondriasis or hysteria"

"The classic diurnal variation of mood in severe depressive illnesses is not seen: the patient with ME will relate their depression to the frustration felt at not being able to do the active things they enjoy doing"

"The depressed patient feels fatigued and will be unmotivated to exercise, but can do most activities if required and sustain them, including climbing a hillside, standing upright for two hours or carrying a heavy object. The sufferer with ME, on the other hand, cannot do more than a fraction of these activities"

"There are also subtle difference between the impairment of concentration in depression and that in ME; in ME, the impairment of concentration tends to be associated with the timing and severity of the fatigue"

"In addition, specific cognitive abnormalities are present in ME, including difficulty in marshalling material, difficulty in finding the correct words in a sentence, and in appropriate syntax; speech is sometimes slurred, and the patient appears more clumsy than usual. They tend to bump into doorways and furniture more frequently, may display old bruises, and may complain of a feeling of dysequilibrium

"The physical symptoms should be an aid to diagnosis, although they may be wrongly attributed to primary psychological illness unless care is taken in eliciting them"

"Under a regime of pushing beyond physical limits, severe relapses occur and physical limits decrease. This is the exact opposite of what happens in a depressed person who is otherwise physically well, where steady pushing beyond physical limits will extend those limits and increase physical fitness"

"People with this illness do not tolerate antidepressants well"

"Patients with postviral fatigue syndrome are often very scared and in considerable pain".

1991

History of Chronic Fatigue Syndrome Stephen E Straus
Review of Infectious Diseases 1991:13: Suppl 1: S2-S7

"It is my goal to review briefly the history of (ME)CFS. In so doing, it becomes apparent that (ME)CFS is not of recent origin"

"Despite the broad divergence of opinion in the medical community, there is little doubt that classic allergy and atopy are inexplicably prevalent in (ME)CFS. In a recent study, a high proportion (50%) of patients were found to be reactive to a variety of inhalant or food allergens when innoculated epicutaneously in the classic manner"

"Because neurologic symptoms have dominated in certain of the case clusters (and even in some sporadic ones), the syndrome has been called benign myalgic encephalitis *(sic)*"

"Certainly patients with (ME)CFS differ immunologically from their healthy counterparts and it is this observation, more than any other today, that is evoked in support of the organic hypothesis of disease causation".

1991

Defining the Chronic Fatigue Syndrome Gary P Holmes
ibid S53-S55

"Preferably, patients with (ME)CFS who have such immune abnormalities might be considered a subset of the larger group: ie. persons with (ME)CFS who have immune dysfunction".

1991

Review of Laboratory Findings for Patients with Chronic Fatigue Syndrome
Dedra Buchwald Anthony L Komaroff
ibid S12-S18

"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 autoantibodies, particularly antinuclear antibodies and antithyroid antibodies; altered levels of immunoglobulins; abnormalities in number and function of lymphocytes"

1991

Chronic Fatigue Syndrome in Northern Nevada Sandra A Daugherty, Daniel Peterson, Sheila Bastien et al
ibid S39 - S44

"Enlargement of the spleen and liver is not unusual"

"The striking distortion of cognitive function along with the abnormal results of the MRI scans observed in these patients suggests a pathologic process in the brain"

"The pattern of focal and lateral impairments in these patients is more consistent with that of an atypical organic brain syndrome"

"This is not the pattern seen in depression, psychosis, anxiety or situational stress".

1991

Cognitive and Mood-state Changes in Patients with Chronic Fatigue Syndrome
Jordan Grafman et al
ibid: S45- S52
"The potential for confusing fatigue induced by virus with fatigue associated with mood is great"

"(Kennedy states that in (ME)CFS the) 'fatigue is the decline in performance that occurs in any prolonged or repeated task' "

"We remain cautious in attributing the cause of (ME)CFS in the vast majority of cases to an underlying psychiatric conflict. The tendency towards such an attribution is currently popular".

1991

Laboratory Abnormalities in Chronic Fatigue Syndrome Dedra Buchwald
In: Postviral Fatigue Syndrome Ed: Rachel Jenkins and James Mowbray Pub: John Wiley & Sons, Chichester, 1991:117-136

"Allergies are a common feature of patients with (ME)CFS".

1991

Postviral Fatigue Syndrome and the Cardiologist RG Gold
ibid: 227-231

"The patient suffering from PVFS (ME) is referred to a cardiologist almost always because of chest pain. The usual cause of the chest pain in these patients is chronic benign pericarditis. When we reviewed this condition in 1967, we felt then that the pericarditis was the final common pathway in an abnormal immunological response"

"The pain of pericarditis has some highly characteristic features which suggest the diagnosis to the clinician who is aware of these"

"(The) chest pain is variable in character. It is sometimes severe, sharp and stabbing, or it may be dull and aching. The pain may last for several hours or even days. It frequently occurs centrally but even in the same patient may recur on a different occasion in the right or left chest or back. It is commonly aggravated by sudden movement, change of posture, respiration, or swallowing"

"The patient may complain of shortness of breath"

"Palpitations are frequent, with sinus tachycardia being a common and at times distressing symptom"

"The presence of the pericardial rub is independent of the intensity of pain"

"The diagnosis of the cause of chest pain as a complication of ME rests almost entirely on careful clinical evaluation. Chronic benign pericarditis may continue or recur for many years and, like ME, be a distressing and debilitating illness. There is, alas, no way of predicting how long the condition will persist, and no reliably successful means of treating it"

"The main role of the clinician is to provide symptomatic relief and sympathetic support".

1991

USA: Multiple chemical sensitivity JB Sibbison
Lancet 1991:337:1469-1470

"Exposure to trace amounts of chemicals in indoor air or common foods has been said to produce symptoms such as headaches, memory loss, dizziness (etc)"

"There is no specfic treatment for MCS, whose existence is widely acknowledged"

"Treatment usually consists of avoidance of the offending substance (by special diets, for example)"

"Some governments will not wait for questions to be answered through research. The Bush administration is already requiring special accommodation for the chemically sensitivie in its housing policy"

"The Chemical Manufacturers Association's senior officials are concerned about the mounting litigation".

1991

Myalgic Encephalomyelitis: Postviral Fatigue Syndrome: Diagnostic and Clinical Guidelines for Doctors
Peter O Behan
Published by UK The ME Association, 1991

"Many different neurological and psychiatric syndromes follow viral infections. Recently, attention has been focused on (a) common postviral neurological syndrome, ie. the postviral fatigue syndrome, termed myalgic encephalomyelitis"

"Guidelines from the Medical Research Council may be unhelpful, since they suggest that "CFS" is a better term"

"The chief organ affected is skeletal muscle and severe fatigue, with or without myalgia, is the main symptom. The fatigue appears clinically to be of central origin in most patients but a peripheral component, ie. muscle involvement, has also been demonstrated by biochemical, electrophysiological, pathological and virological studies"

"Muscle metabolism is undoubtedly disturbed, but other organs, particularly the brain, heart, endocrine system and immune system are also affected".

"The idea that mass hysteria might account for these outbreaks was fashionable at one time, but like the majority of illnesses for which a psychiatric aetiology has been put forward, this hypothesis lacked all scientific merit and with the emergence of hard data, can be totally rejected"

"Some patients never exhibit any psychiatric manifestations whatsoever"

"It is quite clear to anyone who has experience in dealing with these patients that their symptoms differ considerably to those (with) endogenous depression"

"Gastro-intestinal symptoms are often made worse by certain foods and antibiotics"

"Patients who present with labyrinthitis often have a dysequilibrium syndrome, so that they are uncertain of their balance when walking"

"The recent attempt by Oxford psychiatrists to formulate (another case definition) has not taken us any further"

"It should be pointed out that there are definite subgroups who will have signs and symptoms of myocarditis"

"We have seen a large number of patients who presented with classical postviral fatigue syndrome and who continue to have intermittent but definite abnormalities in liver enzymes"

"Some patients exhibit all the symptoms of irritable bowel syndrome in addition to PVFS"

"We have demonstrated mitochondrial abnormalities on electronmicroscopy"

"75% of patients were found, using single fibre EMG, to have prolonged jitter values"

"Our experience with patients who have had the illness for one year or more and in whom there continues to be fluctuation in symptoms intensity but no remission, is that the prognosis is poor for recovery".

1992

Chronic Fatigue Syndrome: A Pamphlet for Physicians
US Department of Health and Human Services
NIH Publictaion No. 92-484, May 1992

"Many patients have a history of allergies years before the onset of (ME)CFS, and allergic symptoms may worsen after these patients become ill. Allergies are so prevalent in (ME)CFS patients that it is important to differentiate those symptoms that are allergy-related"

"(ME)CFS symptoms overlap with those of many well-recognised illnesses, for example, lupus erythematosus (SLE) and multiple sclerosis"

"Psychiatric evaluations fail to identify any psychiatric disorders in some patients"

"Many people with (ME)CFS have neurologic symptoms, including parasthesias, dysequilibrium and visual blurring. A few patients have more dramatic neurologic events such as seizures, periods of severe visual impairment, and periods of paresis"

"Many investigators believe that the illness involves a constant antigenic challenge to the immune system and, as a consquence, a constant immunologic response to that challenge"

"Evidence suggests that several latent viruses may be actively replicating more often in (ME)CFS patients that in healthy control subjects"

"Most investigators believe that reactivation of these viruses is probably secondary to some immunologic challenge"

"For many patients, it is important to avoid situations that are physically stressful"

"A balanced diet and rest enhance well-being"

"For now, physicians do not have all the answers, but in treating people with (ME)CFS, they can offer guidance with compassion".

1992

Ocular manifestations of Chronic Fatigue and Immune Dysfunction Syndrome
Walter Potaznick, Neil Kozol
Optometry and Vision Science 1992:69:10:811-814

"Whatever name is used, the syndrome most often consists of neurological symptoms, immunological abnormalities, cognitive impairments (and) disabling fatigue in a variety of other symptoms reflecting involvement in some if not all body systems"

"(We looked at) over 200 patients and over 200 controls and evaluated the data for each of 25 (ocular) symptoms"

"Statistical analysis shows that the increased rate at which patients with CFIDS report ocular symptoms is not explained by chance alone"

"Many CFIDS patients experience very troubling and disabling symptoms"

"It appears that the ocular symptoms of CFIDS are genuine".

1992

Chronic Fatigue Syndrome N Phillips
Australia and New Zealand Journal of Psychiatry 1992:26:329-330

" It is important for psychiatrists to familiarise themselves with the complexities of this syndrome and to be aware of the rapidly expanding body of new literature on this illness"

"Wessely's work on depression and (ME)CFS is methodologically flawed; (his patients) were not diagnosed using the full diagnostic criteria and therefore included many 'non-pure' (ME)CFS cases"

"Psychiatrists need to utilise such terminologies as 'the sick role' and 'abnormal illness behaviour' with great caution when discussing chronic illness. Not only will they alienate their medical colleagues, but, more importantly, the patients they are trying to help"

1992

CFIDS Chronicle Special Bulletin Walter Gunn (Principal Investigator of CFS studies at the Centres for Disease Control (CDC), USA *February 1992*

"Our surveillance study does not support the notion that CFS is a psychiatric disease and, in fact, suggests that it has an organic basis".

1992

Cell-mediated immunity in patents with chronic fatigue syndrome, healthy controls and patients with major depression A Lloyd I Hickie J Dwyer et al
Clin Exp Immunol 1992:87:76-79

"Evaluation of the psychiatric status of patients with (ME)CFS does not support the contention that (ME)CFS is simply a depressive equivalent"

"Although depression is common in patients with (ME)CFS, the disturbance in cell-mediated immunity in this disorder differs in prevalence and magnitude from those associated with major depression"

"It is likely therefore that this disorder is generated and maintained by an immunopathological process within the central nervous system".

1992

A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes Type 6 infection
Dedra Buchwald, Paul Cheney, Robert Gallo *(co-discoverer of the HIV virus)*, Anthony L Komaroff et al
Ann Intern Med 1992:116:2:103-113

"57% of patients were bed-ridden, shut in or unable to work"

"Immunologic (lymphocyte phenotying) studies revealed a significantly increased CD4 / CD8 ratio. Taken together, the controlled studies cited above and many others, seem to indicate an immune system chronically responding to a 'perceived' antigenic challenge"

"Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with oedema or demyelination in 78% of patients"

"Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic, immunologically-mediated inflammatory process of the central nervous system".

1992

Possible up-regulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome AMO Bakeit, PO Behan, TG Dinan et al
BMJ 1992:304:1010-1012

""In the past few years evidence which shows the organic nature of this condition has accumulated"

"The results suggest upregulation of the hypothalamic 5-hydroxytryptamine (5-HT) receptors in patients with PVFS but not in those with primary depression"

"Most of these patients had objective evidence of muscle damage, as shown by mitochondrial changes and the persistence of enteroviral RNA sequenced in muscle"

1992

Postviral fatigue syndrome Costa DC, Brostoff J, Douli V, Ell PJ
BMJ 1992:304:1567

" (SPECT scans have demonstrated) significant deficits in brain perfusion, particularly in the hypothalamus and pons".

1992

The postviral fatigue syndrome WRC Weir
Current Medical Literature (Royal Society of Medicine) 1992:6:1

"In more acutely affected individuals the advice to 'exercise back to fitness' is a recipe for disaster".

1992

Neuro-opthalmological Manifestations of Chronic Fatigue Syndrome Alfredo A Sadun and Pravin U Dugel *In:* The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome *Ed:* Byron M Hyde, Jay Goldstein and Paul Levine *Pub: The Nightingale Research Foundation, Ottawa, Canada 1992*

"The neuro-opthalmological manifestations of (ME)CFS are myriad and common. Two thirds of the patients complained of blurred vision; one patient (complained of) binocular diplopia. The most obvious objective sign was nystagmus; **it was even more astonishing that approximately one quarter of the patients had a primary nystagmus, since such nystagmus is always pathological**".

1992

How do I diagnose a patients with Chronic Fatigue Syndrome? J Goldstein
In: The Clinical and Scientific Basis of ME CFS. Ed: BM Hyde, J Goldstein, P Levine. Pub: the Nightingale Research Foundation, Ottawa, Canada, pp247-252

"Other disease associations such as irritable bowel syndrome, polycystic ovarian disease, thyroiditis and endometriosis are probably part of (ME)CFS. **It is a rare woman with (ME)CFS who has not had hair loss, usually diffuse**".

1992

Chronic Fatigue Syndrome: Is It a State of Chronic Immune Activiation Against an Infectious Agent?
Jay A Levy, Alan L Landay et al
Contemp Issues Infect Dis 1993:10:127-146

"Since about 1986, clinicians in the San Francisco area have seen an upsurge of (ME)CFS in their practice"

"In the majority of cases, the onset of depression occurred six months after the onset of the illness"

"Three (immune) markers were found to be highly significant: the data indicate a high (90%) probability that an individual with two or more of the CD8+ cell subset changes will have active (ME)CFS"

"We expect that when the clinical data on these individuals are tabulated, severe illness will again correlate with signficiantly abnormal lymphocyte phenotypic findings"

"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 activiation state"

"We speculate that (ME)CFS represents a type of autoimmune disease. Because of the known higher prevalence of (ME)CFS in women, 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 recognized autoimmune diseases and multiple sclerosis".**

1992

Neuropsychological and psychiatric abnormalities in myalgic encephalomyelitis: a preliminary report
Massimo Riccio, Ariel F Lant et al
Brit J Clin Psychology 1992:31:111-120

"At the present time, the term ME is viewed as probably the most satisfactory in encompassing all the features of this distressing illness"

"The acute presentation in all patients followed a similar pattern"

"Muscle pain was common after even trivial attempts at exercise"

"All patients reported difficulty in concentration which was often profound"

"All reported an inability to socialize because of exhaustion"

"Few controversies in modern medicine have raged so fiercely as that over the syndrome which has been called ME"

"(This) study offers an insight into the nature of the central nervous system component of the disorder. The results presented here may point to the presence of an organic aetiology for the neuropsychiatric abnormalities which have bee noted clinically in some patients"

"The neurpsychological abnormalities we have shown are not accountable wholly in terms of depression"

"In the presence of evidence of organic memory impairement, it seems reasonable that the patients should consider themselves to be ill"

"In conclusion, the present study provides evidence that, in some patients with operationally defined ME, cognitive abnormalities which may be compatible with an organic cause can be detected"

1993

Clinical presentation of chronic fatigue syndrome Anthony L Komaroff
In: Chronic Fatigue Syndrome, John Wiley & Sons, Chichester; Ciba Foundation Symposium 173: 43-61

"Many diseases that today are well-established -- for example, multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis – were at one time controversial until definitive objective abnormalities were identified"

"(ME)CFS can last for years and is associated with marked impairment"

"(ME)CFS is) a terribly destructive illness"

"The tenacity and ferocity of the fatigue can be extraordinary"

"On past medical history, the only clearly striking finding is a high frequency of atopic or allergic illness in approximately 50-80%, in contrast to a background prevalence of about 10% in the population at large"

"As for the symptoms that accompany the fatigue, it is striking that these symptoms are experienced not just occasionally but are present virtually all the time"

"In our experience, 80% of patients with (ME)CFS have an exceptional post-exertional malaise"

"(Physical examination findings) include abnormal Romberg test (and) hepatomegaly (and) splenomegaly"

"Anyone who has cared for patients with (ME)CFS will recognize that (the) description of the patient with lupus eloquently describes many patients with (ME)CFS as well".

1993

Information Processing Efficiency in Chronic Fatigue Syndrome and Multiple Sclerosis
John DeLuca Susan Johnson Benjamin Natelson
Arch Neurol 1993:50:301-304

The objective of this study was to compare the cognitive performance of subjects with (ME)CFS, MS, and healthy controls.

"The MS group was added so that the performance of the (ME)CFS group could be compared with a population presenting with a symptoms cluster similar to that of patients with (ME)CFS, but of known organic cause"

"The results of this study clearly demonstrate that subjects with (ME)CFS and MS exhibit difficulties in information processing efficiency compared with matched controls"

"These results indicate that subjects with (ME)CFS and subjects with MS show signficiant impairment when compared with appropriate controls"

"The results of our study indicate that depression alone cannot account for the deficits observed in the (ME)CFS and MS groups".

1993

Biochemical and muscle studies in patients with acute onset postviral fatigue syndrome
VR Preedy et al
J Clin Pathol 1993:46:722-725

"Patients with acute onset PVFS lose muscle protein synthesis potential, but not muscle bulk. Histopathology is consistent with these observations. These peturbations may contribute to the apparent feature of perceived muscle weakness associated with the persistent viral infection in the muscles themselves".

1993

Persistence of enterovirus RNA in muscle biopsy samples suggest that some cases of chronic fatigue syndrome result from a previous, inflammatory viral myopathy
NE Bowles, LC Archard et al
Journal of Medicine 1993:24:2:145-160

"The term PVFS has been widely misused to describe all forms of chronic fatigue"

"Investigation with strand-specific riboprobes demonstrated that in each of the PFS cases found positive for virus RNA, enterovirus persisted in these non-inflammatory muscle biopsies as a replication defective mutant"

"Our data confirm that enterovirus infection of muscle is not a general feature of the population"

"This association of enterovirus infection is compatible with what is often considered an autoimmune disease"

"We propose that in PFS patients, a mutation affecting control of viral RNA synthesis occurs during the initial phase of active virus infection and allows persistence of replication defective virus which no longer attracts a cellular immune response".

1993

Testimony before the US FDA Scientific Advisory Committee, 18th February 1993
Paul Cheney, Professor of Medicine, Capital University, USA; Medical Director of the Cheney Clinic, North Carolina, USA (one of the world's leading exponents on ME/CFS)

"I have evaluated over 2,500 cases. At best, it is a prolonged post-viral syndrome with slow recovery. At worst, it is a nightmare of increasing disability with both physical and neurocognitive components. The worst cases have both an MS-like and an AIDS-like clinical appearance. We have lost five cases in the last six months. The most difficult thing to treat is the severe pain. Half have abnormal MRI scans. 80% have abnormal SPECT scans. 95% have abnormal cognitive-evoked EEG brain maps. Most have abnormal neurological examination. 40% have impaired cutaneous skin test responses to multiple antigens. Most have evidence of T cell activation. 80% have evidence of an up-regulated 2-5A antiviral pathway. 80% of cases are unable to work or attend school. We admit regularly to hospital with an inability to care for self".

1993

Memory deficits associated with chronic fatigue immune dysfunction syndrome
Curt Sandman (Professor of Psychiatry and Human Behaviour, University of California School of Medicine)
Biol Psych 1993:618-623

"The performance of the CFIDS patients was sevenfold times worse than either the control or the depressed group. These results indicated the memory deficit in CFIDS patients was more severe than assumed by CDC criteria. A pattern emerged supporting neurological compromise in CFIDS".

1994

Summary and Perspective: Epidemiology of Chronic Fatigue Syndrome Paul H Levine
Clin Inf Dis 1994:18: (Suppl 1):S57-S60

"Epidemiologists play a number of roles in the study of diseases; the functions of these specialists include case definitions, descriptions of disease patterns, identification of risk factors, and analysis of clinical trials. In the study of a complex illness such as (ME)CFS, for which no definitive diagnostic test exists, the most important aspect is case definition – all other areas of investigation depend on this standard for appropriate interpretation of results"

Most patients affected in a cluster of 'epidemic neuromyasthneia' do not fit the 1988 case definition of (ME)CFS"

"It has been noted for a number of years that a history of allergies appears to be an important risk factor for (ME)CFS"

"**The spectrum of illnesses associated with a dysregulated immune system must now include (ME)CFS**"

"The precipitating factors leading to (ME)CFS were also an important focus of this symposium. In addition to a history of allergy, other factors such as **exposure to chemicals and noxious agents** were noted to be possible triggers"

"It is likely that host response, due to genetic predisposition, contributes to the development of (ME)CFS **as an outcome of the exposure".**

1994

Association between HLA Class II Antigens and the Chronic Fatigue Immune Dysfunction Syndrome
RH Keller, MA Fletcher, N Klimas et al
ibid S154-S159

"The chronic fatigue immune dysfunction syndrome (CFIDS) is a major subgroup of the chronic fatigue syndrome (ME/CFS). We and other investigators have reported a strong association between immune dysfunction and a serological viral reactivation pattern among patients in this group. This finding appeared similar to that for a variety of conditions such as chronic active hepatitis, juvenile rheumatoid arthritis and systemic lupus erythematosus (SLE or lupus), in which a definite association between a particular HLA-DR/DQ haplotype and increased disease frequency has been reported"

"It is possible that DR4 (relative risk for CFIDS 1.6) and DR5 (relative risk for CFIDS 1.8) are also associated with an increased risk of developing CFIDS"

"The data presented herein suggest that CFIDS, together with a variety of immune-mediated diseases, may share similar sequences of pathogenic mechanisms"

"It may be speculated that in a particular sub-population, a genetic predisposition may be triggered immunologically by any of a number of potential stimuli, resulting in a state of chronic immune dysequilibrium"

"This model could easily explain the recent findings with regard to acute viral infection, allergies or other mechanisms that are obscured by the process of chronic immune activation".

1994

Decreased Natural Killer Cell Activity is Associated with Severity of Chronic Fatigue Immune Dysfunction Syndrome EJ Ojo-Amaize et al
ibid S157-S159

"Our results confirm and extend previous reports that low NK cell cytotoxicity is a pronounced immunologic abnormality found in some patients with CFIDS"

"The fact that NK cell activity decreases with the increased severity and duration (of the disorder) suggests that measurement of NK cell function could be useful for stratification of patients and for monitoring the progression of CFIDS".

1994

Immunologic studies of CFS Andrew R Lloyd
ibid S134-135

"Circumstantial evidence suggests that (ME)CFS may result from a disordered immune response to a precipitating infection or **antigenic challenge**"

"Findings from several case reports and one controlled study have suggested that serum levels of IgG subclasses (especially IgG1 and IgG3) may be reduced in patients with (ME)CFS"

"The three most prominent and reproducible findings are (1) impaired lymphocyte proliferation in response to stimulation by mitogens has been repeatedly documented and has also been shown to be dissociated from the potential effect of concurrent mood disturbance on this response; (2) investigators have reported

increased number of peripheral blood lymphocytes bearing activation markers such as HLA-DR and interleukin-2R in these patients; (3) impaired cell-mediated immune function"

"It is likely that conflicting data may arise because of the heterogeneity of the sample populations studied".

1994

Upregulation of the 2-5A Synthetase/ Rnase L Antiviral Pathway Associated with Chronic Fatigue Syndrome Robert J Suhadolnick Daniel L Peterson Dharam Ablashi et al
Ibid S996-104

"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 the pathway is an important indictaor of the antiviral state in (ME)CFS"

"Evidence that this pathway is activated in (ME)CFS was identified in the subset of severely disabled patients as related to virological and immunological status".

1994

Closing Remarks of the Symposium Anthony L Komaroff and Nancy Klimas
ibid S166-167

"Few studies by psychiatrists are presented in this symposium. Many investigators who have argued that (ME)CFS is primarily a psychiatric disorder chose not to present their work".

1994

Simultaneous Measurement of Antibodies to Epstein Barr Virus, Human Herpes Virus 6, Herpes Simplex Virus Types 1 and 2, and 14 Enteroviruses in Chronic Fatigue Syndrome: Is there evidence of Activation of a Nonspecific Polyclonal Immune Response? FA Manian
Clin Inf Dis 1994:19:44-53

"Of the 14 enteroviruses tested for, (only) those to Coxsackie B1 and B4 were present at significant titres in cases versus controls at a percentage significantly higher than that of controls".

1994

Chronic Fatigue Syndrome Up-date: Findings now point to CNS involvement
David S Bell (Instructor in Paediatrics, Harvard Medical School)
Postgraduate Medicine 1994:98:73-81

"Abnormalities of immune function, hypothalamic and pituitary function, neurotransmitter regulation and cerebral perfusion have been found in patients with (ME)CFS. Recent research has yielded remarkable data. The symptoms of (ME)CFS have long been viewed as a neurologic pattern, as confirmed by names such as myalgic encephalomyelitis. A link is being forged between the symptoms of (ME)CFS and objective evidence of central nervous system dysfunction. The view that (ME)CFS is a primary emotional illness has been undermined by recent research".

1994

The ocular signs and symptoms of chronic fatigue syndrome Caffery BE et al
Journal of the American Optometric Association: 1994:65:187-191

"(ME)CFS affects the ocular system in many ways"

"Every patient seen with (ME)CFS presented with at least one ocular symptom"

"There were three major prevalent ocular findings in patients with (ME)CFS: all patients presented with ocular symptoms; (some) patients had reduced accommodation (and some) patients had objective abnormalities of preocular tear film and ocular surface"

"In the past, the ocular signs and symptoms of (ME)CFS have not been considered to be a major component of the disease process. However, it appears that the ocular system may be very much affected by this systemic disease"

"The objective findings of the anterior segment suggests an organic aetiology"

"The number of patients presenting with tear film and ocular surface abnormalities was remarkable"

"There are histological studies that demonstrate lacrimal gland invasion by inflammatory cells in Sjogrens syndrome. One could speculate that there may be similar histological findings in patients with (ME)CFS"

"The ocular neurological symptoms that presented in such a large number of (ME)CFS patients suggests a neurological basis of the disease. The visual symptoms combined with the reduced motor skills of these patients might lead some clinicians to entertain the diagnosis of multiple sclerosis".

1994

Detection of Intracranial Abnormalities in Patients with Chronic Fatigue Syndrome: Comparison of MR Imaging and SPECT
RB Schwartz AL Komaroff et al
AJR (American Roentgen Ray Society) 1994:935-941

"SPECT scans showed more abnormalities than MR scans did in patients with (ME)CFS"

"The complaints of afflicted patients, particularly those involving the central nervous system, can be misdiagnosed or even considered by some to be factitious. The finding of abnormal neuroimaging studies in the vast majority (94%) of patients with (ME)CFS indicates that this condition is associated with physiologic changes that can be observed objectively"

"As with any chronic inflammatory condition affecting the central nervous system, the T2-bright foci on MR in (ME)CFS may represent a perivascular cellular infiltrate and / or reactive demyelination of the surrounding white matter. Alternatively, these abnormalities may reflect the results of a vasculopathy involving the small vessels of the cerebral white matter; indeed, the distribution of lesions on MR in ME/CFS is similar to that observed in occlusive arteriolar disease of any origin"

"The cortical defects measured with SPECT likewise may result from direct infection of neurological elements, from cellular dysfunction due to circulating cytokines, or from decreased flow through cortical arterioles owing to vasculitis"

"Specifically, on the basis of our observations, the white matter abnormalities seen on MR images may represent foci of chronic demyelination which appear to be irreversible".

1994

Anaesthesia in CFIDS Patrick L Class
CFIDS Chronicle, Summer 1994:82

"There is a group of commonly-used anaesthetic agents which are known histamine-releasers and are best avoided by CFIDS patients"

"Since so many of these histamine-releasing agents are commonly used during emergency surgery, it would be advisable (for patients with (ME)CFS) to wear a medical alert bracelet"

1995

SPECT Imaging of the Brain: Comparison of Findings in Patients with Chronic Fatigue Syndrome, AIDS Dementia Complex and Major Unipolar Depression
RB Scwartz, AL Komaroff et al
AJR (American Roentgen Ray Society)1994:162:943-951

"This study demonstrates that (ME)CFS shares some similarities on SPECT imaging with AIDS Dementia Complex (ADC). By this objective standard, the pathophysiologic processes in the central nervous system of patients with (ME)CFS would seem more similar to that in patients with ADC than in patients with unipolar depression"

"The similarity in MCUI data between patients with ADC and (ME)CFS suggests a similar origin for the neurologic dysfunction in these conditions (and) the similarity in appearance on SPECT suggests the possibility of similar underlying abnormalities in ADC and (ME)CFS".

1995

Introduction to Research and Clinical Conference, Fort Lauderdale, Florida, October 1994
Daniel L Peterson
JCFS 1995:1:3-4:123-125

"**In my experience, ME/CFS is one of the most disabling diseases that I care for, far exceeding HIV disease except for the terminal stages".**

1995

Immunology Roberto Patarca
ibid: 195-202

"Several groups have been working on defining immune status variables of relevance to the nosology and follow-up of (ME)CFS patients"

"One rationale for the immunological approach stems from the experience accumulated with similar syndromes of heterogeneous presentations such as autoimmune and environmentally-triggered diseases"

"**The hypothesis was entertained that (ME)CFS may be associated with certain HLA class II antigens, as are some forms of environmental disease"**

"Viruses are frequently reactivated in association with immune system dysregulation in (ME)CFS and may contribute indirectly to the symptomatology"

"**These observations underscore the distinction between (ME)CFS and psychiatric maladies"**

1995

'Abnormal' Illness Behaviour in Chronic Fatigue Syndrome and Multiple Sclerosis
Peter Trigwell Simon Hatcher
BMJ 1995:311:15-18

"Those who see (ME)CFS as primarily a psychiatric disorder regard it as a variety of somatisation. The concept of somatisation overlaps with that of 'abnormal illness behaviour'. There is an explicit judgment to be made in concluding that a patient is exhibiting abnormal illness behaviour: it is that the doctor does not think that the patient's objective pathology entitles him to be placed in the sick role he expects"

"If (ME)CFS is a variety of somatisation, then we should expect to find evidence of abnormal illness behaviour with the syndrome"

"We wanted to confirm whether patients with (ME)CFS have abnormally high levels of disease conviction and if so, whether it is associated with other elements of abnormal illness behaviour or is, indeed, merely a corollary of chronic disease"

"We draw two conclusions from our study. Firstly, the illness behaviour questionnaire seems to be unsatisfactory as a measure of abnormal illness behaviour in (ME)CFS. Secondly, we have confirmed that disease conviction is common in (ME)CFS"

"Scores on illness behaviour questionnaires cannot be taken as evidence that (ME)CFS is a variety of abnormal illness behaviour because the same profile occurs in multiple sclerosis".

1995

Exercise response and psychiatric disorder in chronic fatigue syndrome
Russell JM Lane Leonard C Archard et al
BMJ 1995:311:544-545

"In previous studies patients with (ME)CFS showed exercise intolerance in incremental exercise tests, which seemed to be related to an increased perception of effort. We examined venous blood lactate responses to exercise at a work rate below the anaerobic threshold in relation to psychiatric disorder"

"Our results suggest that some patients with (ME)CFS have impaired muscle metabolism that is not readily explained by physical inactivity or psychiatric disorder".

1995

Brainstem perfusion in chronic fatigue syndrome DC Costa C Tannock J Brostoff
Quarterly Journal of Medicine 1995:88:767-773

"Patients with (ME)CFS have a generalised reduction of brain perfusion, with a particular pattern of hypoperfusion of the brain stem".

1995

Detection of Enterovirus-specific RNA in Serum: the Relationship to Chronic Fatigue
Geoffrey B Clements et al
J Med Virol 1995:45:156-161

"In the study described here, enteroviral sequences were found in significantly more (ME)CF patients than in the two comparison groups. The presence of the enteroviral sequences in a significant number of patients points to some role in (ME)CF"

"A variety of immunological disturbances have been reported for (ME)CF patients which may relate in some way to the enteroviral persistence"

"This study provides evidence for the involvement of enteroviruses in just under half of the patients presenting with (ME)CF and it confirms and extends previous studies using muscle biopsies"

"We provide evidence for the presence of viral sequences in serum in over 40% of (ME)CF patients and also in some buffy coat cells and stool samples".

1995

Pathophysiology of a Central Cause of Post Polio Fatigue Richard L Bruno et al
In: Ann NY Acad Sci 1995:753:257-275

"These relationships and recent empirical comparisons between post polio and chronic fatigue will be described"

"Beginning in Los Angeles in 1934 and continuing for more than 20 years, a dozen outbreaks occurred of a disease that was at first diagnosed as poliomyelitis, then as 'atypical' poliomyelitis and finally named myalgic encephalomyelitis (ME)"

"Most patients were left with a marked exhaustion and fatiguability that were always made worse by exercise and emotional stress"

"A more direct association between the polio virus and ME was seen in 1948"

"More recent support for a relationship between poliovirus and ME came in 1989 when a dangerously rising titre to type III poliovirus was documented in a patient who did not have polio but who had been diagnosed with ME"

"A constellation of symptoms resembling ME was termed 'chronic fatigue syndrome' (CFS) --- like ME and post-polio fatigue, CFS is characterized by complaints of chronic fatigue and impaired concentration that are triggered or exacerbated by physical exertion and emotional stress"

"Hyperintense signal imaged along white matter tracts may have resulted from damage to the brain parenchyma by a local, tissue-toxic effect of the poliovirus"

"Notably, periventricular and deep white (but not grey) matter HS have been imaged in between 40 and 100% of (ME)CFS patients and have been suggested to represent either enlarged, fluid-filled spaces around arterioles, or demyelination"

"Neuroradiologic and neuroendocrine data have indicated damage to brain areas responsible for cortical activation and attention in polio survivors and others with chronic fatigue"

"Word-finding difficulties are reported by 82% of polio survivors with fatigue, and appear similar to word-finding problems reported by (ME)CFS patients".

1996

Prognosis in chronic fatigue syndrome: a prospective study on the natural course
JM Vercoulen et al
JNNP 1996:60:489-494

"Comprehensive assessment of (ME)CFS entails measurement on all dimensions simultaneously"

"The finding that on three out of seven outcome measures these patients did not show improvement underlines the importance of multidimensional assessment in studies on prognosis"

"Psychological well-being (including depression) did not predict improvement in this study, although others (Wessely et al) have suggested that this factor plays a part in the perpetuation of complaints"

"Avoidance of physical activity is also thought to play a part in the perpetuation of complaints (Wessely et al) but the present study is not conclusive on this issue"

"The improvement rate in patients with a relatively long duration of complaints is small".

1996

Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome.
Jan H M M Vercoulen, Caroline Swanink et al
Lancet, 1996:347:858-861

"Antidepressant therapy is commonly used (in (ME)CFS). However, there has been no randomised, placebo-controlled double-blind studies showing the effectiveness of antidepressant therapy in (ME)CFS. We have carried out such a study to assess the effect of fluoxetine *(Prozac)* in depressed and non-depressed (ME)CFS patients"

"There have been anecdotal reports that fluoxetine is poorly tolerated by patients with (ME)CFS. In our trial, 15% of fluoxetine-treated patients withdrew because of side effects, a higher withdrawal rate than in fluoxetine trials in depressed patients on the same regime".

"In our study, fluoxetine was no better than placebo in treating depression".

"Fluoxetine in a 20 mg daily dose does not have a beneficial effect on any characteristic of CFS".

"We conclude that prescription of 20mg fluoxetine in CFS is unwarranted, irrespective of whether depressive symptoms are present; it does not lead to improvement in any area of the patient's functioning".

1996

Chronic Fatigue Syndrome: is total body potassium important? Burnet RB et al
Medical Journal of Australia, 1996:164:6:384

The authors found that total body potassium (TBK) was lower in patients with (ME)CFS and they suggest that abnormal potassium handling by muscle in the context of low overall body potassium may contribute to fatigue in (ME)CFS.

1996

Lung function test findings in patients with chronic fatigue syndrome.
De Lorenzo et al
Australia and New Zealand Journal of Medicine, 1996:26:4:563-564.

The authors found that compared with controls, patients with (ME)CFS showed a significant reduction in all lung function parameters tested.

1996

Abnormality of adrenal function in the patients with chronic fatigue syndrome.
(Abstract of presentation at the Proceedings of the First World Congress on CFS, Brussels, November 9-11,1995) Yamaguti K et al
JCFS, 1996:2:2/3

"The level of DHEA decreases in some patients and the level of DHEA - S decreases in most patients with (ME)CFS. These abnormalities found in (ME)CFS are quite different from those found in patients with mental and physical diseases reported previously".

1996

Eosiniphil cationic protein serum levels and allergy in chronic fatigue syndrome.
Conti F et al
Allergy: 1996:51:124-127

"ECP serum levels were significantly higher in (ME)CFS patients than in controls. In (ME)CFS patients, the prevalence of radio-allergosorbent (RAST) positive responses to one or more allergens was 77%, while no control showed positive RAST".

1996

Chronic Fatigue Syndrome: evaluation of a 30-criteria score and correlation with immune activation. Hilgers A and Frank J.
Journal of Chronic Fatigue Syndrome,1996:2:4:35-47.

The aim of this study was to develop a score to evaluate the severity of (ME)CFS and to correlate the degree of severity with parameters of immune activation; five hundred and five patients were studied using a 45-criteria score and basic laboratory programmes, together with immunological profiles. In most of the patients, further tests of complement system, immune activation markers, hormones and viral serology were evaluated.

385 patients fulfilling the 1994 CDC criteria showed significant differences to healthy controls in 40 of the 45 symptoms assessed. Thirteen symptoms corresponding to CDC criteria were all significant, but 17 further significant criteria were added to improve precision:

respiratory infections; palpitations; dizziness; dyspepsia; dryness of mouth / eyes; allergies; nausea; paraesthesia; **loss of hair**; skin alterations; eczema; dys-coordination *(sic)*; chest pain; personality changes; general infections; urogenital infections; twitches.

A correlation between the 30-criteria score and immunological parameters could be evaluated in 472 of the 505 patients.

Significant positive correlation was found in numbers of CD8+ T lymphocytes, HLA DR+ lymphocytes, gamma globulins, 1gM, lgG, and for the numbers of types of autoantibodies (mainly ANA, ACA, antithyroid and antiparietal cell antibodies).

Significant negative correlation was found in albumin-globulin ratio, eosinophils and lgE.

Most of these parameters also correlated with one another.

"In increasingly larger groups of patients with (ME)CFS and related constellations we often see clinical signs and longer anamnesis of other symptoms beside the classical criteria of (ME)CFS, especially a high prevalence of local and general infections and hints to prolonged inflammation processes…A reduced or unstable immune control can lead to a chronic neuro-immune activation state and autoimmune disorders. Hypersensitivity symptoms of the patients might not be mediated by classical allergies alone but also result from a type IV hypersensitivity".

1996

The neuroendocrinology of chronic fatigue syndrome Scott LV Dinan TG
JCFS: 1996:2:4:49-59

The authors note that there is an increasing volume of evidence to support the view that patients with (ME)CFS have unique neuroendocrinology patterns.

Central to this endocrine dysfunction is altered hypothalamic-pituitary-adrenal axis (HPA) activity.

The cardinal findings include attenuated adrenocorticotrophic hormone (ACTH) responses to corticotrophin-releasing hormone (CRH) and low 24 hour urinary cortisol. These are compatible with a mild central adrenal insufficiency.

Adrenal steroids have widespread impact in the brain, and of particular importance is their dense concentration on serotonergic and noradrenergic neurotransmitter pathways.

The authors propose that the disruption of the HPA axis (which may be triggered by a number of stressors) may represent a primary phenomenon, and that neurotransmitter abnormalities (serotonin and noradrenalin) are in fact secondarily heralded by prolonged HPA dysregulation.

1996

Evidence that abnormalities of central neurohormonal systems are key to understanding Fibromyalgia and Chronic Fatigue Syndrome Leslie J.Crofford Mark A.Demitrack
Rheum Dis Clin North America:1996:22:2:267-284

The concept that disorders such as fibromyalgia (FM) and chronic fatigue syndrome (ME/CFS) are associated with subtle and undetectable disturbances in the central nervous system was introduced in 1869 by Beard. Great strides have been made in recent years towards defining neurochemical abnormalities in FM and (ME)CFS, and both FM and (ME)CFS fall into the spectrum of what might be termed *stress-related illnesses* by virtue of the clinical observation that the onset of both is coincident with physical or emotional stress. The article focuses on abnormalities of the HPA axis and sympathetic nervous system (SNS), ie. the major stress response systems, and the authors point out that it is important to keep in mind that activity of stress response systems is determined by genetic and environmental factors.

The authors present data which supports the view that FM and (ME)CFS could represent different forms of insufficient stimulation of the HPA axis, with both syndromes expressing low hypothalamic CRH but with FM being characterised by *increased* exposure of the corticotrophs to AVP, while (ME)CFS patients have *decreased* AVP levels. Patients with a longer duration of disease tend to have more severe basal abnormalities in cortisol levels.

When oestrogenic stimulation diminishes, relative hypo-function of the HPA axis could follow, contributing to the development or maintenance of FM / (ME)CFS.

Further research into the nature of the neurohormonal peturbations in FM and (ME)CFS may elucidate treatment strategies for these disorders.

1996

Neuroimmune mechanisms in health and disease. Part 2: Disease Anisman H et al.
Can Med Assoc.J: 1996:155(8) 1075-1082

In the second part of their article on the emerging field of neuroimmunology, the authors present an overview of the role of neuroimmune mechanisms in defence against infectious disease and in immune disorders. Profound neuroendocrine and metabolic changes take place: acute phase proteins are produced in the liver; bone marrow function and the metabolic activity of leukocytes are greatly increased, and specific immune reactivity is suppressed. Defects in regulatory processes (which are fundamental to immune disorders and inflammatory diseases) may lie in the immune system, the neurendocrine system or both.

Defects in the HPA axis have been observed in autoimmune disease, chronic inflammatory disease, (ME) chronic fatigue syndrome and fibromyalgia.

Defective neural regulation of inflammation is likely to play a pathogenic role in allergy and in gastrointestinal inflammatory disease.

A better understanding of neuroimmunoregulation holds the promise of new approaches to the treatment of immune and inflammatory disease with the use of hormones, neurotransmitters and neuropeptides and drugs which modulate these newly recognised immune regulators.

1996

Prevalence of irritable bowel syndrome in chronic fatigue Gomborone JE et al
JRCP Lond 1996:30:6:512-513

The purpose of this study was to determine the prevalence of irritable bowel syndrome in chronic fatigue sufferers.

A questionnaire about bowel symptoms was sent to 4,000 members of Action for ME self help group, and was returned by 1,797 (45%).

The people with chronic fatigue reported more bowel symptoms including the Manning criteria than the general population.

Seventy three per cent qualified for the diagnosis of IBS, which greatly exceeds estimates of lBS prevalence of up to 22% in the general population.

1996

Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome
Cordero DL Natelson BH et al.
Clin Auton Res: 1996:6:(6):329-333

The purpose of this study was to determine if patients with (ME)CFS have less vagal power during walking and during rest periods following walking.

Patients had significantly less vagal power than the control subjects, despite there being no significant group-wise differences in mean heart rate, tidal volume, minute volume, respiratory rate, oxygen consumption or total spectrum power.

Notably, patients with (ME)CFS had a significant decline in resting vagal power after periods of walking.

These results suggest a subtle abnormality in vagal activity to the heart in patients with (ME)CFS.

1996

Autoantibodies to Nuclear Envelope Antigens in Chronic Fatigue Syndrome
K.Konstantinov D.Buchwald J.Jones et al
J.Clin Invest 1996:98:8:1888-1896

The authors identified and partially characterised the autoantibodies in sera of 60 patients with (ME)CFS.

The autoantibodies were of the lgG isotype.

The occurrence of autoantibodies to a conserved intracellular protein like lamin BI provides new laboratory evidence for an autoimmune component in (ME)CFS.

The immunological abnormalities described are in accordance with a growing body of evidence suggesting chronic, low-level activation of the immune system 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. Their findings suggest that in addition to the other 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 subjects in control groups I and II. In addition, none of the patients with chronic depression or atopy showed reactivity to NE proteins.

These results confirm that the NE reactivity of some (ME)CFS sera is against lamin B. Autoantibodies to NE proteins are relatively infrequent in routine ANA serology, and most of these fall into the broad category of an unusual connective tissue disease subset characterised by brain or skin vasculitis.

The authors state that future work should be directed at a better understanding of the autoimmune response of (ME)CFS patients to other NE proteins.

1996

Randomized, double-blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndrome Benjamin H.Natelson et al
Psychopharmacology 1996:124: 226-230

The authors investigated the possibility that (ME)CFS was a disorder of reduced central sympathetic drive; their study allowed the authors to evaluate patients for a placebo effect: no evidence for this was found, suggesting that (ME)CFS is not an illness due to patients being overly suggestible, and negating the proposal by some investigators that (ME)CFS is not a disease at all but simply a form of aberrant illness behaviour related to the suggestibility of the patient.

The authors conclude that their results are certainly not consistent with what might be expected in suggestible patients with psychogenic illness.

The authors state that "no clear effect of any commercially available treatment has ever been demonstrated in this devastating illness".

1996

Cognitive Deficits in Patients with Chronic Fatigue Syndrome
Barbara Marcel Anthony L Komaroff et al
Biological Psychiatry 1996:40:535-541

"Subjects with (ME)CFS and healthy controls were administered a lengthy neuropsychological battery"

"The results indicate that (ME)CFS patients have a statistically signficiant impairment in learning and memory"

"It is also significant that impairments in memory, category fluency and word monitoring persisted even after test scores were covaried for psychiatric symptomatology in subjects"

"This suggests that cognitive dysfunction in (ME)CFS is likely to be related to mechanisms independent of any psychiatric symptoms".

1997

Evidence for enteroviral persistence in humans
Daniel N.Galbraith Carron Nairn Geoffrey B.Clements
Journal of General Virology 1997: 78:307-312

The authors present for the first time evidence for enteroviral persistence in humans based on sequence comparison of serial PCR products from the 5' non-translated region (NTR).

A group of (ME)CFS patients was being followed prospectively, and showed closely related enteroviral sequences containing a unique shared pattern detectable in sera of individual patients for up to 24 months, providing good evidence for viral persistence.

The sequences from the (ME)CFS patients form a group demonstrating a close genetic relationship with each other, and fall into a subgroup that is related to Coxsackie B viruses.

The authors point out that co-existence of populations of different enteroviral sequences has been shown in poliovirus where reversion of attenuated vaccine strains to a neurotropic type can occur in an individual.

1997

Biochemical Evidence for a Novel Low Molecular Weight 2-5A-Dependent RNase L in Chronic Fatigue Syndrome
Robert J.Suhadolnik Daniel L.Peterson Paul R.Cheney Kenny de Meirleir et al
Journal of Interferon and Cytokine Research 1997:17:377-385

Previous studies from this laboratory have demonstrated a statistically significant dysregulation in several key components of the 2' 5'A synthetase / RNase L and PKR antiviral pathways in (ME)CFS. The 2-5A synthetase *I* RNase L pathway is part of the antiviral defence mechanism in mammalian cells.

An accumulating body of evidence suggests that (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.

Marked and striking differences have been observed in the molecular mass and RNase L enzyme activity of 2-5A binding proteins in extracts of PBMC from individuals with (ME)CFS compared with healthy controls.

The authors present biochemical evidence for an RNase L enzyme dysfunction in (ME)CFS, in particular for an upregulated RNase L activity associated with (ME)CFS.

The biochemical and immunological data presented in this paper have identified a potential subgroup of individuals with (ME)CFS with an RNase L enzyme dysfunction that is more profound than previously observed in (ME)CFS, and which the authors believe is related to the severity of (ME)CFS symptoms.

1997

Elevation of Bioactive Transforming Growth Factor-ß in Serum from Patients with Chronic Fatigue Syndrome
Adrienne L.Bennett Dedra Buchwald Anthony L.Komaroff et al.
Journal of Clinical Immunology: 1997:17:2:160-166

The authors provide evidence that patients with (ME)CFS had significantly higher levels of bioactive TGF-ß levels compared to the healthy controls, to patients with major depression, patients with SLE, patients with relapsing/remitting multiple sclerosis and patients with CP (chronic progressive) MS, ie. that in patients with (ME)CFS, the levels were significantly higher compared to patients with various diseases known to be associated with immunologic abnormalities and / or pathologic fatigue.

The authors state that perhaps of greatest relevance to CFS are the effects of TGB-β on cells of the immune and central nervous systems, and the evidence that it may play a role in autoimmune and inflammatory disease.

1997

Cognitive Slowing and Working Memory Difficulties in Chronic Fatigue Syndrome
Paul S Marshall et al
Psychosomatic Medicine 1997:59:58-66

A battery of cogntivie function tests was given to (ME)CFS patients and controls.

"(ME)CFS patients did not qualify as having affectve disorder by several diagnostic criteria"

"These cognitive changes (might) have significant adverse consequences for effectiveness and productivity in many daily and work-related activities"

"These (ME)CFS patients had no history of major depression by extensive structured (DIS) interviews, psychometric evlaution, or medical history"

"(ME)CFS patients' pattern of ratings is much more like that of medically ill patients who experience a reactive depression".

1997

Elevated apoptotic cell population in patients with chronic fatigue syndrome: the pivotal role of protein kinase RNA A Vojdani CW Lapp et al
Journal of Internal Medicine 1997:242:465-478

The authors state that a prominent feature of (ME)CFS is a disordered immune system and recent evidence indicates that induction of apoptosis *(programmed cell death)* might be mediated in a dysregulated immune system by the upregulation of growth inhibitory cytokines.

The authors' results are in agreement with previous reports on abnormal cytokine production in (ME)CFS patients.

Quantitative analysis of apoptotic cell population in (ME)CFS patients has shown a statistically significant and marked increase compared with healthy controls. Such an abnormality in cell cycle progression is an indication of abnormal mitotic cell division.

Activation of PKR can result in inhibition of protein synthesis and induction of apoptosis, and activation of the PKR pathway could result from a dysregulated immune system or from chronic viral infection

"PKR-mediated apoptosis in (ME)CFS individuals may contribute to the pathogenesis and the fatigue symptomatology associated with (ME)CFS".

1997

Blunted serotonin-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome Timothy G.Dinan Tahir Majeed Peter Behan et al
Psychoneuroendocrinology 1997:22:4:261-267

The authors state that (ME)CFS is a clinically defined syndrome in which serotonergic activation of the HPA axis is defective, with the release of ACTH (but not cortisol) in response to ipsapirone challenge being significantly blunted, and that patients with (ME)CFS show disturbances of HPA function which differ markedly from those seen in melancholic depression.

The authors note that an increase in peripheral turnover of the major metabolite of 5HT might explain the heightened allergic responsiveness, as well as the musculoskeletal pain seen in CFS patients.

1997

Politics, Science, and the Emergence of a New Disease Leonard A.Jason Karen M.Jordan et al
American Psychologist:1997:52:9:973-983

This significant paper states that many physicians minimised the seriousness of (ME)CFS and interpreted the symptoms as being equivalent to a psychiatric disorder and the authors state that these attitudes have had negative consequences for the treatment of (ME)CFS

They point out that use of the original case definition of (ME)CFS and the type and scoring of psychiatric tests appear to have produced erroneous estimates of the extent of (ME)CFS comorbidity with psychiatric disorders.

The authors specifically mention the work of Wessely, pointing out that he was "influential", and also pointing out that Wessely's findings have led some to conclude that (ME)CFS is solely a psychiatric disorder.

The authors comment on "unfortunate biases" having been introduced, and they point out that the DIS (a structured psychiatric instrument designed for use in community surveys) has frequently been used to assess psychiatric comorbidity in (ME)CFS, when that instrument was not designed for use with *medically* ill populations.

The authors point out that high or low psychiatric rates in (ME)CFS samples may relate to whether symptoms are attributed by physicians to psychiatric or non-psychiatric cause.

The authors consider methodological problems with the "broadened" case definition (as advocated by Wessely et al to include all cases of unexplained "fatigue" lasting for at least one month), and point out that by broadening the (ME)CFS definition, it is important to ensure that those patients with solely a psychiatric disorder are not erroneously included within the (ME)CFS rubric, as to do so could seriously complicate the interpretation of epidemiological and treatment studies.

Professor Jason points out that some (ME)CFS investigators would not see this as a confounding problem because they believe that high rates of psychiatric comorbidity indicate that (ME)CFS is mainly a psychiatric disorder.

The authors urge caution with graded exercise regimes in (ME)CFS, saying that for those (ME)CFS individuals who do not have psychologically mediated reductions in activity, such a directed approach would be inappropriate and could even be counterproductive.

The authors point out that differences observed by investigators (named as Sharpe et al, a UK psychiatrist and close collaborator of Wessely) could well be due to Sharpe's focus on illness beliefs, so Sharpe's sample of CFS patients might have been less impaired than a severely ill group.

The authors re-iterate that biases in the scoring and selection of psychiatric tests contributed to high levels of psychiatric comorbidity in (ME)CFS claimed by this group of psychiatrists, and that these findings were possibly due to the psychiatrists' belief that (ME)CFS was predominantly a psychiatric rather than a medical disorder, and that the findings were influenced by "flawed epidemiological research".

The papers states "Other investigators, such as Wessely et al, believe that (ME)CFS represents an arbitrarily defined end point and that there are no clear cutoff points separating those with severe fatigue from (ME)CFS".

"Psychiatrists and physicians have also regarded fatigue as one of the least important of presenting symptoms (Lewis and Wessely, *1992).* These biases have been filtered to the media, which has portrayed (ME)CFS in simplistic and stereotypic ways".

The authors comment on the disregard of the *severity* of (ME)CFS symptoms; they conclude by commenting "We believe that it is crucial for (ME)CFS research to move beyond fuzzy recapitulations of the neurasthenia concept and clearly delineate precise criteria for diagnosing pure (ME)CFS".

1997

Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease
John de Luca Benjamin H.Natelson et al
JNNP 1997:62:151-155

The authors conclude that impaired cognition in (ME)CFS cannot be explained solely by the presence of a psychiatric condition and is contrary to expectations based on a model of "depression - induced" cognitive impairment in (ME)CFS.

"The results of the present study suggest that at least in a subgroup of patients, (ME)CFS is not simply a manifestation of a primary psychiatric disorder".

1997

Neuroendocrine correlates of chronic fatigue syndrome: a brief review Mark A Demitrack.
J Psychiat Res *1997:31:1:69-82*

The author begins his review by stating "Over time, it has not escaped the view of clinical authors that (ME)CFS and its historical antecedents shares many characteristics with endocrine disease states. Contemporary clinical research efforts have clearly documented that neuroendocrine disturbances are evident in patients with (ME)CFS".

"In almost all studies, at least 25% of subjects show no evidence, either past or current, for formally diagnosable psychiatric illness".

"Indeed, the accumulating body of evidence is contributing to a view of (ME)CFS as a disorder which is, in part, characterised by a novel dysregulation of the stress response".

The author surveys the published literature of neuroendocrine abnormalities in patients with (ME)CFS; he provides confirmatory support for an impairment of the HPA axis (consistent with the view that adrenocortical function is impaired); he notes the overall observation of reduced adrenocortical activation is a common feature to both fibromyalgia and (ME)CFS; he underlines the role of stress in the onset and course of (ME)CFS, and provides concluding remarks on the implications of this work.

1997

Epidemiological Advances in Chronic Fatigue Syndrome Paul H Levine
J Psychiat Res 1997:31:1:7-18

"Epidemiologic studies of (ME)CFS have been hampered by the absence of a specific diagnostic test. Working case definitions have not always been utilized precisely by various investigators. The separation of those patients with and without pre-existing depression and other psychologic diagnoses that are not exclusive to (ME)CFS continues to be of major importance".

The author comments specifically on the fact that all physical findings were dropped from the CDC 1994 case definition of CFS *(note that UK psychiatrist Michael Sharpe is a named co-author of this revised definition and that Simon Wessely is listed as being a member of the International Chronic Fatigue Syndrome Study Group who produced the CDC 1994 definition)*

Levine states: "Not surprisingly, the differences among these and earlier studies persist due to the different populations evaluated".

This author (as others) notes that "The effect of stress on the neuroendocrine and immune function is being increasingly well characterised".

He states: "The data suggest a poorer prognosis in those with more severe debilitation for a prolonged period of time".

This author is another to comment specifically that "The importance of the definition of subgroups is apparent. The heterogeneity of the disorder clearly highlights their existence".

Professor Levine points out that "The most important risk factors for (ME)CFS continue to be gender and a recent history of severe stress".

1997

Precipitating Factors for the Chronic Fatigue Syndrome Irving E Salit.
J psychiat Res 1997:31:1:59-65

This author also points out that "Stressful events were very common in the year preceding the onset of (ME)CFS". He concludes by stating "Even more compelling is the evidence that (ME)CFS can and does occur after physically traumatic events such as motor vehicle accidents".

1997

Visual Dysfunction in Chronic Fatigue Syndrome Lesley Vedelago
Journal of Behavioural Optometry 1997:8:6:149-153 (Reproduced in the CFS Research Review:2000:4-9)

"There are few references in the literature to visual and/or ocular disturbances in (ME)CFS, even though visual problems are common. It becomes very obvious when working with these patients that the ocular system is very much affected by, and turn affects, this systemic condition"

"The visual symptoms typically encountered with (ME)CFS include: blurred or foggy vision (distance or near); difficulty focusing from distance to near or near to distance; inability to focus on objects, particularly near; difficulty tracking lines of print; diplopia or ghosting of images; problems with peripheral vision; misjudging distances; inability to tolerate looking at moving objects; spots, flashes of light, floaters and halos; intolerance to light (glare); gritiness, burning, dryness or itchiness; eyes becoming sore as the day wears on"

"Objective ocular findings: upon examination, findings may include poor oculomotor control; saccades (rapid intermittent eye movements made as the attention switches from one point to another) -- these normally quick eye movements are very slow, with marked jerkiness; conscious effort goes into changing visual fixation; pursuits (tracking an object) are not smooth and cannot be done quickly; exophoria (the tendency for one eye to diverge when the other eye is covered); remote near-point convergence (this may be quite painful in ME/CFS); poor convergence at near; constricted peripheral fields; slow and incomplete blinking; small pupils; tear film and ocular surface abnormalities; visual mid-line shift (a neurological event interferes with vision processing from only one side of the body, and patients tend to have poor balance and tend to lean to one side or the other; nystagmus"

"Because (ME)CFS is an illness of increasing prevalence, it is important that eye specialists are not only fully informed about the condition itself, but also cognizant of the ocular/visual disturbances".

1997

The Quality of Life of Persons with Chronic Fatigue Syndrome JS Anderson CE Ferrans
The Journal of Nervous and Mental Disease l997:185:5:359-367

The purpose of this study was to explore the quality of life (QOL) of persons with (ME)CFS.

Over all scores on the quality of life index, people with (ME)CFS were significantly lower than for other chronic illness groups.

The authors conclude that "The findings suggest that quality of life is particularly and uniquely disrupted in (ME)CFS".

The authors note that there has been little research into this aspect, and their study revealed that 90% of their sample group experienced frequent feelings of isolation, alienation and inadequacy due to (ME)CFS.

They warn that what may be considered a disability for one person may be merely a nuisance for another, and they point out that the quality of life index (QLI) is one of the few available instruments which takes account of this phenomenon, and that the reliability and consistency of the QLI is well established.

All participants stated that (ME)CFS had had a profound impact on every aspect of their lives in ways they had never imagined possible.

All participants related profound and multiple losses, including the loss of jobs, relationships, financial security, future plans, daily routines, hobbies, stamina and spontaneity, and even their sense of self because of (ME)CFS. Activity was reduced to basic survival needs in some subjects.

These profound losses significantly affected the participants' mental health and outlook for the future.

Participants had difficulty in describing their illness because of the marked variability in symptoms.

Symptoms were reported to be multiple, diverse, variable and pervasive. Participants reported that symptom variability tended to impede diagnosis and credibility and made it difficult for them to adjust and cope with the illness.

Symptom variability also made it impossible for those with (ME)CFS to predict their level of functioning, which interfered with efforts to plan activities. For this reason, symptom variability was regarded as an especially frustrating aspect of (ME)CFS, and the uncertainty was one of the most difficult aspects of CFS to deal with.

Patients reported that they were exhausted and could not function, and that "it never goes away".

All participants (100%) felt that (ME)CFS had devastated social relationships and activities: "Friends of 15 years stopped returning my calls and quietly disappeared". A third reported that they had lost most, if not all, of their previous friendships; 18% currently had no friends whatsoever. Several participants reported that they had no family.

The authors conclude that the extent of the losses experienced in (ME)CFS was devastating, both in number and in intensity.

Participants described a sense of hopelessness that was integral to the illness due to symptom variability, length of illness and repeated relapses. Over time, those who were initially optimistic became emotionally exhausted.

Patients were particularly concerned about their long-term financial needs.

The authors note that such fatigued patients may lack the energy to seek out social support, and they may lack the energy to maintain existing relationships.

The authors found that the impact of (ME)CFS on patients' life was so total and so devastating that participants had difficulty in accepting their illness and its consequences.

The authors conclude by stating "(ME)CFS is a poorly understood and often trivialized illness, which in reality causes marked disruption and devastation".

1997

A 56 year old woman with Chronic Fatigue Syndrome: Clinical Crossroads:
Conference Report. Anthony L Komaroff
JAMA, 1997: 278:14:1179 -1185

(This conference took place at the Medicine Grand Rounds of the Beth Israel Deaconess Medical Center, West Campus, Boston, Mass. on June 11th 1997.Dr Komaroff is Professor of Medicine, Division of General Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, Mass. He is a world acclaimed expert on ME/CFS)

Dr Komaroff told the Conference that two themes emerge: (i) the enormous frustration of suffering from an illness that is poorly understood and (ii) the loss of legitimacy that a patient with (ME)CFS feels.

He explained that (ME)CFS is not just a state of chronic fatigue (such as many people experience), but a truly debilitating state, associated with impaired memory / concentration, sore throat, adenopathy, myalgias, arthalgias, new headache, unrefreshing sleep, postexertional malaise, anorexia, nausea, drenching night sweats, intolerance of alcohol and pharmaceuticals that affect the central nervous system, and dizziness.

He reminded those present that objective, biological abnormalities can be found in patients with (ME)CFS, and that the medical literature of the past decade indicates that there are indeed such abnormalities.

Komaroff made the point that it is now evident that this illness is not simply an imaginary one, nor the result of anxiously amplifying normal bodily sensations. Komaroff dealt with the evidence of central nervous system (CNS) involvement in (ME)CFS: in his experience, a majority of (ME)CFS patients have symptoms which could reflect an underlying CNS process, for example, difficulty with memory, concentration and balance; photophobia and paraesthesias; in addition, substantial objective evidence of abnormalities in the CNS is now available: MRI scans have revealed areas which may represent inflammation and / or demyelination.

Komaroff told the Conference that the signal abnormalities in (ME)CFS patients "most closely resemble those seen in AIDS encephalopathy".

Autonomic nervous system testing "frequently reveals abnormalities of the sympathetic and parasympathetic systems".

Komaroff then dealt with the evidence of chronic immune activation in (ME)CFS: he discussed this evidence, and concluded that a state of chronic immune activation could lead to the production of cytokines that disrupt neurotransmitter function, resulting in the symptoms of (ME)CFS.

He made the point that the state of chronic immune activation in (ME)CFS suggests the possibility of a chronic infectious process, saying that some physicians (including himself) believe that infectious agents may trigger and even perpetuate the symptoms of (ME)CFS; he referred to the evidence for a chronic viral infection as demonstrated by Suhadolnick, which showed an abnormality in an antiviral lymphocyte enzyme system (2-5A pathway), which is found to be chronically activated in patients with (ME)CFS.

Komaroff referred to the findings that many (ME)CFS patients have experienced atopic symptoms from childhood, and that the atopic symptoms often flare up in (ME)CFS.

Komaroff stated that perhaps the most important nonpharmacologic intervention was to encourage patients to avoid physical or emotional stress, and to pace themselves.

He stated that it is antitherapeutic for the clinician to dismiss any patient's symptoms out of hand, especially in (ME)CFS, which is a "de-legitimating illness", as "patients often experience rejection by family, friends and physicians. The illness is hardly 'imaginary'".

1997

Chronic Fatigue Syndrome: A Challenge to the Clinical Professions
Derek Pheby (Director, Unit of Applied Epidemiology, University of the West of England, Bristol, UK)
Physiotherapy: 1997:83:2:53-56

"No-one who has experienced this illness, or who has had the responsibility of caring for a family member who has had the misfortune to suffer from it, can have any doubt not only about the extent of the real pain,

suffering and distress that it can cause, but also as to the disastrous effect it can have on social relationships and life in the community".

"The most seriously affected individuals may be bed-ridden most or all of the time and can do little or nothing for themselves".

"In this illness, 'recovery' is very much a relative term: in follow-up studies, after 48 years *(sic)*, eight out of ten patients continued to have some form of disability (Hyde & Bergman 1991). This is in line with Ramsay (1986) who wrote that complete recovery is confined to one third of cases".

"Recent research has made it clear that the view that there were no specific changes demonstrable in patients with (ME)CFS has become untenable".

"The disturbances to the HPA axis in (ME)CFS differ markedly from those found in depression, as do brain vascular perfusion patterns".

"The overall costs associated with the syndrome are likely to be around £90 million per year (National Task Force Report, 1994, page 21). Given the tendency to chronicity, much of this cost is due to the need for long - term supportive care of patients".

"CFS/ME is a major challenge to all health care professionals".

1997

Chronic Fatigue Syndrome —aetiological aspects Dickinson CJ
Eur J Clin Invest: 1997:27:4:257-267

"There is some evidence both for active viral infection and for an immunological disorder in (ME)CFS. Many observations suggest that the syndrome could derive from residual damage to the reticular activating system (RAS) of the upper brain stem and / or to its cortical projections"

"Regional blood flow studies by SPECT have been more consistent (and) have revealed blood flow reductions in many regions, especially in the hind brain. Similar lesions have been reported after poliomyelitis and in multiple sclerosis —in both of which conditions fatigue is characteristically present".

1997

Cardiac Involvement in Patients with Chronic Fatigue Syndrome as Documented with Holter and Biopsy Data in Birmingham, Michigan, 1991 - 1993 A. Martin Lerner et al
Infectious Diseases in Clinical Practice 1997:6:327-333

This study reports the prevalence of abnormal oscillating T-waves on Holter 24 hour monitoring in a consecutive case series of 67 (ME)CFS patients.

Resting 12 lead ECGs were normal, with the presence of labile T-wave abnormalities coming to light only with 24 hour Holter monitoring.

Repetitive T-wave flattening was a sensitive indicator of the presence of (ME)CFS, as every (ME)CFS patient (but only 22.4% of the controls) showed abnormal flattening or inversion on Holter monitoring.

Abnormal cardiac wall motion (at rest and on stress), dilatation of the left ventricle and segmental wall motion abnormalities were present. (Normal left ventricular resting ejection fraction is 50%, but in (ME)CFS, the left ventricular ejection fraction — at rest and with exercise — of as low as 30% was seen).

Abnormal T-wave oscillations (T-wave flattening or inversion) of at least 25 normally conducted beats were necessary to be considered abnormal; they frequently appeared only with the advent of sinus tachycardia.

Two cardiologists unaware of the position of the patients reviewed the Holter tracings.

"This study confirms our earlier report (see *following item)* that (ME)CFS patients uniformly have abnormal oscillating T-wave flattenings and T-wave inversions by Holter monitoring"

"As described here, abnormal Holter monitoring is important to the explicit diagnosis of patients with (ME)CFS (and) are a characteristic of (ME)CFS (and) appear to be an essential element to the pathologic physiology of the cardiomyopathy of (ME)CFS".

1997

New Cardiomyopathv: pilot study of intravenous gangiclovir in a subset of the chronic fatigue syndrome.
Lerner AM et al
Infectious Diseases in Clinical Practice 1997:6:2:110-117

This study involved a subset of (ME)CFS patients with oscillating repetitively abnormal aberrant T waves on Holter 24-hour electrocardiogram (ECG) recording.

None of these patients could work or manage a household.

The type of abnormalities documented in the cardiac study "are not seen in normal persons leading a sedentary life".

1997

Does the chronic fatigue syndrome involve the autonomic nervous system?
Freeman R and Komaroff AL
American Journal of Medicine 1997:102:4:357-364

The aim of this study was to investigate the role of the ANS (autonomic nervous system) in the symptoms of (ME)CFS patients (selected if they had one of three criteria indicating ANS dysfunction).

The (ME)CFS subjects had significant increase in baseline and maximum heart-rate on standing and tilting.

Tests of the parasympathetic nervous system function were significantly less in the (ME)CFS group, as were measures of sympathetic nervous system function.

Deconditioning alone did not fully explain the documented ANS abnormalities.

89% of patients reported that an infectious illness had preceded the onset of (ME)CFS, and in 46%, the ANS symptoms occurred within four weeks of the infection. The authors described "a temporal pattern that is consistent with a postviral, idiopathic autonomic neuropathy".

Symptoms of ANS dysfunction are not related to psychiatric disorder.

1997

A population-based incidence study of chronic fatigue
Lawrie SM, Pelosi AJ et al
Psychological Medicine 1997:27:343-353

Longitudinal studies using appropriate measures have shown that physical attributions do not affect outcome.

1997

Exercise limits in chronic fatigue syndrome Lapp C. (Charles Lapp is Professor of Community Medicine at Duke University, Charlotte, North Carolina, USA)
American Journal of Medicine 1997:103:83-84

This reports a trial involving 31 consecutive new (ME)CFS patients, which allowed them to reach their maximum oxygen consumption within 8 - 10 minutes of exercise.

The results showed that 74% of patients experienced worsening fatigue. None improved.

The average relapse lasted 8.82 days, although 22% were still in relapse at 12 days (when the study ended).

These findings suggest that, pushed to maximal exertion, patients with (ME)CFS may relapse.

1997

Chronic Fatigue Syndrome: A Disorder of Central Cholinergic Transmission
A Chaudhuri T Dinan et al
JCFS 1997:3(1):3-16

"Chronic Fatigue Syndrome is a clinical disorder that is increasingly recognized in most countries as a major health hazard. Its classical clinical feature is fatigue associated with sleep abnormalities, difficulties concentrating, memory impairment and myalgia"

"To this may be added a constellation of other symptoms, including atypical chest pain, gastrointestinal motility disorders, unexplained attacks of sweating and light headedness. The fatigue is clinically identical to that found in multiple sclerosis, Parkinson's disease, Alzheimer's disease, post-polio syndrome and the fatigue that may follow posterior head injury"

"The sleep abnormality is similar to that described in patients with acquired autoimmune myasthenia gravis.

"Abnormalities in muscle, neuromuscular transmission, heart and resting energy expenditure have been found in patients with (ME)CFS"

"These abnormalities may well be secondary to a primary abnormality of central cholinergic transmssion"

"We tested this hypothesis using a neuroendocrine challenge paradigm (and) have shown that the pathogenesis involves up-regulation of post-synaptic cholinergic receptors".

1997

Arguments for a Role of Abnormal Ionophore Function in Chronic Fatigue Syndrome
Abhijit Chaudhuri et al
In: Chronic Fatigue Syndrome, Ed: Yehuda and Mostofsky; Plenum Press, New York, 1997

"Chronic fatigue syndrome is a disorder that is now receiving world-wide attention from the scientific and medical communities"

"All (study participants) had several features which should be stressed, namely, the illness was fluctuating and made worse by exercise"

"Myocarditis, with or without Bornholm-type was a common symptom in an analysis of 1,000 patients of (ME)CFS who were seen in Glasgow over the past 20 years. Several of our patients were referred by cardiologists. Various aetiologies for non-cardiac chest pain have been proposed, including oesophageal reflux and spasm, chest wall pain and microvascular coronary artery disease. We were struck by the often occurring association of patients who develop (ME)CFS with acute chest pain resembling coronary thrombosis. Nuclear magnetic resonance spectroscopy studies of skeletal muscle in patients with syndrome X are identical to those found in patients with (ME)CFS. Waldenstrom et al have suggested that there are abnormal ionophores in the skeletal muscle and cardiac cells of patients with syndrome X.

"There has been anecdotal evidence that some patients with (ME)CFS who presented to cardiologists with chest pain have abnormal thallium-201 SPECT scans (and this) prompted us to carry out cardiac thallium-201 scans on a small group of ME/CFS patients.

"Image analysis revealed moderate defects in the left ventricle of 7 of the 10 patients. This was shown to be significantly different from the expected incidence of abnormal results (and) here again we have similar results in (ME)CFS and syndrome X.

"Additionally, the TBK (total body potassium) results for the (ME)CFS patients were significantly lower than those for controls (which) fits with the hypothesis of abnormal ionophore formation (and) evidence is now accruing that patients with (ME)CFS might have a reduced TBK (which) would probably be a result of an abnormality of membrane permeability consequent to abnormal ionophores"

"These fit well with the other metabolic abnormalities of (ME)CFS patients"

"It is plausible that the defect in (ME)CFS lies at the cellular level in view of the widespread symptomatology so commonly found in this condition"

"There is compelling data to show that a number of different noxae can precipitate (ME)CFS. These include viruses, exposure to organophosphates, and incapacitating stress. It may also occur as a result of exposure to other toxins"

"We propose that ion channels, eg. potassium, sodium or even calcium channels are affected in patients with ME/CFS following exposure to viruses and organophosphates"

"It may not be in the too distant future when (ME)CFS would be considered as an example of channelopathy like many other neurological diseases".

1997

Anaesthesia in the Allergic Patient
Honor Anthony, Sybil Birtwhistle, Keith Eaton, Jonathan Maberly
In: Environmental Medicine in Clinical Practice: BSAENM Publications, 1997: ISBN 0 9523397 2 2

"Patients with Type B allergies, especially those with chemical sensitivity, commonly give a history of slow recovery after an anaesthetic, (with) prolonged severe malaise, nausea, vomiting, pain and other symptoms"

"The risk of reactions is higher in patients who have other evidence of chemical sensitivity, and thiopentone and suxamethonium are best avoided"

"Of the intravenous induction drugs, thiopentone should eb avoided because it can cause anaphylaxis"

"Propofol is an emulsion made up in egg and soya and should be avoided in patients known to be sensitive to these foods"

"Of the inhalation anaesthetics, halothane and enflurane cause more trouble"

"Morphine and pethidine should normally be avoided as they tend to release histamine".

1998

Cardiovascular responses during a cognitive stressor before and after exercise in chronic fatigue syndrome versus sedentary healthy subiects SA Sisto B Natelson et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS. Mass. USA 1998: Abstract:page 48

Patients with (ME)CFS complain of cognitive difficulties that worsen after exercise.

The purpose of this study was to determine if patients with (ME)CFS have similar cardiovascular responses (compared with sedentary controls) during a cognitive test battery, both before and after exercise.

The (ME)CFS group demonstrated a significantly lower change in systolic blood pressure compared with the sedentary controls.

Exercise produces the expected attenuation of the cardiovascular responses in the healthy group, but not so for the (ME)CFS patients.

This hypo-responsiveness may, in part, be responsible for (ME)CFS patients reporting detrimental effects of periods of psychological stressors or excess physical exertion.

1998

CFS severity is related to reduced stroke volume and diminished blood pressure responses to mental stress
Arnold Peckerman Bejamin Natelson et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS, Mass. USA 1998: Abstract page 47

One plausible hypothesis of the pathophysiology of (ME)CFS is a disorder of circulation.

The present study examined whether cardiovascular homeostasis at rest and centrally-mediated haemodynamic responses to behavioural challenges are altered in (ME)CFS.

The results showed that in (ME)CFS patients, a lower stroke volume was highly predictive of illness severity: across three different postures, the most severely affected (ME)CFS patients were found to have a lower stroke volume and cardiac output compared with those with more moderate illness.

These findings suggest a low flow circulatory rate in the most severe cases of (ME)CFS; this may indicate a defect in the higher cortical modulation of cardiovascular autonomic control.

In the most severely affected, situations may arise where a demand for blood flow to the brain may exceed the supply, with a possibility of ischaemia and a decrement of function.

1998

Respiratory symptoms and lung function testing in CFS patients P de Becker, K de Meirleir et al *Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS. Mass. USA 1998: Abstract page 104*

The purpose of this study was to report the prevalence of respiratory symptoms in a cohort of (ME)CFS patients.

The following respiratory symptoms were observed: cough, chest tightness, medical history of allergy, new onset of allergy; the major respiratory complaint was found to be a pronounced exercise-induced dyspnoea.

In 60% of (ME)CFS patients, a marked bronchial hyper-responsiveness was present. (Bronchial hyper-responsiveness was defined as PD 20 *his* < 2 mg histamine).

(ME)CFS patients show a significant decrease in vital capacity (VC), possibly due to a significant increase of residual volume (RV).

The incidence of bronchial hyper-responsiveness in this group is remarkably high.

These observations can, at least partially, explain the respiratory symptoms in these patients.

1998

Chronic Fatigue Syndrome: An Update A.L.Komaroff D.S.Buchwald
Annu Rev Med 1998:49:1-13

Studies indicate that the illness is not simply a manifestation of an underlying psychiatric disorder, but rather is an illness characterised by activation of the immune system, various abnormalities of several hypothalamic pituitary axes and reactivation of certain infectious agents.

The most robust findings are increased numbers of CD8+ cytotoxic T cells that bear antigenic markers of immune activation on their cell surface, and depressed function of natural killer lymphocytes.

Other reported findings of immune activation are elevated levels of circulating immune complexes and immunoglobulin G, and higher frequencies of various autoantibodies.

More circumstantial evidence of a chronic viral infection in many (ME)CFS patients comes from reports of an abnormality in an antiviral lymphocyte enzyme system (the 2-5A pathway) which appears to be chronically activated in patients with (ME)CFS.

These reports provide strong evidence that (ME)CFS can be triggered by an acute infection that has the capacity to produce a chronic infection.

This paper concludes by affirming that **"there is growing evidence that abnormal, objective biologic processes are present in many patients with (ME)CFS -- in particular, subtle abnormalities of the central nervous system, chronic activation of the immune system, and reactivation of several latent viruses".**

1998

Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome
Russell JM Lane Leonard C Archard et al
JNNP 1998:64:362-367

The object of this study was to examine the proportions of types I and II muscle fibres and the degree of muscle fibre atrophy and hypertrophy in patients with (ME)CFS in relation to lactate responses to exercise, and to determine to what extent any abnormalities found might be due to inactivity.

Muscle fibre histometry in patients with (ME)CFS did not show changes expected as a result of inactivity.

The authors note that one of these patients had an inflammatory infiltrate, and it would seem that inflammation and class I MHC expression may occur in biopsies from patients with (ME)CFS.

The authors note that this is of some interest, as they have argued previously that some forms of (ME)CFS may follow a previous virally-mediated inflammatory myopathy.

1998

On symptoms and life events surrounding the onset of chronic fatigue syndrome
Evengard B et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS, Mass. USA: 1998: Abstract page 32

This study was aimed at describing the sequence of psychosocial events and infections preceding the onset of (ME)CFS (related to the temporal development of crucial symptoms).

Sixty seven percent of the (ME)CFS patients had a clearly negative life event preceding infection, which preceded (ME)CFS onset.

1998

Gastrointestinal Manifestations of Chronic Fatigue Syndrome: Symptom Perceptions and Quality of Life
Herbert Hyman Thomas E Wasser
JCFS 1998:4(1):43-52

The authors conclude that the classification of irritable bowel syndrome (IBS) should be modified to include a subset of patients who have a combination of (ME)CFS and lBS.

They enumerate not only functional gastrointestinal (GI) complaints, but also other abdominal complaints, particularly neurologic.

They point out that in (ME)CFS, immunologic abnormalities are regularly found, and that there are more lymphocytes associated with the Gl tract than any other site in the human body.

Since the gut mucosa contains immunologically active lymphoid tissue, the authors believe that a pattern of immune dysfunction exists in (ME)CFS in which immune products are transmitted to the gut via the lymphatic system, reacting on both the lumenal contents and intestinal motor system, and that the GI lymphatic system not only has an effector function, but also transmits characteristic (ME)CFS immune dysfunction to other organs.

The authors also suggest that oral antigens could be similarly effective in (ME)CFS patients by way of the immunological activity of the gut mucosa.

Some (ME)CFS patients had abdominal wall pain due to unilateral segmental neuropathy.

In summary, this study demonstrated three primary findings: (i) (ME)CFS patients showed significantly more symptom dysfunction than those in the functional bowel disease (FBD) group; (ii) (ME)CFS patients had significantly lower Quality of Life scores than the FBD group and (iii) since differences occur between (ME)CFS and FBD patients, the classification of lBS should be modified to include a subset of patients who have a combination of (ME)CFS and lBS.

1998

Chronic Fatigue Syndrome in Children and Adolescents: A Review
Karen M Jordan Leonard A Jason et al
Journal of Adolescent Health 1998:22:4-18

The majority of studies concerning (ME)CFS have concentrated on adults, but the illness does strike younger individuals, and the case definitions do not address the appropriateness for the paediatric population. The lack of specificity to the unique characteristics of children and adolescents is pervasive in much of the research literature.

Several authors reported a preponderance of acute onset with viral-type illness in children and adolescents.

Many previous epidemiological studies (one of Wessely's studies is cited) have relied on physician referral, when (those) physicians are sceptical of the validity of (ME)CFS as a true illness.

Repetitive treatment-seeking is often necessary before a diagnosis of (ME)CFS is made: children may be less able to seek care persistently, so the prevalence rate in those under 18 years has undoubtedly been minimised.

The authors describe the Cheney proposition *(Cheney PR. Proposed pathophysiological mechanism of CFIDS. CFIDS Chronicle: 1994:7: 1-3)* that the common symptoms of (ME)CFS (eg. hyperreflexia, abnormalities of vestibular function, palpable and slightly enlarged discoid shaped lymph nodes, predominantly left-sided tender posterior and cervical lymph nodes) suggest a connection between immune activation and central nervous system injury: as alpha-interferon can be neurotoxic, particularly to the limbic structure and the serotonergic pathways (via opioid receptors), this may account for the abnormalities in corticotrophin-releasing hormone (CRH), and these deficiencies then contribute to a positive feed-back loop which maintains immune activation.

In addition, the decrease in TRH production could lead to reduced cellular metabolism, including impaired oxygen consumption during exercise, which is consistent with mitochondrial dysfunction.

The authors note that there has been minimal controlled study of psychiatric status for children and adolescents with (ME)CFS. However in one study, adolescents with (ME)CFS received higher scores of

psychiatric comorbidity, but on further examination of the somatic complaint items, it was found that this scale was confounded by the presence of many items related to (ME)CFS symptoms (eg. headaches, pain and feeling sick).

The authors state that the overlap of (ME)CFS symptoms with those of psychiatric disorders has been found to lead to an overdiagnosis of psychiatric disorder in adult (ME)CFS populations.

The authors note that a list first supplied by Komaroff provides four discriminating characteristics of fatigue and symptoms which should assist the clinician in distinguishing between (ME)CFS and malingering or somatoform disorders, and these include symptoms which are rarely found in paediatric general practice.

The authors note that the perceived causal role of depression in (ME)CFS may have been inflated in some studies owing to frequent errors.

They note that the Diagnostic and Statistical Manual (DSM) IV criteria for depression do not include any of the primary complaints of patients who present with (ME)CFS.

Further, the DSM IV criteria for somatisation do not mention fatigue symptoms.

The DSM IV states that individuals with somatisation disorder describe their complaints in a colourful, sensational and emotional manner, with specific factual information missing.

On the contrary, people with (ME)CFS describe their symptoms clearly and concisely.

Minimal work has been done in the formal assessment of coping with illness, level of disability or quality of life issues in children and adolescents with (ME)CFS.

Paediatric patients may require assistance obtaining special services or accommodations from their school.

The authors note that several authors (Sharpe and Wessely are named) have proposed the use of cognitive behavioural therapy (CBT), and note that while the Sharpe study may be criticised for its poor subject selection methods, no other studies have reported the effectiveness of CBT with child or adolescent populations.

Several authors have conducted follow-up studies with paediatric (ME)CFS patients; most reported improvement or recovery in over 50% of the patients studied, but the present authors note that some children continued to experience significant disability, and that it is possible these children who do not improve represent a unique subset of paediatric (ME)CFS, perhaps having a more severe form of the illness, including more severe neurologic symptoms such as myoclonus, paraesthsia and seizure-like episodes.

Much of the current literature is confused by the lack of paediatric case definition.

(ME)CFS in children and adolescents remains dramatically understudied.

It is imperative that criteria specific to children and adolescents be adopted and used as a standard in future research.

1998

Severe CFS/ME of Juvenile Onset
R Gibbons, DFH Pheby, C Richards, FI Bray
JCFS 1998:4:4:67-80

"The modal age of onset for this severe group of patients was 11 – 15"

"A relatively larger proportion of the affected child population develop more serious forms of the disease, which may become chronic and lead to severe disability"

"There is a marked tendency towards deterioration (and this) underlines the case for special attention to be given to this particular group of patients, in resource allocation, in planning and providing services to meet their needs, and in the training of health, social care and education professionals involved in their care".

1998

Brain SPET in Chronic Fatigue Syndrome D.di Giuda D.Racciatti et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS, Mass. USA: 1998: Abstract page 112

(ME)CFS is a severely disabling illness.

This study was designed to investigate possible changes in the brain perfusion of patients with (ME)CFS.

Regional brain perfusion impairment (mainly hypoperfusion) was found in 83.9% of (ME)CFS patients.

In 30.8%, a concurrent fibromyalgia syndrome was present. A total of 147 brain regions showed abnormal 99mTc-HMPAO uptake.

This study confirmed previous reports of brain perfusion impairment in (ME)CFS, providing objective evidence of central nervous system dysfunction.

1998

Impaired associative learning in chronic fatigue syndrome Servatius RJ Natelson BH et al
Neuroreport: 1998:9:1153-1157

The researchers tested patients with (ME)CFS in protocols designed to measure memory reactivity and acquisition of the classically conditioned eyeblink response.

The authors conclude that their data suggest organic brain dysfunction within a defined neural substrate in (ME)CFS patients.

1998

Relationship between SPECT scans and buspirone tests in patients with ME *I*CFS
Richardson J Costa DC
JCFS 1998:4:3:23-38

The SPECT scans revealed that all (ME)CFS patients studied had hypoperfusion in the brain: 62% in the brain stem and 51% in the caudate nuclei.

According to the researchers, these findings provide "actual evidence of neurological dysfunction" in (ME)CFS.

1998

Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data
Tirelli U. et al
American Journal of Medicine 1998:105:3A: 54s-58s

The PET images examined 22 cortical and subcortical areas. PET is better than SPECT at detecting small structures such as the brain stem.

The scans revealed significantly reduced glucose metabolism in the brainstem of patients with (ME)CFS compared with depressed patients and healthy controls. The area particularly affected in the brainstem was the pons. There was also significant hypometabolism in the right mediofrontal cortex in the (ME)CFS patients.

Hypometabolism of the brainstem has not been documented in any psychiatric disorder assessed to date.

1998

Neurally Mediated Hypotension and Chronic Fatigue Syndrome
Peter C Rowe Hugh Calkins
Am J Med 1998:105: (3A):15S-21S

This article discusses selected issues in the clinical overlap of (ME)CFS and autonomic dysfunction.

The authors note that frequently in (ME)CFS, patients have symptoms of lightheadedness (88%); cognitive difficulties / problems thinking and concentrating (47%); blurred vision (47%); tremulousness (38%); pallor (31%) and anxiety (29%), and that these neurocognitive symptoms have been attributed to cerebral hypoperfusion.

That fatigue can be associated with neurally mediated hypotension has been appreciated since 1932, when Sir Thomas Lewis demonstrated that a long period of fatigue could follow a single episode of vasovagal (or neurally mediated) hypotension.

One of the patients who prompted the authors' investigation was a 16 year old girl who described becoming tired, shaky, lightheaded and pale after walking more than 10 minutes: one notable physical finding was that her legs and arms developed a purple discolouration after a short period of quiet standing, which is indicative of abnormal venous pooling.

In this study, all the (ME)CFS patients but none of the controls developed orthostatic symptoms during the first stage of the testing, suggesting that orthostatic intolerance may be a defining feature of (ME)CFS.

Three factors which predispose to the development of NMH are a low resting blood volume, excessive pooling of blood in the dependent vessels, and excessive loss of plasma volume during upright posture, all of which can decrease venous return to the heart.

In those with abnormal responses to upright tilt, when cardiac output is consequently decreased, there seems to be a failure to mobilize blood effectively from the dependent splanchnic and limb vasculature: several groups have identified impaired vasoconstrictor responses in the forearm and splanchnic bed, and in microvascular flow to the skin.

Among the neuroendocrine changes that accompany the orthostatic intolerance are an increase in epinephrine, vasopressin, ß-endorphin and vasoactive intestinal polypeptide.

Factors that can contribute to early activation of the vasovagal reflex include stress and sodium depletion.

Conditions with an increased histamine release can also cause a decreased return of blood to the heart.

Such an inappropriate venous return could provoke worse orthostatic tolerance in response to common everyday cognitive stress, which could provide an explanation for why some patients describe worse fatigue after reading or concentrating.

Virtually *all* (ME)CFS patients (regardless of their haemodynamic response) have their symptoms provoked by standing upright.

The authors note that there is a high prevalence of allergic disease in those with (ME)CFS, and suggest that with an association between (ME)CFS and NMH, one would expect to find a mechanism by which allergic disease increases the activation of this reflex pathway: other workers have shown that both viral infection and allergic reactions to food antigens increase the excitability of mechanically sensitive vagal afferents in the airway.

The ability of allergen exposure to enhance the discharge of mechanically sensitive fibres, including C-fibres, provides a potential link between these clinical situations and the development of NMH in CFS patients with allergy, suggesting that efforts to prevent activation of NMH would need to prevent exacerbation of food and inhalant allergies in those with (ME)CFS.

1998

Low levels of serum acylcarntine in chronic fatigue syndrome and chronic hepatitis type C but not seen in other diseases Kuratsune H et al
International Journal of Molecular Medicine 1998:2:1:51-56

This study found significantly lower serum acylcarnitine (ACR) in (ME)CFS patients but not in controls.

It was not present in other medically ill populations such as patients with haematological malignancies, chronic pancreatitis, hypertension or diabetes.

ACR may have an effect as an antioxidant and may be linked to the production of cytokines.

These findings indicate that serum ACR deficiency may be a characteristic of (ME)CFS.

1998

Secretion of growth hormone in patients with chronic fatigue syndrome Berwaerts J et al
Growth Hormone and IGF Research 1998:8:127-129

Serum IGF-l was significantly lower in patients with (ME)CFS than in controls.

1998

Adrenal size in chronic fatigue syndrome Teh J Scott L Dinan E et al
Radiology 1998:209P (Suppl):411-412

A CT scan revealed that the right and left adrenal glands of (ME)CFS patients were reduced by 50% when compared with healthy people.

1998

Increased resting energy expenditure in the chronic fatigue syndrome
Watson WS Chaudhuri A Behan P0 et aI
JCFS 1998:4:4:3-14

When individual resting energy expenditure (REE) was predicted on the basis of total body potassium values, 45.5% of the (ME)CFS patients tested had resting energy expenditure above the upper limit of normal, suggesting that there is upregulation of the sodium-potassium pump in (ME)CFS.

There was no evidence that the results were due to lack of activity (which would have affected total body water estimates).

1998

Parallels between post-polio fatigue and chronic fatigue syndrome: a common pathophysiology?
Bruno RL et al
Am J Med 1998: 105 (3A) 66S-73S

Post-polio fatigue is characterised by subjective reports of difficulty with attention, cognition, and maintaining wakefulness. These symptoms resemble those reported in nearly two dozen outbreaks of post-viral fatigue syndrome (PVFS) that have recurred this century and which are related clinically, historically, anatomically or physiologically to polio virus.

This article reviews studies which relate the symptoms of post-polio fatigue and (ME)CFS to clinically significant deficits on neuropsychologic tests of attention, histopathologic and neuroradiologic evidence of brain lesions, impaired activation of the HPA axis, increased prolactin secretion, and EEG slow-wave activity.

A common pathophysiology for post-polio fatigue and (ME)CFS is described.

1998

Alteration of spatial-temporal parameters of gait in Chronic Fatigue Syndrome
Saggini R et al
J Neurol Sci 1998:154:1:18-25

(ME)CFS has been widely studied and a lot of information is available in the literature regarding immunological, virological, neuroendocrinal and psychiatric aspects of this disease, and great attention has been paid to the alteration of muscular function in (ME)CFS.

The aim of this work was to study the gait of (ME)CFS patients to see if there are objective measures which can better characterise the pathology.

Comparison with reference data from healthy controls revealed significant abnormalities.

The abnormalities were present as from the beginning of the gait, which indicates that they are unlikely to be caused by rapidly increasing fatigue.

These findings strengthen the notion of direct involvement of the central nervous system in (ME)CFS.

1998

A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome
Peterson PK et al
Arch Intern Med 1998:158: (8):908-914

At baseline, study participants reported symptom severity greater than 5 for most symptoms and all had evidence of marked functional impairment.

Five patients withdrew from the trial.

The incidence of adverse experience was similar in patients and controls.

The authors conclude that low dose fludrocortisone (0.1 - 0.2mg for six weeks) does not provide sufficient benefit to be evident in a blinded trial of unselected patients with (ME)CFS.

1998

Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomised controlled trial
Mckenzie R Dale J Demitrack M et al
JAMA 1998:280: (12): 1061-6

The object of this study was to evaluate the efficacy and safety of low-dose oral hydrocortisone as a treatment for CFS (oral hydrocortisone, 13 mg /m2 of body surface area every morning and 3 mg /m2 every afternoon for approximately 12 weeks).

The authors conclude that the degree of adrenal suppression precludes the practical use of hydrocortisone in (ME)CFS.

1998

Immunological Status Correlates with Severity of Physical Symptoms in Chronic Fatigue Syndrome Patients S Wagner N Klimas et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS 1998: Mass. USA. Abstract page 28

The purpose of this study was to investigate the relationship between immunologic status and physical symptoms in (ME)CFS patients.

The findings suggest that the degree of cellular immune activation is associated with the severity of (ME)CFS physical symptoms.

Specifically, elevations in the T-helper / inducer cells, activated T-cells, activated cytotoxic / suppressor T-cells, and CD4 / CD8 ratio are associated with greater disease severity.

Furthermore, reductions in T-suppressor / cytotoxic cells also appear related to greater severity of (ME)CFS physical symptoms and illness burden, suggesting that greater symptoms are associated with lower availability of regulatory T-cells.

1998

A study of the Immunology of the Chronic Fatigue Syndrome: Correlation of Immunologic Parameters to Health Dysfunction I.S.Hassan W.Weir et al
Clin Immunol lmmunopathol 1998:87:60-67

Surface and intracellular immunologic and apoptotic markers and functional lymphocyte assays after stimulation with anti-CD3 / anti-CD28 antibodies or phytohaemagglutinin (PHA) were studied.

Patients with increased HLA-DR expression had worse pain and poorer physical functioning scores.

The increased expression of Class II antigens and the reduced expression of the co-stimulatory receptor CD28 (which is a marker for terminally differentiated cells) lend further support to the concept of immunoactivation of T-lymphocytes in CFS and may be consistent with a viral aetiopathogenesis in (ME)CFS.

The authors demonstrated changes in different immunological parameters, each of which correlated with particular aspects of disease symptomatology and measures of disease severity.

1998

Co-incidental splenectomy in chronic fatigue syndrome Brian J Miller et al
JCFS 1998:4(1): 37-42

The authors describe the removal of a ruptured spleen in a female with (ME)CFS following a road traffic accident.

At operation, the splenic parenchyma was unusually spongy and friable.

There was a generalised infiltration of the splenic sinuses by atypical lymphoid cells. These cells appeared blastic and had large, vesicular nuclei, multiple large nucleoli and a moderate amount of dense, eosinophilic cytoplasm.

In immunohistochemical studies, they were strongly reactive for the T-lymphocyte markers CD45RO and CD43.

In addition to this cellular infiltrate, there was a reduction in the volume of the white pulp.

Histological examination of the spleen revealed chronic inflammatory changes of uncertain aetiology.

These histopathological changes in the spleen of a patient with (ME)CFS have not been described before.

The reduction in white pulp and infiltration of the splenic sinuses by atypical lymphoid cells are not features of traumatic rupture, and suggest a chronic inflammatory process likely to be associated with (ME)CFS.

(At the Second World Congress on Chronic Fatigue Syndrome and Related Disorders, Brussels, 9-12th September 1999, Dr L Lambrecht from Belgium spoke on "Chronic Fatigue Syndrome: Clinical, Immunological and Neuroimaging Correlations in 500 Patients', noting that splenomegaly was reported in 29% of CFS patients, saying that this finding has not previously been reported – which was not quite accurate, since there are reports of splenomegaly in the early literature).

1998

T-Lymphocytes in CFS -- in vitro reaction to mutagens I Hauspie K de Meirleir et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS 1998: Mass. USA. Abstract page 70

Many studies in (ME)CFS patients suggest a virally-triggered onset, associated with an abnormal immune function.

The results from this study add information to the existing knowledge of intracellular abnormalities in (ME)CFS, and point towards abnormalities in intracellular protein metabolism, with increased sensitivity to alcohol.

The authors believe that lymphocytic cell membrane permeability is altered in (ME)CFS.

1998

Lymph node morphology and phenotype in chronic fatigue syndrome Nancy Klimas et al
Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS 1998: Mass, USA. Abstract page 73

(ME)CFS is an illness which is associated with immune dysfunction, including abnormalities in the function and activation status of peripheral blood lymphocytes. There has been no study of the lymph node compartment in this illness.

The authors conclude that the distribution of lymphocyte subsets in the lymph nodes in (ME)CFS patients offers confirmation regarding the immunopathogenesis of (ME)CFS.

The data here presented indicate a preponderance of activated T-cells that is even higher than that reported in peripheral blood.

The findings are compatible with a chronically activated immune status in this patient group.

1998

CD4 T Lymphocytes from Patients with Chronic Fatigue Syndrome have Decreased Interferon - γ Production and Increased Sensitivity to Dexamethasone Jeroen Visser et al
The Journal of Infectious Diseases 1998:177:451-4

To the authors' knowledge, this study was the first to compare properties of purified CD4 T cells from (ME)CFS patients with those of cells from healthy controls.

The CD4 cells were studied to determine whether they have an altered sensitivity to dexamethasone (DEX).

CD4 T cells from (ME)CFS patients produced less interferon - γ than did the cells from controls, indicating an increased sensitivity to DEX.

The authors suggest that their observation of low interferon - γ production in (ME)CFS might be due to an increased sensitivity of the CD4 T cells for glucocorticoids, which are known to modulate T cell responses.

1998

Decreased immunoreactive beta-endorphin in mononuclear leucocytes from patients with chronic fatigue syndrome Conti F et al
Clinical & Experimental Rheumatology 1998:16:6:729-732

Beta-endorphin concentrations were measured in peripheral blood mononuclear cells (PBMC) by radioimmunoassay performed with antibodies specific for the C-terminal portion of human beta-endorphin.

Beta-endorphin concentrations in the PBMC of (ME)CFS patients were significantly lower than in the healthy subjects.

Beta-endorphin concentrations in PBMC seem to mirror the central nervous system homeostasis of the opioid, thus the fatigue and weakness typical of (ME)CFS could be related to low beta-endorphin concentrations at the CNS level.

1998

The in vitro immunomodulatory effects of glyconutrients on peripheral blood mononuclear cells of patients with chronic fatigue syndrome See DM et al
Integrative Physiological and Behavioural Science 1998:33:3:280-287

A glyconutrient compound was added to PBMC isolated from 90 normal controls and 91 patients with (ME)CFS.

Cell surface expression of the glycoproteins CD5, CD8 and CD11a were significantly lower in patients with (ME)CFS compared with normal controls.

Furthermore, natural killer (NK) cell function was reduced in (ME)CFS patients.

Importantly, apoptosis was significantly higher in patients with (ME)CFS, but the percentage of apoptotic cells was significantly decreased in PBMC of (ME)CFS patients which had been incubated for 48 hours with glyconutrients.

Thus glyconutrients improved immune parameters in vitro in patients with (ME)CFS.

1998

Chronic fatigue in overlap syndromes Abhijit Chaudhuri Peter Behan
Neurology 1998:1:2:16-20

The authors state that (ME)CFS is a disabling neurological illness which may be precipitated by infections, toxins, and physical and mental stress.

They point out that only when a poliomyelitis epidemic swept California in the summer of 1934 was CFS distinguished as a separate epidemic illness, when it was called ‘atypical poliomyelitis’.

Most (ME)CFS cases now occur sporadically; clinical symptoms include generalised muscular aches and pains (fibromyalgia), weakness, sleep disorder, impaired memory and mental concentration, paroxysmal (usually nocturnal) sweating, intermittent dysequilibrium, mild myoclonus, cervical adenopathy (early in the illness), vertigo, palpitations and angina-like chest pain.

The authors state that the organic nature of (ME)CFS soon became apparent from detailed study of symptoms and from neuroendocrine tests.

The authors state that in a number of diseases, fatigue similar to that in (ME)CFS may be the only symptom before other signs become apparent: multiple sclerosis (MS), chronic inflammatory demyelinating polyneuropathies (CIDP), sarcoidosis and haemachromatosis are common examples where fatigue can antedate other symptoms; such (ME)CFS-associated or (ME)CFS-overlap syndromes can be grouped into four divisions:

(i) syndromes commonly associated with postviral or idiopathic (ME)CFS (eg. dysequilibrium syndrome, Gilbert's disease, atopic disorders, including gluten sensitivity, syndrome X and irritable bowel syndrome)

(ii) (ME)CFS-like syndromes following exposure to chemicals (eg. after ciguatera fish poisoning, or following exposure to low dose organophosphate compounds, organochlorine exposure, multiple chemical sensitivities, fatigue induced by medication, including anaesthetics)

(iii) medical or neuropsychiatric diseases where the severity of the fatigue is independent of the underling illness (eg.sarcoidosis, Sjogren's syndrome, SLE and other vasculitides, demyelinating neuropathies, Parkinson's disease, metabolic myopathies, HIV infection, post-head injury)

(iv) other (ME)CFS-like syndromes, where the precipitating factor is uncertain (eg. Gulf War syndrome, sick building syndrome, a (ME)CFS-like syndrome following silicone breast implants).

The authors state that Syndrome X is characterised by typical anginal chest pain but with a normal coronary angiogram. Angina-like chest pain, similar to Syndrome X, is a common symptom in (ME)CFS patients: the two syndromes share many similarities, including an identical clinical course.

A similar exaggerated GH-release response is seen in patients with chronic low-dose exposure to OPs, who develop a syndrome identical to (ME)CFS.

The irritable bowel syndrome which occurs in (ME)CFS is identical to 'idiopathic' IBS.

Cases of (ME)CFS may develop after physical trauma.

(ME)CFS has bee reported in multiple chemical sensitivity

In summary, (ME)CFS should be considered multifactorial in origin, with infection and stress being the two most common triggers.

The mechanism of fatigue in various neurological disorders, including (ME)CFS, may be related to an abnormal cell membrane ion channel and / or membrane-associated ATPase function.

1999

Impaired oxygen delivery to muscle in chronic fatigue syndrome
Kevin K McCully Benjamin H Natelson
Clinical Science 1999:97:603-608

"Complaints of muscle weakness and pain are common, and abnormal muscle metabolism has been reported to occur in (ME)CFS"

"Autonomic dysregulation could affect blood flow to active muscles, could explain the alterations in muscle metabolism we have found, and could partially explain the post-exertional fatigue that is a characteristic of the illness"

"(**ME)CFS patients had recovery rates for oxygen saturation that were 60% lower than those for recovery of oxygen saturation in normal subjects"**

"The impaired oxygen delivery seen in the (ME)CFS subjects in the present study could result in reduced exercise capacity"

"The present study has demonstrated direct impairments in oxygen delivery in (ME)CFS patients compared with normal controls. These impairments were more clearly seen after exercise".

"The magnitude of the alteration in oxygen delivery may be sufficient to impair exercise capacity".

1999

Demonstration of delayed recovery from fatiguing exercise in chronic fatigue syndrome
Lorna Paul Leslie Wood Wilhemina M.H.Behan William M.Maclaren
European Journal of Neurology 1999:6:63-69

The purpose of this study was to try to confirm the observations that patients with (ME)CFS complain consistently of delay in recovery of peripheral muscle function after exercise.

The use of 31 P-nuclear magnetic resonance (31 P-NMR) has now provided positive evidence of defective oxidative capacity in (ME)CFS.

Patients with (ME)CFS reach exhaustion more rapidly than normal subjects, in keeping with an abnormality in oxidative metabolism and a resultant acceleration of glyolysis in the working skeletal muscles.

When the rate of resynthesis of phosphocreatinine (PCr) following exercise is measured, this abnormality is confirmed

The authors' study provides a conclusive demonstration that recovery is significantly delayed in patients with (ME)CFS.

It also supports the fact that patients with (ME)CFS produce maximum voluntary contractions during exercise. The authors are confident that the differences observed in recovery in this study represent true effects.

The results demonstrate that patients with (ME)CFS fail to recover properly from fatiguing exercise and that this failure is more pronounced 24 hours after exercise.

Some of the patients demonstrated more severe effects than others.

Indeed, while the recovery of force in the controls was complete by 200 minutes post-exercise, "an even further decline in force" was observed among the (ME)CFS group at 24 hours post-exercise.

This delayed recovery is unlikely to be the result of de-conditioning.

The findings support the clinical complaint of delayed recovery after exercise in patients with (ME)CFS.

The authors note that recent experiments by others *(Bouwer & Packer: Corticospinal excitability in patients in patients diagnosed with CFS. Muscle Nerve 1994: 1210-1212; Samii et al: Decreased post-exercise facilitation of motor-evoked potentials in patients with CFS or depression. Neurology 1996:1410-1414)* have demonstrated a significant reduction in motor evoked potentials following exercise in (ME)CFS patients compared with controls. This is in keeping with a reduction in the excitability of the motor cortex and could account for a reduction in voluntary motor output leading to the decline in muscle force observed in this study.

1999

Interferon-induced proteins are elevated in blood samples of patients with chemically or virally induced chronic fatigue syndrome
Vojdani A Lapp C
Immunopharmacol Immunotoxicol 1999:21: (2): 175-202

Professors Vojdani and Lapp state that 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.

"We conclude that 2-5A and PKR are not only biomarkers for viral induction of (ME)CFS, but biomarkers for others stressors that include (chemicals)".

1999

Chronic Fatigue Syndrome is a Acquired Neurological Channelopathy
Abhijit Chaudhuri Peter Behan
Hum Psychopharmacol Clin Exp 1999:14:7-17

Review article noting that the fatigue in (ME)CFS is distinct from the fatigue of neuromuscular disorders but similar to that found in disorders of the central nervous system such as multiple sclerosis, Parkinsons disease and multiple system atrophy.

The authors note that many symptoms of (ME)CFS, including severity of fatigue, may be induced by physical trauma and stress.

In this paper, the authors propose dysfunctional ion channels in the cell membrane as the key abnormality in (ME)CFS, which may also be responsible for the altered neuroendocrine function found in (ME)CFS.

A significant proportion of patients with (ME)CFS suffer from irritable bowel syndrome.

Autonomic dysfunction in (ME)CFS is also well recognised.

(ME)CFS patients have a supersensitivity of cortisol response to exogenous ACTH: both physical trauma and emotional stress (such as bereavement) can precipitate (ME)CFS, directly activate the HPA axis and modify the immune system. Chronic activation of the HPA axis may cause a relative decrease by the adrenals of delta 3 - adrenal androgens. This process, in turn, may alter the helper Tcell phenotype in chronically affected patients.

Cytokine levels increase during stress: it has been shown clearly that breakdown of the blood-brain barrier (BBB) can occur during periods of stress.

At the cellular level neurochemicals use second messengers and ion channels for their desired actions.

It is therefore possible that neurochemical abnormalities can lead to alterations in the normal receptor and ligand-gated ion channel function.

Abnormal ion channel functions as the mechanism of neurological disorders now constitute a new group of diseases termed *channelopathies.*

Changes in the ion channel function from time to time offer a rational basis to explain the fluctuating fatigue and related symptoms in (ME)CFS. Known channelopathies provide excellent examples of neurological conditions where the symptoms are periodic, fluctuating, and are induced by physical activities, stress and fasting.

If the sodium channels are blocked in the open mode, this causes entry of sodium into neural tissues and muscles. This ingress of sodium is followed by water, which in turn leads to swelling of the neural tissues, a phenomenon observed both electron microscopically and by laser scanning microscopy.

Acquired ion channel abnormalities in myocardium could explain the pathogenesis of Syndrome X and may form the basis of cardiac dysfunction in both Syndrome X and in (ME)CFS — a highly significant proportion of (ME)CFS patients have cardiomyopathy, as shown in the epidemiological study by Lerner et al

Ion channel abnormality leading to selective neuronal instability may be the common disease mechanism in (ME)CFS and other disorders affecting brain function such as migraine and epilepsy.

The authors believe that (ME)CFS is *acquired* rather than inherited, making any therapeutic attempts to correct an ionophoric defect difficult.

1999

Dehydoepiandrosterone (DHEA) response to i/v ACTH in patients with chronic fatigue syndrome De Becker P, de Meirleir K et al
Hormone and Metabolic Research 1999:31:1:18-21

In order to investigate the dynamic response of the adrenal glands, the researchers measured serum levels of DHEA at intervals during 60 minutes after ACTH stimulation. Patients in the study were severely affected, with no psychiatric illness.

The patients had a blunted serum DHEA response curve to intravenous ACTH injection.

This observation adds to the large amount of evidence of endocrinological abnormalities in (ME)CFS.

Relative glucocorticoid deficiency might contribute to the overall clinical picture in (ME)CFS and could explain some of the immunological disturbances observed in this syndrome.

1999

Chronic fatigue syndrome Pagani M and Lucini D.
Clinical Science 1999:1:117-125

In (ME)CFS there are reported disturbances in autonomic activity and in other homeostatic mechanisms, such as hormonal and immune systems.

There are alterations in cardiovascular autonomic control, as can be assessed by spectral analysis of R-R interval and systolic arterial pressure variability.

Indices of sympathetic modulation could provide quantifiable signs of the interaction between the patients' efforts and their environmental demands, independently of self description; this could provide convenient measurable outcomes, both for diagnosis and treatment titration.

1999

Chronic fatigue syndrome: assessing symptoms and activity level Jason LA et al
J Clin Psychol 1999:55:4:411-424

Current approaches to the diagnosis and assessment of (ME)CFS rely primarily on scales which measure the occurrence of various symptoms in (ME)CFS.

Such approaches do not provide information on either the severity of symptoms or on the fluctuations in symptom severity, or on activity level over time. As a result, these measures do not reflect the complexities and the inter-reactions among symptoms.

By obscuring the fluctuating nature of (ME)CFS and its high variability, commonly used assessment procedures may prevent health care professionals from understanding the complexities of this disease.

1999

Natural History of Severe Chronic Fatigue Syndrome
NF Hill, LA Tiersky, BH Natelson et al
Arch Phys Med Rehab 1999:80:1090-1094

"Objective: to evaluate the natural history of (ME)CFS in a severely ill group of patients"

"Neither the 1988 (Holmes et al) nor the 1994 (CDC Fukuda et al) case definition identifies the sickest patients because information about symptom severity is not required to make the diagnosis of (ME)CFS"

"Within the homogenous group of severe (ME)CFS patients, the prognosis for recovery was poor"

"The majority of (ME)CFS patients continued to have severe problems and to be unemployed due to their illness over the course of this 4-year study. Thus, not only do patients with severe (ME)CFS not recover to full health, but they remain quite severely ill over many years.

"As this study reveals, the majority of severely ill (ME)CFS patients become disabled because of their illness and remain so for many years"

"The data reported here indicate a poor prognosis for patients receiving standard medical care".

1999

Presentation in Orlando, Florida at the International Congress of Bioenergetic Medicine, February 1999
Paul Cheney MD, Director of the Cheney Clinic, Charlotte, North Carolina, USA

"The most important thing is not to have (ME/CFS patients) do aerobic exercise"

"I believe that even progressive aerobic exercise is counter-productive. If you have a defect in mitochondrial function and you push the mitochondria by exercise, you kill the DNA".

1999

A Subgroup Analysis of Cognitive Behavioural Treatment Studies Fred Friedberg
JCFS 1999:5:3/4:149-159

"Several studies of graded activity-oriented cognitive behavioural treatment for (ME)CFS, all conducted in England, have reported dramatic improvements in functioning and substantial reductions in symptomatology"

"On the other hand, cognitive behavioural intervention studies conducted in Australia and the United States have not found signficiant improvements in functioning or (ME)CFS symptoms"

"Furthermore, descriptive studies of (ME)CFS patients in England, the US and Australia suggest that the (ME)CFS patient population studied in England shows substantial similarities to depression, somatisation or phobia patients, while the US and Australian research samples have been clearly distinguished from primary depression patients and more closely resemble fatiguing neurological illnesses"

"The differentiation of (ME)CFS subgroups by symptoms and disability may plausibly suggets protocols that are specific to these widely divergent clinical presentations".

1999

A review of multiple chemical sensitivity RA Graveling et al
Occup Environ Med 1999:56:73-85

Note: This review was commissioned by the UK Government's Health and Safety Executive.

"Several phrases have been used to describe patterns of generalized hypersensitivity to chemical exposure including environmental illness, 20th century disease, chemical AIDS and total allergy syndrome"

"Conditions such as chronic fatigue syndrome and gulf war syndrome have symptoms which overlap with multiple chemical sensitivity (MCS)"

"There is convincing evidence that some people report a consistent set of symptoms which they attribute to previous chemical exposure and which recur on subsequent exposure to the same or structurally unrelated chemicals"

"The evidence is made more convincing in cases where the illness has produced considerable social and financial hardship with no apparent benefit and is associated with a strong motivation to be made well"

"(Study results) do favour the idea that patients with MCS tend to have different immune patterns"

"A recent appraisal of the literature on a psychogneic origin for MCS examined ten articles and identified extensive methodological deficiencies in nine. In particular, eight of the ten confused association with cause"

"Once MCS is initiated, symptoms are provoked by exposures at concentrations well below any considered remotely of relevance by mainstream toxicologists"

"The amygdala has been implicated in chemical sensitivity (and) it has conncections with the hypothalamus, which governs a range of physiological response in multiple organ systems"

"There is evidence to suggest that in some people, exposure to chemicals can initiate a clinical response to subsequent exposures to very low doses of that chemical and to structurally unrelated chemicals"

"The evidence is convincing"

"Recent research has suggested that certain chemicals are able to directly penetrate areas of the brain and to exert an effect at doses much lower than previously considererd possible".

2000

Editorial: Anthony Komaroff, Assistant Professor of Medicine, Harvard Medical School
JAMA 2000:108:2:169-171

"Objective biological abnormalities have been found significantly more often in patients with the syndrome than in comparison groups"

"The evidence indicates pathology of the central nervous system and immune system"

"What is the evidence of central nervous system pathology? Magnetic resonance imaging has revealed areas of high signal in the white matter. SPECT signal abnormalities are also found more often in patients, abnormalities like those seen in patients with encephalopathy due to the acquired immune deficiency syndrome (AIDS) and unlike the findings in patients with depression"

"Autonomic nervous system testing has revealed abnormalities of the sympathetic and parasympathetic systems that are not explained by depression or physical deconditioning"

"Studies of hypothalamic and pituitary function have revealed neuroendocrine abnormalities not seen in healthy control subjecys and opposite to those found in depression"

"There is considerable evidence from different investigators, using different technologies and studying different groups of patients, of a state of chronic immune activation"

"In summary, there is now considerable evidence of an underlying biological process in most patients (which) is inconsistent with the hypothesis that (ME/CFS) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest".

2000

Symptom patterns in long-duration chronic fatigue syndrome
Fred Friedberg et al
Journal of Psychosomatic Research 2000:48:59-68

"Our objective was to evaluate symptom patterns in patients with (ME)CFS who were ill for 10 or more years"

"Patients who have been persistently ill for more than ten years have not been described in the literature"

"Recognition of this long-duration group is important to the conceptualisation of (ME)CFS as an illness that may not lead to recovery or significant improvement for a substantial number of patients"

"Evidence of possible cardiac involvement has been reported. (ME)CFS patients showed abnormal left ventricular dynamic function, a possible sign of viral infection. A subsequent study revealed significantly higher levels of oscillating T wave abnormalities in the cardiac output of (ME)CFS patients"

"Chemical sensitivities were assessed. Chemical sensitivity scores were significantly higher in the long - duration group compared with the short-duration participants"

"Allergy history, confirmed by allergy testing, was the most frequently reported medical condition (88.8%). (ME)CFS symptom severity scores were significantly correlated with measures of allergy symptoms severity and frequency of allergies"

"(ME)CFS symptoms severity scores were significantly associated with chemical sensitivity scores"

"Evidence for hypersensitivity in (ME)CFS was found. A related finding suggests the presence of drug hypersensitivity as well"

"This study may shed light on previously unexplored factors in (ME)CFS that have implications for illness severity, persistence, and outcome"

"A review of outcome studies in (ME)CFS generally showed very low recovery rates for stringently defined adult cases"

"This study suggests that a hypersensitivity mechanism and viral infection may contribute to illness persistence in (ME)CFS".

2000

Proton magnetic resonance spectroscopy and morphometry of the hippocampus in Chronic Fatigue Syndrome Brooks JCW Roberts N Whitehouse G Majeed T
Brit J Radiol 2000:73:1206-1208

In his review of this paper in the Summer 2001 Newsletter for the 25% Severely Affected ME Group, Dr John Breward wrote:

"This paper from a research group in Liverpool provides some interesting evidence for the existence of functional abnormalities in the hippocampus of ME patients"

"It is yet another piece of evidence of an organic disease process in ME, and a pointer to the underlying cellular pathology"

"There is now a substantial body of evidence documenting brain abnormalities using a variety of brain scanning techniques, ie. MRI, PET, SPECT etc. The cumulative evidence is now incontestable: there are **measurable physical abnormalities** in the brain in ME".

2000

A 37 kDa (kiloDalton) 2-5A Binding Protein as a Potential Biochemical Marker for Chronic Fatigue Syndrome Kenny De Meirleir et al
Am J Med 2000:108:99-105

"A 37 kDa 2-5A binding polypeptide was found in 88% of the patients with (ME)CFS compared with 28% of the controls: when present, the amount of 37 kDa protein was very low in controls"

"When expressed as the ratio of a 36 kDa protein to the 80 kDa protein, 72% of patients with (ME)CFS had a ratio of more than 0.05 compared with 11% of the healthy subjects and none of the patients with fibromyalgia"

"This 37 kDa 2-5A binding protein has not been reported in healthy subjects or in other diseases"

"This low molecular weight 2-5A binding protein may be useful as a biological marker for (ME)CFS".

2000

Exercise Capacity in Chronic Fatigue Syndrome
Pascale de Becker Neil McGregor Kenny De Meirleir et al
Arch Intern Med 2000:160:3270-3277

"The standard for measuring exercise capacity has always been the maximal oxygen uptake (VO_2 max) during high intensity whole body exercise"

"A total of 450 consecutive female patients who met the CDC's 1988 or 1994 criteria for (ME)CFS were enrolled in the study"

"Our patients with (ME)CFS had an average VO_2 max just below 20 mL/kg per minute, representing significant impairment relative to the controls"

"**Comparing the exercise capacity in our patients with data from other studies shows a functionality similar to that of individuals with chronic heart failure, patients with chronic obstructive pulmonary disease, and those with skeletal muscle disorder"**

"The decrease in physical capacity in patients with (ME)CFS appears to be associated with disease severity".

2000

Disturbed neuro-endocrine-immune interactions in chronic fatigue syndrome
Kavelaars A et al
J Clin Endocrinol Metab 2000:85:2:692-696

"We examined the sensitivity of the immune system to the glucocorticoid agonist dexamethasone in (ME)CFS and controls"

"The maximal effect of dexamethasone on T-cell proliferation is significantly reduced in (ME)CFS as compared with controls"

"Baseline adrenaline levels were significantly higher in (ME)CFS patients"

"We conclude that (ME)CFS is accompanied by a relative 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 neuro-endocrine-immune communication".

2000

Enhanced sensitivity of the Peripheral Cholinergic Vascular Response in Patients with Chronic Fatigue Syndrome VA Spence Faisel Khan JJF Belch
Am J Med 2000:108:736-739

"The results of this study show enhanced cholinergic activity in the peripheral microcirculation of patients with (ME)CFS"

"Many of the symptoms of (ME)CFS such as temperature sensitivity, gastrointestinal difficulties, problems with sleep, and orthostatic intolerance, are consistent with altered cholinergic activity"

"The response of skin microvessels to actylcholine is typical of blood vessels elsewhere in the body. Thus, our findings might have important implications for features of (ME)CFS that involve vascular integrity".

2000

Immunologic Status Correlates with Severity of Physical Symptoms and Perceived Illness Burden in Chronic Fatigue Syndrome Patients Stacy E Cruess Nancy Klimas et al
JCFS 2000:7:1:39-52

"Specifically, elevations in 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".

2000

Comparative Analysis of Lymphocytes in Lymph Nodes and Peripheral Blood of Patients with Chronic Fatigue Syndrome Mary Ann Fletcher Nancy Klimas et al
JCFS 2000: 7:3:65-75

"Blood and lymph node samples were obtained from patients with (ME)CFS"

"While a greater proportion of T lymphocytes from both lymph nodes and blood of control subjects 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 it is interesting to note that the decreased populations of naïve T cells are also seen in the peripheral blood of patients with autoimmune disease".

2000

Review: Immunology of Chronic Fatigue Syndrome
Roberto Patarca Timothy Mark Mary Ann Fletcher Nancy Klimas
JCFS 2000: 6: 3-4:69-107

This extensive review of the immunology in (ME)CFS contains 212 references.

"A review of the literature on the immunology of (ME)CFS reveals that people who have (ME)CFS have two basic problems with immune function that have been documented by most research groups: (1) immune activation, as demonstrated by elevation of activated T lymphocytes, including cytotoxic T cells, as well as elevations of circulating cytokines, and (2) poor cellular function, with low natural killer cell cytotoxicity, poor lymphocyte response to mitogens in culture, and frequent immunoglobulin deficiencies, most often IgG1 and IgG3"

"These findings have a waxing and waning temporal pattern which is consistent with episodic immune dysfunction (which) can account for the perpetuation of disease with remission/exacerbation cycles"

"The data summarized herein indicate that (ME)CFS is associated with immune abnormalities that can account for symptomatology"

"Future research should further elucidate the cellular basis for immune dysfunction in (ME)CFS and its implications".

2000

Treating Paediatric CFS David S Bell
The CFIDS Research Review, Autumn 2000

"(ME)CFS is widely recognized in adults but it is not as well known that children and adolescents can have the illness"

"(ME)CFS has been found in children as young as age five"

"The illness can and often does present differently in children than in adults and can be difficult to diagnose".

2000

Faces of CFS: Case Histories of Chronic Fatigue Syndrome
David S Bell
Lyndonville Publications, New York, 2000 ISBN 097 00770 200

"Nearly every patient with (ME)CFS thinks of suicide at one time or another. Sufferers are driven to suicide by loneliness and self-doubt. Although they are ill every day of their lives, neighbours and family insist they look 'just fine'. (ME)CFS carries a terrible stigma, the burden of which weighs more heavily on them even than the burdens borne by most victims of chronic disease. The world seems to believe that people with (ME)CFS could 'snap out of it' if they really wanted to. This utterly false perception of the disease is widespread"

"I continue to see a great many (ME)CFS patients in my practice. Sadly, I find it exceedingly difficult to help such patients meet even their most basic needs"

"Medicine has moved from an epoch of scientific curiosisty to a period in which money-minded bureaucrats dominate and possibly even retard scientific progress"

"Just last year (ie. 1999), a shocking article appeared in a widely read medical journal, The Annals of Internal Medicine, that seemed to turn back history. The authors argued that all somatic illnesses, those without a clear explanation of cause, are fake. Such diseases, these psychiatrists argued, are little more than the expressions of unhappy people who are desperate for attention. The authors further stated that doctors

who appear to be 'symptathetic' to such patients only encourage these bogus maladies to persist" *(The article in question was Review: Functional Somatic Syndromes by Arthur Barksy and Jonathan Borus; Ann Int Med 1999:130:910-921).*

"After more than a decade of studying this devastating disease, I can report that (ME)CFS is not a psychosomatic illness"

"I do have a problem with the lack of respect given to patients with poorly understood neurologic disease. Science has created a false aura of mastery, and if there is an area where mastery does not apply, it is an area to be disregarded, ignored, and even ridiculed"

"Neurologic symptoms appear to be the most direct window into the heart of this illness; they both define and explain (ME)CFS, (which) is a unique blend of numerous neurologic symptoms, none of which are well understood"

"Neurologists define myoclonus as a sudden and generalized jerking contraction of the muscles. Although myoclonus is a markedly abnormal finding, it is also the ultimate humiliation for the patients with (ME)CFS. Although this finding may be one of the most important signs of neurological disease, doctors typically dismiss it as 'hysterical' when they are examining (ME)CFS sufferers.

"Publishing scientific papers about (ME)CFS has become so difficult in the last decade (that) a group of researchers decided in 1995 to establish a journal specifically for the disease, one that would afford clinicians and scientists a forum in which to report on developments in the field" *(The Journal of Chronic Fatigue Syndrome).*

"The terms 'fatigue' or 'exhausted' do not even describe the sensation experienced. 'Collapse' is more accurate"

"One of the oddest symptoms of (ME)CFS is the complaint by many patients that they are losing their hair"

"There exists a strange kind of medical discrimination against patients with (ME)CFS"

"I have learned so much from (my (ME)CFS) patients), particularly from their courage to persist despite this illness".

2001

Cytokines and chronic fatigue syndrome Patarca R
Ann New York Acad Sci 2001:933:185-200

"(ME)CFS patients show evidence of immune activation. Nevertheless, immune cell function of (ME)CFS patients is poor"

"Immune dysfunction in (ME)CFS, with predominance of T-helper type 2 and pro-inflammatory cytokines, can be episodic (and) can account for the perpetuation of the disease with remission/ exacerbation cycles"

"A T-helper type 2 predominance has been seen among Gulf War syndrome patients and this feature may also be present in other related disorders, such as multiple chemical sensitivity".

2001

Detection of Immunologically Significant Factors for Chronic Fatigue Syndrome Using Neural-Network Classifiers SJ Hanson W Gause B Natelson

"Neural-network classifiers were used to detect immunological differences in groups of (ME)CFS patients"

"A sensitivity analysis of the network found differences between the groups that are consistent with the hypothesis that (ME)CFS symptoms are a consequence of immune system dysregulation"

"Of signficiant interest was the fact that, of all the cytokines evaluated, the only one to be in the final model was interleukin-4 (IL-4). Seeing an increase in IL-4 suggests a shift to a type 2 cytokine pattern. Such a shift has been hypothesised, but until now, convincing evidence to support such a hypothesis has been lacking".

2001

Enteroviral and Toxin Mediated Myalgic Encephalomyelitis / Chronic Fatigue Syndrome and Other Organ Pathologies John Richardson
The Haworth Medical Press Inc., New York, 2001

"In ME, there are chronic sequelae and the effects may be neurological, hormonal, autoimmune and myalgic, which may affect the myocardium".

2001

Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity
Bazelmans E et al
Psychological Medicine 2001:31:107-114

"(ME)CFS patients often complain that physical exertion produces an increase in complaints. It has been suggested that this is due to physical deconditioining"

Twenty patients with (ME)CFS were compared with 20 matched controls. Measures included heart rate, blood pressure, oxygen consumption and saturation, carbon dioxide consumption and blood-gas values (of arterial capillary blood).

"Wessely et al (*JRCGP 1989:39:26-29*) hypothesized that physical deconditioning might play an important role in (ME)CFS"

"Based on this hypothesis, the role of avoidance of physical activity in (ME)CFS has been emphasized more and more"

"In the present study, (ME)CFS patients did not have a worse physical fitness compared with controls"

The researchers conclude that "physical deconditioning does not seem a perpetuating factor in (ME)CFS".

2001

Role of impaired lower-limb venous innervation in the pathogenesis of chronic fatigue syndrome
Streeten DH
Am J Med Sci 2001:321: (3):163-167

"In patients with acute orthostatic hypotension, there is excessive pooling of blood in the legs. The common occurrence of delayed orthostatic hypotension and / or tachycardia in (ME)CFS led to the present studies"

"Inconsistently excessive increases in heart rate were found in (ME)CFS patients, in whom venous compliance in response to infused norepinephrine was significantly reduced"

"In these patients with (ME)CFS, delayed orthostatic hypotension was clearly demonstrable (implying) impaired sympathetic innervation of foot veins"

"(This suggests) that excessive lower body venous pooling, perhaps by reducing cerebral perfusion, is involved in the orthostatic component of fatigue in these patients".

2001

Increased sensitivity to glucocorticoids in peripheral blood mononuclear cells of CFS patients
Visser J et al *J Investig Med 2001:49(2):195-204*

"In this study we tested the hypothesis that the increased sensitivity to glucocorticoids in (ME)CFS patients can be attributed to an altered functioning of their glucocorticoid receptors (GR)"

"In (ME)CFS patients, 0.01 micromol dexamethasone suppressed PBMC proliferation by 37%, whereas the controls were only suppressed by 17%"

"In conclusion, PBMC of (ME)CFS patients display an increased sensitivity to glucocorticoids which should be attributed to molecular processes beyond the actual binding of the ligand to the GR".

(NB. This is evidence of a biological marker).

2001

Muscle metabolites detected in urine of fibromyalgia and chronic fatigue syndrome may suggest ongoing muscle damage SCM Richards A Cleare et al
British Society of Rheumatology, Edinburgh, 14th-27th April 2001: 382

"Creatine has previously been shown to be a sensitive marker of muscle inflammation (measured in the urine) in myositis"

"We assessed whether patients with fibromyalgia (FM) and (ME)CFS showed evidence of ongoing muscle damage as measured by the loss of creatine in the urine"

"We also measured several other metabolites known to be released from damaged muscle"

"Significant levels of creatine were detected in the urine of 29 of 60 patients with FM (ie. 48%) and 32 of 60 patients with (ME)CFS (ie. 53%) compared to none (ie. 0%) in healthy controls"

"There was *(sic)* also significantly higher levels of urinary excretion of choline and glycine in (ME)CFS compared to controls"

"This study reveals that approximately half these patients with FM and (ME)CFS were excreting creatine and other muscle related metabolites in their urine in detectable levels"

"This may well represent ongoing muscle damage in FM and (ME)CFS".

2001

PRESS RELEASE, CFIDS ASSOCIATION OF AMERICA, 15th July 2001

"New Survey reveals Chronic Fatigue Syndrome (ME) is as disabling or debilitating as lupus, multiple sclerosis and rheumatoid arthritis. Many medical professionals are acknowledging it as a seriously disabling condition. Three quarters of medical professionals responding to the survey believe that (ME)CFS, also known as CFIDS, is as or more disabling than other chronic diseases"

2001

AMERICAN MEDICAL ASSOCIATION STATEMENT *Co-Cure, 17th July 2001*
Anthony Komaroff, Assistant Professor of Medicine, Harvard Medical School

"**There is considerable evidence already that the immune system is in a state of chronic activation in many patients with (ME)CFS"**

2001

The effect of exercise on gait an balance in patients with chronic fatigue syndrome
Paul LM Wood L Maclaren W
Gait Posture 2001:14(1):19-27

"This study investigated anecdotal reports of gait and balance abnormalities in subjects with (ME)CFS (compared with controls)"

"There were significant differences in gait parameters between the two groups, confirming anecdotal evidence"

"Heart rate responses were perceived to be higher by the (ME)CFS group".

2001

Physiological response to incremental exercise in patients with chronic fatigue syndrome
Inbar O et al
Med Sci Sports Exerc 2001:33(9):1463-1470

"The purpose of this investigation was to characterize the physiological response profiles of patients with (ME)CFS to an incremental exercise test, performed to the limit of tolerance"

"As a group, the (ME)CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values at peak exercise, compared with the control group"

"These results could indicate either cardiac or peripheral insufficiency embedded in the pathology of (ME)CFS"

"We conclude that indexes from cardiopulmonary exercise testing may be used as objective discriminatory indicators for evaluation of patients with (ME)CFS".

2001

Haemodynamic instability in chronic fatigue syndrome: Indices and diagnostic significance
Naschitz JE et al
Semin Arthritis Rheum 2001:31:3:199-208

The objective of the study was "To evaluate the cardiovascular response to postural challenge in patients with (ME)CFS and to determine whether the degree of instability of the cardiovascular response may aid in diagnosing (ME)CFS"

"The haemodynamic instability score differed significantly between (ME)CFS and other groups (ie. a healthy control group, patients with fibromyalgia, patients with generalized anxiety disorder and patients with essential hypertension) except for generalized anxiety disorder"

"The haemodynamic instability score adds objective criteria confirming the diagnosis of (ME)CFS".

2001

Extracts from Over-view of the Alison Hunter Memorial Foundation ME/CFS Clinical and Scientific Meeting, December 2001, Sydney, Australia
Margaret Williams (*with grateful acknowledgment to Dr Rosamund Vallings)*
(for the complete over-view, see http://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind0207c&L=co-cure&T=0&F=&S=&P=3579)

The mission of the Alison Hunter Memorial Foundation is to reduce the impact in the community of the disease myalgic encephalomyelitis / chronic fatigue syndrome. The Foundation was established in 1998 and works with international researchers and ME/CFS societies to advance scientific knowledge and medical care. The Foundation is an enduring memorial to Alison Hunter and to all those whose lives have been devastated by ME/CFS. Alison died aged 19 in 1996 from severe ME, suffering seizures, paralysis, gastrointestinal paresis, severe recurrent mouth ulcers and overwhelming infection, having courageously fought ME/CFS for ten years.

The December 2001 Sydney Conference hosted world-renowned experts on ME/CFS such as Professor Anthony Komaroff from Harvard, Professor Kenny de Meirleir from Brussels, Professor Neil McGregor from the Department of Biological Sciences, University of Newcastle, New South Wales, Dr Dharam Ablashi from Colorado and Dr Susan Levine from New York, who variously presented evidence on the biology of ME/CFS, gastro-intestinal symptoms and gastric emptying studies, ME/CFS and multiple sclerosis (MS) as subsets of a group of cellular immunity disorders, active HHV6 infection and its correlation with RNaseL low molecular weight protein (37KDa) in ME/CFS patients, objective evidence of brain impairment, regional cerebral blood flow, pathophysiological mechanisms of ME/CFS, biochemical anomalies, food intolerance and channelopathy in ME/CFS.

Komaroff A. (Professor of Medicine, Harvard)
"The Biology of ME/CFS"

Professor Komaroff gave a presentation which reviewed the epidemiological context and symptoms, pointing out that some patients are completely disabled by the symptoms and noting that impairment of

these patients, as measured by the SF-36 instrument, is comparable with that of patients with congestive heart failure.

Past medical history is notable primarily for a high frequency of atopic or allergic illness in up to 80% of patients.

Physical examination is notable for posterior cervical adenopathy in about 35% and for abnormal tests of balance (Romberg and tandem gait) in about 25%.

A growing literature reports a number of objective laboratory findings that clearly distinguish patients from healthy controls. In his experience, several findings are seen more often in patients: low levels of circulating immune complexes, elevated total complement (CH50), elevated IgG, atypical lymphocytosis and low levels of antinuclear antibodies (ANA).

Neuroendocrine findings demonstrate that patients have a variety of abnormalities of the HPA axes, for example there is reduced hypothalamic production of corticotrophin releasing hormone (CRH) leading to diminished pituitary release of ACTH, leading to basal hypocortisolism; this axis is the opposite of that seen in depression. CT scans have demonstrated that the adrenal glands of patients are half the size of those in healthy controls.

Neuroimaging studies report that in 78% of cases MRI scans reveal punctate areas of high signal in the white matter, particularly in the subcortical areas. Single photon emission computerised tomography (SPECT) reveals defects of perfusion and metabolism much more often in patients with ME/CFS than in healthy controls.

Autonomic nervous system testing studies from Johns Hopkins, Harvard and other institutions find evidence of both sympathetic and parasympathetic neuropathy in ME/CFS patients. Clinically, 50% of patients meet criteria for neurally mediated hypotension and postural tachycardia syndromes.

There is evidence from several controlled studies of the reactivation of various chronic viral infections; in Komaroff's opinion this evidence is strongest for HHV6 (a neurotropic and immunotropic virus). HHV6 can lead to neural sequelae, and there is good evidence of a strong association between HHV6 and MS.

Immunological studies have revealed a variety of immunological abnormalities, especially impaired function of natural killer cells and increased numbers of activated CD+T cells. Whilst neither finding is specific enough to constitute a diagnostic marker, they are nevertheless consistent with a chronically activated immune system in ME/ICD-CFS.

Two groups have reported what appears to be a more specific immune system abnormality in ME/CFS: an increased activity of the 2-5A enzymatic pathway in lymphocytes. Patients with ME/CFS were very different from those with depression, fibromyalgia and healthy controls.

From a psychiatric perspective, probably only a small proportion of patients who seek help for fatigue have ME/CFS. Most ME/CFS patients become depressed and anxious *after* the onset of the illness, with up to 50% developing depression or anxiety in the years after the onset of ME/CFS.

What is ME/CFS? In Komaroff's view, the evidence indicates an organic basis.

Burnett RB (Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide)
Chatterton B (Dept Nuclear Medicine, Royal Adelaide Hospital, Australia)
"Gastro-Intestinal Symptoms and Gastric Emptying Studies in ME/CFS"

Gastro-intestinal symptoms are particularly common in ME/CFS patients but have never been properly assessed even though after the fatigue and central symptoms they are the commonest group and cause considerable distress.

These patients all had increased large bowel symptoms of faecal urgency, nocturnal diarrhoea, loose consistency of the stools and increased frequency.

88% of patients had one or more upper gastro-intestinal symptoms and 91% of patients had an abnormal gastric emptying study; 46% had a delay in oesphageal emptying; 89% had a delay in the liquid phase and 67% had a delay in the solid phase.

This study indicates that the cause is an abnormality of gut motility. The main abnormality was a delay in the liquid phase rather than the solid phase. This suggests a central rather than a peripheral causation for the gastric delay. The delay in mobility may well lead to bacterial overgrowth.

Behan WHM (Professor of Pathology, Glasgow)
"Research Update on ME/CFS"

Much controversy has been caused by the fact that fatigue has both central and peripheral components and the mechanisms are complex; however, in other disorders such as multiple sclerosis (MS) there is a significant decrease in muscle phosphocreatine resynthesis after exercise, while in chronic obstructive pulmonary disease (COPD) reductions in muscle aerobic capacity appear to play almost as important a role as defects in lung ventilation. Professor Behan used detailed exercise studies to compare and contrast the response in well-characterised groups of patients with ME/CFS, MS and COPD. The muscle chemistry features associated with fatigue all seem to be the same.

There is a general manifestation of problems with the muscles, such as changes in enzymes and muscle mass. Professor Behan described a pathway for exercise from brain to nerves to muscle to muscle metabolism, and from lungs to circulation to muscle metabolism; she had found that in ME/CFS there seemed to be abnormalities in all these processes.

She described two kinds of muscle fibre – "fast" (used for bursts of energy) and "slow" (used for endurance). ME/CFS patients had up to 20% less of the "slow" muscle fibres, which helps to explain why sufferers tire so easily.

Deconditioning is not a perpetuating factor in ME/ICD-CFS.

The muscle involvement includes weakness, delayed recovery, decreased aerobic activity, mitochondrial abnormalities and metabolic abnormalities.

Tests showed that patients are doing their best, and that 24 hours after exercise all patients were worse in strength, with the reduction being most severe after 24 hours. This is because the metabolites are slow at resynthesising. Patients have the metabolites but cannot use them properly, so supplements are unlikely to be of help either.

Resting energy expenditure (REE) is elevated in ME/CFS patients unable to exercise and this may relate to cytokine abnormalities and to autonomic dysfunction.

In relation to cardiovascular involvement, the heart is slow to get going with exercise and remains at low peak value. This may be due to increased vagal tone or an intrinsic heart muscle effect. Autonomic function may play a role.

CNS involvement has been shown in SPECT and MRI scans, and neuroendocrine studies show HPA axis abnormalities.

Stress can affect the CNS providing a changed micro-environment in the brain and increased permeability of the blood brain barrier. This can lead to changes in gene expression, which in turn affects production of neurotransmitters. All these events have an impact on the exercise pathway.

One new finding in ME/CFS is that convincing evidence of cardiovascular impairment can be demonstrated.

The whole process is likely to have been precipitated by a severe insult to the body.

It is hoped that these studies will lead to a better understanding of the interference in normal exercise capacity.

Sargent C, Scroop GC, Burnett RB, Buckley JD and Nemeth PD
(Adelaide Chronic Fatigue Syndrome Research Unit, Department of Physiology, University of Adelaide)
"Excess lactic acid is not a cause of fatigue in Chronic Fatigue Syndrome"

It is commonly assumed that the restricted lifestyle of ME/CFS patients leads to a progressive reduction in physical fitness, thus perpetuating the condition. It is on that basis that both the Australian and British Colleges of Physicians recommended exercise training programmes.

The conclusion from this study is that ME/CFS patients have normal physical fitness and that there is no physiological basis for recommending graded exercise training programmes.

Early work suggested that excessive lactic acid accumulation might be a factor in the muscle pain and fatigue experienced by patients during exercise so the authors completed an investigation of plasma lactate responses during incremental exercise to volitional exhaustion in patients and matched sedentary controls.

Increases in plasma lactate concentration with exercise intensity were not different from control subjects and these results indicate that the production and clearance of lactic acid in ME/CFS patients is normal and does not contribute to their fatigue and reduced power output during exercise.

Englebienne P, de Meirleir K et al (Free University of Brussels, Belgium)
"Chronic Fatigue Syndrome (CFS) and Multiple Sclerosis (MS) as Subsets of a Group of Cellular Immunity Disorders"

Apoptosis (programmed cell death) is a critical component of adaptive cellular immunity. When challenged by infection, type I interferons elicit apoptotic responses by inducing the expression of 2-5A synthetase (2-5OAS), RNaseL and the p68 dependent kinase (PKR).

Results from the authors' laboratories point to an improper activation of 2-5OAS in monocytes of both patients with ME/CFS and with chronic (but not in relapsing / remitting) MS, which results in an inappropriate activation of RNaseL.

This process ultimately leads to a blockade of the RNaseL-mediated apoptotic programme and it supports the involvement of environmental factors. Such cellular stress is capable of generating small RNA fragments and / or of inducing the transcription of endogenous retrovirus sequences. The 'abnormal' RNA

sequences are responsible for the inappropriate activation of 2-5OAS and have been implicated in the aetiology of both ME/CFS and MS.

Depending on their origin and structure, these RNA fragments are capable of either activating or down-regulating PKR. This results in a differential effect not only on the PKR/RNaseL-mediated apoptotic programmes but also on the activation of by PKR of the inducible NO synthetase. A release of nitric oxide at either high rates (as in ME/CFS) or low rates (as in chronic MS) by lymphocytes has corollary consequences, triggering the skeletal and cardiac muscle ryanodine receptors (calcium channels), NK cell function, COX2 activation and glutamate release by activated T-cells in the brain.

Glutamate upregulation leads to oligodendrocyte excitotoxicity in MS, whilst glutamate downregulation in ME/CFS impairs hypothalamic CRH secretion.

These results suggest that ME/CFS and MS are extremes of an array of dysfunctions in the 2-5A/RNaseL/PKR pathways into which other autoimmune diseases such as lupus might fit.

Ablashi D (1), Gupta S (2), Peterson D (3), Levine S (4) et al
(1) ABI Inc, Columbia, MD,USA (2) University of California, Irvine CA (3) Sierra Internal Med, Incline Village, NV, USA (4) CFS Clinic, New York)
"Evidence of Active HHV-6 Infection and its Correlation with RNaseL Low Molecular Weight Protein (37KDa) in ME/ICD-CFS"

The authors studied HHV-6 frequency of active infection in ME/CFS patients by coculture of PBMCs, IgM response, presence of HHV-6 DNA by nested and real time TaqMan PCR.

Since the levels of RNaseL and LMW protein (ie. 37KDa) is consistently detected in PBMCs of patients with ME/CFS, the authors correlated the 37 KDa protein with active HHV-6 infection.

More than 65% of ME/CFS patients had active HHV-6 infection, with cerebro-spinal fluid from 26.7% showing HHV-6 DNA.

HHV-6 DNA was also detected in the plasma of 34% by nested PCR, but using TaqMan PCR, it was demonstrated that more than 48.5% plasma and 40% cerebro-spinal fluid contained HHV-6 DNA (showing higher sensitivity of the TaqMan assay).

HHV-6 IgM levels ranged from 1:20 to 1:320.

HHV-6 Variant A infection was identified by TaqMan PCR in almost all the positive patients. HHV-6 infection was present in 65% of ME/CFS patients.

Correlation of HHV-6 infection and 37 KDa protein was significant.

In conclusion, higher frequency of HHV-6 reactivation was detected in ME/CFS patients, using various assays. HHV-6 Variant A infection was predominant in ME/CFS. HHV-6 infection also correlated with 37KDa protein.

Casse R, Burnett R et al (The Queen Elizabeth Hospital, Adelaide, Australia)
"Regional cerebral blood flow in chronic fatigue syndrome"

ME/CFS is a complex disorder characterised by profound fatigue and neuropsychiatric dysfunction, including mental fatigue, impaired concentration and slowness of thinking. Patients with this disorder have been studied with radionuclide perfusion scans but most previous studies were performed on inhomogeneous patient populations and were not analysed with Statistical Parametric Mapping (SMP). To

address these issues, a study was performed with Tc-99m HMPAO SPECT and a triple head gamma-camera.

Visually, a deficit in regional cerebral blood flow (rCBF) in the medial temporal lobe was definite in over 50% of patients. The location, amplitude and corrected p-value of significant focal deficits in ME/CFS were: brainstem 19%; right medial temporal lobe 22%; frontal lobe 17% and anterior cingulate gyrus 12%.

There appears to be objective evidence that patients with moderately severe ME/CFS have focal cortical and brainstem hypoperfusion.

Robinson GL, McGregor NR et al (University of Newcastle, New South Wales)
"Biochemical anomalies in people with chronic fatigue syndrome who have visual problems: implications for immune system dysfunction and dietary intervention"

There has been identification of biochemical anomalies in people with ME/CFS and the range of symptoms includes visual problems which are similar to those reported by people identified as having a visual sub-type of dyslexia called Irlen Syndrome (IS).

These visual problems have been associated with abnormal fatty acid metabolism.

The primary investigation identified a number of biochemical markers associated with symptom incidence related to a dysregulation of fatty acid metabolism.

A more detailed analysis found significant differences in the metabolic profiles, indicative of differences in connective tissue turnover due to infection or stress. There were also indications of alterations of neuronal functioning due to changes in neurotransmitters.

Preliminary results for the third study found differences in linoleic acid, tyrosine, aspartic acid and glutamic acid. The IS subjects also had a significantly higher incidence of allergies, gastrointestinal problems, kidney infections, photophobia, headaches, fatigue and impaired concentration.

The results of these studies confirm the association between ME/CFS and visual processing problems, with essential fatty acid metabolism likely to be an indicator. A large percentage have visual processing problems. The results also suggest a need for investigation of immune system dysfunction.

Butt HL, McGregor NR, Dunstan RH (School of Biological and Chemical Sciences,
University of Newcastle, New South Wales)
"Food intolerance exists as a co-morbidity in Chronic Fatigue Syndrome"

It has been estimated that food intolerance is a significant factor in 20-30% of patients with ME/CFS.

Patients reporting gastro-intestinal or food-induced problems were assessed for possible food and chemical intolerance via an elimination diet protocol.

89.5% reported a positive outcome from dietary exclusion: gastrointestinal symptoms synonymous with irritable bowel syndrome (IBS) decreased following the intervention.

Food and chemical intolerance may therefore be of aetiological significance in the development of IBS symptoms in ME/CFS, but such investigation of intolerances remains an under-utilised intervention.

Speight N et al
Paediatric Department, University Hospital of North Durham, UK
Paediatric Chronic Fatigue Syndrome in one Health Authority

This study looked at the prevalence, demography and natural history of (ME)CFS in the catchment area of one Healh Authority over a ten year period. The study included cases across the whole spectrum of severity.

There was a steadily increasing incidence (and) cases were found in all social classes.

School loss was considerable, with a total of 89 academic years being lost of out a possible 220 years.

The average school loss per child was 1.8 years.

Poster Presentations

Wilhelmina Behan (Scotland): "Cardiovascular function and exercise intolerance in chronic fatigue syndrome"

Professor Behan presented evidence that there is cardiovascular impairment during dynamic exercise, as judged by the cardiac output response to moderate exercise.

Pascale de Becker (Belgium): "Monitoring a Hypothetical Channelopathy in Chronic Fatigue Syndrome"

This team presented another poster providing further evidence for a channelopathy in a subset of patients. More than 50% of patients presented with abnormal whole body potassium content. Discriminant function analysis revealed that patients and control subjects could be discriminated on immunophenotyping, with the predominant cell differences being the increase in CD19+CD5+ (mature B-) cells and the decrease in CD3-CD16+CD56+ (NK) cells. The fall in NK cells was very strongly associated with increases in the RNaseL ratio and with falls in serum calcium levels.

These observations provide evidence for a channelopathy in an important subset of ME/CFS patients, probably induced by the deregulated 2-5ARNaseL antiviral pathway.

Ann Harvey (Wellington, New Zealand)

A meta-analysis looking at cortisol levels in ME/CFS patients found that patients seen in tertiary care show more endocrine abnormalities.

P Clifton Bligh (Royal North Shore Hospital CFS Research Unit, New South Wales)

This presentation concluded that the fall in urinary succinic acid seen in ME/CFS patients was associated with deregulation of energy availability and protein synthesis suggestive of a cytokine - mediated nitric oxide mediated change in chemistry, causing an increase in protein turnover and increase in glucose dependence; a fall in oxydative phosphorylation is occurring, which relate to the expression of fatigue.

Conference Conclusion

Richard Burnett's final words echoed the consensus of the conference that the brain, limbic system and gut are implicated in ME/CFS.

2002

Evidence that (ME)CFS is likely to be an autoimmune disorder
Professor Kenny de Meirleir, Brussels
Personal communication, 9th February 2002, but see also the book "Chronic Fatigue Syndrome: a biological approach" edited by Patrick Englebienne and Kenny de Meirleir, ISBN 0 8493 1046 6, published by CRC Press 2002 pp 291

"For me as a clinician "CFS" is no longer a mystery but a treatable autoimmune disorder. We have given it a place between lupus, Type I diabetes and multiple sclerosis. We explain all the symptoms of "CFS", which we now call "AFS" (autoimmune fatigue syndrome) by cellular and immune abnormalities".

2002

Blood volume and its relation to peak O_2 consumption and physical activity in patients with chronic fatigue
William B Farquhar et al
Am J Heart Physiol Heart Circ Physiol 2002:282(1):H66-H71

"We hypothsised that hypovaolaemia, through its interaction with central haemodynamics, would contribute to the exercise intolerance associated with (ME/CFS)"

"Patients displayed a trend for a 9% lower blood volume and had a 35% lower peak oxygen consumption"

"Peak ventilation (was) significantly lower in the patients"

"In conclusion, individuals with (ME)CFS have a significantly lower peak oxygen consumption compared with controls".

2002

Immune dysregulation may be caused by environmental toxins in pesticides, herbicides and fungicides
Colette Bouchez
Health ScoutNews Reporter, 8th April 2002

Commonly found among ME/CFS and MCS (multiple chemical sensitivity) patients, immune system dysregulation may be caused by environmental toxins in pesticides, herbicides and fungicides.

"The research, conducted at Tenessee State University, found an ingredient commonly found in a fungicide used to protect potato and sugar beet crops and in a pesticide used to control potato beetles could cause irreversible damage to human killer (NK) cells, the immune system's first line of defence against cancer and viruses"

" 'Our study showed that, at least in laboratory tests, natural killer cells that were exposed to the chemical compound Triphenyltin (TPT) were rendered almost totally helpless within hours after exposure' says chemistry professor Margaret Whelan"

"The research was the first to demonstrate the effect in human blood cells and the findings are a cause for concern"

"The damage appeared to be permanent".

2002

Cytokine response to physical activity, with particular reference to IL-6: sources, actions and clinical implications Shepherd RJ
Crit Rev Immunol 2002:22:3:165-182

"The present review examines the cytokine response to acute exercise stress"

"Many environmental factors also modulate cytokine release"

"The main source of the exercise-induced IL-6 production appears to be exercising muscle"

"The exercise-induced release of cytokines may have relevance"

"Cytokine concentrations are increased in (ME)CFS"

"Exercise-induced modulations in cytokine secretion may contribute to allergies".

2002

Gynaecological concerns in women with Chronic Fatigue Syndrome
Rosemary Underhill
CFIDS Chronicle, Summer 2002

"A number of gynaecological conditions have been found to occur more frequently in women with (ME)CFS"

"Endometriosis is reported to occur in up to 20% of women with (ME)CFS. These endometrial cells are normally removed by the immune system scavenger cells. In women with immune abnormalities such as (ME)CFS, the scavenging cells may be overwhelmed"

"Cystic enlargement of the ovaries may be present. This can be seen on ultrasound scan"

"20% of (ME)CFS patients have dysuria. Interstitial cystitis is thought to be associated with immune system abnormalities"

"A history of ovarian cysts, including polycystic ovaries, and uterine fibroids was found in one study to be more common in (ME)CFS patients than controls *(Reproductive correlates of chronic fatigue syndrome. Harlow BL et al Am J Med 1998:105:3A:94s – 99s)"*

"Patients with (ME)CFS are signficiantly more likely than controls to have had a hysterectomy. This may be associated with the increased numbers of patients with fibroids, ovarian cysts or endometriosis".

2002

Symptoms occurrence in persons with chronic fatigue syndrome
LA Jason et al
Biological Psychology 2002:59:1:15-27

"This investigation compared differences in the occurrence of symptoms in participants with (ME)CFS, melancholic depression, and controls"

"The findings suggest that other symptoms in addition to the eight symptoms listed as part of the definitional criteria may be important and occur frequently in persons with (ME)CFS. In addition, other fatigue/weakness related, sleep related, neuropsychiatric, infectious, rheumatological, cardiopulmonary, gastrointestinal, neurological and reproductive symptoms not specified in the current case definition were examined"

"Several cardiopulmonary and neurological symptoms in the present investigation occurred with higher frequency and uniquely differentiated the (ME)CFS group from the controls. Shortness of breath, chest pain, dizziness after standing, skin sensations, general dizziness, dizzy moving the head, and alcohol intolerance uniquely differentiate those with (ME)CFS from controls"

"Results of the current investigation also indicated that muscle weakness differentiated the (ME)CFS group from controls. Furthermore, it appeared that the muscle weakness in the (ME)CFS group occurred at multiple sites, with weak legs being the most frequently reported form of weakness. These findings concur with those of Hartz et al (1998), and therefore provide further support for the inclusion of muscle weakness in the case definition of (ME)CFS".

2002

ME/CFS in the 21st Century
Abhijit Chaudhuri (Senior Clinical Lecturer in Neurology, University of Glasgow)
Medical Update: Perspectives: Medical & Welfare Bulletin, Issue 6, Spring 2002 ME Association

"(ME)CFS is recognized worldwide and in all age groups"

"Full recovery is unlikely in the majority of adults who have been symptomatic for over four years"

"One set of clinical diagnostic criteria (the Oxford Criteria) is far too imprecise to be clinically useful but has been widely used in the (UK) epidemiologic and intervention trials of (ME)CFS"

"Since patients with neurogenic chronic fatigue (ICD G93.3) are sufficiently distinct from somatising or psychogenic chronic fatigue (ICD F48.0), it is difficult to see how the proposed interventions (graded exercise therapy and cognitive behavioural therapy) might equally apply to the ME/PVFS subgroup, especially when these interventions were based on the psychogenic paradigm of chronic fatigue"

"The failure to segregate neurogenic and somatising subgroups of chronic fatigue lies at the heart of the controversies surrounding (ME)CFS"

"Some may even record (ME)CFS as a 'non-disease'. There are few examples in the history of medicine where an unproven hypothesis has been so retrogressive"

"Present clinical data indicate that psychological co-morbidity in (ME)CFS is modest and has been over-emphasised in the psychiatric literature probably as a result of selection bias"

"There have been sufficient clues beyond the simplistic model of functional somatic syndrome propagated in the past decade".

2002

Quality of Life of Patients with Chronic Fatigue Syndrome Gus L van Heck Jolanda de Vries
JCFS 2002:10(1):17-35

"The purpose of this study was to compare quality of life between patients with (ME)CFS and healthy controls"

"An ever growing body of literature has pointed to a wide range of debilitating symptoms that individuals with (ME)CFS have to face"

"Compared with the general population control group, the (ME)CFS group was impaired on all scales"

"The (ME)CFS group had more problems in nearly every area compared with the five other disease groups"

"In summary, the quality of life of patients with (ME)CFS was impaired on practically all aspects"

"The impact of (ME)CFS on the patients' lives was very profound"

"**It can be concluded that in comparison with a wide range of healthy and sick populations, the quality of life of the (ME)CFS group is particularly and uniquely disrupted".**

2002

Utility of the blood for gene expression profiling and biomarker discovery in chronic fatigue syndrome
Suzanne D Vernon William C Reeves et al
Disease Markers 2002:18:193-199

"Demonstration of the utility of the blood for gene expression profiling and biomarker discovery would have implications into the pathophysiology of (ME)CFS"

"Some features of (ME)CFS resemble diseases associated with chronc infection, immunologic peturbtation and neuroendocrine disorders"

"We selected a well-charcaterised group of (ME)CFS cases and examined the expression of 1764 genes"

"**The approach successfully distinguished the majority of (ME)CFS patients from controls**"

"Subjects were grouped based in disease status ((ME)CFS versus controls). Nineteen genes were identified as different between these two groups"

"Several of the diferentially expressed genes are associated with immunolgic functions (eg. CMRF35 antigen, IL-8, HD protein)"

"It is noteworthy that one gene, the CMRF35 antigen, was detected as differentially expressed by all analytical approaches. This gene encodes a cell membrane antigen that is a member of the immunoglobulin superfamily (and) plays a role in regulating cytokine expression capabilities of immune cells"

"None of the genes identified in this analysis have been previously characterized in (ME)CFS cases"

"The CMRF35 antigen was highly expressed in the (ME)CFS group".

2003

Left Ventricular Function in Chronic Fatigue Syndrome: Data from Nuclear Ventriculography Studies of Response to Exercise and Postural Stress Arnold Peckerman Benjamin Natelson et al
Experimental Biology: American Physiological Society Conference, 11-15th April 2003, San Diego, CA

Also reported in FASEB 2003:17 (5 SUPPL: Part 2): A853-A853)

PRESS RELEASE 9th April 2003 (American Physiological Society): In Some Patients with Chronic Fatigue Syndrome, Left Ventricular Function may be at the Heart of the Matter

"(ME)CFS is a clinically defined illness"

"The main symptom of the (ME)CFS patient, ie. chronic fatigue that is greatly exacerbated by even minor effort, is similar to that of a patient with left ventricular dysfunction"

"Growing evidence points to a problem with circulation. Previously reported findings include autonomic dysfunction, lower plasma volume and/or red cell mass, as well as abnormalities in neurohormonal systems of circulatory control"

"**Other studies have found that patients may have reduced blood flow in exercising muscles**"

"The researchers used the radioisotopic multiple gated acquisition (MUGA) blood pool method of ventriculography to perform a series of dynamic studies of the heart to assess for evidence of abnormalities with myocardial function"

"MUGA ventriculography uses a radionuclide tracer to label red blood cells, allowing visualization of cardiac blood pools with a gamma camera. The emission counts are processed to estimate volumes of blood in the left ventricle at the end of relaxation and at the end of contraction periods. Their ratio (the ejection fraction or EF) is a measure of myocardial contractility and is considered the best non-invasive indicator of left ventricular function"

"This study provides indication of reduced cardiac function in some patients with (ME)CFS"

"It raises the possibility that some (ME)CFS patients may have cardiac disorders that are subtle enough to escape the current net of clinical cardiological diagnoses, but may be significant enough to lead to the clinical symptoms of (ME)CFS".

"These data support the hypothesis that some cases of (ME)CFS may be explained and potentially treated as a problem with left ventricular function".

2003

Abnormal impedance cardiography predicts symptoms severity in Chronic Fatigue Syndrome
Peckerman A Natelson BH et al
Am J Med Sci 2003:326:2:55-60

"Findings indicative of a problem with circulation have been reported in patients with (ME)CFS"

"Impedance cardiography and symptoms data were collected from patients with (ME)CFS grouped into cases with severe and less severe illness and compared with matched sedentary control subjects"

"(Our) results provide evidence of reduced cardiac output in severe (ME)CFS"

"They suggest that in some patients with (ME)CFS, blood pressure is maintained at the cost of restricted flow, possibly resulting in a low circulatory state"

"Thus there may be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes in at least some vascular compartments"

"Several deficiencies capable of affecting cardiac output have been reported in (ME)CFS, including lower blood volume, impaired venous regulation, and changes in autonomic, endocrine and cardiac function"

"The abnormalities causing a reduction in cardiac output in (ME)CFS thus may be dispersed over multiple systems"

"The reduction in stroke volume in these patients (indicated) worsened cardiac performance under conditions of augmented preload"

"Secondary analyses relating cardiac output to specific symptoms found that postexertional fatigue (was) the most characteristic complaint in patients with severe (ME)CFS, and severity was associated with a lower cardiac output"

"(Further research) should be directed at conditions that may not be overtly expressed in symptoms of (ME)CFS, such as underperfusion in the kidneys and the gut, as the organs in which the initial conservation of cardiac output takes place"

"The patients with severe (ME)CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients

"In summary, this study provides indication of reduced cardiac output in some patients with (ME)CFS".

2003

Assessment of cardiovascular reactivity by fractal and recurrence quantification analysis of heart rate and pulse transit time JE Naschitz et al
Journal of Human Hypertension:2004:17:111-118

Three groups were studied (patients with essential hypertension, patients with (ME)CFS, and healthy controls.

"The FRAS (Fractal & Recurrence Analysis-based Score) differed significantly between the groups"

"The HIS (haemodynamic instability score) distinguished (ME)CFS from healthy controls with 97% sensitivity and 97% specificity"

"Based on these data, it appears that the HIS can reinforce the clinician's diagnosis by providing objective criteria".

2003

Associations between Bronchial Hyper-responsiveness and Immune Cell Parameters in Patients with Chronic Fatigue Syndrome Nijs J De Becker P De Meirleir K McGregor N et al
Chest 2003:123:4:998-1007

This study set out to examine whether bronchial hyper-responsiveness (BHR) in patients with (ME)CFS is caused by immune system abnormalities.

"(ME)CFS is a multisystem disorder in which the immune system is of cardinal importance"

"We observed a significantly higher incidence of BHR in (ME)CFS patients compared to healthy controls"

"These two reports provided sufficient evidence for the increased prevalence of BHR in Belgian (ME)CFS patients"

"BHR has been defined as an exaggerated broncho-constrictive response of smooth muscles with airway narrowing in response to a small quantity of a nonallergic stimulus that does not provoke such a reaction in healthy subjects"

"Airway hyper-responsiveness is frequently observed in patients with COPD, cystic fibrosis, TB and sarcoidosis"

"The group of patients in whom bronchial hyper-responsiveness was present (BHR+) differs 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 compared to BHR – patients, which is consistent with the significant reduction in percentage naïve T cells"

"Immunophenotyping of our sample confirmed earlier reports of chronic immune activation in patients with (ME)CFS compared to healthy control subjects"

"BHR positive + (ME)CFS patients have more evidence of immune activation compared to BHR negative patients".

2003

Variability in Diagnostic Criteria for Chronic Fatigue Syndrome may result in substantial differences in patterns of symptoms and disability
Leonard A Jason et al
Evauation & the Health Professions, March 2003:26:1:3-22

"Although post-exertional malaise and impairment of memory and concentration are essential for the ME criteria, they are not required for the Fukuda et al (CDC 1994) criteria"

"A key question is how important post-exertional malaise (is) for identifying patients with this syndrome"

"We decided to examine a lager group of symptoms than just those in the Fukuda criteria because a recent study (Jason et al, 2002) found that participants with (ME)CFS differed from controls in the occurrence of various cardiopulmonary, neurological and other symptoms not included in the current (Fukuda 1994) case definition"

"Participants with ME were significantly more likely to report the occurrence of weakness in the back and neck (and) significantly more participants with ME reported post-exertional malaise"

"The occurrence of unrefreshing sleep was reported with significantly greater frequency in the ME group"

"(The ME group had significant differences) in memory and concentration, eye sensitivity to lights, forgetting recent conversations and events, disorientation in familiar places, difficulty retaining information, slow to process visual and auditory information, and frequently losing one's train of thought"

"The occurrence of lymph node pain was significantly greater in the ME group"

"The ME group reported significantly more muscle (and) joint pain"

"The CFS group reported significantly more sharp shooting pains in the chest"

"The ME group had significantly more pain in the abdomen"

"The ME group had significantly more tingling or numbness in arms and legs, feeling weak or dizzy after standing, and feeling dizzy when moving the head suddenly"

"The ME criteria appear to select a more symptomatic group than the Fukuda (CDC 1994) criteria but these individuals do not demonstrate more psychiatric impairment than those selected according to the Fukuda criteria"

"**Given the seriousness of the neurological symptoms, it is possible to conclude that the ME group has a more serious illness"**

"**It is possible to use symptom patterns to conclude that the ME group does select individuals with greater illness severity (and) the symptoms can interfere with daily living and occupational performance".**

2003

Test – Retest Reliability of the Aerobic Power Index Test in Patients with Chronic Fatigue Syndrome
Karen Wallman et al
JCFS 2003:11: (4):19-32

"Use of maximal aerobic exercise testing in a chronically ill population may not only deter potential subjects from participating in trials, but may also result in the exacerbation of symptoms related to (ME)CFS"

"Questions arise regarding the suitability of employing maximal exercise testing in a population characterized by debilitating physical fatigue, particularly when this fatigue is reported to be exacerbated by physical activity"

" This concern is reinforced by Lapp, who reported that 74% of subjects diagnosed with (ME)CFS experienced worsening fatigue after VO_2 max testing that resulted in an average relapse period of 8.82 days"

"Research studies in (ME)CFS that employ VO_2 max testing may attract only the more robust subjects, resulting in the exclusion of a vast and perhaps more representative section of the population under study from being assessed"

2003

RNase L in Health and Disease – What did we learn recently? Patrick Englebienne
JCFS 2003:11:2:97-109

"RNase L is central to the innate cellular defence mechanism induced by type 1 interferons during intracellular infection"

"In absence of infection, the protein remains dormant"

"Recent evidence indicates, however, that the protein is activated in absence of infection and may play a role in immune activation"

"A deregulation of this pathway has been documented in immune cells of (ME)CFS patients"

"This protein escapes the normal regulation which implies the development of a cascade of unwanted cellular events"

"Abnormal activation of the innate immunity IFN-alpha/beta pathway is progressively surfacing in the pathogenesis and maintenance of (other) poorly understood clinical condition, including not only (ME)CFS but also lupus"

"Data indicate that the RNase L/RLI 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"

"Observations from our laboratory are likely to indicate the presence of abnormally high levels of oligonucleotides in the serum of (ME)CFS patients when compared to healthy controls. Abnormally high oligonucleotides levels are capable of deregulating the 2-50AS".

2003

The Complexities of Diagnosis
Byron Hyde
In: Handbook of Chronic Fatigue Syndrome Leonard A Jason et al John Wiley & Sons, Inc. 2003

"ME in adults is associated with measurable changes in the central nervous system and autonomic function and injury to the cardiovascular, endocrine and other organs and systems"

"The patient with the diagnosis of ME/CFS is chronically and potentially seriously ill"

"These ME/CFS patients require a total investigation and essentially a total body mapping to understand the pathophysiology of their illness and to discover what other physicians may have missed"

"The chronic ME/CFS patient deserves, at least once, a complete investigation that includes mapping of (i) body structure (ii) organs and (iii) systems. Patients routinely arrive in my office telling me they have had a complete workup, but few of these patients have had what I consider to be even basic investigation"

"The underlying pathophysiologies are so varied that it is unreasonable and perhaps even dangerous to suggest or embark on an uniform treatment"

"Physician(s) and even Government agencies have increasingly tended to speak about "CFS" as a specific disease entity with specific treatments. Whether this treatment protocol employs pharmaceuticals (or)

cognitive retraining, these treatment modalities and philosophies are not medically justifiable and are often potentially dangerous to the patient"

"The development of Western medicine was based on autopsy, physiology, pathology, and reproducible tests. The goals were to define and, where possible, treat the causes of the disease process. This philosophy has been the basis for almost all of the great medical cures and treatments for specific diseases. To date, however, this approach has largely been missing in the investigation and understanding of ME/CFS"

"There has been an immoral intervention by the insurance industry into the philosophy of physicians treating this group of disease entities"

"This corporate insurance company intervention has used the mechanism of sponsoring medical symposiums to produce a uniform, insurance-friendly policy"

"Some of these pain mechanisms are probably vascular (which) may suggest injury to the autonomic nervous system"

"A patient with ME is a patient whose primary disease is central nervous system change, and this is measurable"

"The gradual onset group is of particular concern to me. It is in this group that occult disease, whether malignant or vascular injury of the CNS or cardiac system, is most frequently observed"

"Whether a patient fell ill abruptly or gradually, or has been ill for many years, is no excuse not to search for a potentially treatable cardiac, vascular, or other organ illness"

"Without being able to understand and measure the nature of the underlying disease, it is impossible to measure the effectiveness of any treatment"

"The severity of ME/CFS illness is not usually accompanied by significant observable changes in the regular physical examination. This causes some physicians to assume that there is no major disease present in patients with ME/CFS"

"These patients have obvious CNS injury but simply do not fit into neat categories. A physician who saw some of these patients for only up to one hour would conclude that (there was) nothing wrong. During the course of a day's examination, the patient may change from a brighter than normal person to one who resembles a blank-faced zombie, a patient who can talk and walk only with difficult, or not at all"

"Of the 20 abnormal physical findings in these patients, none is strong enough to excite most neurologists "(*the findings include pallor of the face; Parkinsonian rigidity of facial expression; altered walk; scanning and disjointed speech, with slurring; Sicca syndrome; drenching sweats; Raynaud's phenomenon; unequal pupils; tongue tremor; positive modified Romberg; cogwheel leg raising and lowering; frequently reported muscle twitching; marked falling pulse pressure in arterial pressures taken first when prone, then when sitting and then when standing; rapid heart rate on minor activity such as standing; unusual sensitivity of cervical vertebrae area; laryngeal stridor when fatigued, nodular thyroid).*

"Even with major thyroid disease, the TSH may be normal. I do a thyroid ultrasound on all ME/CFS patients. Their thyroid pathology is part of a general autoimmune dysfunction, certainly involving the CNS but other areas as well"

"NeuroSPECT scans in these patients, as well as their immune tests, tend to be grossly abnormal. The SPECT immune abnormalities tend to persist"

"Low levels of elevated ANA are almost to be expected in many ME/CFS patients, particularly early in their illness"

"It is amazing how few patients have had a chest X-ray, and at times I find major lung, mediastinum and cardiac pathology"

"Gross observable pituitary anomalies occur with increased frequency in this group"

"Most physicians would not find (such) tests alarming unless they believe that ME/CFS is an invented phenomenon"

"During the early days or weeks of the disease, the patient may have a significant increase in intracranial pressure"

"Many patients with acute onset ME/CFS may demonstrate oligoclonal bands in their spinal fluid"

"The most important tests that I do are Doppler scans and echocardiograms. They are more productive than MRIs or almost any other group of tests in uncovering pathology in ME/CFS patients"

"Dr John Richardson in Newcastle upon Tyne has followed ME patients for three to four generations. He has repeatedly demonstrated that many ME patients go on to develop structural heart injury"

"In patients with ME/CFS it is possible to demonstrate spasmodic disease of both major and smaller arteries"

"Left middle cerebral arterial field hypoperfusion is typical of ME"

"Early on in ME/CFS disease, you will find a small number with enlarged spleens"

"I routinely find pelvic pathology in as many as 30% of females"

"Patients with ME/CFS frequently cannot do exercise tests"

"I have seen some ME patients with a circulating blood volume of less than 50% and a very large number with the range 60% to 70%. What this means is that there may be a reduced perfusion of oxygen"

"When blood flow to the heart decreases sufficiently, the organism has an increased risk of death"

"When blood flow decreases, pressoreceptors decrease blood flow to non-cardiac organs and shunt blood to the heart to maintain life. This, of course, robs those areas of the body that are not essential for maintaining life and means the brain, muscles, and peripheral circulation are placed in physiological difficulty"

"It probably suggests an intrinsic autonomic failure in these patients"

"Another finding that we frequently discover is referred to as a vasculitis pattern. This change is identical to what one finds in a patient with HIV dementia. Patients with this vasculitis pattern are some of our most severely affected"

"Patients who arrive at the office (have sometimes) been dismissed as psychiatric or faking. It is in these patients that I find all of the pathology, and some of it is obvious"

"Rarely do physicians do more than a routine series of tests"

"The belief that ME/CFS is a psychological illness is the error of our time"

"Thirty years ago when a patient presented to a hospital clinic with unexplained fatigue, any medical school physician would have told the students to search for an occult malignancy, cardiac or other organ disease, or chronic infection. The concept that there is an entity called CFS has totally altered that essential medical

guideline. Patients are now being diagnosed with CFS as though it were a disease. It is not. It is a patchwork of symptoms that could mean anything".

2003

Functional Status, Neuropsychological Functioning, and Mood in Chronic Fatigue Syndrome
Lana A Tiersky Benjamin Natelson et al
J Nerv Ment Dis 2003:191:324-331

"Individuals with (ME)CFS face chronic physical debilitation, reduced neuropsychological functioning, and changes in emotional well-being that signficiantly detract from quality of life"

"The role of psychiatric disturbance remains unclear"

"The findings of the current investigation lend support to the notion that there is a subgroup of patients with (ME)CFS but no psychiatric illness"

"The patients with (ME)CFS in the current investigation showed a worse health-related quality of life than did healthy controls in almost every domain. In fact, the patients with (ME)CFS (indicated) profound physical impairment. These scores tended to be below the published norms for patients with Type II diabetes, arthritis, cancer, congestive heart failure, hypertension, and myocardial infarction".

2004

Quotation from Charles Lapp, Professor of Community and Family Medicine, Duke University, Charlotte, North Carolina, USA
Co-Cure, 3rd June 2004

"There is no word in the English lexicon that describes the lack of stamina, the paucity of energy (and) the absolute malaise that accompanies this illness"

2004

Chronic fatigue syndrome: intracellular immune deregulations as a possibly aetiology for abnormal exercise response Jo Nijs Kenny De Meirleir et al
Med Hypotheses 2004:62:5:759-765

"The exacerbation of symptoms afer 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 deregulation in (ME)CFS patients"

"This manuscript (explains) that the deregulation of the 2-5A synthetase / RNase L pathway may be related to a channelopathy, 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"

2004

Standing up for ME Vance Spence and Julian Stewart
Biologist 2004:51(2):65-70

"It has been argued by some that orthostatic intolerance is nothing more than cardiovascular deconditioning associated with bed rest (but) vascular dysfunction appears to be best supported by the available data"

"Some subjects show autonomic dysfunction in their internal organ vasculature"

"Evidence points towards enhanced pooling within the internal organs and pelvic regional circulations"

"(ME)CFS patients are sensitive to the endothelium-dependent acetylcholine. Such sensitivity is unusual if not unique and it is clear that the sensitivity is specific to (ME)CFS patients"

"There is clearly a problem with local vasodilator and vasoconstrictor mechanisms in these patients"

"Of further interest are potential autoimmune mechanisms"

"There is a significant body of evidence pointing to vascular dysfunction in the peripheral circulation of patients with (ME)CFS and this is in addition to references to blood flow abnormalities with the central nervous system using SPECT imaging"

"Despite this data being widely available, the research interest in the illness is fragmented, largely due to problems of nomenclature".

2004

Prevalence of abnormal cardiac wall motion in the cardiomyopathy associated with incomplete multiplication of Epstein-Barr Virus and/or cytomegalovirus in patients with chronic fatigue syndrome
Lerner AM et al
In Vivo 2004:18:4:417-424

"We report a prospective consecutive case control study from 1987-1999 of cardiac dynamics in 98 (ME)CFS patients"

"The prevalence of abnormal cardiac wall motion at rest in (ME)CFS patients was 11%"

"A progressive cardiomyopathy caused by incomplete virus multiplication of EBV and/or HCMV in (ME)CFS patients is present".

2004

The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfil the criteria Gwen Kennedy Vance Spence et al
Ann Epidemiol 2004:14:95-100

"The Centres of Disease Control (CDC) 1994 definition of (ME)CFS is very broad and there have been suggestions that it lacks specificity. To test this, we have compared three groups of patients, all of whom fulfil the criteria but self-report different aetiologies"

"Differences in simple, easily performed clinical outcome measurements can be observed between groups of patients, all of whom fulfil the CFS criteria for (ME)CFS. It is likely that their response to treatment may also vary"

"The specificity of the (ME)CFS case definition should be improved to define more homogenous groups of patients for the purposes of treatment and research".

2004

Exercise lowers pain threshold in chronic fatigue syndrome
Alan Whiteside Stig Hansen Abhijit Chaudhuri
Pain 2004:109:3:497-499

"Pain is considered to be an important reason for disability in (ME)CFS. Patients with (ME)CFS experience muscle pain and post-exertional malaise following sustained exercise"

"In this study we compared the pain threshold of (ME)CFS patients with age and sex matched control subjects following exercise"

"This is the first study which has looked objectively at the effect of graduated physical exercise on pain threshold in patients with CDC defined (ME)CFS"

"Post-exertional myalgia and chronic muscle pain have implications for successful rehabilitation programmes in (ME)CFS"

"In our experiment, male and female (ME)CFS patients did not differ from healthy controls in terms of their pain threshold at the beginning of the exercise protocol but had a progressive decline in sensory threshold to pain after exercise"

"Our results indicate that in comparison to the healthy controls, (ME)CFS subjects had incremental reduction in pain threshold after modest exercise"

"(This) may be indicative of a dysfunction associated with the central anti-nociceptive mechanism".

2004

Advances in the biomedical understanding of ME Neil Abbot Vance Spence
InterAction: May 2004

"For thousand of people with ME, living day to day with debilitating malaise and pain, the future must sometimes seem bleak. People remain unwell with a physical illness and struggle to get appropriate recognition and help from healthcare professionals"

"It is becoming clear from a range of studies that altered biochemical processes can be reproducibly observed in groups of ME patients, as seen from investigations of anti-viral pathways and oxidative stress"

"The ability to reproduce a finding is crucial and at the core of scientific investigation. Indeed it is the basis of evidence-based medicine"

"Research papers from at least five different research groups have shown excessive free radical generation in blood, urine and muscle tissue of (ME)CFS patients. One research group has reported that oxidative by-products were raised by as much as 40% in these patients compared with healthy control subjects"

" It is important to discover the source(s) of these molecules, whether from excessive immune activity, chronic infections, or abnormalities within muscle tissue. There is sufficient evidence to implicate all three of these pathways"

"This Unit has found that vascular responses to acetylcholine are increased compared with matched control subjects. (*Acetylcholine is a substance produced by the layer of endothelial cells lining all blood vessels and which causes them to open*). This finding is in contrast to research into a wide variety of cardiovascular diseases. Why should (ME)CFS patients have this seemingly unique thumbprint of increased blood vessel sensitivity to acetylcholine?"

"In addition, we have found that levels of high-sensitivity C-reactive protein, recognized as a robust marker of the inflammatory process, are significantly increased in (ME)CFS patients"

"We have also observed that a type of white blood cell (called neutrophils) from these patients had a larger proportion of dying (apoptotic) cells than in healthy subjects"

"These findings are consistent with an activated inflammatory process"

"Reports in the older literature (1950s and 1960s) included the presence of clinical signs (eg, muscle weakness/swelling, sensory nerve changes etc). If these results can be reproduced by other researchers, the implications for further research and for the management of patients are significant. Will the presence of clinical signs – believed by many healthcare professionals today to be non-existent in ME patients – come to be recognized as important markers of physical illness?"

"Our purpose is to show that dedicated investigators who receive sufficient funding can uncover biological anomalies that might help to explain many of the clinical features associated with the illness"

"The (label) 'CFS' makes no attempt to differentiate patients on the basis of severity of illness or level of disability"

"The results of at least seven scientific studies have highlighted the desirability of the extraction of 'research-based subsets' of 'CFS' patients. Our own research (demonstrated that three separate groups --- (ME)CFS, fibromyalgia and Gulf War veterans ---all fulfilled the CDC 1994 criteria for 'CFS')"

"Shockingly, the mean QOL (quality of life) scores for all three groups as regards limitations on physical functioning were very low, similar to those found in people with AIDS and multiple sclerosis"

"The seemingly obscure point about diagnostic classification is actually very important, because the treatment and resources that patients receive is determined, to a large part, by the diagnosis they are given".

2004

Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome
Okada T et al
BMC Neurol 2004:4:1:14

"The diagnosis of (ME)CFS can be made only after alternative medical and psychiatric causes of chronic fatigue have been excluded"

"Recent studies found biochemical and genetic characteristics in (ME)CFS patients, such as a decreased concentration of serum acetyl-L-carntine, a serotonin-transporter gene-promoter polymorphism, and autoantibodies against the muscarinic cholinergic receptor"

"In (ME)CFS patients, a significant decrease in the uptake of acetyl-L-carnitine was found in several regions of the brain"

"To measure the reduction in gray-matter volume, we conducted voxel-based morphometry with high-resolution magnetic resonance imaging (MRI)"

"All (ME)CFS patients were unable to carry out normal activities"

"The present study provides the first report of focal gray-matter atrophy in the prefrontal cortex of (ME)CFS patients"

"Prefrontal pathology has been reported in MS with pathological fatigue"

"Although MS should be excluded in the diagnosis of (ME)CFS, the similar clinical manifestations of the illnesses suggest that a common pathogenesis underlies the symptoms of fatigue in both disorders"

"In the present study, right dorsolateral prefrontal-cortex atrophy was significantly correlated with the severity of fatigue"

"The results of the present study suggest that the dorsolateral prefrontal cortex might be an important component of the neural substrates that regulate the sensation of fatigue".

2004

Illness and Disability in Danish Chronic Fatigue Syndrome patients at diagnosis and five year follow-up
MM Anderson et al
Journal of Psychosomatic Research 2004:56:2:217-229

In this Danish study, patients meeting both the 1988 and the 1994 criteria were assessed at diagnosis and at five year follow-up.

"Five years (after diagnosis), work disability was very high, social isolation remained high (but) emotional adjustment improved"

"There were increased problems with reading and with allergies"

"(ME)CFS patients exhibit severe, long-term impairment. Substantial improvement is uncommon (at) less than 6%".

2004

Quality of Life and Symptom Severity for Individuals with Chronic Fatigue Syndrome: Findings from a Randomised Clinical Trial Renee R Taylor
American Journal of Occupational Therapy 2004:58:35-43

"Chronic fatigue syndrome (ME) is an often trivialized, yet profoundly disabling condition"

"Much energy has been directed towards controversy over whether its cause is predominantly physical or psychological (labeled as a 'somatoform disorder or functional somatic syndrome') "

"Perhaps as a result there has been a corresponding lack of attention to the impact of this syndrome on quality of life and everyday functioning"

"**In comparison with other chronic illnesses such as multiple sclerosis, untreated hypothyroidism, end-stage renal disease, and heart disease, individuals with (ME)CFS show markedly higher levels of disability"**

"These physical, psychological and social limitations, in conjunction with experiences of social stigma (and) public misunderstanding about (ME)CFS, (as well as) frequently strained relationships with healthcare providers, have led individuals with (ME)CFS to report consistently low levels of quality of life"

"In a growing body of research, quality of life issues have been investigated in (ME)CFS samples. Findings from these studies demonstrate the wide-ranging impact of (ME)CFS in quality of life"

"It is possible that the disabling, severe nature of the fatigue, cognitive difficulties and multiple physical symptoms of (ME)CFS influence the rate of responsiveness to certain kinds of rehabilitative interventions such as those which focus on life-style change, coping, and changes in role functioning".

2004

Altered central nervous system signal during motor performance in chronic fatigue syndrome
Aiemionow V Calabrese L et al
Clin Neurophsyiol 2004:115:10:2372-2381

"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"

"Major findings include: (i) motor performance of the (ME)CFS patients was poorer than the controls (ii) relative power of EEG theta frequency band was significantly greater in the (ME)CFS than the control group (iii) the amplitude of MRCP negative potential was higher in the (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".

2004

Fatigue in neurological disorders Abhijit Chaudhuri Peter O Behan
Review: Lancet 2004:363:978-988

"Chronic fatigue is a typical symptom of neurological diseases, and is most disabling in multiple sclerosis, postpoliomyelitis, poststroke, and in (ME)CFS"

"Our understanding of the neurobiological basis of fatigue is imperfect. As a result, (ME/CFS) has been regarded by some as a medically unexplained symptoms due to somatisation"

"Premature exertional muscle fatigability, exercise-induced cramps and myalgia are the symptoms triad of metabolic myopathies. These symptoms are absent at rest and are induced by exercise"

Exertional fatigue, muscle fatigability, and exercise intolerance, with or without muscle weakness, are symptoms of neurological diseases attributable to mutations in mitochondrial DNA"

"The pattern of muscle weakness in mitochondrial myopathy involves muscles outside the pelvic and shoulder girdles, eg. muscles of the eye and diaphragm"

"Anaesthetic procedures should be carefully reviewed in people with fatigue. Failure to recover from anaesthesia is a recognized complication in patients with neuromuscular junction transmission disorders"

"Cerebral vasculitis (is) symptomatic (of) neurological disorders of central fatigue"

"In susceptible individuals, environmental stressors induce changes in the neuroendocrine axis mainly through the HPA axis and the norepinephrine system"

"Conventional antidepressants could precipitate or worsen fatigue because of their side effects"

"Many doctors prefer to invoke a psychiatric explanation for fatigue when patients' symptoms do not fit a typical medical or neurological diagnostic category"

"**To imply that fatigue is a medically unexplained, non-organic symptom in patients who do not have a primary psychiatric diagnosis would be incorrect and inappropriate. As in other complex medical disorders, only open minded people – who are willing to consider observations and explanations at many different levels – are likely to succeed in offering the right solutions".**

2004

Selective monocyte and Granulocyte Apheresis as a Possible New Treatment for Chronic Fatigue Syndrome
Boye B et al
Journal of Psychosomatic Research 2004:56:6:633

"Immune dysfunction in patients with (ME)CFS has been widely reported, and in some patients (there are) cytokine abnormalities that include perturbations in plasma levels of pro-inflammatory cytokines and (a) decrease in the ratio of Type 1 to Type 2 cytokines"

"Selective monocyte and granulocyte apheresis is approved for treatment of certain immune disorders in Europe and Japan (that) has been shown to improve symptoms in disorders such as inflammatory bowel disorder, Bechet disease and cancer"

"Many (ME)CFS patients do not respond to medical or behavioural therapy and new treatment options are needed for the severely affected patients"

"((ME)CFS) patients do not have major psychopathology explaining the symptoms"

"Clinical observation and assessment of vital signs for the first four (ME/CFS) patients indicated that the patients showed greater autonomic instability than other patient groups that have received this treatment".

2004

Increased neutrophil apoptosis in chronic fatigue syndrome Kennedy G Spence V et al
J Clin Pathol 2004:57:8:891-893

"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 high numbers of apoptotic neutrophils, lower numbers of viable neutrophils, increased annexin V binding, and increased expression of the death receptor, tumour necrosis factor receptor-1 on their neutrophils than did the healthy controls"

"Patients with (ME)CFS also had raised concentrations of active TGFbeta 1"

"These findings provide new evidence that patients with (ME)CFS have an underlying detectable abnormality in their immune cells".

2004

Differential-display PCR of peripheral blood for biomarker discovery in chronic fatigue syndrome
Steinau M, Unger ER, Vernon SD, Jones JF, Rajeevan MS
J Mol Med 2004: (e-Pub ahead of print)

"We used differential-display PCR of peripheral blood mononuclear cells to search for candidate biomarkers for (ME)CFS"

"Differential-display PCR is a powerful tool for identification of candidate biomarkers"

"Most (86%) of the differences between (patients and controls) were present at baseline"

"Six of the ten genes with verified differential expression have functions related to immune response"

"This adds strength to the theory that dysregulation of immunity plays a major role in the biology of (ME)CFS"

"In (ME)CFS patients, intracellular perforin was reduced in natural killer and cytotoxic T cells cells" (*note: one would expect high levels of peforin in viral infection*)

"We determined that a (significant) sequence was upregulated threefold in (ME)CFS"

"Eighteen novel transcripte were discovered"

"We found seven bands with sequences that did not match any known human or pathogen DNA"

"In summary, the majority of the candidate genes identified in this biomarker discovery study are related to immune function"

"These candidate biomarkers must be validated. These validation studies should also include comparison groups of subjects with illness attributed to immune alterations such as inflammatory bowel disease, Sjogrens syndrome, systemic lupus erythematosus and multiple sclerosis".

2004

Press Release: AACFS, 7th October 2004

Charles Lapp, Professor of Community Medicine, Duke University, Charlotte, USA was the contact person for this Press Release by the American Association of Chronic Fatigue Syndrome, which was unequivocal: CDC researchers Dr Williams Reeves, Chief of the (ME)CFS research programme, reported that (ME)CFS patients "**are more sick and have greater disability than patients with chronic obstructive lung or cardiac disease, and researchers found that the strongest predictor of the development of (ME)CFS is the severity of the acute ullness at onset, and that psychological factors played no role".**

2005

Spinal Fluid Abnormalities in Patients with Chronic Fatigue Syndrome Benjamin Natelson et al
Clin Diagn Lab Immunol 2005:12:1:52-55

"Arguments exist as to the cause of (ME)CFS. Some think that it is an example of symptoms amplification indicative of functional or psychogenic distress, while our group thinks that some (ME)CFS patients may have brain dysfunction"

"We did spinal taps (*lumbar puncture)* on (ME/CFS patients) fulfilling the 1994 case definition and on healthy controls"

"We found that signficiantly more (ME)CFS patients had elevations in either protein levels or number of cells than healthy controls (30% versus 0%)"

"13 (ME)CFS patients had protein levels and cell numbers that were higher than laboratory norms"

"Patients with abnormal fluid had a lower rate of comorbid depression than those with normal fluid"

"These results support two hypotheses: that some (ME)CFS patients have a neurological abnormality that may contribute to the clinical picture of the illness, and that immune dysregulation within the central nervous system may be involved in this process".

2005

Exercise capacity and immune function in male and female patients with chronic fatigue syndrome
Snell CR et al
In Vivo 2005:19:2:387-390

"Hyperactivation of 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 capacities of (ME)CFS deregulation of the RNase L pathway and (ME)CFS patients with normal regulation"

"A significant multivariate main effect was found for immune status, with no gender effect or interaction"

"These results implicate abnormal immune activity in the pathology of exercise intolerance in (ME)CFS and are consistent with a channelopathy involving oxidative atress and nitric-oxide-related toxicity".

2005

Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise Jammes Y et al
J Intern Med 2005:257:3:299-310

"Our observations corroborate several previous observations based on nearly the same exercise protocol"

"Oxidative stress is highly expressed in skeletal muscles because their antioxidant defences are poor"

"The early changes in blood redox status here measured in (ME)CFS patients during exercise have real significance"

"Data in the literature also indicate an increased blood oxidative stress in resting (ME)CFS patients. Another observation is in favour of an increased activity of intramuscular antioxidants"

"Such an accentuated exercise-induced oxidative stress in (ME)CFS patients could explain the enhanced oxygen uptake by the exercising muscles suggested by our measurement of an elevated arterio-venous oxygen difference"

"The present study in (ME)CFS patients shows marked alterations of muscle excitability which began early after the exercise had stopped and culminated at the end of the 30- minute recovery period"

"The postexercise-altered muscle membrane excitability reported here in (ME)CFS is not explained by any impairments of potassium outflow during muscle excitation or inflow during the recovery period"

"In (ME)CFS patients, the accentuated and prolonged postexercise oxidative stress may be responsible for muscle membrane alterations with the consequences of the impaired membrane excitability described here"

"Thus, as in inherited muscular dystrophy, an increased level of free radical damage may be a contributor to the underlying defects and symptom presentation".

2005

Exercise responsive genes measured in peripheral blood of women with Chronic Fatigue Syndrome and matched controls Toni Whistler James F Jones Elizabeth R Unger Suzanne Vernon
BMC Physiology 2005:5:5

" Chronic fatigue syndrome is defined by debilitating fatigue that is exacerbated by physical or mental exertion. To search for markers of (ME)CFS-associated post-exertional fatigue, we measured peripheral blood gene expression profiles of women with (ME)CFS and matched controls before and after exercise"

"Activities that are physiological stressors, such as physical exercise, exacerbate the symptoms that define (ME)CFS"

"We used gene expression profiling of peripheral blood to evaluate differences between (ME)CFS subjects and sedentary healthy controls both before and following an exercise challenge"

"Of importance, most differences were present prior to the exercise challenge. These differences were in G protein-coupled receptor and ion transport and ion channel activity ontologies"

"21 genes were identified as being differentially expressed"

"Among the 21 genes, 16 could be categorized in the Gene Ontology (GO) of biological processes and 15 in molecular function. The most significant categories pertained to the biological process of transport (both vesicle-mediated and protein transport). 5 of the 21 genes were involved in this process"

"5 genes classified in vesicle-mediated and protein ontologies differed between (ME)CFS and control subjects"

"For the chromatin architecture category, the (ME)CFS comparison highlighted 7 overlapping ontologies (containing 59 unique genes), compared with 1 ontology of 33 genes in the control subjects"

"**Exercise-related changes that were seen only in (ME)CFS subjects were related to G-protein-coupled receptor signaling"**

"Baseline differences between (ME)CFS subjects and controls that continued after exercise involved GO terms relating to ion transport. After exercise, these differences appear to be amplified"

"Interestingly, complement activation was one of the exercise-induced differences between subjects and controls that was present only after challenge"

"Gene expression profiling affords a unique opportunity to characterise (ME)CFS at a systems biology level"

"We found that (ME)CFS patients had different blood mononuclear cell gene expression patterns than controls"

"**Because this difference in gene expression is so dramatic, it implicates a fundamental peturbation in the biochemical activity of lymphocyte and monocyte peripheral blood fractions from (ME)CFS subjects compared with control subjects that does not affect classical immunologic markers that have been shown to be unaffected in (ME)CFS patients"**

"It is evident that ion transport and ion channel activity segregate cases from controls and that exercise seems to intensify these differences"

"Several other conditions have been reported that are known to be caused by abnormal ion channels. These include myasthenic syndromes, multiple sclerosis, and polyneuropathies"

"The most obvious exercise-induced changes in (ME)CFS cases pertain to gene regulation at the point of chromatin structure"

"It is hoped that this more encompassing approach to (ME)CFS research will open many doors to the understanding of this syndrome".

2005

Chronic Fatigue Syndrome: The Need for Subtypes Leonard A Jason et al
Neuropsychology Review 2005:15:1:29-58

"(ME)CFS represents a heterogenous syndrome and the lack of consistency in studies might very well be (due) to the failure to routinely classify (ME)CFS cases into subtypes"

"It is clear that the current cohort of individuals diagnosed with (ME)CFS is a diverse group"

"The current method of grouping together all individuals who meet diagnostic criteria is complicating the identification of biological biomarkers of the subgroups"

"When diagnostic categories lack reliability and accuracy, the quality of treatment and clinical research can be significantly compromised"

"If a specific treatment is indicated for a given disorder, a misdiagnosis may lead to improper treatment and in cases of severe illness, the matter of an incorrect diagnosis can have serious consequences"

"**If inappropriate use of a case definition leads to the inclusion of individuals who have a purely psychiatric condition, this heterogeneity of patients with (ME)CFS and psychiatric conditions will present difficulties in interpreting the results of epidemiologic and treatment studies"**

"Groups need to be differentiated and analysed separately as opposed to being collapsed into one category"

"The identification of clinically significant subgroups is the logical next step in furthering (ME)CFS research"

"Subgrouping is the key to understanding how (ME)CFS begins, how it is maintained, how it can be prevented, treated, and cured".

2005

Urinary and plasma organic acids and amino acids in chronic fatigue syndrome Jones MG et al
Clinica Chimica Acta; International journal of Clinical Chemistry: Epub June 28 2005

"We have made a detailed analysis of plasma and urinary amino acids and of urinary organic acids from patients with (ME)CFS and from matched control groups"

"Result provide some evidence in patients with (ME)CFS for underlying inflammatory disease and for a lowered threshold for muscle micro-injury. These factors may provide a basis for the fatigue and muscle pain that are the major symptoms in these patients".

2005

Gray matter volume reduction in the chronic fatigue syndrome Floris P de Lange et al
http://www.meresearch.org.uk/archive/grayymatter.html

"The chronic fatigue syndrome is a disabling disorder of unknown aetiology. The symptomatology suggests that this disorder could be related to alterations at the level of the central nervous system. In this study we have used an automated and unbiased morphometric technique to test whether (ME)CFS patients display structural cerebral abnormalities"

"We observed significant reductions in global gray matter volume in (ME)CFS patients, as compared with matched control participants"

"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 pathophsyiology of (ME)CFS".

2005

Syndrome linked to neurological abnormalities: research provides more evidence that chronic fatigue syndrome is a legitimate medical condition James N Baraniuk et al
BMC Neurology:2005:November (online)

Researchers at Georgetown University Medical Centre have found that (ME)CFS may be rooted in distinct neurological abnormalities that can be medically tested.

This research provides objective, physiological evidence that (ME)CFS can be considered a legitimate medical condition.

"One reason that (ME)CFS is difficult to diagnose is because it shares symptoms with many other diseases, including multiple sclerosis and lupus.

The Georgetown study reveals that patients with (ME)CFS have a set of proteins in their spinal cord fluid that were not detected in healthy individuals.

James Baraniuk, Assistant Professor of Medicine at Georgetown, said: "Our research provides initial evidence that (ME)CFS may be (a) legitimate neurological disease and that at least part of the pathology involves the central nervous system".

By examining spinal cord fluid in patients with (ME)CFS and in healthy individuals, the researchers found that (ME)CFS patients have 16 proteins that healthy individuals do not.

Five of these 16 proteins are found in all patients with the illness but in none of the controls.

The results indicate that those 16 proteins could possibly serve as a 'biosignature' for the disease.

2005

Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms
Gwen Kennedy Vance Spence et al
Free Radical Biology and Medicine 2005:39:584-589

"There is mounting evidence that oxidative stress and, more specifically, lipid peroxidation, contribute to the disease process and to some of the symptoms in (ME/CFS)"

"The term oxidative stress is used to describe a number of chemical reactions involved in the production of free radicals and other reactive molecules that are potentially able to induce cellular injury"

"While free radicals may generate tissue oxidative injury, it is evident that other oxidative by-products, especially isoprostanes (*highly noxious by-products of abnormal cell membrane metabolism*) may be even more pivotal in the pathological process"

"Such biological effects may be instrumental in the development of some of the vascular features that charactise patients with (ME)CFS"

"The novel findings in this study are that patients with (ME)CFS have significantly elevated levels of F_2 isoprostanes alongside other key markers of oxidative stress and that these correlate with various (ME)CFS symptoms"

"This is the first time that elevated levels of isoprostanes have been reported in patients with (ME)CFS"

"Isoprostanes have been shown to be powerfully vasoconstricting and are involved in endothelial injury"

"Research has demonstrated that incremental exercise challenge potentiates a prolonged and accentuated oxidant stress that might well account for postexercise symptoms in (ME)CFS patients"

"(ME)CFS is also associated with immune activation and an equally compelling case can be made for free radicals and reactive molecular internmediates being generated by activated white blood cells as a consequence of either persistent infection or environmentl stressors"

"It could be suggested that (ME)CFS is an inflammatory condition (which) could explain many of the pathological manifestations that underlie the illness".

2005

Decreased DHEA sulphate but normal insulin-like growth factor in Chronic Fatigue Syndrome
Maes M et al
Neuro Endocrinol Lett:2005:26:5

"There are reports that (ME)CFS may be accompanied by changes in hormones such as DHEA and insulin-like growth factor (IGF1)"

"This study examines serum concentrations in patients with (ME)CFS and controls"

"We found signficiantly lower serum DHEAS concentrations in (ME)CFS. The decrease in serum DHEAS was highly sensitive and specific for (ME)CFS"

"The results show that (ME)CFS is accompanied by lowered levels of DHEAS and that the latter may play a role in the immune defect and the inflammatory pathophysiology of (ME)CFS".

2005

Chronic fatigue syndrome is associated with diminished intracellular perforin
Maher KJ Klimas NG Fletcher MA
Clin Exp Immunol 2005:142:3:505-511

"Diminished NK cell cytotoxicty is a frequently reported finding (in ME/CFS)"

"Perforin is a protein found within intracellular granules of NK and cytotoxic T cells and is a key factor in the lytic processes mediated by these cells"

"A significant reduction in the NK cell 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 to suggest a T cell associated cytotoxic deficit in (ME)CFS"

"Because perforin is important in immune surveillance and homeostasis of the immune system, its deficiency may prove to be an important factor in the pathogenesis of (ME)CFS".

2005

Gene expression in peripheral blood mononuclear cells from pateitns with chronic fatigue syndrome
N Kaushik SCM Richards ST Holgate JR Kerr et al
J Clin Pathol 2005:58:826-832

"Although (ME)CFS is now recognized as a genuine clinical entity, the pathological basis remains poorly understood"

"To investigate the hypothesis that abnormalities of gene regulation occur in (ME)CFS, we studied gene expression in peripheral blood mononuclear cells of patients with (ME)CFS and normal blood donors"

"Sixteen genes were confirmed as having an expression profile associated with (ME)CFS"

"The expression of 16 genes was signficiantly different in patients compared with controls"

"These genes may be important in the pathogenesis of (ME)CFS and can be grouped according to immune, neuronal, mitochdonrial and other functions that have particular relevance to our present knowledge of the epidemiology of (ME)CFS"

"These findings are consistent with previous work showing that patients with (ME)CFS have evidence of immune activation, such as increased numbers of activated T cells and cytotoxic T cells, and raised circulating cytokine concentrations"

A neuronal component is identified that is associated with central nervous system hypomyelination and encephalopathy (the authors specifically note the association of organophosphates and chemical warfare agents) and that neuronal gene involvement in (ME)CFS has also been reported by Vernon et al.

The authors provide evidence of mitochondrial gene upregulation and observe: "The upregulation identified in our present study may represent a common host response to persistent infection with several different viruses"

"The involvement of genes from several disparate pathways suggests a complex pathogenesis involving T cell activation and abnormalities of neuronal and mitochondrial function, and suggests possible molecular bases for the recognized contribution of organophosphate exposure and virus infection respectively".

2005

Can the Social Model Explain All of Disability Experience? Perspectives of Persons with Chronic fatigue Syndrome Renee R Taylor
Am J Occupational Therapy 2005:59:497-506

*"*The social model of disability has had a major influence on the academic field of disability studies and on contemporary understandings of the causes and experience of disability"

"The purpose of this study was to examine the adequacy of the social model for explaining the disability experience of persons with (ME)CFS"

"(A) factor that differentiates the experiences of (ME)CFS from that of a more traditional disability is its invisibility"

"As a consequence of professional misinformation, individuals with (ME)CFS consistently report negative experiences with health care workers characterized by disbelief, lack of knowledge, misunderstanding, minimization of symptoms, over-emphasis on psychological explanations, and a general lack of responsiveness (as well as a) lack of validation of symptoms"

"It is important to recognize that (the social model) may not capture the full reality of disability".

POSTSCRIPT

No-one disputes that, as with virtually all serious and chronic diseases, there may be accompanying psychological problems, which is very different from asserting that the disorder is a primary psychiatric (behavioural) disorder.

As noted, the above examples are merely illustrative of the extensive evidence base that now exists about the organic nature of ME/CFS.

Many other equally relevant papers could have been included and have been omitted due only to space limitations.

The only possible explanation for the irrational denial and suppression of so much scientific evidence over so many years is the vested interests of all those who have gained materially from such continuing denial and suppression.

RECOMMENDED READING

1988

Myalgic Encephalomyelitis and Postviral Fatigue States A. Melvin Ramsay; second edition
Gower Medical Publishing, London, for the ME Association, 1988; pp 68

1991

The Disease of a Thousand Names David S Bell
Pollard Publications, PO Box 180, Lyndonville, New York, 1991; pp 198

1992

The Clinical and Scientific Basis of ME/CFS Ed: BM Hyde, J Goldstein, P Levine
The Nightingale Research Foundation, Ottawa Canada, 1992; pp 724

2002

Chronic Fatigue Syndrome and the Body's Immune Defence System. Roberto Patarca-Montero (Assistant Professor of Pathology, Harvard Medical School, Boston, USA)
The Haworth Medical Press, New York, 2002: pp122

2002

Chronic Fatigue Syndrome: A Biological Approach. Ed: Patrick Englebienne and Kenny De Meirleir
CRC Press, New York, 2002: pp 291

APPENDIX 1

Illustrations of actual quotations about patients with ME/CFS from Professor Simon Wessely

1988

Postviral fatigue syndrome: time for a new approach David AS Wessely S Pelosi AJ
BMJ 1988:296:696-699

"Future investigations and clinical practice must take into account the similarities between the symptomatology of the post-viral fatigue syndrome and that of common psychiatric disorders in the community".

1988

Myalgic encephalomyelitis, or what? Anthony David Simon Wessely Anthony Pelosi
Lancet 1988:July 9th, 100-101

"Though disordered immunity and persisting viral infection have recently attracted attention, it is important that immunologists do not deflect attention away from the wider (ie. psychiatric) aspects of the chronic fatigue / postviral syndrome".

1989

What your patients may be reading Wessely S
BMJ 1989:298:1532-1533

"Beard and Mitchell have returned to obscurity, but their disease (neurasthenia) is back with a vengeance. My local bookshop has just given ME the final seal of approval, its own shelf. **A little more psychology and a little less T-cells would be welcome".**

1989

Management of chronic (post-viral) fatigue syndrome Simon Wessely Anthony David Sue Butler Trudie Chalder
Journal of the Royal College of General Practitioners 1989:39:26-29

"Many patients referred to a specialized hospital with chronic fatigue syndrome have embarked on a struggle"

"This may take the form of trying to find an acceptable diagnosis, or indeed any diagnosis and may involve reading the scientific literature"

"One of the principal functions of therapy at this stage is to allow the patient to call a halt without loss of face"

"[ME patients are in] a vicious circle of increasing avoidance, inactivity and fatigue"

"The patient should be told that it is now time to 'pick up the pieces' (and) the process is a transfer of responsibility from the doctor to the patient, confirming his or her duty to participate in the process of rehabilitation in collaboration with the doctor"

"Occasionally patients may say they cannot take drugs (but) there is no clinical evidence that allergies exist in anything but a small number of sufferers, and their existence may be coincidental"

"Anxiety is often part of the syndrome (and) sexual problems occur in the majority of patients referred to hospital"

"The notion of allergies reinforces the view that the sufferer is under attack from outside elements which have nothing to do with himself or herself".

1989

Myalgic encephalomyelitis – a warning: Discussion Paper Simon Wessely
JRSM 1989:82:215-217

"It can be concluded that affective disorder is a common condition which shows systematic overlap with CFS. Sadly, few of the current workers in the field of CFS seem aware of this problem".

1989

Fatigue syndromes: a comparison of chronic 'postviral' fatigue with neuromuscular and affective disorders
S Wessely R Powell
JNNP 1989:52:940-948

"Seventy two percent of the CFS patients were cases of psychiatric disorder using criteria that excluded fatigue as a symptom"

"Attribution of symptoms to physical rather than psychological causes was the principal difference between matched CFS and psychiatric controls"

"Any abnormalities in muscle structure or function may result from physical inactivity"

"An alternative hypothesis is that all cases of CFS can be explained by disorder of mood".

1990

Attribution and self-esteem in depression and Chronic Fatigue Syndrome. R Powell R Dolan S Wessely
J Psychosom Res 1990:34:6:665-67.

"This research shows that in CFS, (patients) experience less guilt: such an external style of attribution has certain advantages; external attribution protects the patient from being exposed to the stigma of being labelled psychiatrically disordered, (affording) diminished responsibility for one's own health"

"Our results are close to those predicted by 'learned helplessness' "

"Inappropriate referrals to physicians can lead to extensive physical investigation that may then perpetuate the symptom pattern of physical attribution".

1990

Chronic fatigue and myalgia syndromes Wessely S. *In: Psychological Disorders in General Medical Settings. eds: N Sartorius et al pub: Hogrefe & Huber 1990*

"Most CFS patients fulfil diagnostic criteria for psychiatric disorder" "

Symptoms include muscle pain and many somatic symptoms, especially cardiac, gastrointestinal and neurological. Do any of these symptoms possess diagnostic significance? The answer is basically negative"

"**It is of interest that the 'germ theory' is gaining popularity at the expense of a decline in the acceptance of personal responsibility for illness"**

"Such attribution conveys certain benefits, in other words, there is avoidance of guilt and blame"

"It is this author's belief that the interactions of the attributional, behavioural and affective factors is responsible for both the initial presentation to a physician and for the poor prognosis".

1990

Old wine in new bottles: neurasthenia and ME Simon Wessely.
Psychological Medicine 1990:20:35-53

"It is assumed that ME is an organic disorder of the peripheral or central nervous system. In the initial reports this was indicated by frank neurological signs (but) the concept of ME has shifted. As in neurasthenia, the emphasis is on muscle fatiguability"

"In a current leading neurology text book (Adams and Victor, 1985) chronic fatigue, neurasthenia and depression are seen as synonymous"

"Mood disorder is found in many cases of ME but it is not the only psychiatric disorder (and) some patients do satisfy the criteria for anxiety and phobic disorders. Beard's neurasthenia began as a physical disease -- it provided the most respectable label for distressing, but not life-threatening complaints, one that conferred many of the benefits - and fewest of the liabilities- associated with illness. It was preferable to the alternatives --- hypochondria, malingering and insanity. There is little evidence of any change in the current era"

"Suggestible patients with a tendency to somatize will continue to be found among sufferers from diseases with ill-defined symptomatology until doctors learn to deal with them more effectively"

"The social processes that govern the creation of such illnesses remain obscure but one may argue that they represent culturally sanctioned expressions of distress"

"It has been shown that some patients have always preferred to receive, and well-meaning doctors to give, a physical rather than a psychological explanation for ill-defined illnesses associated with fatigue"

"Such uncritical diagnoses may reinforce maladaptive behaviour".

1990

Possible ME Simon Wessely.
The Practitioner 8 March 1990:234:195-198

"ME is a description, not a diagnosis".

1990

The chronic fatigue syndrome—myalgic encephalomyelitis or postviral fatigue.
S.Wessely PK Thomas
In: Recent Advances in Clinical Neurology. ed: Christopher Kennard. pub: Churchill Livingstone 1990 pp85-131

"There is now a consensus that physical signs are few or absent"

"A number of patients diagnosed as having benign myalgic encephalomyelitis who complained of persistent muscle weakness were examined neurologically by one of the authors of this chapter. In many of them, the usual findings of simulated muscle weakness were present"

"A physical diagnosis implies the illness has an external (physical) cause"

"Such attribution always confers certain benefits, irrespective of accuracy. In other words, there is avoidance of guilt and blame"

"Patients who fail to respond (to antidepressants) should be treated along similar lines to those proposed for treatment-resistant depression, especially (with) lithium"

"Exercise is necessary as a specific therapy. **There is no evidence that physical activity worsens the underlying process"**

"Efforts are made to over-interpret laboratory findings"

"It is regrettable that ME has become a disease of fashion, even a 'fad' "

"Suggestible patients with a tendency to somatise will often be found among the ranks of sufferers from disease with ill-defined symptomatology until doctors learn to cope with them more effectively"

"Over-enthusiastic espousal of new illnesses can be harmful. It may legitimize some of the maladaptive behaviour already described".

1990

Chronic Fatigue and Myalgia Syndromes Simon Wessely
In: Psychological Disorders in General Medical Settings Ed: N Sartorius et al Hogrefe & Huber, 1990

"Most CFS patients fulfill diagnostic criteria for psychiatric disorder"

"Other symptoms include muscle pain and many somatic symptoms, especially cardiac, gastrointestinal and neurological. Do any of these symptoms possess diagnostic significance? The answer is basically negative"

"The description given by a leading gastroenterologist at the Mayo Clinic remains accurate: 'The average doctor will see they are neurotic and he will often be disgusted with them' ".

1991

Editorial Wessely S
Journal of Neurology, Neurosurgery and Psychiatry 1991:54:669-671

"Studies of dynamic muscle function have demonstrated essentially normal muscle strength, endurance and fatigability, other than as a consequence of physical inactivity. Advice that antidepressants may be counter-productive is misguided".

1991

Cognitive behaviour therapy in chronic fatigue syndrome Butler S Chalder T Ron M Wessely S
JNNP 1991:54:153-158

"Continuing attribution of all symptoms to a persistent 'virus' preserves self-esteem".

1991

The psychological basis for the treatment of CFS Wessely S
Pulse of Medicine 14th December 1991:58

"The prognosis may depend on maladaptive coping strategies and the attitude of the medical profession".

1992

The epidemiology of fatigue: more questions than answers Lewis G Wessely S
Journal of Epidemiology and Community Health 1992:46:92-97

"We suggest that many patients currently labelled as having 'CFS' may lie at the extreme end of a continuum that begins with the common feeling of tiredness"

"Studies usually find a high prevalence of psychiatric disorder amongst those with CFS, confirming that physicians are poor at detecting such disorders".

1992

Chronic fatigue syndrome: current issues Wessely S
Reviews in Medical Microbiology 1992:3:211-216

"Validation is needed from the doctor. Once that is granted, the patient may assume the privileges of the sick role (sympathy, time off work, benefits etc)"

On 10th January 1992 Wessely wrote a letter to Dr Mansel Aylward at the Department of Social Security in which he stated:

"It is certainly true that I and my colleagues consider that anxiety about the consequences of activity is one of the factors perpetuating disability in CFS. I have previously been involved in advising the DSS that CFS should not be grounds for permanent disability".

Following Wessely's advice, the 1994 Disability Living Allowance Handbook entry on CFS states "The general consensus of informed medical opinion is that treatment should be by graded exercise and rehabilitation (and) antidepressant drugs may be helpful".

1993

The psychology of multiple allergy LM Howard S Wessely
BMJ:1993:307:747-748

"Many people present to their doctor with multiple unexplained symptomatology which they attribute to allergy. Those at the extreme end of this range often attract a diagnosis of total allergy syndrome, multiple chemical sensitivity, or environmental illness"

"A recent study confirmed that psychological symptoms were a central component of chemical sensitivity"

"Inherent in the concept of allergy is the avoidance of any blame. Sufferers from allergies feel no guilt about their condition and are not subject to moral sanction"

"Sufferers from mysterious conditions that lie outside conventional medical practice no longer consider themselves to be oppressed by spirits and demons but by mystery gases, toxins and viruses. This is particularly visible in the changing nature of mass hysteria".

1993

Chronic Fatigue, ME, and the ICD-10 David A Wessely S
Lancet 1993:342:1247-1248

"The inclusion in the tenth revision of the International Classification of Diseases (ICD-10) of benign myalgic encephalomyelitis as a synonym for postviral fatigue under Diseases of the Nervous System seems to represent an important moral victory for self-help groups in the UK"

"Neurasthenia remains in the Mental and Behavioural Disorders chapter under Other Neurotic Disorders. Neurasthenia would readily suffice for ME"

"Applying more stringent criteria for CFS in the hope of revealing a more neurological subgroup succeeds only in strengthening the association with psychiatric disorders"

"We believe this latest attempt to classify fatigue syndromes will prevent many people from seeing the world as it actually is".

(The authors seem curiously unaware that ME was first classified and included as a neurological disorder by the WHO in 1969)

1994

Patients with medically unexplained symptoms Alcuin Wilkie Simon Wessely
British Journal of Hospital Medicine: 1994:51:8:421-427

"Most doctors in hospital practice will be familiar with patients who complain about a wide variety of symptoms but whose physical examination and investigations show no abnormality. (Such) symptoms have no anatomical or physiological basis"

"Patients at the severe end of the spectrum exert a disproportionately large and avoidable financial burden on the health and social services"

"Patients with inexplicable physical symptoms are usually strongly resistant to any psychological interpretation (and) are generally viewed as an unavoidable, untreatable and unattractive burden".

1994

Population based study of fatigue and social distress Pawlikowska T Chalder T Wallace P Wright DJM Wessely S
BMJ 1994:308:763-766

"In recent years, fatigue has attracted renewed attention, largely because of the prominence given to the chronic fatigue syndrome"

"The infective characteristics may be the result of referral patterns and illness behaviour"

"The chronic fatigue syndrome may represent a morbid excess of fatigue rather than a discrete entity. The definition may have arisen as a result of referral patterns to specialists. Muscle pain was related to psychological morbidity".

1994

The patient with chronic fatigue Simon Wessely et al
West of England Medical Journal

"The aims of treatment were to provide alternative explanations for symptoms. The methods chosen included the use of established techniques to treat depression, namely, dothiepin".

1994

A cognitive-behavioural approach to chronic fatigue syndrome Alicia Deale Simon Wessely
The Therapist 1994:2;1:11-14

"Behavioural, attributional and cognitive factors are central to the perpetuation of fatigue"

"It is important to note that the rates of depression and anxiety in CFS are far too high to be explained solely as reactions to chronic illness".

1995

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

"Many doctors are frequently consulted by patients with persistent unexplained symptoms attributed to allergy or chemical sensitivity. When patients are told there is no evidence of any underlying immunological or allergic cause, they can be difficult to manage"

"In some cases patients claim allergy to almost all of the environmental products of the Western world"

"The illness is usually sporadic but epidemics have been described. Such epidemics overlap with the related subject of mass psychogenic illness, a term which has partly replaced mass hysteria"

"The epidemiology of environmental illness is reminiscent of the difficulties encountered in distinguishing between the epidemiology of myalgic encephalomyelitis (ME), a belief, and chronic fatigue syndrome, an operationally-defined syndrome"

[***Note: The World Health Organisation does not regard ME as " a belief", but as a neurological disorder*** **].**

"These patient populations recruited from the environmental subculture are a subgroup of patients who can be expected to show unusually strong beliefs about the nature of their symptoms, associated with a high prevalence of psychiatric disorder"

"These patients typically resist any attempt to discuss the possibility of a psychological cause"

"Somatization sufferers consume vast amounts of health resources for little benefit"

"Between a quarter and a half of new patients attending medical clinics do not have an organic explanation for their symptoms, (receiving) a diagnosis of chronic fatigue syndrome"

"The risk of psychiatric diagnosis is known to increase linearly with the number of symptoms with which the patient presents"

"Attribution of unexplained symptoms to a "virus", as happens in most patients with the label of ME, may preserve self-esteem and protect against the stigma of psychiatric disorder"

"These total allergy syndromes are akin to culture-bound syndromes afflicting modern developed societies where sufferers from unexplained symptoms no longer see themselves as possessed by devils or spirits but instead by gases, toxins and viruses"

"When a psychiatric disorder is not recognised, patients are often investigated extensively for organic disease; there are hazards in these inappropriate investigations, as patients' beliefs in organic pathology are reinforced. Further investigations will add nothing to the management but will reinforce the patient's beliefs in organic pathology (and) add to the cost of the consultation"

"Patients will benefit from training in cognitive coping skills; (and some) patients should be treated with psychotropic drugs"

"Liaison between the physician and the liaison psychiatrist is necessary so that patient acceptance of psychiatric referrals can be facilitated".

1996

Chronic fatigue syndrome: an update Anthony J Cleare Simon C Wessely
Update 1996:14 August:61

"Chronic fatigue may be better understood by focusing on perpetuating factors and the way in which they interact in self-perpetuating vicious circles of fatigue, behaviour, beliefs and disability"

"The perpetuating factors include inactivity, illness beliefs and fear about symptoms, symptom focusing, and emotional state"

"CFS is dogged by unhelpful and inaccurate illness beliefs, reinforced by much ill-informed media coverage; they include fears and beliefs that CFS is caused by a persistent virus infection or immune disorder"

"Increased symptom focusing occurs in CFS sufferers; (this) increased concern leads to selective attention and 'body watching': this can intensify the perceived frequency of symptoms, thereby confirming illness beliefs and reinforcing illness behaviour".

1996

Chronic fatigue syndrome: a stress disorder? Anthony J Cleare Simon C Wessely
British Journal of Hospital Medicine: 1996:55:9:571-574

"Between half and two thirds of patients with CFS have a co-morbid psychiatric disorder".

1997

Chronic fatigue syndrome: a practical guide to assessment and management
Sharpe M Chalder T Wessely S et al
General Hospital Psychiatry 1997:19:3:185-199

"The majority of patients seen in specialist clinics typically believe that their symptoms are the result of an organic disease process, and resent any suggestion that they are psychological in origin or psychiatric in nature. Many doctors believe the converse"

"(Patients') beliefs are probable illness-maintaining factors and targets for therapeutic intervention"

"Many patients receive financial benefits and payment which may be contingent upon their remaining unwell. Gradual recovery may therefore pose a threat of financial loss"

"Abnormal physical signs should not be accepted as compatible with a diagnosis of CFS"

"The only treatment strategies of proven efficacy are cognitive behavioural ones. We have developed a more intensive (CBT) therapy (which) is acceptable to patients, safe, and more effective than either standard medical care or relaxation therapy. It has also been shown to be cost-effective"

"An important task of treatment is to return responsibility to the patient for management and rehabilitation without inducing a sense of guilt, blame or culpability for his / her predicament".

1998

Clinics in Controversy: Chronic Fatigue Syndrome Anthony J Cleare Simon C Wessely
Update 20 May 1998:1016-1026

"CFS may be better understood as the extreme end of a spectrum that starts with 'feeling tired all the time'"

"Many people suggest that the condition should be called ME, but doctors and the editors of journals have taken a firm stand against this label"

"The GP's response may be important. A sick note and unclear diagnosis are both associated with development of CFS".

1999

Functional somatic syndromes: one or many? S Wessely C Nimnuan M Sharpe
Lancet 1999:354:936-939

"We postulate that the existence of specific somatic syndromes is largely an artefact of medical specialization"

"That is to say that the differentiation of specific functional (ie. psychiatric) syndromes reflects the tendency of specialists to focus on only those symptoms pertinent to their speciality, rather than any real differences between patients"

"Various names have been given to medically unexplained symptoms. These include somatisation, somatoform disorders and functional somatic symptoms"

"We define a functional somatic symptom as one that, after appropriate medical assessment, cannot be explained in terms of a conventionally defined disease"

"Functional somatic syndromes pose a major challenge to medicine. Those symptoms are associated with unnecessary expenditure of medical resources"

"Chronic fatigue syndrome is associated with worse disability than conditions such as heart failure"

"Three quarters of patients had symptoms more than 10 years after presentation. Thus, functional somatic complaints constitute a large and costly health-care issue that urgently requires improved management"

"Many of these (functional somatic) syndromes are dignified by their own formal case definition and body of research. We question this orthodoxy and ask whether these syndromes represent specific diagnostic entities (eg. irritable bowel syndrome, premenstrual syndrome, fibromyalgia, hyperventilation syndrome, tension headaches, globus hystericus, multiple chemical sensitivity, chronic fatigue syndrome) or are rather more like the elephant to the blind man --- simply different parts of a larger animal?"

"Such patients may have variants of a general functional somatic syndrome. If we accept that functional somatic syndromes are considered together, we open the way for more general strategies for their management"

"Functional somatic symptoms and syndromes are a major health issue. They are common, and may be costly. Most of the current literature pertains to specific syndromes. We have put forward the hypothesis that the acceptance of distinct syndromes as defined in the medical literature should be challenged. We contend that the patients so identified have much in common"

"We propose an end to the belief that each different syndrome requires its own particular sub specialist"

"A previous generation of physicians noted overlaps between "psychosomatic syndromes". Unfortunately, none of these theories were accompanied by empirical support and consequently have disappeared from our current thinking. We argue that their re-instatement is overdue".

2000

Responding to Mass Psychogenic Illness. Editorial: Simon Wessely
The New England Journal of Medicine 2000:342:2:129-130

"Such outbreaks are not novel. In a previous era, spirits and demons oppressed us. Although they have been replaced by our contemporary concern about invisible viruses, chemicals and toxins, the mechanisms of contagious fear remain the same"

"The term 'psychogenic illness' and its predecessor 'mass hysteria' exemplify the problem. To the majority of observers, including most professionals, these symptoms are indeed all in the mind"

"It is now commonplace to blame our environment for many of our ills. Should we investigate at all?"

"How do you convey the message that the main mechanisms for the transmission of distress are psychosocial and behavioural? A firm public message that certain symptoms are probably psychological in origin will probably help prevent their spread".

2001

Chronic fatigue syndrome: Symptom and Syndrome Wessely S
Annals of Internal Medicine 2001:134: 9S:838-843

"Social, behavioural and psychological variables are important in both chronic fatigue and chronic fatigue syndrome"

"The lack of congruence between the patient's report of feeling tired and exhausted and objective measures of fatigability further frustrate clinicians and investigators"

"Compelling evidence of abnormal neuromuscular fatigability in patients with the chronic fatigue syndrome is lacking"

"Fatigue can be related to psychological variables such as belief and expectation"

"Some of the desire to split the chronic fatigue syndrome into subgroups is driven by emotion. It is interesting to note how some of those who advance this argument assume that "their" condition (the one they suffer from, research or treat) will fall on the physical side of the divide"

"The greater the number of symptoms and the greater the perceived disability, the more likely clinicians are to identify psychological, behavioural or social contributors to illness"

"The pressure to reify the chronic fatigue syndrome comes from the way in which the developed world organizes medical services and reimbursement systems"

"Some of the modern impetus to 'allow' a specific chronic fatigue syndrome arises from the various compensation and social insurance schemes operating in developed countries"

"If the chronic fatigue syndrome did not exist, our current medical and social care systems might force us to invent it"

"Other symptoms identified in the chronic fatigue syndrome (include) increased symptom-monitoring and increased anxiety".

(In correspondence arising from this paper, Wessely wrote "I can sleep easy at night when it comes to treatment. I know that we have done more good than harm. You mention the views of Paul Cheney, but I must say I disagree profoundly with them – and more importantly, so does every neurologist I have ever met. All I know is that I am quietly proud of what our group has achieved over the years").

2001

How many functional somatic syndromes? C Nimnuan S Rabe-Hesketh Simon Wessely Matthew Hotopf
Journal of Psychosomatic Research 2001:51:4:549-557

"Experiencing symptoms is part of normality. Most of these symptoms are not associated with clear-cut biomedical diagnosis and are then referred to as "medically unexplained" or "functional" "

"Functional somatic symptoms are an important problem in general medicine on account of the high associated consumption of health service resources"

"Such symptoms may be elevated to the status of a syndrome to which a specific name is attached. These include irritable bowel syndrome, pre-menstrual pain, fibromyalgia and chronic fatigue syndrome"

"Physicians instinctively seek and treat only conditions they know well. Patients may be seen in several clinics, which increases the risk of over-investigation. We argue that such an approach is outdated. Instead, an appreciation of the fundamental unity of those syndromes may reduce the potential for iatrogenic harm ".

2002

Modern worries, new technology, and medicine Keith Petrie Simon Wessely
Editorial: BMJ 2002:324:690-691

"People's suspicion of modernity has increased to such an extent that it has increased their worries about environmental causes of poor health and fostered a migration to complementary medicine"

"We believe that these concerns have important implications for the way patients interact with health services. In clinical settings patients are reluctant to start medication for fear of putting 'unnatural chemicals' into their body. At the same time the consumption of unproved herbal and alternative 'natural' remedies is increasing"

"This anxiety is reflected in the presentation of psychosomatic illness: the number of illnesses attributed to environmental factors --- for example, multiple chemical sensitivity, total allergy syndrome --- has increased"

"Normal everyday symptoms such as headache and fatigue are now more easily interpreted as signs of disease or ill health. Attributions made by patients about the cause of their illness often involve environmental pollution, and they see the effects of modern life as undermining the effectiveness of their immune system"

"Distrust of experts is now commonplace, and at its extreme it can merge into the conspiratorial thinking that is part of a modern paranoid style. Mismanaged environmental incidents add to the fear of the public.

New and unsubstantiated health worries can be instantly transmitted to an internet audience eagerly seeking information on health, or to special interest networks such as illness support groups. We believe it is only a matter of time before a mass psychogenic illness is identified as being spread electronically".

2003

Managing patients with inexplicable health problems B Fischhoff Simon Wessely
BMJ 2003:326:595-597

"Those with medical mysteries will find some explanation. When a medical explanation is slow in coming, physicians, officials and companies often bear the brunt of (patients') anger, for example in chronic fatigue syndrome and Gulf war sickness, authorities who denied sufferers' claims met with scorn and contempt"

"In this article we discuss how illness beliefs arise and suggest principles for dealing with patients"

"It is only human for doctors to view the public as foolish, uncomprehending, hysterical or malingering"

"One challenge arises when patients have named their condition in a way that leaves doctors uncomfortable, as occurred with chronic fatigue syndrome"

"It may seem that adopting the lay label reinforces the perceived disability. A compromise strategy is 'constructive labelling': it would mean treating chronic fatigue syndrome as a legitimate illness while gradually expanding understanding of the condition to incorporate the psychological and social dimensions. The recent adoption by the UK Medical Research Council and the chief medical officer's report of the term CFS/ME reflects such a compromise, albeit it an uneasy one".

2003

Medically unexplained symptoms: exacerbating factors in the doctor-patient encounter.
LA Page, S Wessely
Journal of the Royal Society of Medicine 2003:96:223-227

"This paper proposes that well-intentioned actions by medical practitioners can exacerbate or maintain medically unexplained symptoms (MUS). This term is now used in preference to 'somatisation' "

"The medical specialties employ shorthand descriptions for particular clusters of MUS, including irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome"

"Examples of precipitating events include muscle ache after unaccustomed exercise. As one expert notes, 'It is a commonplace clinical observation that somatising patients --- more than any other group ---resent psychiatric referral' "

"Once a patient feels discredited, the opportunity to explore psychosocial factors is lost. For patients with MUS, the sensory experiences tend to outweigh the negative results of a doctor's examination or investigations"

"Thus one sees how the cycle of excessive investigation can begin. If enough investigations are performed, minor and irrelevant abnormalities will be detected and themselves become hypothesis-generating"

"Reassurance is particularly important in patients who have hypochondriasis or MUS".

"The adoption of a label such as CFS affords the sufferer legitimacy --- in other words, it allows entry into the 'sick role' "

"The external acknowledgement that the condition is 'legitimate' is both reassuring and enabling"

"However, the conferring of a label is not a neutral act, since specific labels are associated with specific beliefs and attitudes. In CFS for example, use of this term or the alternative 'myalgic encephalomyelitis' implies underlying assumptions about aetiology and treatment for both patients and doctors"

"(In relation to treatment), there is evidence to suggest that harm occurs at the hands of non-medical practitioners (who) colluded with patients' abnormal illness beliefs"

"If sections of the media advocate an exclusively organic model, as has happened with CFS, the biomedical model may become firmly enshrined for patients and families at the expense of psychosocial models"

"Clearly there are implications for the way doctors are taught to assess and treat these patients".

2003

Chronic fatigue syndrome Reid S Chalder T Cleare A Hotopf M Wessely S
Clin Evid 2003: (9): 1172-1185

"A systematic review of studies of prognosis found that outcome was influenced by the presence of psychiatric disorders and beliefs about causation".

2004

Unloading the trunk: neurasthenia, CFS and race A Luthra S Wessely
Social Science and Medicine 2004:58:2363-2369

"The history of neurasthenia, the predecessor of the modern chronic fatigue syndrome (CFS) suggests that anxiety about technology is not only a modern phenomenon. Intrinsic to neurasthenia was a class bias which characterized it as a disease of the 'civilised' "

"Alongside this class bias existed a gender and race bias "

"Some researchers have mapped the shift of neurasthenia from a neurological entity in the 19th century to a psychological one in the 20th century"

"Overall, CFS (or ME) is represented as a Western disease"

"We would argue that the descriptions of race in the CFS/ME lay literature represents a 20th century re-emergence of the 19th century race bias around neurasthenia"

"Differential exposure to new technologies is used to explain the racial differences in CFS"

"Neurasthenia patients were seen as 'neurologically vulnerable', whereas CFS patients are 'immunologically vulnerable' "

"We conclude from this that cultural/racial biases remain alive and well"

"The dramatic under-representation of ethnic minorities in our CFS clinic is more likely to represent a combination of diagnostic and referral bias rather than any lack of vulnerability to CFS"

"This paper aimed to show how 19th century racial thinking intrinsic to neurasthenia has developed over the last hundred years with CFS/ME".

2004

There is only one functional somatic syndrome Simon Wessely
Brit J Psychiat 2004:185:95-96

"Why did our (1999 Lancet article on functional somatic syndromes) provoke so much reaction? To be fair, this was rarely among professionals, most of whom had no problem in accepting our thesis"

"First, many sufferers did not accept the thesis and continue to have strong emotional attachments to their label"

"Second, some felt that what we were saying was that all these syndromes are psychiatric"

"Five years later, Sharpe and I stand by our thesis".

2005

The Placebo Response in the Treatment of Chronic Fatigue Syndrome: A Systematic Review and Meta-Analysis Cho HJ Hotopf M Wessely S
Psychosom Med 2005:67 (2):301-313

"The placebo response is conventionally asserted to be high in CFS because of the latter's subjective nature"

"It is known that CFS patients attending specialist clinics often have strong physical attributions regarding causation. If so, the placebo response in CFS may be influenced by the type of intervention according to its perceived rationale"

"The placebo response was lower than predicted and lower than in some other medical conditions"

"In contrast with the conventional wisdom, the placebo response in CFS is low".

2005

What advice do patients with infectious mononucleosis report being given by their general practitioner?
Bridget Candy Trudie Chalder Anthony J Cleare Simon Wessely Matthew Hotopf
J Psychosom Res 2005:58:435-437

"(The) majority of patients make rapid recoveries from infectious mononucleosis. However, approximately 9-22% of patients develop chronic fatigue syndrome"

"The main advice given in medical textbooks frequently includes the need for the patient to rest. We are aware of no systematic evidence to support this. There is no evidence to support a prescription of rest, and some suggest this might be harmful"

"In this study, the majority of patients reported receiving advice to rest"

"Giving unqualified advice to rest may encourage patients to prolong their convalescence and thereby increase their expectations of a delayed recovery. This fits into a wider literature suggesting that rest may be harmful in other illnesses".

2005

Chronic fatigue syndrome: an overview Hyong Jin Cho Simon Wessely
Rev Bras Psiquiatr. September 2005:27:3: Sao Paulo

"Medically unexplained symptoms (MUS) lacking identifiable underlying physical disease are common and can be associated with severe disability and high cost to health services"

"Functional somatic syndromes refer to groups of symptoms lacking demonstrable abnormalities of structure. They include chronic fatigue syndrome"

"A multifactorial approach has been proposed to explain the pathogenesis of CFS, integrating psychological, social and physical factors into a coherent model"

"A person might be pre-disposed to develop CFS by life-style factors"

"Perpetuating factors have particular importance in understanding CFS"

"Firstly, many consider that amplification of somatic symptoms that happen in our daily lives is a core factor underpinning the perpetuation of many unexplained medical syndromes. Secondly, modification of these factors is the main focus of what are the currently most successful treatments for CFS, ie. cognitive behavioural therapy and graded exercise therapy"

"Several factors have been reported to be associated with the perpetuation of CFS. These include a fixed somatic attribution, which may be associated with avoidance behaviour related to exercise or activity"

"Physical deconditioning as a consequence of reduced activity may contribute to towards greater experience of symptoms"

"There are numerous articles that claim CFS is associated with a high placebo response. This is because CFS is associated in the minds of many with the features that are thought to maximize the placebo effect: highly subjective symptoms and a fluctuating nature often influence by patients' selective attention"

"The disorder has a poor prognosis".

2005

Biopsychosocial Medicine: An integrated approach to understanding illness ed. Peter White
OUP 2005

This book arose out of a two-day conference held in autumn 2002 at the Novartis Foundation in London.

The entire conference was chaired by Professor Simon Wessely.

It provides evidence of the intention of Wessely School adherents and members of One-Health company (a company that was "established in order to promote a system of healthcare based on the biopsychosocial model of ill-health") to indoctrinate State agencies with their own model of "medically unexplained" disorders such as (ME)CFS.

Professor White states that the book was written because "some people believe that medicine is currently traveling up a 'blind alley' (and) this 'blind alley' is the biomedical approach to healthcare. The biomedical model assumes that ill-health and disability is directly caused by diseases and their pathological processes (but) there is an alternative approach: the biopsychosocial approach is one that incorporates thoughts, feelings, behaviour, their social context and their interactions with pathophysiology".

For further information on the Wessely School beliefs about modern medicine, see "PROOF POSITIVE? Evidence of the deliberate creation via social constructionism of "psychosocial" illness by indoctrination of State agencies" by Eileen Marshall and Margaret Williams, available on Co-Cure ACT, 2nd September 2005, also online at http://www.meactionuk.org.uk/PROOF_POSITIVE.htm

In summary, Simon Wessely is on record as affirming that ME is a "myth" and a "non-existent disease": between February and April 2002 the BMJ ran a poll of "non-diseases" with which Wessely is widely known to have been involved and to have proposed ME as a "non-disease". When the results of the poll were published, ME – along with freckles and big ears -- was found to be a non-disease that is best left medically untreated.

APPENDIX II

Quotations from the published works of Dr Michael Sharpe on ME/CFS

As with Wessely, it is not just a matter of noting the more offensive statements but rather it is the relentlessness of the same message over more than a decade (and the fact that the message does not adapt to, but actively dismisses, the strength of emerging biological evidence) which shows Wessely School psychiatrists to be out of touch with international scientific knowledge.

1991

Psychiatric management of Post Viral Fatigue Syndrome M Sharpe
British Medical Bulletin 1991:47:4:989-1005

"Psychiatric assessment distinguished factors that perpetuate the condition from those that may have precipitated it. Treatments are targeted at perpetuating factors.

"To exclude (patients with a psychiatric diagnosis) is practically restrictive.

"**Psychiatric management may be defined as the assessment and treatment of the mentally ill.**

"Multiple perpetuating factors may operate (and) the following have been suggested in CFS:

"Viral infection is of theoretical interest but of minor importance in managing established cases

"The possibility that immune function is impaired by psychosocial factors and may be improved by psychiatric treatment is a tantalising possibility

"Several physiological factors may perpetuate symptoms. These include the consequences of inactivity and hyperventilation

"Syndromes conventionally termed "psychiatric" have been shown to occur in the majority of patients with CFS. Extensive physical investigation is unlikely to be fruitful and should be limited

"Personality factors (attitudes, beliefs and thoughts) and behaviour have been shown to perpetuate disability. These unhelpful or "dysfunctional" cognitions include the beliefs that recovery from the illness is not under personal control or that the illness is poorly understood"

"It has been suggested that dysfunctional cognitions and maladaptive behaviour interact with the physiological factors and psychiatric illness to perpetuate the disability that comprises CFS. Increasing physical deconditioning may lead to helplessness.

"Because of their possible importance in CFS (social factors) deserve discussion. One such factor is our cultural attitude to symptoms occurring in the absence of demonstrated physical disease"

"Such symptoms are frequently regarded as revealing personal weakness and as not being a valid reason for exemption from daily demands"

"Physical disease, on the other hand, particularly if validated by a doctor, is rarely considered to be the responsibility of the afflicted, merits sympathy, and excuses the sufferer from meeting the demands of others"

"Patients without a "physical" disease label for their illness may consequently experience difficulty in explaining their disability to friends, family or employers. Hence they may request a "physical diagnosis" from doctors"

"In response to the lack of acceptance of the "reality" of the symptoms of CFS, support has been sought for the existence of a disease called myalgic encephalomyelitis or "ME". The insistence that "ME" is an exclusively physical disease with a poor prognosis may have been unhelpful for sufferers (and) such a restricted conception of the problem may have perpetuated illness in some individuals"

"The use of extensive laboratory investigation may be psychologically harmful to the patient by reinforcing their beliefs about serious physical disease

"Even if shown to be beneficial, such (immunological) treatment is unlikely to be feasible on a wide scale because of cost.

"There are many anecdotal reports (of the efficacy of antidepressant drugs) in CFS.

"Cognitive behaviour therapy is a development of Behaviour Therapy in which emphasis is placed on changing the patients' cognition as well as their behaviour. The aim is to show that the patient can regain control of their lives and that their illness is not so mysterious as to be untreatable".

"Excessive investigation should be avoided"

"Problems may arise if the patient requires a diagnosis the doctor feels is inappropriate or wants certification of permanent invalidity (ie) "ME".

"There is evidence that psychiatric treatment can reduce disability in CFS. In some patients it can be 'curative' ".

1991

Mania and recovery from chronic fatigue syndrome MC Sharpe BA Johnson
JRSM 1991:84:51-52

"There is anecdotal evidence that (antidepressants) can reduce disability in CFS.

"Psychosocial factors may maintain disability. Family members may reinforce both beliefs and avoidance"

"We suggest that the clinical assessment should consider mood, beliefs, avoidance of inactivity and the role of the family".

1992

Fluctuations in perceived energy and mood among patients with chronic fatigue syndrome
C Wood, M Sharpe et al
JRSM 1992:85:195-198

"Because of its suspected viral aetiology, CFS is becoming an increasingly frequent presentation seen by specialists in infectious diseases. Current thinking *(here Sharpe quotes a self-reference)* does not require the presence of a viral aetiology in defining the syndrome"

"(Patients') higher levels of depression serve to reinforce the now widely current notion that such patients may be suffering from a depressive illness, of which physical fatigue is a somatic manifestation."

1994

The Chronic Fatigue Syndrome: A Comprehensive Approach to its Definition and Study.
K. Fukuda S.Straus M Sharpe et al
Ann Int Med 1994:121:12:953-959

"The use of tests to diagnose the chronic fatigue syndrome should be done only in the setting of protocol-based research"

"In clinical practice, no additional tests, including laboratory tests and neuro-imaging studies, can be recommended"

"Examples of specific tests (*which should not be done*) include serologic tests for enteroviruses; tests of immunologic function, and imaging studies, including magnetic resonance imaging scans and radionuclide scans (such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) of the head. We consider a mental status examination to be the minimal acceptable level of assessment"

"The exclusion of persons (*with psychiatric disorders*) would substantially hinder efforts to clarify the role that psychiatric disorders have in fatiguing illness"

"We dropped all physical signs from our inclusion criteria ".

1995

Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Wessely S and Sharpe M.
In: Treatment of Functional Somatic Symptoms. Ed: Mayou R, Bass C and Sharpe M. (chapter 16): OUP 1995

On the issue of patients' organisations making medical research information available to members, Sharpe states "Such information may have a considerable and often unhelpful influence on patient attributions of illness."

1996

Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial
Michael Sharpe, Tim Peto et al
BMJ 1996:312:22-26

"Cognitive behaviour therapy offers a novel approach to the treatment of the chronic fatigue syndrome…(it) aims at helping patients to re-evaluate their understanding of the illness….**it was both acceptable and more effective than medical care alone."**

(One of the trial participants (Catherine Rye) had a letter published in the Independent on 30 March 1996 in which she made valid points: "I participated in the Oxford trial…the article implies that a new successful treatment has been found for ME but that sufferers do not want to accept it. There are facts about the trial that throw into doubt how successful it is. It is stated that patients in the control group received standard medical care. I was in that group but I received nothing. Also, patients receiving treatment had to attend weekly hospital visits, thus excluding the most severely

affected sufferers. Patients who "improved significantly" only increased their score from 70 to 80 on a scale of general functional ability.")

1997

Treating medically unexplained symptoms. EDITORIAL (Editor's Choice).
Richard Mayou and Michael Sharpe.
BMJ 1997:3:15:561-562

"Evidence for the superiority of new ways of thinking about and managing such patients is growing. These new treatments, often referred to as cognitive behavioural therapies, take a new approach (which) is in keeping with the evidence that the perpetuation of unexplained somatic symptoms is best understood in terms of psychological factors (such as) misinterpretation of bodily sensations and unhelpful coping behaviour."

1997

Chronic Fatigue Syndrome: A Practical Guide to Assessment and Management
Sharpe M. Wessely S et al
Gen Hosp Psychiatry 1997:19:3:185-199

"The only treatment strategies of proven efficacy are cognitive behavioural ones.

"The clinical problem we address is the assessment and management of the patient with a *belief* that he / she has a fatiguing illness such as CFS, chronic fatigue and immune deficiency syndrome (CFIDS) *[CFIDS in fact stands for chronic fatigue and immune dysfunction syndrome]* or myalgic encephalomyelitis (ME)"

"The patients who cause the greatest clinical difficulty are those with both severe symptoms and strong beliefs. The majority of patients believe that their symptoms are the result of an organic disease process. Many doctors believe the converse.

"It is particularly important to focus on factors which may be perpetuating the illness. A large number of somatic symptoms suggests a greater likelihood of psychiatric disorder. A conviction of a solely physical cause for symptoms is the single most consistent predictor of poor outcome.

"Beliefs are probable illness-maintaining factors and targets for therapeutic intervention

"Many patients receive financial benefits and payments which may be contingent on their remaining unwell. Recovery may therefore pose a threat of financial loss

"Personality is important. The account of an informant *(about the patient's personality)* is often helpful

"Most sufferers are seeking confirmation of their own intuition that they are suffering from a particular condition, rather than reassurance that they are not

"Abnormal physical signs should not be accepted as compatible with a diagnosis of CFS

"In our experience, postural hypotension usually resolves with increased activity

"Reports from specialist settings have shown statistically increased rates of abnormal results on tests for parameters such as antinuclear factor, immune complexes, cholesterol, immunoglobulin subsets

and so forth. Their significance is for researchers rather than clinicians and we feel that testing for such variables is more likely to result in iatrogenic harm *(caused by doctors)* than good

"Many physicians are reluctant to make the diagnosis of CFS (because of) reinforcing unhelpful illness beliefs

"Patients need a diagnosis in order to organise their dealings with the world of benefits

"Perpetuating factors (include) reinforcement of sick role by mother and doctor

"An important task of treatment is to return responsibility to the patient for rehabilitation without inducing a sense of guilt

"(CBT) is acceptable to patients, safe and more effective than standard medical care
(*"standard medical care" is not defined*)

"It is usually possible to persuade these patients to try antidepressants

"Disability systems and insurance agencies are sceptical about CFS. When asked to comment in benefits or insurance claims, we do not support claims for permanent disability until all reasonable efforts at rehabilitation have been tried."

1997

Chronic fatigue syndrome and occupational health A Mountstephen and M Sharpe
Occup Med 1997:47:4:217-227

"(The term myalgic encephalomyelitis) has been used to define a supposedly specific disease associated with viral infection. Despite this, the existence of ME as a specific syndrome remains unestablished. Use of the term is best avoided

(ME as a specific syndrome has been classified since 1969 as a neurological disorder by the World Health Organisation, so it is diffcult to know on what evidence these authors rely to support their statement that "the existence of ME as a specfic syndrome remains unestablished").

"**The label of CFS avoids the connotations of pseudo-disease diagnoses such as ME**

"Patients' beliefs and behaviour are often a prominent part of the clinical presentation (which) is most commonly diagnosed in young and middle aged females

"The evidence for an association between immunologic abnormalities and CFS remains unclear

"Both self help books and the media have tended to emphasise medical explanations at the expense of psychiatric conceptualisations

"CFS may serve as a culturally defined function which allows a socially acceptable expression of distress

"Illness perpetuating factors are more important than predisposing or precipitating factors

"Psychiatric assessment is recommended in *every case*

" In most cases of chronic fatigue, few laboratory investigations are necessary

"Important aspects are the individual's beliefs about their illness

"Exercise therapy may be considered for patients who are physically inactive

"The only psychological treatment supported by the evidence is cognitive behavioural therapy (which) is well fitted to the task of helping patients achieve a more helpful view of the illness

"Referral to 'specialists' should be avoided as they can entrench illness behaviour

(*Presumably the authors exclude referral to specialist psychiatrists)*

"A process of education to address inaccurate and unhelpful attitudes and beliefs may be a necessary preliminary step

Under "Eligibility for benefits", the authors state "The DSS's Handbook advises adjudication officers that in CFS there is unlikely to be a need for assistance with attending to bodily functions or with mobility. It will be unfortunate if the (Disability Discrimination) Act leads to an undue focus on long term disability at the expense of efforts directed at rehabilitation and recovery."

1997

Treating medically unexplained physical symptoms. Effective intervention available.
EDITORIAL: EDITOR'S CHOICE Richard Mayou Michael Sharpe.
BMJ 1997:315:561-562

"Chest pain, back pain, headache, muscular pains, bowel symptoms, breathlessness, dizziness and fatigue often remain unexplained after medical assessment. Such cases may be referred to as functional syndromes of chronic fatigue or as somatoform disorders"

"When symptoms are found not to result from "genuine physical illness", they are often attributed to mental illness"

"Evidence for the superiority of new ways of thinking about and managing such patients is growing. These new treatments, often referred to as cognitive behavioural therapies, take an approach in keeping with the evidence that perpetuation of unexplained somatic symptoms is best understood in terms of an interaction between physiological processes, psychological factors and social context.

"This integrative approach (consists of) identifying the principal factors that perpetuate illness, including misinterpretation of bodily sensations, abnormalities of mood and unhelpful coping behaviour.

"Implementation of this new approach will require changes in both medical practice and the organisation of services. Innovative service developments such as dedicated liaison psychiatry services will provide for patients who require more intensive treatment"

"The small but conspicuous group of patients who present with recurrent and multiple physical symptoms will be given co-ordinated care aimed at limiting unnecessary medical interventions

(The statistics are that it is not a "small but conspicuous group": the incidence is rising phenomenally. As long ago as 1994, the medical insurance company UNUMProvident -- one of the largest disability insurers – reported that in the five years from 1989 to 1993, mens' disability claims for ME/CFS increased 360%, whilst womens' claims for ME/CFS increased 557%. ***No other disease category surpassed these rates of increase. In order of insurance costs, ME/CFS came second in the list of the five most expensive chronic conditions, being three places above AIDS****).*

"If these changes in practice and service provision could improve patient care, why have they not been implemented? One reason is the widespread lack of awareness that effective evidence based treatments are available. There are welcome signs of change, as evidenced by the recent joint royal colleges' reports".

1998

Cognitive Behaviour Therapy Michael Sharpe
A Research Portfolio on Chronic Fatigue. Ed: Robin Fox; published by The Royal Society of Medicine for The Linbury Trust, 1998

"Cognitive behaviour therapy offers patients a new way to think about their illness. The first application of CBT to chronic fatigue syndrome was by Wessely and colleagues (who proposed) a vicious-circle model of the perpetuation of chronic fatigue whereby patients' beliefs about the illness lead to avoidance of activity and thus to chronic disability

"Our group (ie. the Wessely School) wanted to develop the behavioural approach and the first step was to gain a systematic view of their beliefs and behaviour

(*No mention is made about obtaining a systematic view of patients' brain perfusion patterns, or of their immune status, or of their neuroendocrine function)*

"CBT helps patients to re-evaluate their beliefs (and) encourages them to change their behaviour. Change in the belief is an important factor in recovery.

"The trials of CBT have shown that 'psychological' treatment is effective in patients with CFS. (CBT) is currently the most effective treatment we have for CFS."

1998

Doctors' Diagnoses and Patients' Perceptions: Lessons from Chronic Fatigue Syndrome
EDITORIAL Michael Sharpe
Gen Hosp Psychiat 1998:20:335-338

"For many patients, the more clearly 'biomedical' the diagnosis is, the more likely they are to welcome it

"These patients want a medical diagnosis for a number of reasons. First, it allows them to negotiate reduced demands and increased care from family, friends and employer. Without such a diagnosis, the patient is open to the social stigma of psychiatric illness. In short, (a biomedical label) admits them to a bona fide 'sick role'. Second, it may open the way for practical help in terms of financial and other benefits from government, employers and insurers

"Why are many physicians reluctant to provide a medical diagnosis? (Because) to make such a diagnosis, especially if it is suggested by the patient, may risk the censure of peers

"The application of (a psychiatric diagnosis) may give the physician the satisfaction of having applied a label of which most of his peers would approve. The problem is that many patients not only fail to accept this diagnosis but respond to it with frank hostility because a psychiatric diagnosis may offer lower financial benefits

"For many patients, obtaining an acceptable diagnosis becomes their main preoccupation."

1999

ME. What do we know (real physical illness or all in the mind?)
Lecture given in October 1999 by Michael Sharpe, hosted by the University of Strathclyde

"In my lecture this evening, I would like to talk to you about myalgic encephalomyelitis (ME), also known as chronic fatigue syndrome or CFS (which) for convenience I will refer to as CFS.

"We know that in the majority of cases CFS can be effectively treated. CBT has been shown to have substantial benefits for patients with CFS (and) can reduce disability in most patients.

"I shall argue that patients themselves have played a part in denying themselves this type of treatment

"Despite a lot of media comment and much hypothesising relating CFS to modern concerns such as toxic exposures, there is very clear evidence that a condition which appears identical caused similar concerns a hundred years ago (and) the causes were thought to lie in the concerns of that time namely, the changing role of women; in our time it is allergy and toxins.

"The conventional wisdom is that illnesses are made real when they are legitimised by a doctor's diagnosis

"Does CFS have biology? Yes (but) not conventional disease pathology

"The majority of patients with CFS have no doubt how they prefer their conditions to be seen

"The vehemence with which many patients insist that their illness is medical rather than psychiatric has become one of the hallmarks of the condition

"Clinically, it appears that interpersonal stress appears to be a major factor giving rise to development of CFS

"Over-solicitousness and the reinforcement of unhelpful illness beliefs can have an unhelpful effect on patients' attitude and coping

"Purchasers and Health Care providers with hard pressed budgets are understandably reluctant to spend money on patients who are not going to die and for whom there is controversy about the "reality" of their condition (and who) are in this sense undeserving of treatment.

"Those who cannot be fitted into a scheme of objective bodily illness yet refuse to be placed into and accept the stigma of mental illness remain the undeserving sick of our society and our health service."

2000

Chronic Fatigue Syndrome (Myalgic Encephalomyelitis) Michael Sharpe
NETDOCTOR.CO.UK February 2000

"Chronic Fatigue Syndrome is not a new disease. A very similar description was described more than a hundred years ago and was given the name Neurasthenia"

"Special investigation such as brain scans do not help the diagnosis of this condition"

"It is not usually necessary to have very extensive investigations"

"It is helpful to make a plan of management for the illness as soon as possible in order to reduce its duration and effect on your life"

"Your doctor may refer you for a rehabilitative programme. There is good evidence that a form of rehabilitation called cognitive behavioural therapy or CBT helps people with CFS cope effectively with the illness"

"Some patients who were doing stressful jobs find that they do not wish to return to their previous employment"

"There are a number of patient support groups (which) tend to be oriented towards the patient who has developed long-term illness".

2000

Insurance Medicine. Chronic fatigue syndrome and its management. Dr Michael Sharpe, University of Edinburgh. Conference rapporteur: Ian Cox MA MRCP, Chief Medical Officer, Prudential UK, Reading. *JRCP 2000:34:394-396*

"Psychosocial factors are important in CFS. Prognostic factors include family factors and social factors; work could also mitigate against a full recovery.

"Reports from doctors for employers, insurance companies and benefit agencies could reinforce beliefs and behaviour to delay full recovery.

"The belief that there is no treatment is incorrect; correcting obvious misconceptions about the disease process and avoiding unnecessary investigations all help patients.

"Cognitive behaviour therapy caused improvement in 60% of patients with CFS

"Secondary prevention (ie. preventing chronicity) includes early identification and treatment; keeping the individual in contact with the workplace helps to reduce the chronic problems.

"There was general agreement that all doctors have a responsibility to aid their patients' return to employment.

"Social attitudes and differing health beliefs can slow down or even prevent a return to work and such beliefs are increasingly being promulgated through the media and doctors have to be aware of these issues.

"The problem of communication between doctors and insurers or benefits agency personnel were discussed throughout the meeting, which was an excellent first step towards improved links between the Royal College and doctors working in insurance and benefit agencies".

2001

Interpretation of symptoms in chronic fatigue syndrome Dendy C Cooper M Sharpe M
Behaviour Research and Therapy 2001:39(11):1369-1380

"It has been suggested that patients with CFS tend to interpret their symptoms as indicating physical illness"

"Most (ME/CFS) patients believe that their symptoms are primarily caused by physical disease"

"Psychological factors play a role in the aetiology of ME/CFS (but) patients often actively resist this suggestion"

"The tendency to interpret symptoms in terms of physical disease rather than emotion is potentially of clinical importance as it has been shown to predict a poor outcome"

"A cognitive model of ME/CFS has been proposed (Sharpe et al, 1991). The model attempts to explain how early experiences lead to the formation of assumptions that, combined with life stressors, may precipitate ME/CFS in predisposed individuals"

"According to this model, the interpretation of symptoms predominantly in terms of physical illness, and not in terms of emotional states, plays a particularly important role in the maintenance of the disorder"

"Unexpectedly, the ME/CFS group made more normalizing interpretations than the MS and depressed groups"

"Patients with ME/CFS may have had experiences of being told by others, including medical staff, that their symptoms are best explained by physical illness. It seems likely that such experience will contribute to the development of beliefs"

"The finding that (ME/CFS) patients have a greater tendency even than MS patients to view (their symptoms) as non-emotional needs explanation ---MS patients experience symptoms related to a known physical illness, so we expected them to interpret them as such"

"The cognitive model (of ME/CFS) might be useful in assessing the outcome of treatment using cognitive therapy, which aims to change cognitive processing in ME/CFS".

2001

Unexplained somatic symptoms, functional syndromes and somatisation: do we need a paradigm shift?
Michael Sharpe Alan Carson
Ann Int Med 2001:134:9:2:926-930

"Medically unexplained symptoms are somatic complaints that are not adequately explained by disease"

"We suggest that there is much to learn from physicians of the pre-Freudian era (as) their clinical practice provided a way of making psychological treatment acceptable"

"Although there is a research literature suggesting the presence of biochemical and physiological abnormalities in many of these disorders, they share a lack of pathologically defined changes that dignify medical conditions such as cancer as disease"

"Unexplained symptoms were often referred to as hysterical"

"It was only at the turn of the 19th century that an explicitly and exclusive psychological or mental origin for these symptoms was proposed"

"Consequently the treatment of unexplained somatic symptoms became explicitly psychological"

"Somatisation was proposed as a process to explain how mental problems could manifest as somatic symptoms"

"Large numbers of patients with somatic symptoms present to physicians for assessment. Treatments that are regarded as psychiatric or psychological have substantial proven efficacy in such patients but they are not in widespread use"

"It does seem that the neglect of the psychological impact can be harmful, for example, by suggesting to the patients that they are sick when they are not"

"Given the predominant psychological model of explanation, it is not surprising that there has been substantial development of psychiatric and psychological therapies. The most commonly recommended form is behavioural or cognitive behavioural therapy"

"This is an explicitly psychological treatment that aims to achieve recovery by helping the patient to change illness perpetuating beliefs and behaviours"

"We suggest that much can be learned from the clinical management of unexplained somatic complaints employed by clinicians over 100 years ago. The predominant model was the functional paradigm. This model explicitly acknowledged the influence of psychological influences. Recent evidence is now beginning to provide support for this viewpoint"

"There is an urgent need to make these (psychological) treatments more available and acceptable"

"These studies give us clues about how we may psychologically augment the standard medical consultation by the incorporation of cognitive behavioural techniques into it. It is possible to integrate the principles of psychological and psychiatric treatment into medical care"

"Such a paradigm shift would also influence the research agenda"

"We need to evaluate the effectiveness of medical assessments augmented by the inclusion of proven cognitive behavioural principles".

2002

The English Chief Medical Officer's Working Parties' report on the management of CFS/ME: Significant breakthrough or unsatisfactory compromise? Michael Sharpe
Journal of Psychosomatic Research 2002:52:6:437-438

"In 1998, the UK Chief Medical Officer took the unusual step of commissioning a special working group (on CFS). The working group was not the first to report in the UK. The (Joint) Royal Colleges published one in 1996. This new one was novel in that it was composed of not only medical experts but also patients and representative of patients' organizations"

"What does it say? Some recommendations are controversial. The first of these is about a matter as basic as what to call the illness. The term CFS was welcomed by researchers when it was introduced in 1988"

"The operational definition has been changed, but the term CFS retained. The main alternative term widely used by patients' organizations in the UK is ME. The report comes down on a compromise term CFS/ME"

"The second issue is whether CFS/ME is best regarded as a 'medical' or a 'psychiatric' illness. Again, the report skirts around this issue (and) the compromise recommendation is that management should be by 'multidisciplinary' teams"

"Perhaps the most controversial issues refers to the original brief of the report: the choice of treatment. Only the behavioural rehabilitative treatments of CBT and graded exercise therapy (GET) emerged as having significant empirical support"

"Also presented in the report was a patient survey carried out by one of the patients organizations. This reported that a substantial minority felt that these treatments had actually made them worse. This controversy over what treatment to recommend split the committee"

(*Note that Sharpe is inaccurate in referring to a 'substantial minority' --- the figure is exactly 50%).*

"Little that was previously controversial has been resolved; the conclusion often read as an uneasy compromise"

"The name CFS/ME symbolizes the fudge adopted regarding the issues of psychiatric care and of the choice of treatment"

"My own view has long been that the issues around CFS/ME are the same as those surrounding the acceptance and management of (patients) who suffer conditions that are not dignified by the presence of what we call disease".

2002

Clinical Review: ABC of psychological medicine Michael Sharpe David Wilks
BMJ 2002:325:480-483

"Fatigue can refer to a subjective symptoms of malaise and aversion to activity"

"Patients generally regard fatigue as important, whereas doctors do not"

"Fatigue may be regarded as the final common pathway for a variety of causal factors. These can be split into predisposing, precipitating, and perpetuating factors"

"Predisposing factors include being female"

"Perpetuating factors include physical inactivity (and) emotional disorders"

"**Other factors such as immunological abnormalities are of research interest but not of clinical value"**

"Fatigue is a major symptoms of many psychiatric disorders"

"Psychiatric disorders commonly associated with fatigue (include) somatisation disorder"

"Chronic fatigue syndrome is a useful descriptive term for prominent physical and mental fatigue"

"A preoccupation with medical causes seems to be a negative prognostic factor"

"Immunological and virological tests are generally unhelpful"

"Perpetuating causes (are) excessive inactivity, unhelpful beliefs, avoidance of activity"

"Persistent fatigue requires active management (and) a broader biopsychosocial management strategy is required"

"Patients should be told that they are suffering from a common and treatable condition for which behavioural treatment can be helpful"

"While patients may be concerned about the need for medical investigation, it can be explained that no disease has been found"

"Rehabilitation based on behavioural principles is currently the most effective specialist treatment approach".

2002

Functional Symptoms and Syndromes: Recent Developments Michael Sharpe
In: Trends in Health and Disability 2002, Report of UNUM Provident Insurance Company

"It is becoming increasingly clear that the problem of patients who have illness that is not clearly explained by disease is a large one"

"There is a great deal of confusion about what to call such illness. A wide range of general terms has been used including 'hysteria', 'abnormal illness behaviour', 'somatisation' and 'somatoform disorders' "

"Recently the terms 'medically unexplained symptoms (MUS) and 'functional' symptoms have become popular amongst researchers"

"Classification is also confusing as there are parallel medical and psychiatric classifications. The psychiatric classifications provide alternative diagnoses for the same patients"

"The majority will meet criteria for depressive or anxiety disorders and most of the remainder for somatisation disorders of which hypochondriasis and somatoform disorder have most clinical utility"

"The psychiatric classification has important treatment implications. Because patients may not want a psychiatric diagnosis, this may be missed"

"There is strong evidence that symptoms and disability are shaped by psychological factors"

"Especially important are the patients' beliefs and fears about their symptoms"

"**Possible causal factors in chronic fatigue syndrome:**

Psychological: personality, disease attribution, avoidant coping style.

Social: information patients receive about the symptoms and how to cope with them; this information may stress the chronicity and promote helplessness. Such unhelpful information is found in 'self-help' books. Unfortunately doctors may be as bad.

"Obstacles to recovery:

"**The current system of state benefits, insurance payment and litigation remain potentially major obstacles to effective rehabilitation"**

"Furthermore patient groups who champion the interest of individuals with functional complaints (particularly chronic fatigue syndrome) are increasingly influential; they are extremely effective in lobbying politicians. The ME lobby is the best example"

"Functional symptoms are not going to go away. However, the form they take is likely to change. Possible new functional syndromes are likely to include those associated with pollution (chemical, biological and radiological)"

"As the authority of medicine to define what is a legitimate illness is diminished, increasingly consumer oriented and privatised doctors will collude with the patient's views that they have a disabling and permanent illness"

"In other words, it may be difficult for those who wish to champion rehabilitation and return to work to 'hold the line' without seeming to be 'anti-patient' "

"It will be imperative that health and social policy address this problem. This will not be easy. However, there are glimmers of progress. An example is recent developments in the politics of CFS. One of the major charities (Action for ME) is aligning itself with an evidence-based approach. These are early days but if this convergence of rehabilitation oriented clinicians and a patient advocacy group is successful, there could be very positive implications for insurers"

"Funding of rehabilitation by commercial bodies has begun in the UK with organisations such as PRISMA and is likely to continue"

"An increased availability of rehabilitative treatment facilities is highly desirable. The NHS is not likely to pay for these"

"Both health services and insurers now need to take a more positive approach".

2004

Somatoform disorders --- new approaches to classification, conceptualization and treatment
Winfried Rief Michael Sharpe
Editorial: Journal of Psychosomatic Research 2004:56:387-390

"In February 2002, an international group of clinical scientists working in the area of somatoform disorders meet in Marburg, Germany, to discuss new approaches to classification and treatment"

"Every medical specialty has its own syndrome of 'medically unexplained' or 'functional' somatic symptoms. Fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, pelvic pain syndrome and non-cardiac chest pain are just some examples"

"Recent evidence suggests that these categories are not as distinct as they initially appear"

"The core diagnostic category of the somatoform disorders is somatisation disorder"

"For these disorders, a wider range of phenomena are included in the diagnostic criteria, including the patients' beliefs and behaviour"

"The core of somatoform disorders must remain as somatic complaints unexplained by disease"

"Many patients with somatoform disorders manifest a tendency to interpret benign bodily complaints as signs of disease"

"As well as perceptions, we might wish to include behaviour. Abnormal illness behaviour was described as seeking verification of a medical diagnosis by multiple doctors ('doctor-shopping'), urging doctors to do unnecessary investigations, inability to go working, and many others"

"As somatoform disorders are more frequently seen by non-psychiatric physicians than by psychiatrists, it could be argued that they should be placed in a completely new category in ICD-10 instead of under the F-category of psychiatric disorders"

"Somatoform disorders are an essential keystone to maintaining the integrity of both medicine and psychiatry" "

Modern psychiatry is based on the concept of psychopathology. That is, patients are assumed to have 'mental disease' "

"Hence, somatoform disorders serve both medicine and psychiatry by providing a disposal for the patients who would otherwise challenge the theoretical models upon which practice is based"

"An exciting new development is the attempt to translate specialized CBT treatments for use in primary care. A number of studies aimed to train GPs in the use of CBT are in progress"

"The stage of developing a clinically meaningful classification (and terminology) is work in progress"

"The ultimate aim will be the creation of an evidence-based psychologically sophisticated healthcare system".

2004

Somatoform disorders: a help or hindrance to good patients care? Michael Sharpe Richard Mayou
British Journal of Psychiatry 2004:184:465-467

"The prevalence of (somatoform disorder) has major implications for medical services"

"The main limitation is that the psychogenic implication is simply unacceptable to many patients, making it a poor basis for collaborative management"

"Somatoform disorders do not relate to the more widely used general medical classification of functional somatic syndromes such as chronic fatigue syndrome that are used in primary care to describe the same patients"

"The value of somatoform diagnoses is often taken simply to indicate a need to minimize access to medical care"

"The ambitious programme to prepare for the forthcoming DSM-V and ICD-11 offers an opportunity to reconsider the somatoform disorders"

"If somatoform disorders are to be abolished, with what should replace them? We should adopt a new terminology that is acceptable to patients. A variety of alternative terms have been suggested, including 'medically unexplained symptoms' and 'functional somatic symptoms'. We have found that the diagnosis of 'functional symptoms' is relatively acceptable to patients"

"The new classification could accommodate behaviour disturbances"

"In the 'post-somatoform' world we envisage that there will be a renewed interest by all parts of medicine in an integrated approach to patients' symptoms. Such a development will require that psychological assessment and intervention are fully integrated into medical care".

2005

The Science of the Art of Medicine Michael Sharpe
Inaugural Lecture, University of Edinburgh, 12th May 2005

In his inaugural lecture, attended by Simon Wessely, Sharpe (who now hold a Personal Chair in Psychological Medicine and Symptoms Research) spoke on "functional medicine" and how to treat diseases with "no pathology".

Sharpe highlighted medicine's 'blind spot' in dealing with symptoms that are not expressions of disease, including patients with controversial syndromes such as chronic fatigue syndrome or ME.

"We need a science of what was previously thought to be the 'art' of medicine. In order to do this, we must consider psychological as well as biological aspects of treatment as important"

"There are a number of examples of current scientific research aimed at treating patients' symptoms by addressing psychological aspects of medical care"

"These include exploration of the therapeutic impact of investigation and diagnosis in patients whose symptoms are disproportionate to disease and different forms of management programmes to help patients manage chronic fatigue syndrome".

In summary, it can fairly be said that Michael Sharpe regards ME/CFS as having **no pathology** and sufferers as being the **"undeserving sick of our society and our health service"**.

It seems he is unaware of – or simply dismisses – the evidence of multisystem pathology (illustrations of which are set out above) that has been demonstrated in ME/CFS.

APPENDIX III

Wessely's Wisdom? Some more open questions for Professor Wessely

Margaret Williams 16th January 2005

Professor Wessely, in your reply to John Sayer's open letter to you of 5th January 2005 you made some interesting statements that have raised important issues concerning what you refer to as "CFS/ME", so perhaps you would be good enough to clarify your current position with specific reference to the issues set out below.

It is to be hoped that you will understand the reason you are being asked to address these issues: it is because the ramifications are of such crucial and fundamental importance to many sick people. You are therefore asked to give the matters raised here your very serious attention.

By way of introduction, you must surely be aware that many well-informed people consider the real stumbling block to the advancement of medical understanding of the discrete disorder myalgic encephalomyelitis (ME) to be the various non-homogenous case definitions currently in use, especially the 1991 Oxford criteria (which you helped to formulate) and the 1994 Fukuda criteria (with which you were also involved).

This is because both these case definitions expressly exclude those with physical signs (as distinct from symptoms), thereby excluding those with Ramsay-described ME but automatically including anyone with what you choose to call "medically unexplained" tiredness or fatigue --- as distinct from post-exertional incapacitating exhaustion and malaise that are the cardinal features of ME --- for longer than six months.

Such dilution of the case description of ME has resulted in uncountable numbers of people being included in a distorted, grossly inflated and heterogenous construct now known as chronic fatigue syndrome ("CFS") which also includes those with psychiatric disorders in which "fatigue" is a feature.

Flowing from this is the disunity and confusion generated by the fact that the alternative name for ME listed in the WHO ICD-10 is CFS: the problem is that although the name is identical, "CFS" means different things to you and your psychiatrist colleagues in the so-called "Wessely School" than it does to other, non-psychiatrist, researchers and clinicians.

This has resulted in considerable unrest about the inclusion criteria to be used in the forthcoming Medical Research Council trials on "CFS", especially as the MRC itself confirmed (on 19th March 2004, in writing) that: "The Oxford criteria are to be used since they are perceived to be broader and more inclusive", and indeed the Trial Identifier itself states: "We chose these broad criteria in order to enhance recruitment" (para 3.6). Although not an issue arising from your reply to John Sayer, perhaps you would explain how the intentional inclusion of different disorders will be of benefit to sufferers from a specific disease such as ME/CFS that you claim will be included in those MRC studies on "CFS/ME"?

On this important issue of scientific exactitude and rigorousness, did you know that Nancy Klimas, Professor of Medicine at Miami, is on record as stating "The research effort is hampered by poorly conceived, constantly changing, even non-existent standards" (*CFS Research: the Need for Better Standards: Co-Cure 5th August 2002*)?

The issues arising from your reply that require your clarification are itemised below.

1. **The concept of ME/ICD-CFS as a nosological entity**

In your reply to John Sayer you state: "When we make a diagnosis of CFS/ME we are merely making a descriptive diagnosis". On what evidence do you rely to substantiate such an assertion that flies in the face

of so much published evidence to the contrary? Why do you persistently reject the evidence that since 1969 ME has been listed by the World Health Organisation as a neurological disorder in the ICD and that ME has been accepted by The Royal Society of Medicine as a nosological entity since 1978?

In your Joint Royal Colleges' Report on CFS (CR54, 1996) why did you entirely dismiss ME as an entity and assert that "Previous studies have counted people with ME, but these studies reflect those who seek treatment rather than those who suffer the symptoms" (13.3)? How curious that the WHO overlooked this.

Can you really be unaware that ME/CFS is a multi-system disorder of extraordinarily incapacitating dimensions from which complete recovery is unlikely?

Are you not aware that Professor Leonard Jason from De Paul University, Chicago, states that (ME)CFS can affect virtually every major system in the body and that for years, investigators have noted many biological abnormalities in ME/CFS, including an over-activated immune system, biochemical dysregulation in the 2-5A synthetase/RNase L pathway, cardiac dysfunction, EEG abnormalities, abnormalities in cerebral blood flow in certain areas of the brain and autonomic dysfunction (*Subtypes of Chronic Fatigue Syndrome: A Review of Findings. Leonard Jason et al. JCFS:2001:8:3-4:1-21*).

On what basis do you still disregard and dismiss the significance of the published findings of such an eminent and experienced expert, given that such abnormalities as he documents cannot be psychosocial in origin?

Will you explain why (apart from expediently relying on the fact that the 1991 Oxford criteria that you helped to formulate specifically exclude neurological signs and symptoms from your version of "CFS") you reject the documented evidence of neurological signs and symptoms in ME such as vertigo, nystagmus, ataxia, positive Romberg, abnormal tandem, abnormal gait, fasciculation, neuromuscular incoordination and autonomic dysfunction (especially frequency of micturition and nocturia) that are so frequently present in ME/CFS?

Despite claims from you and your associates (and despite what you stated in your reply to John Sayer that "no-one has yet provided compelling evidence that there is a subgroup of CFS which is 'neurological'), there is indeed published evidence (if you look for it) of inflammation of the central nervous system. Just a few examples 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. What is your own explanation for such findings?

Why do you refuse to acknowledge the existence and significance of other well-documented problems in ME/CFS, including delayed muscle recovery that has been shown not to be due to "deconditioning" (as you claim), cardiovascular symptomatology, particularly vasculitis (with convincing laboratory evidence of disruption of microvascular integrity), respiratory problems, gastro-intestinal dysfunction, pancreatic dysfunction, an enlarged liver with disruption of liver enzymes, severe and recurrent mouth ulcers, hair loss, adrenal and thyroid dysfunction (including low free T3), the many visual problems that are documented as occurring in ME/CFS and the well-documented increased incidence of allergies and hypersensitivities, none of which is present in your version of "CFS" or in other, non-specific, states of chronic fatigue in which "fatigue" is the predominant complaint?

Despite the published evidence of organic pathology that has been demonstrated in ME/CFS, you are on record as asserting that ME is nothing more than a "belief system".

And then there is your article in which you categorically assert that "there lies at the heart of CFS not a virus (or) immune disorder, but a distortion of the doctor-patient relationship" (*Chronic fatigue syndrome: an update. Anthony J Cleare, Simon C Wessely. Update (Recent Advances): 14th August 1996:61-69*).

Compare your own view with that of Professor Komaroff: "The report by De Meirleir, Bisbal and their colleagues is another strong piece of evidence that is consistent with the hypothesis that the immune system is under attack. Furthermore the report is inconsistent with the hypothesis that (ME)/chronic fatigue syndrome involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest" (*Editorial: The Biology of the Chronic Fatigue Syndrome: Am J Med 2000:108:99-105*).

By contrast, you and your colleagues proclaim (frequently) that ME is perpetuated by "dysfunctional illness beliefs" (specifically, the belief that the disorder is a physical illness) and by "avoidant coping", these precise quotations being taken from the Presentation of Dr Peter White to the Scientific Workshop sponsored by the National Institutes of Health that was held at Bethesda, Maryland on 12th-13th June 2003.

Can you be unaware that your view that ME/CFS is a functional somatic syndrome that is amenable to compulsory psychotherapy regimes has had a catastrophic impact, not only on adults but especially on children and young people with ME, which as far as children are concerned is certainly unproven, since there have been no trials on children?

Does it not trouble you that (quote) "every school system in the nation seems to be more familiar with the phrase 'Munchausen's Syndrome By Proxy' than 'Chronic Fatigue Syndrome'. The situation for children and adolescents with the disease – and their families – is grim. The stories are so horrible, frightening, terribly sad. Threatening to take a sick child away from his / her parents because the school system doesn't 'believe' in a disease that the CDC calls 'a major life-altering illness' is too obviously wrong" (*acknowledgment to Mary Schweitzer, Co-Cure ACT: 16th January 2005*).

Will you explain how such abnormalities as those mentioned above can possibly be the consequence of aberrant beliefs?

For you to have dismissed ME as an aberrant belief is surely gravely erroneous yet you once wrote that you are proud of your own contribution to the advancement of understanding about the disorder. Are you still proud of yourself?

The researchers whose work is mentioned here are not quacks and they did not rely on "subjective questionnaires, theories, personal feelings or sociological musings to support their ideas" (*M.E.Advocacy. Maupin C*: http://cfidsreport.com).

Do you know what Dr Peter Rowe, paediatric cardiologist of Johns Hopkins University, Baltimore, said about the somatisation theory of ME/CFS in his invited presentation to the CFS Advisory Committee on 10th January 2005? At that meeting, Professor Charles Lapp noted that when he went to the international body of literature on paediatric (ME)/CFS, he found that much of the research claimed that children with (ME)/CFS were "psychosomatic" and he asked Rowe what he thought of that. Rowe was emphatic: "When there is depression or anxiety, it is co-morbid". Lapp said that one quarter of articles found on paediatric (ME)/CFS were from the United Kingdom and that of these, 62% insisted that it was purely a psychiatric problem or one that would be outgrown. Lapp concluded that a paediatrician who went to the world literature for information on (ME)/CFS would get the wrong impression. Rowe's reply was "With information, good doctors will pick up (the correct facts). On the other hand, the psychiatrists have gotten very good at picking out the patients…so what we need are good psychiatrists" *(with acknowledgment to Mary Schweitzer: Co-Cure ACT: 12th January 2005).* Would you be good enough to comment on this?

Have you ever read Osler's Web by Hillary Johnson? Perhaps you prefer not to read it, but you may have seen Johnson's recent reminder on the internet (*Back to the Future, 14th January 2005*) about how other well-respected physicians regard ME/CFS, for example, as long ago as the late 1980s Philip Peterson,

Professor of Infectious Diseases at the University of Minnesota, found by using a morbidity scale first published in JAMA in 1989 (the Medical Outcome tool) that whilst healthy controls scored on average 75 and those with rheumatoid arthritis scored in the 40s range, those with ME/CFS scored an average of only 16.

Also in the late 1980s, Mark Loveless, an HIV expert from Oregon, found that ME/CFS patients whom he saw had far lower scores on the Karnofsky performance scale than his HIV patients even in the last week of their life.

By 1990, Peterson was unequivocal: "It is, potentially, an immunologic disease".

Then there is world expert Professor Klimas herself on this same issue, who has described this disorder in very specific terms: it is "a form of acquired immunodeficiency, with natural killer (NK) cell dysregulation being the most consistent abnormality" (*Immunologic Abnormalities in chronic fatigue syndrome. J Clin Microbiol 1990:1403-1410*).

Do you recall that in 1992, international experts including Cheney, Komaroff and Gallo et al found that "neurologic symptoms, MRI findings and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic, immunologically mediated inflammatory process of the central nervous system" (*Ann Int Med 1992:116:103-113).*

And on the same issue, do you remember that in 1994, Professor Paul Levine (from the National Cancer Institute in Bethesda) is on record as advising that "the spectrum of illnesses associated with a dysregulated immune system must now include (ME) CFS"? (*Clin Inf Dis 1994:18: (Suppl 1):557-560*).

Do you remember that from his first hand experience of ME/CFS patients, Dr Dan Peterson confirmed that "In my experience (ME)CFS is one of the most disabling diseases that I care for, far exceeding HIV disease except for the terminal stages" (*JCFS 1995:1:3-4:123-125*).

Moving on to 2001, do you recall the work of Cook et al? You can hardly overlook that they demonstrated that brain abnormalities detected by MRI are significantly related to low physical function in ME/CFS, and that the abnormalities were grouped into five categories: (i) lateral ventricular enlargement (ii) grey matter and / or brain stem hyperintensities (iii) subcortical white matter hyperintensities (iv) cerebral atrophy and (v) L – R cerebral hemisphere asymmetries. 52% of patients examined showed abnormalities that fell into one of the five categories and the authors suggest that the brain abnormalities in ME/CFS are "as functionally significant as has been shown in the case of multiple sclerosis" *(Intern J Neuroscience 2001:107:1-6).*

However, you are on record as advising ardently that people with ME/CFS should receive only the most basic routine screening and you specifically advised Government that "no investigations should be performed to confirm the diagnosis, which is a clinical one" (*Joint Royal Colleges' Report, 1996: Summary for Commissioners, page 45).*

And then there is your advice to the CMO: were you content that the advice contained in the CMO's Working Group Report was that it is inappropriate and unnecessary even to look for such pathology in those who are thought to have the disorder?

Unless such abnormalities as those demonstrated by Cook et al are looked for, how can they be found? You might argue that even if abnormalities are found, they would not change the management or outcome, but how can you justify this argument in the light of such data as that mentioned in this document?

Do you recall that in 2001, Susan Levine found indisputable evidence of infectious agents in the spinal fluid of ME/CFS patients? (*JCFS 2001:9: (1-2):41-51*). Some of the infectious agents found have previously been shown to invade the central nervous system. The author commented that it was surprising to obtain

such a relatively high yield of infectious agents on cell free specimens that had not been centrifuged. What is your view on these findings?

Then we move right up-to-date: as a self-proclaimed expert on this disorder, you would be expected to be at the forefront of knowledge on your speciality, so you will know that Ben Natelson et al from New Jersey have published some very interesting and important results supporting the view that some patients with ME/CFS have a neurological abnormality and that immune dysregulation within the central nervous system may be involved in this process *(Clinical and Diagnostic Laboratory Immunology. January 2005:12:1:52-55*). It is noteworthy that Natelson says about the disorder: "Some think that it is an example of symptom amplification indicative of functional or psychogenic illness, while our group thinks that some (ME)CFS patients may have brain dysfunction". By testing spinal fluid, Natelson found that 30% of those with (ME)CFS had protein levels that were higher than controls (all of whom had normal levels), with some patients having levels that were higher even than the laboratory norms. Significantly, those with the highest protein levels had a lower rate of co-morbid depression than the controls. Natelson concludes that this confirms a neurological cause for the disorder. Would you explain why you disagree?

What is your interpretation of Jonathan Kerr's finding from Imperial College, London that supports a genetic basis for this disorder, as reported by James Le Fanu in The Sunday Telegraph on 9th January 2005? Do you regard it as significant that the identified genetic abnormality is present in no less than 15 genes involved in the functioning of "the nerves and the 'batteries' that provide the energy for the cells"?

Despite all this (and what is mentioned here barely scratches the surface of what is known and published about ME/CFS), you are seemingly determined to deny reality in that you ride rough-shod over such findings as those illustrated above. Why is this so?

From your own published (and audio-recorded) views on people with ME/CFS, it would be unreasonable to expect you to show compunction, but does it not concern you at all that the ME community is understandably outraged by your statement that ME is simply a "belief system"?

Why are you so opposed to looking diligently and relentlessly for evidence of disrupted biological processes in ME/CFS patients? What drives your resistance?

You are on record as stating that it is not necessary to know the *cause* of a disorder before treating it, but what countless people find so unacceptable is the denial by you and your group of psychiatrists of the need even to look for the cause, as well as your denial and dismissal of the very existence of the symptoms that so comprehensively wreck so many lives.

You are also on record many times as expressing the need to control NHS costs, in particular for what you regard as the substantial and costly problem of "non-existent" and "medically unexplained" syndromes (in which you include "CFS/ME"), but is there something perhaps more self-serving than cost control involved?

On the matter of "medically unexplained syndromes", did you know that in his item in the current BMJ (*A new era of psychospiritualism*), Abhijit Chaudhuri, Senior Lecturer in Neurosciences at the University of Glasgow, writes that Medically Unexplained Syndromes (MUS) is an artificial construct that is entirely synthetic; that it is created by psychiatrists and lies outside the natural territory of medicine? How do you respond to this?

2. <u>Cognitive Behavioural Therapy and the Mind-Body Movement</u>

In the CMO's Working Group Report of January 2002, cognitive behavioural therapy is described as "a tool for modifying attitudes and behaviour".

It is known that it is Government policy to promote CBT as widely as possible for conditions for which medicine currently has no answer. After all, in 2002 the BMJ made the position clear: "The trend started

with the 1996 NHS Strategic Review 'Psychotherapy Services in England'. This set out a programme for coordinated, evidence-based, comprehensive, safe and equitable provision of psychotherapy. Psychological therapies increasingly form an integral part of government planning for mental health care and cognitive behavioural therapy tends to be seen as the first line treatment for many psychiatric disorders….for most diagnoses, cognitive behavioural therapy tends to get the accolade of 'level 1' evidence ….a similar theme emerges in the Department of Health's guidelines: cognitive behavioural therapy comes first for depressive disorders, panic disorder and chronic fatigue" *(All you need is cognitive behavioural therapy. Jeremy Holmes et al BMJ 2002:324:288-294).*

However, correctly delivered CBT is very expensive and time consuming, as one of your named collaborators in the current MRC PACE trial (Tony Johnson from the MRC Biostatistics Unit at Cambridge) has previously confirmed when he challenged the validity and cost effectiveness of CBT in a critical analysis of the methodology of psychiatric trials: you will doubtless be aware that he found that a course of psychotherapy typically lasted for 12 weeks and a major limitation is its cost (Clinical trials in psychiatry: background and statistical perspectives. T. Johnson. Statistical Methods in Medical Research 1998:7:209-234). As you know, the trial statistician is named as Dr Tony Johnson in the PACE Trial Identifier, which says: "Prof. Simon Wessely will oversee the CTU (Clinical Trial Unit), with the support of Dr Tony Johnson" (para 4.4).

In your reply to John Sayer on the issue of cognitive behavioural therapy for those with ME/CFS, you write: "what I know is that these are treatments that have a reasonable chance of helping you irrespective of the cause. I can say from the evidence of the randomised trials that more people who receive them do better than those who do not. I am entitled to say that because that is what the trials, reviews and meta analyses show".

How many meta-analyses have there been? How can there be a secure evidence-base of "best practice" for the cost-effective benefit of CBT when not enough attention has been given to the fact that in the systematic review of the literature that was commissioned for the CMO's Working Group (the York review) there were only three randomised controlled trials (RCTs) of graded exercise therapy and five RCTs of CBT that were of sufficiently acceptable standard to have been included?

Those RCTs that were included in the York Review found the possibility of **some** benefit to **some** patients in broadly-defined cohorts, not that CBT was specifically or universally efficacious.

The Review is unequivocal: "overall, sufficient research evidence was lacking and the quality was not optimal".

Would you accept so low a figure of RCTs as a viable evidence base for "best practice" in support of homoeopathy, for example? As Abbot and Newton say, if a similar evidence base existed for Shamanic healing, it would arouse little clinical interest (http://bmj.bmjjournals.com/cgi/eletters/325/7362/480).

Given the prolific evidence that ME/CFS is not a primary psychosomatic disorder (which you cannot deny but only reject), why were you and your colleagues so specific in your recommendations in the 1996 Joint Royal Colleges' Report on CFS (CR54), about which in regard to the provision of future services in the UK for those with "CFS" you (a liaison psychiatrist) said: "such services could arise out of existing liaison psychiatry provision" (CR54:13.10)?

Moving forwards by six years, why do the recommendations to the Chief Medical Officer about the necessary direction of health service planning (CMO's Report, January 2002) say: "Government investment in research on CFS/ME should encompass behavioural and social science (and) the research programme should include sufficient resource allocation for investigator-generated studies on the condition". Is it only by chance that in the UK, "investigator-generated studies" are firmly in the psychiatric domain?

Why do you disregard the substantial evidence that CBT stops being effective when the sessions with the therapist end?

Is there perhaps even more at stake? For instance, is it because of your allegiance to and involvement with the Mind-Body movement which, as you will know, arose in Germany and Austria, its aim being to counteract laboratory-based medicine by emphasising mental and behavioural aspects of disease management?

You will be aware that under a $50 million initiative, the US National Institutes of Health established 10 centres around the country in just two years (between 1999 and 2001) for the promotion of behavioural management strategies. Could the recent funding of £8.5 million by the UK Government for the setting up of new centres to deliver CBT regimes for "medically unexplained syndromes" have anything to do with this growing movement that seems to have access to unlimited corporate funds?

In the light of the research findings mentioned in this document, have you any regrets that the report by the CMO's Working Group states that the management of "CFS/ME" is to be psychiatric and that future NHS service provision (quote) "ideally would adopt a biopsychosocial model (and that) the components of such a service are facilities for activity management"?

Would you be good enough to comment on the fact that CBT has been shown to be at best ineffective and at worst actively harmful for those with ME/CFS (it is unnecessary for you to claim that the MRC trials are intended to resolve this issue, since the obfuscation of the trial entry criteria referred to above precludes any such resolution).

3. <u>The classification issue: is it also connected to the Mind-Body Movement?</u>

There can be no doubt that you and your colleagues have worked assiduously to effect the reclassification of ME/CFS from its present category of neurological to psychiatric, even to the extent of misclassifying ME/CFS as a mental disorder in the WHO Guide to Mental Health in Primary Care without the WHO sanction or approval--- a fact that was unacceptable to the WHO (who on 16th October 2001 confirmed in writing that such a view (quote) "is at variance with WHO's position").

It was eventually also unacceptable to the UK Government, as Health Minister Lord Warner's letter of 11th February 2004 to the Countess of Mar made clear: "The Department (of Health) accepts that it might have been clearer to say that chronic fatigue syndrome is indexed to the neurology chapter and fatigue states to the mental health chapter".

Even the CMO's Working Group Report of 2002 (with which you were involved) was misleading on this point, because it stated: "Currently, CFS and ME are classified as distinct illnesses in the World Health Organisation's International Classification of Diseases". Given that the Working Group was notified of this error on more than one occasion before the final report was published, to have included such an erroneous statement in a report of such significance was either inexcusable editorial carelessness or it was deliberate promulgation of misinformation in accordance with what appeared to be a pre-determined agenda.

The whole issue of correct classification is a serious matter, yet you are on record as being dismissive about it, referring to it in a statement entitled "What's in a classification?" on your King's College website as nothing more than "a storm in a teacup". Your comments were also reported in the newsletter of the UK ME Association (*ME Essential, March 2004, page 10*).

On the troubled issue of the correct ICD classification code for ME/CFS, in your reply to John Sayer you refer to the letter that you and Tony David wrote to the Lancet about the classification of ME (and for the sake of accuracy, it was in November 1993, not in 1992 as you state in your reply to Sayer), in which you said "neurasthenia would readily suffice for ME" *(Chronic fatigue, ME and ICD 10. David A, Wessely S. Lancet 1993:342:1247-1248).*

As you will know, Charles Shepherd, Medical Adviser to the UK ME Association, commented on the letter you and Tony David sent to the Lancet in the following terms: "Despite (Wessely's) view that (the inclusion of ME/CFS in ICD-10 as a neurological disorder) was a 'moral victory' for self-help groups, there

was a very strong and growing campaign at this time, mainly involving psychiatrists on both sides of the Atlantic, to completely eradicate the term myalgic encephalomyelitis from medical language. And they had a considerable degree of success as it became almost impossible to use the term ME in the medical journals" (*Co-Cure 26th July 2002).*

You specifically confirm to Sayer that what you said in that (1993) letter was true: ("nevertheless, what I wrote was true"). You then say to Sayer: "most doctors, even those involved in CFS/me (*sic*) research, are not bothered by the issue of F or G codes. I don't myself think it does much good to get too hung up on the business of what code the WHO uses. Remember, if you look at the descriptions, you will see beyond a shadow of doubt that what is being described under the two headings is the same condition".

This is clearly erroneous, because the WHO itself confirmed in writing (on 23rd January 2004) that "it is not permitted for the same condition to be classified to more than one rubric as this would mean that the individual categories and subcategories were no longer mutually exclusive".

If you believe that ICD codes are not of significance, why are you so determined to get the existing classification of ME changed from neurological to psychiatric?

This being so, on what evidence-base do you maintain your view? Why do you persist in ignoring not only the distinguishing difference in symptomatology but also the enormous body of biomedical evidence that ME/CFS is not the same as medically unexplained idiopathic chronic fatigue to which you ascribe the term "CFS/ME" (and the F code) and assert that it is indistinguishable from ME (which carries the G code)?

In your reply to John Sayer, you mention depression. In your earlier work you seemed certain that ME/CFS was a form of depression and you are on record as advising the use of anti-depressants; indeed, despite the published evidence that anti-depressants do not work in ME/CFS and that those with ME/CFS have a high frequency of adverse reactions to such medication, you have argued for their use more recently even in people with ME/CFS who are not depressed.

This inevitably brings to mind the fact that the House of Commons Health Select Committee is currently holding an inquiry into the influence of the pharmaceutical industry: you will doubtless be aware that this industry has come under intense scrutiny and has been criticised for, amongst other disturbing things, "disease-mongering" and the creation of "life-style" illnesses, especially in the field of mental health. This is apparently with a view to creating a market for long-term dependence on prescribed medication. In view of your persistent efforts to reclassify ME/CFS as a mental disorder, could this be one of the reasons why you wish to reclassify ME/CFS from neurological to psychiatric?

The classification issue is important and correct classification does matter because it impacts on correct referral to an appropriate specialist, correct investigations, correct diagnosis, correct management and / or treatment, correct State benefit support, correct insurance policy payments and, as part of correct management, the provision of home tuition for young people.

Are you really unaware that ICD codes are used to plan the provision and delivery of NHS services? It is a fact that software systems in the NHS use ICD-10 to encode diagnostic data. For this reason alone, ICD codes matter very much, so it is hardly surprising that people find your views dismissive and patronising. Have you really no contrition about this, especially when the consequences of misdiagnosis and the imposition of inappropriate management regimes have been (and remain) so serious?

Do you promote the re-coding of ME as a mental disorder and the further funding of psychiatric services for "CFS/ME" in order to secure funding for the maintenance of what is described as your current status as world leaders and your Centre of Excellence in this field? Given the significant amount of evidence that ME/CFS is not a psychiatric disorder, how can recommending such resources for your own speciality be in the best interests of patients with ME?

Conclusion

In the letter that you and Tony David wrote to the Lancet in November 1993 (to which you referred in your reply to John Sayer), you ended by affirming: "We believe that this latest attempt to classify fatigue syndromes will prevent many people from seeing the world as it actually is". That seems remarkably arrogant and presumptuous. Although that letter was written over a decade ago, it is obvious from your subsequent publications that despite the ever-mounting evidence that shows you to be wrong in your belief about the nature of ME/CFS, you still hold such a view.

You claim to have read "Denigration by Design?" which as you know, documents your own involvement in the current perception of ME/CFS in the UK. You may therefore recall what the internationally respected psychologist Dr Dorothy Rowe states: "People who know absolutely that they are right are very dangerous" (Observer, 14th November 1993). You may not, however, be aware of what Cormac Rigby, former BBC Radio 3 announcer who became a Catholic priest has to say on the same issue: "The greatest enemies of truth are those who think they have a monopoly of truth" (The Lord be with you -- a book of sermons. Fr. Cormac Rigby. Family Publications, Oxford 2004). Do you agree with such a view?

APPENDIX IV

Unanswered Questions: do inconsistencies matter in medicine?

Margaret Williams 10th September 2005

Following recent posts about the intention of members of the Wessely School / One-Health company to persuade Government agencies to implement a national programme of cognitive behavioural therapy and graded exercise regimes for those with alleged "behavioural" disorders in which they include "CFS/ME" (see Co-Cure ACT: "Proof Positive?": 2nd September 2005 and "More Proof Positive?": 4th September 2005), there are numerous inconsistencies that seem to remain unaddressed by One-Health company lobbyists. They include (i) the irrationality of drawing conclusions across differing patient populations (for example, lumping together those with primary psychiatric disorder and those with primary organic disorder and then claiming that this amalgamation represents one single "behavioural" disorder); (ii) the absurdity of relying on assumptions as the basis for a compulsory management regime (for example, that ME/CFS patients obtain secondary gain); (iii) the divergent assertions about the efficacy of cognitive behavioural therapy; (iv) the inherent danger of applying a "one-size fits all" management policy to those with "CFS/ME" and (v) the opposing evidence of these psychiatrists' intention to claim "CFS/ME" as a psychiatric disorder.

The irrationality of drawing conclusions across differing patient populations

Although Wessely began attacking the validity of ME in 1987 (see, for example, "Mass Hysteria: Two Syndromes?" Wessely S. Psychological Medicine 1987:17:109-120), there is substantial evidence that since the creation of "CFS" in 1988 *("Chronic Fatigue Syndrome: A Working Case Definition". Holmes et al. Ann Int Med 1988:108:387-389*), Wessely and his colleagues have assiduously attempted to subsume ME within the heterogeneous label "CFS", asserting that it is a functional somatic disorder (ie. a primary psychiatric disorder) whose sufferers must be made to alter their beliefs and behaviour (see http://www.meactionuk.org.uk) but it needs to be asked on what evidence One-Health company members rely that enables them to subsume the discrete entity ME into their own definition of "CFS/ME" when, by virtue of the criteria they used, most of their studies could not have included those with authentic ME?

Because of the irrationality of drawing conclusions across differing patients populations, in the first (1996) volume of "Denigration by Design?" (copies available at cost price from Mrs DM Jones, telephone 0208-554-3832) 34 questions were listed which it was believed Wessely should be required to answer; almost a decade later, most of those questions remain unanswered but are equally relevant and include the following:

1. On what grounds do Wessely et al justify their selection of patients for their studies when the criteria they use exclude the criteria necessary for a diagnosis of ME (which they now refer to as "CFS/ME"), for example, the Ramsay diagnostic triad? (*see: Myalgic Encephalomyelitis: A Baffling Syndrome with a Tragic Aftermath. A. Melvin Ramsay. Published by the UK ME Association, November 1981)*

2. Why do Wessely et al ignore the world-wide literature on the severity and chronicity of ME?

3. What are their views on the fact that patients with ME are not permitted to donate blood, whereas patients with a psychiatric diagnosis are not excluded?

4. In how many of their patients have they requested tests of vestibular function, of pancreatic exocrine function, of liver function, of cardiac function and of levels of oxygenation, perfusion and pulsatilities; in how many patients have they asked for measurement of patients' CD4:CD8 ratio; of IgG3 levels; of circulating immune complexes and of NK cells; what percentage of their patients have abnormal vascular changes and what percentage of their patients have undergone nuclear medicine imaging studies?

5. Where is their evidence of secondary gain in ME patients who they claim have "adopted the sick role"?

The answers to these questions are important: without answers, why are people trained in other professional disciplines to make factual observations and to collect and analyse data taking Wessely School psychiatrists' studies seriously?

The absurdity of relying on assumptions as the basis for a compulsory management regime

On the issue of secondary gain, in 1996 the question was asked why Wessely never addresses the losses sustained by those with ME/CFS: "Why does (Wessely) assume that there are invariably benefits in the sick role? If he wishes to claim there are benefits (which he does), then he needs to ascertain in each individual case that patients *are* benefiting from adopting the sick role for what they can get out of it: this needs to be proved before it can be stated as fact. No expensive tests would be required to ascertain whether or not patients do benefit in any way, and this should not be stated as a universal fact merely on Wessely's assertion that it is so".

What "secondary gain" can possibly compensate for the loss of health, employment, financial security, social life and – far too often – loss of home, partner, family and friends? If "adopting the sick role" brings people with ME/CFS to the point of such despair that they consider or commit suicide, how can it be thought to be "rewarding"?

However, as was shown in "Proof Positive?", Wessely and his co-lobbyists still seem to hold the same beliefs because Professor Michael Von Korff said: "If we start with the assumption that (these patients) are motivated largely by secondary gain ….". To depend on such an assumption defies logic, so the question therefore needs to be repeated: where are the published studies which demonstrate that such patients obtain secondary gain? As Von Korff made plain, the psychiatrists' view is an assumption -- with much being built on it -- but assumptions are hardly "evidence-based medicine" upon which Wessely et al claim to place such store.

Divergent assertions about the efficacy of CBT

The documented inconsistencies about the efficacy of cognitive behavioural therapy (CBT) seem to present another paradox: in his "Reply to our critics" that followed the publication of the paper "Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome" by Pauline Powell, Richard Bentall, Fred Nye and Richard Edwards (*BMJ 2001:322:387*) in which the authors – all of whom could be regarded as being supportive of "Wessely School" beliefs about "CFS/ME" -- cite Sharpe's 1996 BMJ paper, Richard Bentall asserted: "There is now a consistent and impressive body of evidence that shows that psychological interventions that facilitate a graded return to normal activity are effective in many cases of CFS". (*eBMJ: 27th February 2001*).

What seems to have been overlooked is that although Sharpe contributed much of the cited (allegedly supportive) literature, Sharpe himself substantially undermined it by stating on 3rd November 2000: "There is a tendency for the difference between those receiving CBT and those receiving the comparison treatment to diminish with time due to a tendency to relapse in the former" (see: http://www.cfs.inform.dk). Curiously, in the same document Sharpe referred to a five-year follow-up study of CBT as showing "some persistent benefit".

It is important to be aware that the authors of the study to which Sharpe referred conceded that CBT "has been shown to improve functional impairment for up to 8 months after treatment" and state about the efficacy of CBT that "observed gains may be transient". The conclusion was: "It seems that once therapist contact ended at six months after treatment, some patients may have become vulnerable to relapse", so (unsurprisingly) the authors suggest that "It may be useful to extend the duration of treatment to include more attention to core beliefs that could leave patients vulnerable to relapse". Crucially, the findings were that after five years, "almost one-half (of participants) still fulfilled the criteria for chronic fatigue

syndrome" ("*Long-Term Outcome of Cognitive Behaviour Therapy Versus Relaxation Therapy for Chronic Fatigue Syndrome: A 5-Year Follow-Up Study". Alicia Deale, Trudie Chalder, Simon Wessely et al. Am J Psychiatry 2001:158:2038-2042*).

Of more relevance is by what reasoning a management regime that delivered "some" benefit lasting for only six months can be deemed to be cost-effective to the extent that it is being promoted as the national management regime of choice for the much-abused sufferers of ME/CFS. Is this the calibre of "evidence" that One-Health members will rely on to convince the Establishment that they are right?

It is not only Sharpe but also Wessely himself who has conceded the limited efficacy of CBT: in his editorial "Chronic Fatigue Syndrome – Trials and Tribulations" (JAMA: 19th September 2001:286:11) Wessely stated that CBT and graded exercise are only "modestly effective" and that neither is "remotely curative"; one wonders why he confided this insight to a leading American journal, while he continues to withhold it from the readership of the BMJ and from Government policy-makers.

<u>The inherent danger of applying a "one size fits all" policy of management in ME/CFS</u>

Of note is that the same Richard Bentall referred to above (professor of experimental clinical psychology at the University of Manchester) is on record as stating: "The idea that there is a clear division between 'mad' and 'sane' is resulting in the mass-application of treatments which, while benefiting some, are very harmful to others"; of significance in relation to ME/CFS is that he also said that identifying and addressing the problems the sufferer, rather than the psychiatrist, perceives is far more scientific, humane and effective than a blanket diagnosis (*Madness of labelling mental illness. Michelle Roberts. BBC News health reporter; BBC 2nd September 2005, 23:50 GMT*).

Are Bentall's two quotations consistent in relation to ME/CFS, especially as those with ME/CFS are indeed the subjects of "blanket diagnosis" (ie. somatisation disorder) by One-Health company members and are also subject to the mass application of CBT and graded exercise and it is beyond dispute that the problems identified by patients with ME/CFS are not only not addressed but are comprehensively ignored by One-Health company psychiatrists?

Yet again, it needs to be asked why there is special pleading in relation to ME/CFS?

<u>The opposing statements from One-Health company members concerning the intention of psychiatry to claim "CFS/ME" as a psychiatric disorder</u>

It seems unequivocal from what was disclosed in "Proof Positive?" that the psychiatric lobby believes "CFS/ME" to be a somatisation disorder. It is widely understood that this psychiatric lobby is intent on the creation of a new category for "somatisation" disorders in the next edition of International Classification of Diseases (ICD-11) into which category "CFS/ME" will be placed, as proposed by Professor Mike Sharpe (*see "Sinister Science": Co-Cure:ACT 6th June 2004*). Sharpe believes that this new category should accommodate "behavioural" disturbances such as CFS/ME: "The ambitious programme to prepare for the forthcoming DSM-V and ICD-11 offers an opportunity to reconsider somatoform disorders" (*see: British Journal of Psychiatry 2004:184:465-467).*

This seems inconsistent with the written assurances from Wessely, who in November 2001 wrote to a correspondent: "I am aware that some people see (the inclusion of ME as a mental disorder in the WHO Guide to Mental Health in Primary Care) as a plot for WHO to surreptitiously switch CFS/ME from neurological to psychiatric. I can tell you that is nonsense. I am afraid there is no conspiracy to claim CFS/ME for psychiatry". In a second letter, Wessely re-iterated his earlier assurances: "I know one or two people detect a plot by psychiatry to claim CFS/ME for itself --- I promise you that the idea is preposterous. If the real issue is that this is all a sinister plot to get CFS transferred into the clutches of psychiatry --- forget it".

How do such assurances match the facts?

As Wessely et al seem intent on enticing the Chancellor of the Exchequer and the policy-makers with a national programme of CBT for those with "CFS/ME" that is promised to save money (presumably by removing patients from State benefits, after which what subsequently happens to them is of little interest to this cabal), should someone not tell them that the psychiatrists' own existing evidence is already clear that such programmes do not deliver lasting improvement? The policy-makers are unlikely to save money in the long-term by allowing themselves to be indoctrinated by One-Health company members, especially as any such claim seems to be based on nothing more than unsustainable assumption and assertion.

It would surely be more cost effective to fund appropriate research into causation, ie. biomedical research that stands a realistic chance of delivering actual treatment that leads to what sufferers regard as the ultimate goal – a cure.