Evidence of cardiovascular problems in ME/CFS that NICE disregarded

Margaret Williams 4th August 2008

Executive Summary

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) is an organic, multi-system disorder involving major systems and organs, particularly the neurological system (central and autonomic), the immunological system, the endocrine system, the cardiovascular system, the respiratory system, the muscles, the gastro-intestinal system, the urological system, the reproductive system, the auditory system, the ocular system and the skin, and pain is often a significant feature. There is abundant published evidence of multi-system dysfunction in ME/CFS but this document looks at some of the evidence concerning just one system that is dysfunctional in ME/CFS: the cardiovascular system.

Cardiovascular dysfunction in ME/CFS patients has been well documented for many years. As long ago as 1957, Dr Andrew Wallis recorded ***"myocarditis, with dyspnoea on slightest exertion"***. Professor Peter Behan wrote in 1988 that "***evidence of cardiac involvement may be seen",*** and Dr Jay Goldstein noted in 1990 that "***a significant group have cardiac symptoms"***. An important study by Professor Benjamin Natelson and Dr Arnold Peckerman published in 2003 **demonstrated that there might be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes, including the possibility of under-perfusion in the kidneys and gut**.

It may, therefore, be seen as both inexplicable and inexcusable that the NICE Guideline Development Group (GDG) who on 22nd August 2007 produced the NICE Guideline CG53 on "CFS/ME" chose to ignore – and was directed to disregard - an evidence-base of over 4,000 published studies showing underlying biological abnormalities in ME/CFS patients, studies that include extensive evidence of cardiovascular problems: the Guideline specifically stipulates that "***signs and symptoms of cardiorespiratory disease should not be attributed to CFS/ME"*** and refers instead to ***"perceived exertion"***.

The Guideline makes no reference to the fact that people with ME/CFS are not permitted to be blood-donors.

The GDG also ignored calls for the subgrouping of ME/CFS patients, with the result that the NICE Guideline has recommended the national implementation of a behavioural management regime (cognitive behavioural therapy and graded exercise therapy) for all patients with "CFS/ME", a regime that may be potentially **fatal** for an unknown number of patients.

Where it does refer to subgrouping, the Guideline seems only to be talking about the difference between the mildly, or moderately, or severely affected patients, not to distinct clinical categories.

Of particular note is the fact that in its Comments on Stakeholder submissions, NICE states that it advised that "CFS/ME" is a physical disorder; **NICE has not recommended behavioural interventions as the only intervention for any other physical disorder for which it has produced a Guideline**.

As a result of these failings by NICE, this document seeks to look in particular at the following key areas:

(i) **The need for an accurate case definition of ME/CFS**

- There are now at least eleven different case definitions of supposedly the same disorder
- NICE insists that "CFS/ME" is the same as ME/CFS – but the World Health Organisation (WHO) does not agree, classifying ME/CFS as a discrete neurological disorder (ICD-10 G93.3)
- The most significant obstacle to accurate diagnosis is the continued failure (particularly in the UK) to adopt the most effective case-definition (i.e. the 2003 Canadian case definition).

(ii) **The need for subgrouping of "CFS /ME"**

- Flaws in the case definition and in the design of (mostly UK) epidemiological studies have "***led to inaccurate and biased characterisation of CFS"*** which incorrectly favour a psychiatric view of the disorder
- Subgrouping of "CFS/ME" is important and necessary and there is extensive literature supporting the need for it
- A significant percentage (at least 20%) of people with ME/CFS as distinct from "CFS/ME" **die** from cardiac failure.

(iii) **Evidence and illustrations of cardiovascular dysfunction in ME/CFS that the NICE GDG was directed to disregard**

- "***The blood vessels throughout the nervous system were distended with red blood cells … the most characteristic change was infiltration of the blood vessel walls"***
- *"ME is a multisystem syndrome including nervous, cardiovascular, endocrine and other involvement. Vasculitic skin lesions, autonomic dysfunction, especially circulation and thermoregulation"*
- ***"These chronic ME/CFS patients complain of severe chest pain and shortness of breath as if suddenly stopped by an invisible barrier"***
- *"Evidence of cardiac involvement may be seen: palpitations, severe tachycardia with multiple ectopic beats and occasional dyspnoea may occur and are quite distressing. It is of great interest that some patients have evidence of myocarditis"*
- ***"There is a high incidence of cardiomyopathy in CFS patients"***
- ***"Convincing evidence of cardiovascular impairment can be demonstrated"***
- *"As a group, the ME/CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values compared with the control group.* ***These results indicate either cardiac or peripheral insufficiency embedded in the pathology of ME/CFS"***
- *"Several groups have shown that ME/CFS patients have abnormal regulation of heart rate and blood pressure, as well as high rates of allergic disease"*
- *"Many people with ME/CFS may have a serious heart problem. When you exercise, your heart pumps out more blood. But these patients' hearts actually pump less blood"*
- **Without exception, every disabled CFIDS (ie ME/CFS) patient is in heart failure**
- "Q" stands for cardiac output in litres per minute. In ME/CFS patients, Q values correlated – with great precision – with the level of disability. **When disabled ME/CFS patients stand up, they are on the edge of organ failure due to extremely low cardiac output as their Q drops to 3.7 litres per minute (a 50% drop from the normal of 7 litres per minute)**
- ***"All disabled ME/CFS patients, all of whom have post-exertional fatigue, have low Q and are in heart failure"***
- In order to improve cardiac output in ME/CFS, patients need to lie down, as this increases the cardiac output by 2 litres per minute. Some ME/CFS patients need to lie down all the time to augment their blood volume in order to survive
- **Aerobic exercise may kill the patient with ME/CFS. There is an objective database in key medical literature that includes evidence of diastolic dysfunction and heart failure in ME/CFS**
- After 10 years of illness, there is only a 30% chance of any functional recovery
- ME/CFS is a compensatory response to down-regulate energy production and oxygen transport in order to reduce tissue damage. Attempts to push beyond energy limits will cause injury
- **Diastolic failure begins when the body can no longer compensate and there is a reduction in cardiac output. This is seen in 80% of ME/CFS patients**
- **In order to stay relatively stable, it is essential for the ME/CFS patient not to create metabolic demand that the low cardiac output cannot match**

- **Graded exercise therapy is ill-advised – if a patient has abnormal oxygen consumption, muscles will not have enough oxygen and exercise will result in relapse**
- **The cardiac index of ME/CFS patients is so severe that it falls between the value of patients with myocardial infarction (heart attack) and those in shock.**

(iv) **Conclusion**

- It is essential to ascertain how, in the light of so much evidence of serious heart and vascular problems in a subset of ME/CFS patients (all of which the GDG was directed to disregard) incremental aerobic exercise as recommended in the NICE Guideline can help such patients remain as functional as possible
- Evidence should be produced by NICE as to why such an important Guideline was so restricted in its remit that it was not allowed to consider the totality of the existing evidence-base on ME/CFS
- A credible explanation should be sought from NICE as to why only those professionals who support a behavioural model of "CFS/ME" were selected to be members of the GDG.

Evidence of cardiovascular problems in ME/CFS that NICE disregarded

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) is a complex disease affecting all the major systems and organs of the body, including the cardiovascular system, where extensive damage has been identified (M Hooper. J Clin Pathol 2007:60:466-471).

There are over 4,000 peer-reviewed papers documenting the biomedical underpinnings of ME/CFS.

However, a group of UK psychiatrists and their adherents known as the Wessely School (Hansard [Lords] 19th December 1998:1013) deny and dismiss this scientific and biomedical evidence and have spent the last two decades proclaiming their belief that ME/CFS does not exist as a nosological entity and that it is *"like the elephant to the blind man – simply (a) different part of the same animal"*, the elephant being a single somatoform (behavioural) disorder (S Wessely et al. Lancet 1999:354:936-939).

These psychiatrists are advisers to UK Government agencies and to the medical insurance industry and they have assiduously published their beliefs; it is largely their studies that form the basis of the Systematic Reviews upon which NICE has relied as its "evidence-base" for its recommended management regime in its Guideline CG53 on "CFS/ME" published on 22nd August 2007. Since virtually all the papers on the management of "CFS/ME" that were included in the Systematic Reviews had been written by the Wessely School psychiatrists and adherents themselves, those Systematic Reviews support the Wessely School's view that behavioural interventions are the management regime of choice.

In the current issue of the British Medical Journal there is an Editorial by Professor Sir Iain Chalmers entitled "Confronting therapeutic ignorance. Tackling uncertainties about the effects of treatments will help to protect patients" (BMJ 2008:337:a841). Sir Iain writes:

"*This week's BMJ includes the first of a series of articles on areas of practice where clear and robust evidence is lacking, and where uncertainty exists about management.* ***Our failure to confront uncertainty about the effects of treatment has resulted in the suffering and death of patients, sometimes on a massive scale. Thousands of systematic reviews have shown that the existing evidence does not answer important questions about the effects of many treatments****. More fundamental changes are needed to reduce the damage being done to patients by failure to confront uncertainties. Hyper-regulation has made it easier for clinicians simply to acquiesce in therapeutic ignorance. The consequences for patients of acquiescing in therapeutic ignorance can be disastrous, yet current attitudes are powerful disincentives to people who wish to confront uncertainties about the effects of treatments".*

Nowhere is this more apposite than to the national management regime recommended in the NICE Guideline CG53 on "CFS/ME".

Because of the failure to confront management uncertainty, and in defiance of the well-documented evidence of contra-indications that were submitted to it (for which it claimed that it could not find any evidence), **NICE has recommended the national implementation of a management regime for all patients with "CFS/ME" that may be potentially fatal for an unknown number of patients.**

The need for an accurate case definition of ME/CFS

Including its own new case definition for "CFS/ME" that, without due consultation, was introduced by NICE itself in its Guideline on "CFS/ME", there are now at least eleven different case definitions of supposedly the same disorder.

Apart from the case definition introduced by NICE and the widely-acclaimed Canadian Case Definition (Carruthers B et al. 2003: ISBN 0-7890-227-9, see below), nine case definitions are listed on page 88 of The National Task Force Report on Chronic Fatigue Syndrome/Post Viral Fatigue Syndrome/Myalgic

Encephalomyelitis, 13th September 1994 (produced by Westcare, now part of Action for ME, and supported by the Department of Health).

Advised by Wessely School psychiatrists and adherents, NICE insists that "CFS/ME" is the same as "ME/CFS" but the World Health Organisation (WHO) does not agree, classifying ME/CFS as a discrete neurological disorder (ICD-10 G93.3) and classifying states of chronic fatigue as behavioural disorders (ICD-10 F48.0). The Wessely School, however, does not accept the WHO classification of ME/CFS: Wessely asserts that: "*Neurasthenia would readily suffice for ME"* (Lancet 1993:342:1247-1248), and he subsumes the distinct disorder ME into the psychosomatic label "CFS/ME" that he has constructed (BMJ 2003:326:595-597).

It is notable that the Guideline Development Group (GDG) states on page 36 of the GDG Comments on Stakeholder submissions on Chapter 2: *"a recommendation that CFS/ME should be recognised as a physical illness has been made"*, but this is not explicit in the published Guideline and, significantly, the only management recommendation is a behavioural modification programme.

NICE has not recommended a behavioural modification programme as the only intervention for any other physical disorder for which it has produced a Guideline.

The GDG further states: "*Support for specific physical features of the syndrome was weak and inconsistent in the studies reviewed for this Guideline"*. Herein lies the nub of the problem, because the studies on which NICE has based its recommended management regime are limited to those of the Wessely School and ignore an evidence-base of over 4,000 peer-reviewed published papers that show the Wessely School to be wrong.

The Canadian Criteria

There is international agreement that the most significant obstacle to accurate diagnosis is the continued failure (particularly in the UK) to adopt the most effective case definition (i.e. the 2003 Carruthers et al Canadian case definition, **this being the one that distinguishes the discrete disorder ME/CFS from the heterogeneous "CFS/ME", yet its use is specifically proscribed by NICE**).

The Canadian Guidelines are critical of the UK trials upon which the GDG relied for its alleged evidence-base (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Carruthers B et al. JCFS 2003:11 (1): 7-115).

During the UK Guideline consultation period, at least 40 submissions to NICE drew attention to the importance of the Canadian Guidelines (CFS / ME: stakeholders comments and GDG responses: see http://www.nice.org.uk/guidance/index.jsp?action=folder&o=36179).

Those submissions came not only from patients and support groups, but from professionals who do not subscribe to the Wessely School (behavioural) model and from ME/CFS charities. All made valid points, for example:

- LocalME wrote: "*(The Canadian) Guidelines were based on the international panel's collective extensive clinical experience diagnosing and treating more than 20,000 ME/CFS patients, and are widely believed to be the most detailed and comprehensive definition of ME/CFS in the world. They have informed Southern Australia as a basis for their own GP guidance and are endorsed by scientists here in the UK"*

- BRAME (Blue Ribbon Awareness for ME) wrote: "*Not to give credence (to) and recognition of the Canadian Guidelines, the most comprehensive clinical diagnostic criteria, and which provide a wealth of evidence-based advice, created by worldwide experts on (ME/CFS) is diabolical. One of our medical advisers (wrote): 'The reluctance to accept the biomedical model suggested in the Canadian document is unhelpful'. Adoption of the Canadian Clinical Guidelines would really*

have helped medical professionals, not only to have the information they need to make an accurate diagnosis of ME/CFS, but would also give them constructive information and skills to help manage their patients' chronic illness. The Canadian Guidelines manage to give a detailed account of pharmacological symptoms control, detailing which drugs are most likely to help, and those with the worst side effects. If that Guideline can do this, then why can't this one?"

- the UK charity Action for ME wrote: "*Diagnostic criteria remains a contentious issue, with many questioning the omission of the Canadian criteria"*

- the West Midlands Consortium wrote: "*The Canadian Case Definition was produced by a team of international specialists in (ME/CFS), with experience of over 20,000 patients. These guidelines are widely believed to be the most detailed and comprehensive (available). By comparison, the NICE Guidelines appear to endorse an extraordinarily weak definition of CFS/ME which amounts to chronic unexplained fatigue plus one other symptom"*

- SWAME (South West Alliance for ME) wrote: "*We believe that clinical guidelines need to go much further in describing the range of symptoms, as do the Canadian Clinical Guidelines"*

- The ME Association wrote: "*We are very disappointed to find the GDG appear to have totally rejected the way in which the Canadian Guidelines have moved towards a much tighter clinical definition that clearly recognises the importance of subgrouping under the ME/CFS umbrella".*

One of the world's leading researchers into ME/CFS, Professor Leonard Jason (see below), is on record about the need for the Canadian Guidelines to be used: commenting on his own group's comparison of the Canadian Guidelines with other Guidelines, Jason was clear: "*The Canadian Criteria selected patients with more physical impairment, more fatigue and weakness, and neurocognitive and neurological symptoms. The findings suggest that the Canadian criteria point to (the) designating post-exertional malaise and fatigue, sleep dysfunction, pain, neurocognitive and autonomic / neuro-immuno-endocrine symptoms as major criteria. The selection of diagnostic signs and symptoms has major implications for which individuals are diagnosed with ME/CFS and how seriously the illness is viewed by healthcare providers (and) disability insurers. I hope the results of this comparison study will encourage more physicians to use the Canadian Clinical Criteria"* (Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: An Overview of the Canadian Consensus Document". Bruce M Carruthers; Marjorie I van de Sande http://www.cfids-cab.org/MESA/me_overview.pdf).

Dr David Bell, a leading paediatrician specialising in ME/CFS, also endorsed the Canadian Guidelines: "*In the past few years, science has made extraordinary strides in understanding the basic mechanisms of ME/CFS, yet little of this science has reached medical practitioners to be used in relieving the suffering of patients affected by the illness. It is now possible to define abnormalities in the neurological, immune, autonomic and neuroendocrine systems in a concise way that can paint a portrait of this disabling illness. The Canadian consensus definition of ME/CFS is a concise summary of these advances and permits a clear diagnosis for patients. (It) should be read and studied by every medical provider"* (http://www.cfids-cab.org/MESA/me_overview.pdf).

The GDG, however, proscribed the use of the Canadian Guidelines.

In rejecting the use of the Canadian Guidelines, the GDG gives as its reason: "*The Canadian criteria are based on expert opinion and not on research evidence"*, repeating this on pp 15, 16, 81, 86, 87, 155, 163 and 195 in its comments on Stakeholders' submissions.

Another version of the reason given by the GDG is risible: "*The Canadian Guideline is a consensus document and does not provide an evidence-base for their guidance".*

Not only is it demonstrably untrue that the Canadian Guideline provides no evidence-base for its guidance, (which is based on world-class evidence and contains 237 references), but **for the GDG to reject the Canadian Guideline because it is a "consensus" document demonstrates the double standards and**

fundamental bias employed by the GDG, who themselves used "consensus" in the formulation of their own Guideline: "*Aware that the GDG might find difficulty in reaching agreement on some of the more controversial issues,* ***NICE set up two new procedures to help us make our recommendations: a formal consensus method*** *and consultation with a wider group nominated by stakeholders"* (Dr Fred Nye, GDG member: J Inf 2007:55:6:569-571). That consensus was used was also confirmed by the GDG itself: *"Consensus was used"* (page 36 of the GDG Comments on Stakeholder submissions on Chapter 2).

It is perhaps relevant that Professor Anthony Pinching (the patients' "Champion") who in the Guideline Acknowledgements is singled out by the GDG for special thanks and who, according to NICE, was instrumental in formulating the GDG's remit -- and who is lead adviser on "CFS/ME" to the UK Department of Health and who was responsible for the setting up of the "CFS" Centres that will deliver only behavioural interventions for "CFS/ME" -- advised NICE that: *"The Canadian definition has not been tested or validated as a set of criteria".*

The Canadian Criteria advocate the subgrouping of patients into three distinct categories (autonomic, which includes cardiovascular; inflammatory and endocrine symptoms), but the GDG ignored the many calls for subgrouping of "CFS/ME" and subsumed all states of "medically unexplained fatigue" – in which it includes ME/CFS -- into a single somatoform construct and based its management recommendation on this heterogeneous population, claiming -- as the Wessely School claims -- that there is no evidence of the need to subgroup "CFS/ME". Given the extent of the international evidence that subgrouping is essential, such a statement by NICE is insupportable.

In support of its recommended management regime, NICE relied mostly on the Oxford criteria for "CFS" which were published in 1991 by psychiatrists of the Wessely School and which specifically include in their own case definition of "CFS/ME" those patients with pre-existing psychiatric disorder and exclude those with neurological disease (Sharpe M, Wessely S et al. JRSM 1991:84:118-121).

<u>The need for subgrouping of "CFS" (known as "CFS/ME" by UK Departments of State whose advisers are Wessely School psychiatrists and adherents)</u>

In response to representations from Stakeholders pointing out the urgent need for subgrouping (for example, the patients' representative group BRAME [Blue Ribbon Awareness for ME] was clear: "*If sub-groups were identified it would help in offering appropriate treatment"*), the GDG's invariable response was: "*The evidence reviewed in this guideline does not allow us to distinguish between these groups when making recommendations"* (GDG response to Stakeholders' comments on chapter 5, page 56 of 279). This mantra is repeated throughout, for example: *"No research evidence was found for defined subgroups or different management strategies"* (GDG Comments, page 455 of 575); "*The GDG did not find evidence of sub-groups"* (GDG Comments, page 459 of 575). Where subgrouping is referred to, the GDG seems only to consider those who are mildly affected, those who are moderately affected, or those who are severely affected, and not the distinct clinical subgroups.

In 1997 Jason et al were clear about the psychiatric bias in "CFS/ME" research: **in a Review article, Jason et al stated that flaws in the case definition and in the design of (mostly UK) epidemiological studies have "*led to inaccurate and biased characterisation of CFS"* which incorrectly favour a psychiatric view of the disorder.** Jason et al noted that the Australian and British case definitions do not consider pre-existing psychiatric disorder to be exclusionary for a diagnosis of "CFS" and stated: "***the erroneous inclusion of people with primary psychiatric conditions in CFS samples will have detrimental consequences for the interpretation of both epidemiologic and treatment efficacy findings.*** *Until more differentiated subgroups are developed, it will be exceedingly difficult to identify characteristics that are common for all people with the diagnosis of CFS"* (American Psychologist 1997:52(9):973-983).

Leonard Jason is one of the foremost researchers into the disorder. He is Professor of Psychology and Director, Centre for Community Research, DePaul University, Chicago; he is also Vice President of the International ME/CFS Association and is a member of the CFS Advisory Committee to the US Secretary of Health and Human Services.

Subgrouping of "CFS/ME" is important and necessary and the extensive literature supporting the need for it cannot be denied.

Prominent US researchers, including Martin Lerner, Arnold Peckerman, Benjamin Natelson and Paul Cheney (see below) have found that one subgroup contains people with ME/CFS who have a particular form of cardiomyopathy, as described by Cheney (Professor of Medicine at Capitol University, Washington DC, see below).

Wessely, however, does not agree: in correspondence arising from his article "Chronic fatigue syndrome: Symptoms and Syndrome" (Annals of Internal Medicine 2001:134:9S:838-834, in which he wrote: ***"[There] is a debate about subgroups. Some of the desire to split the chronic fatigue syndrome into subgroups is driven by emotion"),*** Wessely said: *"What matters is the evidence. Here I am on firmer ground. The approach that we have developed (CBT and GET) is safe and cost effective and it represents a reasonable way forward, reducing symptoms and disability. All I can say is that the results of our approach have really made a difference****. So I can sleep easy at night when it comes to treatment – I know 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"*** (personal communication, 17th May 2001).

However, Wessely is not a cardiologist, nor a neurologist, nor an immunologist, nor a virologist, nor an expert in gene expression. He is a psychiatrist.

This is important, because the current issue of the BMJ (2nd August 2008:337:263) is clear that "experts" must not succumb to the temptation to speak outside their own core area of expertise: "*Staying within your area of expertise is one of the key rules highlighted this week in a new GMC guide for expert witnesses.* ***Another pitfall it warns against is being too partisan and too wedded to pet theories****. Where there is a range of opinion on a subject, (an expert) must outline this and explain how he reached his own views".*

It is a matter of record that Wessely promotes himself as a "*world expert in the field of medically unexplained illnesses including Chronic Fatigue Syndrome*" (PRISMA Company Information, 2001).

While it remains the case that the precise aetiology of ME/CFS is as yet unknown (as is the case in many other diseases), it is incorrect that the cause of the symptomatology is unknown. For example, there is a significant literature on evidence of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in ME/CFS, which results in many of the symptoms. What is not yet known is what causes the HPA dysfunction.

Despite Wessely's denial, **a significant percentage (at least 20%) of people with ME/CFS as distinct from "CFS/ME" die from cardiac failure** (Causes of Death Among Patients with Chronic Fatigue Syndrome. Jason L et al. Healthcare for Women International: 2006:27:615-626). Although denied by the GDG, there is abundant documented evidence of cardiac and vascular problems in ME/CFS (see below), yet the GDG stipulates that: "***signs and symptoms of cardiorespiratory disease should not be attributed to CFS/ME"*** (52 page version, page 15:1.2.1.4) and instead refers to ***"perceived exertion"*** (52 page version, page 30:1.6.2.17).

The ignoring by NICE of this important subgroup is just one of the many deficiencies of the Guideline, some of which become more apparent when the Guideline is compared with the advice provided for Scottish clinicians about the same disorder.

Comparison of the Scottish Good Practice Statement with the NICE Guideline for England, Wales and Northern Ireland

Whilst NICE is overly inclusive about what constitutes "CFS/ME", it is unduly proscriptive about which interventions apart from psychotherapy may be used in management. The position adopted by NICE should be compared with that taken about the same disorder in Scotland ("Scottish Good Practice

Statement on ME/CFS: A Guide for GPs to use in the consulting room". Dr Gregor Purdie, on behalf of the Scottish Government; produced in consultation with Scottish Medical Practitioners, people with ME in Scotland and their representatives, ME charities and support groups and professionals in health, social care and research; 23rd July 2008).

The Scottish Good Practice Statement (SGPS) is very different from the NICE Guideline:

"*The purpose of this Scottish Good Practice Statement on ME/CFS is to provide general practitioners with a simple, straightforward document that can be easily used in the consulting room. National and international debate is ongoing as to the appropriate terminology but for the purposes of this statement we will use the composite ME/CFS, the term recommended by the Scottish Public Health Network.*

"The NHS has recognised that the physical symptoms can be as disabling as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, congestive heart failure and other chronic conditions and that the illness places a substantial burden on people with the condition, their families and carers, and on society.

"ME/CFS is experienced by patients as a range of symptoms and it is therefore necessary to adopt a holistic approach to treatment and care. Empathetic listening is vital.

"Some people are described as being severely affected by ME/CFS. It is estimated that 25% will fall into this category at some stage in their illness. They will often spend periods of time bed-bound, housebound, or wheelchair bound, and perhaps be unable to tolerate movement, bright light, noise, certain scents or chemicals (including prescribed drugs). Neurological symptoms can be extreme -- with for example, difficulty swallowing requiring nutritional support, and the investigations of vitamin deficiencies ".

The Scottish statement informs clinicians that people with ME/CFS "*are often sensitive to the side-effects of drugs, particularly anti-depressants, anaesthetics and those which act on dopaminergic transmission (eg. metoclopramide / Maxalon). Sensitivities and intolerances to various foods are often experienced by people with ME/CFS and contribute to gastrointestinal problems".*

Advised by the Wessely School, the NICE Guideline states that there is no evidence of adverse reactions to prescribed medication, or of multiple chemical sensitivity (MCS): "*No research evidence was found to support the experience of some people with CFS/ME that they are more intolerant of drug treatment and have more severe adverse / side effects"* (52 page version of Guideline, page 18, section 1.4.1.2). Such a statement ignores the compelling evidence to be found in the work of Martin Pall, Professor of Biochemistry and Basic Medical Sciences, School of Molecular Biosciences, Washington State University (for an explanation of his work, see http://www.meactionuk.org.uk/Resume_of_Pall_MCS_paper_-_August_2002.htm). It also disregards the fact that since 2000, MCS is listed in the ICD (ICD-10-SGBV, version 3.1:T78.4).

NICE also specifically proscribes the use of vitamin supplementation.

The Scottish Statement advises that ME/CFS commonly follows some form of viral infection, and that it can be precipitated by "*vaccinations, toxins (and) pesticide exposure".*

Despite the large body of literature documenting viral persistence in ME/CFS, the NICE GDG did not include a virologist. Only those professionals who believe in the behavioural model of "CFS/ME" were chosen to be GDG members, as confirmed by NICE: "*We had a large number of nominations for this guideline development group from professional organisations wishing to contribute (but) we gave preference to those with day to day clinical experience for managing this condition"* (letter dated 23rd December 2004 from Nancy Turnbull, Chief Executive, National Collaborating Centre for Primary Care to Dr Charles Shepherd, Medical Director, ME Association, rejecting his offer to be on the GDG). Since the only NHS management is behavioural interventions, restricting the choice of GDG members to those engaged in delivering such interventions meant that the Guideline's management recommendations were a foregone conclusion.

Importantly, the GDG made no mention of the fact that the Parliamentary Under Secretary of State The Lord Warner confirmed in writing on 11th February 2004 in a letter to the Countess of Mar that **people with ME/CFS (also known as Postviral Fatigue Syndrome and classified as such by the World Health Organisation [WHO] in the International Classification of Diseases ICD-10 G93.3) are not permitted to be blood donors**. Lord Warner was unambiguous: "*We have checked with the National Blood Service and they have provided the following information.* ***The NBS guidelines on donor selection on ME refer to those on Post Viral Fatigue Syndrome. The Guidance is: defer from blood donation until recovery. The underlying logic is that this condition is possibly viral and therefore the NBS cannot accept the risk of possible transmission by blood.*** *Since the condition is very variable and sometimes prolonged, it could become a lifetime ban in any particular case. I have copied this letter to the House (of Lords) library".*

Notably, those with behavioural disorders are not prevented from being blood donors.

The Scottish Statement continues: "*Key symptoms (include) exercise-induced muscle fatigue; post-exertional malaise; pain that is often persistent and difficult to control (and) a general feeling of ongoing malaise".*

Again in contrast, the NICE Guideline relies heavily on Random Controlled Trials (RCTs) produced by the Wessely School, whose own case definition does not include exercise-induced muscle fatigue or post-exertional malaise.

The Scottish Good Practice Statement is unambiguous: "*Other symptoms (include) dysequilibrium; autonomic dysfunction, disturbed thermoregulation, night sweats and heat sensitivity; sensory disturbances; hyperacusis and/or photophobia; arthralgia; irritable bowel-type symptoms (and) alcohol intolerance, drug and chemical sensitivities".*

It is notable that psychiatrist Professor Peter White, a key member of the Wessely School, advised NICE that bowel problems are not a feature of "CFS/ME": "*bowel symptoms are not part of CFS/ME"* (St Bartholomew's Hospital Chronic Fatigue Service Stakeholder Comments on Chapter 6, page 143). There is a significant literature documenting gastrointestinal problems in ME/CFS (which the Wessely School refers to as "CFS/ME"), so it is disturbing that Professor White's Unit seems to be unaware of it, especially as he is lead adviser on "CFS/ME" to the Department for Work and Pensions.

It is not clear why a psychiatrist should be advising the DWP about a multi-system neuro-immune classified organic disorder.

The Scottish Statement differs markedly from the NICE Guideline in advising Scottish clinicians that appropriate investigations may include testing for adrenal insufficiency; immunodeficiency and autonomic function, and that tests may include nuclear medicine scans (MRI); muscle biopsy and serum 25-hydroxyvitamin D status.

These are specifically proscribed by NICE for patients with the same disorder in England, Wales and Northern Ireland.

Regarding the management regime recommended by NICE as the primary (indeed only) treatment option, the Scottish Statement could not be more different. Referring to graded exercise therapy (GET), it states: **"*The following treatments have a varying rate of success and in some cases have been harmful to individuals.*** *Graded exercise therapy makes use of an exercise programme involving a progressive increase in aerobic exercise on a day to day basis (and) is intended to restore physical fitness which has declined due to inactivity imposed by ME/CFS. Cognitive behavioural therapy (CBT) is a psychological intervention.*

"In England, there are special clinics which offer these therapies as specific treatments for ME. There has been much concern expressed about the evidence-base for these treatments*. In Scotland, these treatments are being evaluated in the PACE trial* (a Medical Research Council trial run by Wessely School

psychiatrists) *which is at present underway in Edinburgh.* ***It would be prudent, therefore, to await the evaluation before making any pronouncements on the specific place of these therapies".***

In contrast, NICE pre-empted the results of the same trials in England and, further supporting the widely-held expectation that, like the NICE Guideline, the outcome of the trials is a foregone conclusion, recommended the national implementation of behavioural interventions that are promoted by the Wessely School.

Evidence of cardiovascular dysfunction in ME/CFS that the GDG was directed to disregard

NICE claims that there is little good research evidence for most aspects of "CFS/ME" apart from the psychosomatic (behavioural) model put forward by the Wessely School (GDG comments on Chapter 2). Although NICE acknowledged the need for "consensus" methods and paid lip-service to this need, the GDG largely ignored the expert patients' consensus, claiming that it was "biased".

Not only did NICE ignore the expert patients' evidence, as well as the evidence of clinicians and notable biomedical researchers who challenged the basis of the Wessely School's beliefs about the nature of ME/CFS, it also ignored the significant body of research which shows that patients with ME/CFS may be in a particular form of heart failure and should not, therefore, be subject to incremental aerobic exercise as recommended by NICE.

It is notable that the draft Guideline of September 2006 advised patients and clinicians that an exercise programme should not be maintained if there is active infection, but that this explicit warning to cease exercising during active infection was removed from the final Guideline (*cf* Draft Guideline page 142 and Full Guideline page 150).

Illustrations of cardiovascular dysfunction in ME/CFS include the following:

1957

One of the most useful and important descriptions of ME is that of Dr Andrew Wallis as contained in his doctoral thesis (An Investigation into an Unusual Disease seen in Epidemic and Sporadic Form in a General Practice in Cumberland in 1955 and subsequent years. Andrew Lachlan Wallis. Doctoral Thesis, University of Edinburgh, 1957). For a summary, see http://www.meactionuk.org.uk/Vade_MEcum.htm .

Wallis particularly noted **myocarditis (heart rate was accelerated during the illness), with dyspnoea on slightest exertion.** The post-mortem histopathology report from one (female) case stated:

"There are in the entire diencephalon, particularly round the third ventricle, numerous small haemorrhages, which extend into the adjacent parts of the mid-brain. Similar haemorrhages can be seen in the corpora mamillare. The haemorrhages are mostly around the small vessels but some are also to be seen in the free tissue. This is a significant finding."

Comparison of the Wallis findings with other published findings

The post-mortem histopathology report in Wallis' thesis was particularly interesting, given the subsequent documented evidence of vascular abnormalities and impaired blood flow in ME/CFS. For example, references in one textbook of ME/CFS to vasculopathy include the following:

"lymphocytes in the cerebrospinal fluid congregate in the perivascular (Virchow Robin) spaces of the brain…these findings do suggest that the disease may involve the perivascular spaces of the brain

"dilatation of the Virchow Robin spaces could also suggest intracranial arterial or periarterial pathology, in particular, one would expect to find a congregation of lymphocytes in the perivascular spaces around the central nervous system arteries ***…(Wallis) revealed an artefact that is in an anatomical position similar to that suggested by MRI studies***

re: the Los Angeles 1934 epidemic*: "****The blood vessels throughout the nervous system were distended with red blood cells…the most characteristic change was infiltration of the blood vessel walls***" (The present consensus on MRI in ME/CFS. Royce J Biddle. In: The Clinical and Scientific Basis of ME/CFS. ed: BM Hyde; The Nightingale Press, Ottawa, Canada 1992).

Other references to vasculopathy in ME/CFS in the same textbook include:

page 42 (Chapter 5 / BM Hyde): *"We routinely observe patients with severely cold extremities and a visible line demarcating the cold from the area of normal skin temperature. The fact that the loss of normal blood flow may be persistent has been indicated by Gilliam* (1938)"

page 62: *"Patients will complain of severe blanching of their extremities, nose, ears, lower arms and hands as well as lower legs and feet. Observation will often reveal a blanched clearly demarcated line separating warm from icy cold tissue. The whitened extremities may persist for hours and can be extremely painful"*

page 70: "***The haemorrhages are mostly around small vessels, but some are also to be seen in the free tissue"***

page 73: Hyde discusses the occurrence of Raynaud's Disease in ME/CFS: "*This is common in ME/CFS. These acute Raynaud's Disease changes are visible"*

page 89 (Chapter 8 / John Richardson): *"****A liver biopsy showed a vasculitis of the liver"***

paqe 91: *"Liver Function Tests are sometimes abnormal and signify a vasculitis of the liver"*

page 250 (Chapter 23 / Jay Goldstein): *"SPECT scanning may justify vasodilator therapy with calcium channel blockers"*

page 286 (Chapter 28 / EG Dowsett): *"ME is a multisystem syndrome including nervous, cardiovascular, endocrine and other involvement. Symptoms and Signs (table 2): Vasculitic skin lesions, autonomic dysfunction, especially circulation and thermoregulation"*

page 376: (Chapter 42: Hyde and Jain: Cardiac and Cardiovascular Aspects of ME/CFS): reference is made to *"frequent vasomotor abnormalities"*

page 377: *"vasomotor disturbances were almost constant findings, with coldness and cyanosis. It was the impression of most observers that a generalised disturbance of vasomotor control occurred in these patients"*

page 377: "*Findings included sinus tachycardia, abnormal T waves in two or more leads (and) prolongation of Q-T interval"*

page 377: "*Myocarditis in the acute phase: the heart rate was accelerated (and) tachycardia was considered to be a diagnostic feature. In four cases there was a persistent rise in blood pressure (which) slowly lowered over a period of many months"*

page 378: *"Cardiovascular symptoms: angina-like pain; vascular headache; orthostatic hypertension; oedema; dyspnoea; transient hypertension* (note that on page 42, Hyde states about blood pressure

regulation: "***Some seem to be unable to adjust blood pressure with body activity, resulting in high blood pressure on modest activity and very low pressure when reclining****")*

Page 378: referring to Professor Peter Behan's CIBA lecture in 1988: "*using SPECT scan techniques,* ***his team was regularly able to demonstrate micro-capillary perfusion defects in the cardiac muscle of ME patients"***

page 380: ***"These chronic ME/CFS patients complain of severe chest pain and shortness of breath as if suddenly stopped by an invisible barrier"***

page 381: "*Arrhythmias are frequently noted in the first few weeks of illness, then decrease in frequency, only to return in a chronic form 20 years later"*

page 433 (Chapter 49 / Ismael Mena): referring to the need for SPECT scans in ME/CFS patients, Mena states: ***"The accuracy and reproducibility of these measurements are justification to evaluate cerebral perfusion abnormalities in patients with ME/CFS. Most probably, temporal lobe perfusion defects may fingerprint primary inflammatory changes or secondary vascular impairment in these patients"***

(It is notable that SPECT scans are specifically proscribed by NICE).

page 437: "*the diminished uptake of this oxime can be interpreted as due to a) diminished rCBF* (regional cerebral blood flow)*, b) inflammatory regional changes (present in 71% of patients studied)"*

page 598 (Chapter 65 / LO Simpson): *"if the stasis did not resolve, focal lesions of ischaemic necrosis would develop"*

page 673 (Chapter 75 / J Russell): Dr Jon Russell is a world expert on fibromyalgia (which may be a comorbidity with ME/CFS: *"Fibromyalgia appears to represent an additional burden of suffering amongst those with ME/CFS"*. Buchwald D et al. Rheum Dis Clin N Am 1996:22:2:219-243) and says about the prevalence of vasculitis*: "It is apparent that some patients with fibromyalgia also exhibit vasculitis with a frequency that has caught the attention of clinicians".*

Wessely disagrees, asserting that fibromyalgia (FM), like ME, is but part of a single somatoform (behavioural) disorder (Lancet 1999:354:936-939) and consequently FM is included within "CFS/ME" in the MRC trials, even though FM is classified as a quite separate disorder by the World Health Organistion (ICD-10 M79). Furthermore, the National Fibromyalgia Association's FAME (Fibromyalgia Assessment, Management and Education) programme has received CME accreditation (continuing medical education) from the American Academy of Family Physicians (http://www.FMaware.org).

Other references in the literature to cardiovascular problems in ME/CFS

1976

From the earliest reports of ME/CFS, autonomic vasomotor instability has been noted (AM Ramsay, Update: September 1976:539-541).

1984

There have been many reports of impaired bloodflow in the microcirculation (LO Simpson, NZMJ:1984:698-699).

1988

"Evidence of cardiac involvement may be seen: palpitations, severe tachycardia with multiple ectopic beats and occasional dyspnoea may occur and are quite distressing. It is of great interest that some patients have evidence of myocarditis" (Behan P. Crit Rev Neurobiol 1988:4:2:157-178).

1989

"*The data are compatible with latent viral effects on cardiac pacemaker cells, or their autonomic control, and skeletal muscle, that are unmasked by the stress of exercise*" (Montague TJ et al. Chest 1989:95:779-784).

1989

"Persistent viral infections impair the specialised functions of cells. ***Evidence of persistent enterovirus infection has been found in both dilated cardiomyopathy and in myalgic encephalomyelitis***. *Immunological and metabolic disturbances in ME may result from chronic infection, usually with enteroviruses, providing the organic basis of the postviral fatigue syndrome. This condition is charcterised by recuperation through rest. The myocardium, however, cannot rest – except terminally"* (NR Grist. BMJ 1989:299:1219).

1990

"*A significant group have cardiac symptoms*" (Professor Peter Behan, Cambridge Conference Report, 17th March 1990; ME Association Medical Update 1990: 2).

1990

"There is a high incidence of cardiomyopathy in CFS patients" (Dr Jay Goldstein, Director of the CFS Institutes, Anaheim Hills; member of the Faculty of the Department of Psychiatry, University of California; CFIDS Reporter, Oregon, October 1990).

1991

"The patient with Post-viral fatigue syndrome (ME) is referred to a cardiologist almost always because of chest pain. In viral pericarditis, as with ME, there is now abundant evidence that the disease process arises from an abnormal response to a viral infection. *Chest pain is variable in character. It is sometimes severe, sharp and stabbing, or it may be dull and aching. It is unrelated to exertion, although the patient frequently feels the pain to be worse after a day of increased physical activity.* ***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 the back. It is commonly aggravated by sudden movement, change of posture, respiration or swallowing.* ***Palpitations are frequent, with sinus tachycardia being a common and troublesome symptom.*** *The diagnosis of the cause of chest pain in ME rests almost entirely on careful clinical evaluation.* ***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"* (Post-viral Fatigue Syndrome and the Cardiologist. RG Gold. In: Postviral Fatigue Syndrome. Ed: Rachel Jenkins and James Mowbray. John Wiley & Sons, 1991).

1993

Evidence of repetitively negative to flat T waves on 24-hour ECG monitoring was found in some ME/CFS patients (Lerner AM et al. Chest 1993:104:1417-1421).

1994

Abnormal left ventricular dynamics (i.e. an abnormal pumping mechanism) were demonstrated in ME/CFS patients, including abnormal wall motion at rest; dilatation of the left ventricle, and segmental wall motion abnormalities (Dworkin HJ, Lerner AM et al. Clinical Nuclear Medicine 1994:19:8:675-677).

1994

"As with any chronic inflammatory condition affecting the central nervous system, the T2-bright foci on MR (magnetic resonance) ***in ME/CFS may represent perivascular cellular infiltrate and / or reactive demyelination of the surrounding white matter….these abnormalities may reflect the result of a vasculopathy specifically 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 may result 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 chronic demyelination, which appears to be irreversible****"* (Detection of Intracranial Abnormalities in Patients with Chronic Fatigue Syndrome: comparison of MR imaging and SPECT. Schwartz RB, Komaroff AL et al. Am J Roentgenol 1994:162:935-941).

1995

"The use of cardiopulmonary exercise testing is not only valid and reliable, but also serves as an objective indicator for assessing disability. Maximal cardiopulmonary exercise testing provides two objective markers of functional capacity. The first is maximal oxygen consumption. The most important determinant of functional capacity is not maximal oxygen consumption, but anaerobic threshold. ***Typically ME/CFS patients achieve less than 80% of predicted maximal oxygen consumption with an anaerobic threshold lower than 40% of predicted peak oxygen consumption levels.*** *In ME/CFS patients, we have not found re-conditioning to be possible.* ***In fact, attempts to re-condition patients consistently results in exacerbation of symptomatology.*** *Cardiopulmonary exercise testing can be used to provide ME/CFS patients with another objective marker that will aid them in obtaining disability status"* (SR Steven. JCFS 1995:1:3-4:127-129).

1996

At the State of Massachusetts educational workshop given by Professor Paul Cheney, evidence was presented of the complexity of ME/CFS (referred to as "CFIDS", or Chronic Fatigue and Immune Dysfunction Syndrome).

According to Cheney, 80% of ME/CFS patients display medication and environmental sensitivities; there is evidence of lymphatic involvement, with the thoracic duct being tender, and the swollen areas on the neck or upper chest being a back-up of lymphatic fluid.

Cheney biopsied 16 digits of people with ME/CFS and found a vasculitis not uncommon in immune activation and similar to that which is found in SLE / systemic lupus erythematosus (The Massachusetts CFIDS Update).

1997

"Myocarditis was a common symptom in an analysis of 1,000 patients of ME/CFS who were seen in Glasgow over the past 20 years*. We were struck by the often-occurring association of patients who develop ME/CFS with acute chest pain resembling a coronary thrombosis. On subsequent clinical follow-up, all these patients had a clinical course that was indistinguishable from patients who presented with Syndrome X. Nuclear magnetic resonance spectroscopy studies of skeletal muscle in patients with Syndrome X show abnormalities that are identical to those found in patients with ME/CFS. We, in examining muscle biopsies of patients with ME/CFS, showed an increase in calcium ATPase activity in skeletal muscles. These data strengthen the relationship between ME/CFS and Syndrome X and suggest that an increased energy expenditure, with a consequent reduction of intra-cellular ATP* (adenosine triphosphate) *and an increase in ATPase activity could account for the abnormalities in these two conditions.* ***Thallium cardiac scans (thallium-210 SPECT scans) in patients with ME/CFS revealed moderate defects in the left ventricle****"* (Arguments for a role of abnormal ionophore function in CFS. A Chaudhuri et al. In: Chronic Fatigue Syndrome. Ed: Yehuda and Mostofsky; Plenum Press, New York, 1997).

1997

"We report the prevalence of abnormal oscillating T waves at Holter monitoring in a consecutive case series of ME/CFS patients from an infectious diseases centre. ***Every ME/CFS patient, but only 22.4% of the non-ME/CFS patients, showed abnormal oscillating T wave flattenings or inversions at Holter monitoring. Abnormal cardiac wall motion at rest and stress, dilatation of the left ventricle, and segmental wall abnormalities were present. Left ventricular ejection fractions, at rest and with exercise, as low as 30% were seen in ME/CFS patients.*** *The abnormal (results) which we confirm here appear to be an essential element to the pathologic physiology of the cardiomyopathy of ME/CFS"* (Cardiac Involvement in Patients with CFS as Documented with Holter and Biopsy Data in Michigan, 1991-1993. AM Lerner et al. Infectious Diseases in Clinical practice 1997:6:327-333).

This research was summarised by Dr PD Corning, having been reviewed and approved by Dr Lerner:

"***Dr Lerner, an Infectious Diseases specialist at Wayne State University, and his colleagues have found evidence that ME/CFS may be caused by a persistent (virus) infection of the heart****. This research is significant and well-documented.* ***In this study, 100% of the ME/CFS patients showed abnormal oscillating T waves at 24-hour Holter monitoring*** *and 24% showed weakened function on the left side of the heart (the side that pumps oxygenated blood to all the body except the lungs).* ***The data showed that patients exhibited evidence of cardiomyopathy, or disease of the heart muscle. This finding is so consistent (and) it distinguishes ME/CFS from those with fatigue of unexplained origin. This work offers hard evidence to back up ME/CFS patients' much disbelieved claim that exercise is harmful and causes disease progression in ME/CFS. In many cases, the resulting disease process is progressive. (The virus) attacks the heart tissue producing exercise intolerance, the hallmark of ME/CFS. These researchers have backed up their work with biopsies of the cardiac tissue in ME/CFS patients. They found heart muscle disorganisation, muscle fibre disarray, abnormal formation of fibrous tissue in place of heart muscle cells, fat infiltration and increases in mitochondria within heart muscle cells. All these results are indicative of cardiomyopathy. The weakened heart is aggravated by physical activity, accounting for post-exertional sickness so common in this disease. When the heart muscle tissue is infected, overactivity causes death of cardiac tissue and disease progression. This is in direct conflict with conclusions that ME/CFS symptoms are caused by underactivity due to a sedentary lifestyle****. Dr Lerner and associates have also documented abnormal fraction ejection in ME/CFS. Normally, over half the blood in the left ventricle is ejected when the left ventricle contracts.* ***In Dr Lerner's subjects, the ejection fraction is decreased. Some patients had a reduced ejection fraction at rest. Others had an ejection fraction that decreased during exercise from 51% to 36%. In a normal subject, the ejection fraction will rise over 5% during exercise. Declining ejection fractions are not seen in normal persons leading sedentary lives".***

The full summary is at http://www.ncf.ca/ip/social.services/cfseir/naneir/news/28FEB98.html .

1998

At the Fourth International AACFS Research and Clinical Conference held in Massachusetts in October 1998, Arnold Peckerman and Benjamin Natelson et al presented evidence of a disorder of the circulation in ME/CFS. As a group, patients with ME/CFS displayed similar cardiovascular function status on most of the parameters, but a lower stroke volume was found to be highly predictive of illness severity. These findings indicate a defect in the higher control modulation of cardiovascular autonomic control**. In the more severe cases, 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** (CFS Severity is Related to Reduced Stroke Volume. Peckerman et al. AACFS, October 1998).

1999

Watson et al reported that perfusion defects seen in thallium cardiac scans of ME/CFS patients were unlikely to be explained by occlusive coronary vessel disease and that in their studies (as well as in other independent studies), **cardiac thallium SPECT scans were shown to be abnormal in the majority of patients with ME/CFS and perfusion defects were common. Cardiac SPECT scanning is a nuclear medicine technique used to identify regions of under-perfused myocardial tissue** (A Possible Cell Membrane Defect in Chronic Fatigue Syndrome and Syndrome X. Walter S Watson et al. In: Kaski JC (Ed). Chest pain with normal coronary angiogram: pathogenesis, diagnosis and treatment. Kluwer Academic Publishers, London 1999: chapter 13:143-149).

1999

"This study examined the cardiovascular response to orthostatic challenge. Among subjects who completed the test, those with ME/CFS had higher heart rate and smaller stroke volume than corresponding control subjects. ***These data show that there are baseline differences in the cardiovascular profiles of ME/CFS patients when compared with control subjects****"* (La Manca JJ et al. Clinical Physiology 1999:19:2:111-120).

2000

"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. ***Our findings might have important implications for features of ME/CFS that involve vascular integrity****"* (V Spence et al. Am J Med 2000:108:736-739).

2001

"Convincing evidence of cardiovascular impairment can be demonstrated" (Research Update presentation to the Alison Hunter Memorial Foundation Third International Clinical and Scientific Conference on ME/CFS held in Sydney, Professor Mina Behan, University of Glasgow).

2001

According to David Streeten, Professor of Endocrinology at Upstate Medical Centre in Syracuse, NY: **"*Inconsistently excessive increases in heart rate were found in ME/CFS patients, in whom venous compliance was significantly reduced*** *(and in whom) delayed orthostatic hypotension was clearly demonstrable, implying impaired sympathetic innervation. Excessive lower body venous pooling, perhaps*

by reduced cerebral perfusion, is involved in the orthostatic component in these patients" (Streeten DH. Am J Med Sci 2001:321:3:163-167).

2001

Erich Ryll, Assistant Clinical Professor of Medicine, Division of Infectious and Immunology Diseases, University of California, believes that in ME/CFS there is an infectious venulitis: "*Troublingly (in the literature) very few vascular features were mentioned.* ***I have followed these patients since 1975. Because of this, I have learned all the nuances, all the signs and symptoms of the disease. In studying this disease, one must always have an open mind. This disease teaches the physician to be humble***. *The extremity discomfort is often described as a burning, searing sensation. Numbness and tingling of the extremities is common (and) cases have spontaneous bruises that occur without any injury.* ***The disease is frightening to patients because of its severity and its many unusual features. Physicians are not trained to diagnose an illness that encompasses so many signs and symptoms. Two common statements patients make are: 'I hurt all over' and 'I am going to die'. During relapse, many can be totally helpless and unable to care for themselves. Dizziness often occurs and for some patients, it is constant***. *They are uncoordinated and lurch about. They state that their legs just give way, causing them to fall.* ***The autonomic nervous system that controls blood vessels is deranged in the disease. Sweating, flushing, icy and blue hands and feet, hot sweaty hands, red and blotchy hands are common. Pain can be the most severe aspect of this disease. There is partial paralysis of the gastrointestinal tract (which) can lead to nausea. Small veins can suddenly rupture. Deep veins can remain inflamed and are not visible on the surface. An electromyogram is frequently abnormal, showing damage to nerves***. ***The MRI brain image often reveals evidence of demyelination. A SPECT scan invariably shows impairment of brain blood circulation. Muscles may be damaged but do not waste away.*** *There is currently no treatment that can cure this disease.* ***Treatments are geared to making life more bearable"*** (http://home.tampabay.rr.com/lymecfs/ryll.htm).

2001

"***As a group, the ME/CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values compared with the control group. These results indicate either cardiac or peripheral insufficiency embedded in the pathology of ME/CFS***" (Inbar O et al. Med Sci Sports Exerc 2001:33:9:1463-1470).

2001

"***The haemodynamic instability score differed significantly between ME/CFS and other groups***" (Naschitz JE et al. Semin Arthritis Rheum 2001:31:3:199-208).

2002

According to Peter Rowe, Professor of Paediatrics at Johns Hopkins and an ME/CFS specialist: "***Several groups have shown that ME/CFS patients have abnormal regulation of heart rate and blood pressure, as well as high rates of allergic disease***. *About a third of ME/CFS studies have identified low urinary and serum levels of cortisol"* (Co-Cure MED: 3rd May 2002; see also Peter C Rowe, Journal of Paediatrics 2002:140:387-388).

2003

"The main symptom of the ME/CFS patient, i.e. chronic fatigue that is greatly exacerbated by even minor effort, is similar to that of a patient with left ventricular dysfunction. *We performed nuclear ventriculography (MUGA / radioisotopic multiple gated acquisition used to perform a series of dynamic*

studies of the heart to assess for evidence of abnormalities with myocardial function) stress tests in ME/CFS patients and controls. ***During maximal exercise, ejection fraction (EF) increased in controls but declined in ME/CFS patients. The decreases tended to be greater in patients with more severe symptoms. These data support the hypothesis that some cases of ME/CFS may be explained and potentially treated as a problem with left ventricular function****"* (A Peckerman B Natelson et al. FASEB 2003:17:5 Suppl: Part 2: A853).

This study was summarised by Donna Krupa, APS Newsroom, 10th April 2003: "*Growing evidence points to a possible problem with circulation. Studies have found that ME/CFS patients may have reduced blood flow in exercising muscles. A new 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 in some patients to lead to the clinical syndrome of ME/CFS".*

2003

"*Cardiovascular reactivity is defined as the change on blood pressure, heart rate, or other haemodynamic parameters in response to physical or mental stimuli.* ***13 variables showed significant differences between ME/CFS patients and controls.*** *The degree of arterial stiffness of the large arteries affects both the cardiovascular reactivity and the pulse wave velocity. The FRAS (Fractal & Recurrence Analysis-based Score) differs between the groups of healthy persons, hypertensives, and ME/CFS patients.* ***The HIS (haemodynamic instability score) distinguished ME/CFS from healthy subjects with 97% sensitivity and 97% specificity.*** *Based on these data, it appears that the HIS can provide objective criteria (in) the assessment of ME/CFS"* (JE Naschitz et al. Journal of Human Hypertension 2003:17:111-118).

2003

"CFS is a clinically defined illness. ***Patients frequently report an infection as a precipitating event. Accumulating evidence points to a problem with circulation in ME/CFS. Although abnormalities in single systems may be insufficient to cause a circulatory dysfunction, cumulatively they could produce significant deficiencies in organ blood flow and symptoms.*** *Supporting this possibility, a magnetic resonance spectroscopy study indicated that patients with ME/CFS may have reduced blood flow in exercising muscles, and another study using nuclear magnetic imaging found evidence of post-exercise reduction in brain blood flow in ME/CFS. Based on this evidence, we hypothesised that patients with ME/CFS have reduced cardiac output. This present study tested this hypothesis using noninvasive impedence cardiography.* ***These results provide evidence of reduced cardiac output in severe ME/CFS (and) there might be periods in daily life when demands for blood flow are not adequately met, compromising metabolic processes in some vascular compartments. Some percentage of patients (with) ME/CFS may in fact have covert heart disease. The abnormalities causing a reduction in cardiac output in ME/CFS may be dispersed over multiples systems. Even marginal reductions in cardiac output can result in selective underperfusion during activities that increase demand for blood flow. Inquiries 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 initial conservation of cardiac output takes place"*** (A Peckerman, B Natelson et al. Am J Med Sci 2003:326:2:55-60).

Media coverage of this important paper included the following:

WebMD Medical News: 14th April 2003: "***Many people with ME/CFS may have a serious heart problem. When you exercise, your heart pumps out more blood. But these patients' hearts actually pump less blood. 'Basically we are talking about heart failure' Peckerman tells WebMD. 'ME/CFS is a progressive disease'. Emory University cardiologist Joseph I Miller III MD, says Peckerman's findings are very interesting (and) he agrees that these patients have serious heart problems".***

2003

"ME/CFS is a debilitating condition of unknown aetiology. Recent studies using brain spectroscopy have revealed metabolic disturbances with significantly elevated choline levels in various regions of the central nervous system. In addition, ***we have recently shown that abnormalities specific to the cholinergic pathway also exist in the peripheral microcirculation of ME/CFS patients (and) our findings might have important implications for vascular integrity in ME/CFS****. **ME/CFS is commonly associated with viral onset and immunological disturbance sometimes linked to persistent viral infection. The work described here provides new evidence of disruption to ACh pathways specifically within the peripheral circulation of ME/CFS patients**"* (F Khan, V Spence et al. Clin Physiol Funct Imaging 2003:23:282-285).

2004

"Aberrations of cardiovascular reactivity (CVR), an expression of autonomic function, occur in a number of clinical conditions. Recently, a CVR pattern particular to ME/CFS was observed. *Pathological disturbances may alter cardiovascular reactivity. Our data support the existence of disease-related CVR phenotypes. The importance of recognising disease-specific CVR phenotypes may (offer) supporting data for the diagnosis of certain disorders. Recognising the ME/CFS reactivity phenotype has been found useful in supporting the clinical diagnosis of ME/CFS. Furthermore, CVR phenotype may provide an objective criterion to monitor the course of dysautonomia in ME/CFS"* (Naschitz JE et al. QJM 2004:97:3:141-151).

2004

"Research into ME/CFS is hindered by considerable heterogeneity. There has been speculation that many of the neurological symptoms might be cholinergically mediated. As well as these neurological findings, there has been a recent report of autoantibodies specifically to muscarinic receptors in many ME/CFS patients, suggesting that there might be subgroups withion the ME/CFS construct that are associated with autoimmune abnormalities of cholinergic muscarinic receptors. Apart from its neurotransmitter functions, acetylcholine is a prominent vasodilator whose action is dependent upon an intact layer of endothelial cells that line the lumen of all blood vessels. In most medical conditions associated with cardiovascular disease there is a blunted response to acetylcholine. However, we have reported increased responses to acetylcholine in the cutaneous microcirculation of ME/CFS patients. There was a significantly increased response to substance P in ME/CFS patients and this was often accompanied by a spreading flare and localised oedema, a finding not observed in control subjects. (This may be due to) a heightened sensitivity to substance P in terms of its histamine releasing properties. ***Indeed, sensitivity to histamine has been implicated in ME/CFS pathogenesis.*** *The data demonstrated that the dynamics of the acetylcholine-stimulated blood flow response is significantly different in ME/CFS patients compared with control subjects, possibly via a viral mechanism. (This) acetylcholine sensitivity is specific to a sub-group of patients within the ME/CFS construct (and) points to a problem on the vascular endothelium of ME/CFS patients.* ***We are confident that the findings of increased sensitivity to acetylcholine in ME/CFS patients are robust and unusual. Our results are important in terms of vascular control mechanisms in this patient group and may be relevant to the problems of orthostatic instability that is so evident in most ME/CFS patients****"* (VA Spence et al. Prostaglandins, Leukotrienes and Essential Fatty Acids 2004:70:403-407).

2004

"While the cause of ME/CFS remains to be elucidated, extensive literature exists on the role of a variety of infectious agents; up-regulation of anti-viral pathways; immune abnormalities; disruption to the hypothalamic-pituitary-adrenal (HPA) axis; neuropsychological impairments; dysfunction of the autonomic nervous system; oxidative stress; and lipid peroxidation. Looking at the literature as a whole, there are various strands of evidence suggesting that the vascular system in ME/CFS is compromised.

Many ME/CFS patients are unaware that something as simple as being upright can trigger a cluster of symptoms such as dizziness, altered vision, nausea, fatigue, headache, sweating and pallor. ***Orthostatic intolerance is characteristic of so many of these ME/CFS patients that it could very well serve as a definable subset. It has been suggested by some that orthostatic intolerance in ME/CFS is nothing more than deconditioning associated with bed rest (but) vascular dysfunction appears to be best supported by the data.*** *Some subjects show autonomic dysfunction in their internal organs vasculature (and)* ***evidence points towards enhanced pooling within the internal organs and pelvic circulation.*** *The onset of orthostatic symptoms in many ME/CFS patients is often predated by a viral infection.* ***There is clearly a problem with local vasodilator and vasoconstrictor mechanisms in these patients. 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 blood flow abnormalities within the central nervous system****"* (V Spence & J Stewart. Biologist 2004:51:2:65-70).

2004

Lerner et al demonstrated abnormal cardiac wall motion at rest and in cardiac biopsies: *"A progressive cardiomyopathy caused by incomplete virus multiplication in ME/CFS patients is present"* (Lerner AM et al. In Vivo 2004:18:4:417-424).

2005

A study of adolescents with ME/CFS looked at blood pressure, arterial stiffness and arterial wall thickness. Arterial stiffness, expressed as common carotid distension, was lower in adolescents with ME/CFS, indicating stiffer arteries. "*Pain perception differed considerably between patients and controls (and) this is the first study to confirm this difference. The unexpected finding of stiffer arteries in patients with ME/CFS warrants additional investigation"* (EM van de Putte et al. Paediatrics 2005:115:4:415-422).

2005

"Orthostatic intolerance certainly causes breathlessness. ***The cause of the breathlessness is probably a reduction in blood flow through the heart and lungs. Patients with ME/CFS cannot hold their breath as long as healthy people.*** *This was first noted by Dr Paul Cheney"* (DS Bell. http://www.davidsbell.com/LynNewsV2N2.htm).

2005

On 10th April 2005 Carol Sieverling posted on the internet (Co-Cure) "The Heart of the Matter: CFS and Cardiac Issues" – a 41 page exposition of Professor Paul Cheney's experience and expertise, from which the following notes are taken and to both of whom grateful acknowledgement is made.

Cheney's focus is based on the paper by Dr Ben Natelson (clinical neurologist and Professor of Neurology) and Dr Arnold Peckerman (cardiopulmonary physiologist) at New Jersey Medical Centre (ref: "Abnormal Impedance Cardiography Predicts Symptom Severity in Chronic Fatigue Syndrome": Peckerman et al: The American Journal of the Medical Sciences: 2003:326:(2):55-60).

This important paper says that, without exception, every disabled CFIDS (i.e. ME/CFS) patient is in heart failure.

There are two kinds of heart failure: one that any cardiologist can diagnose in about a minute (which ME/CFS patients do not have); the other is Compensated Idiopathic Cardiomyopathy (CIM). Given that at least 35% of those with CIM will die within 5 years unless they receive a heart transplant, but given that in 20 years' experience of ME/CFS Cheney has never seen one patient go on to transplant, why aren't those

with ME/CFS-induced CIM not dead? Cheney believes it's because ME/CFS itself is protecting patients from a deeper problem that is often missed because it is so well-hidden.

The problem

The New Jersey team looked at many things in ME/CFS patients and they found something: a "Q" problem. "Q" stands for *cardiac output in litres per minute*. **In ME/CFS patients, Q values correlated -- with great precision – with the level of disability.** Q was measured using impedance cardiography, a clinically validated and Government agency-recognised algorithm that is not experimental.

Normal people pump 7 litres per minute through their heart, with very little variance, and when they stand up, that output drops to 5 litres per minute (a full 30% drop, but this is normal). Those two litres are rapidly pooled in the lower extremities and capacitance vessels. Normal people do not sense that 30% drop in cardiac output when they stand up because their blood pressure either stays normal or rises -- the body will defend blood pressure beyond anything else in order to keep the pulse going. This is critical to understanding what happens in ME/CFS patients.

However, **what the New Jersey team found in people with ME/CFS was astonishing –when disabled ME/CFS patients stand up, they are on the edge of organ failure due to extremely low cardiac output as their Q drops to 3.7 litres per minute (a 50% drop from the normal of 7 litres per minute).**

The disability level was exactly proportional to the severity of their Q defect, without exception and with scientific precision.

Symptoms

The New Jersey team then looked to see if there were any symptoms that were observable in disabled ME/CFS patients but not in others and they found that there was only one such symptom that was seen in patients with a Q problem: post-exertional fatigue. To quote Cheney: "That is, **when you push yourself physically, you get worse"**.

ME/CFS patients have a big Q problem; to quote Cheney again: "**all disabled ME/CFS patients, all of whom have post-exertional fatigue, have low Q and are in heart failure"**.

Post-exertional fatigue (long documented as the cardinal feature of ME/CFS but not of non-specific states of chronic fatigue) is the one symptom that correlates with Q. **Among disabled ME/CFS patients, 80% had muscle pain; 75% had joint pain; 72% had memory and concentration problems; 70% had unrefreshing sleep; 68% had fever and chills; 62% had generalised weakness; 60% had headaches, but 100% had post-exertional fatigue.**

In Cheney's model, symptoms in ME/CFS reflect the interaction between Q and how the body compensates for too low a Q, so depending on the nature of the compensation (which is individually distinct), there is an array of symptoms that is individually determined and which will arise out of factors unique to each person.

Cheney posits that when faced with a low Q, the body sacrifices tissue perfusion in order to maintain blood pressure: ie. microcirculation to the tissues of the body is sacrificed to maintain blood pressure so that the person does not die in the face of too a low Q. **This compensation is what is going on in the ME/CFS patient.**

In the Peckerman study, the data on the disabled ME/CFS patients reveals that even when they are lying down, their Q is only 5 litres per minute (not 7 as in normals). When disabled ME/CFS patients stand up, the Q of 5 litres per minute drops to 3.7 litres per minute, so these patients do not have adequate Q to function. The lower the Q, the more time the patient will spend lying down because lying down is the only time they come close to having sufficient cardiac output to survive.

Compensated Idiopathic Cardiomyopathy

Cheney states that it is important to note that the body does not sacrifice tissue perfusion equally across all organ systems: instead, it prioritises the order of sacrifice and one can observe the progression of ME/CFS by noting this prioritisation.

Two organ systems in particular have a protective mechanism (the Renin Angiotensin System, or RAS) against restricted tissue perfusion: the lung and the kidneys. These organs can sustain the greatest degree of Q problems because of this extra protection. Additionally, the heart and the brain also have this extra protection, even in the face of an extremely low Q. Therefore the lung, the brain, the kidneys and the heart are a bit more protected than the liver, the gut, the muscles and the skin from a drop in Q.

In what order is tissue perfusion sacrificed, and what are the consequences? Certainly, Cheney's submission seems to tally with the experience of long-term ME/CFS sufferers.

The first is the skin: if the microcirculation of the skin is compromised, several problems can arise. One is that without adequate microcirculation to the skin, the body cannot thermoregulate anymore: the patient cannot stand heat or cold and if the core temperature rises, the patient will not be able to sleep and the immune system will be activated. In order to regulate that problem, the body will activate thyroid regulation which will down-regulate in order to keep the body temperature from going too high. The result of this is that the patient develops compensatory hypothyroidism, which means that now the patient will have trouble with feeling cold. Also, the body will not be able to eliminate VOCs (volatile organic compounds), which are shed in the skin's oil ducts, so VOCs build up in the body's fat stores and the patient becomes progressively chemically poisoned by whatever is present in the environment -- **in other words, the patient develops Multiple Chemical Sensitivity (MCS).**

The second effect: if things get worse, **the next microcirculation to be sacrificed is that to the muscles and the patient will have exercise intolerance and s/he cannot go upstairs**. If things get still worse, the patient begins to get fibromyalgic pain in the muscles. Cheney posits that if microcirculation to the joints becomes compromised, it may precipitate pyrophosphoric acid and uric acid crystals and the patient starts to have arthralgia linked to this circulatory defect.

The next system to be compromised is the liver and gut. **One of the first things the patient may notice in this stage of disease progression is that there are fewer and fewer foods s/he will be able to tolerate, partly because microcirculation is necessary for proper digestion. Also the body will not secrete digestive juices so whatever food is tolerated will not be properly digested: if food cannot be digested, there will be peptides that are only partially digested and therefore are highly immune-reactive; they will leak out of the gut into the bloodstream, resulting in food allergies and / or sensitivities**. The body will be unable to detoxify the gut ecology, so the gut will begin to poison the patient, who will feel a sense of toxic malaise, with diarrhoea, constipation, flatulence and all kinds of gut problems. If this gets worse, a malabsorption syndrome will develop, resulting in increasing toxicity in which the patient feels "yucky" and which can manifest as a variety of skin disturbances (for instance, a rash), as well as problems in the brain.

The fourth affected system is the brain: **Cheney posits that there is a devastating effect in the brain as a result of liver / gut dysfunction, which can quickly toxify the brain**, resulting in disturbances of memory and of processing speed. **Also, the hypothalamus begins to destabilise the patient from the autonomic nervous system perspective. In all probability, the brain and heart suffer simultaneous compromise, but patients usually notice the brain being affected much earlier than the heart – this is because heart muscle cells have the greatest mitochondrial content of any tissue in the body, so when the mitochondria are impaired, the heart muscle has the greatest reserve.** Even if the patient is sedentary with not too much demand on the heart, s/he can still think and make great demands on the brain, and energy is energy, whether it is being used physically or cognitively.

The fifth affected system is the heart: Cheney posits that the effect of compromised microcirculation upon the heart has an "a" part and a "b" part: part "a" is the manifestation of microcirculation impairment and part "b" is "the event horizon".

Part "a": manfestation of microcirculation impairment: **the initial manifestation of microcirculatory impairment of the heart is arrhythmia with exercise intolerance: when the patient goes upstairs, more cardiac output is needed but the patient cannot sustain it.** As it gets worse, there will be mitral valve prolapse (MVP) because of inadequate capillary function. **Finally, when there are even more severe microcirculatory problems, the patient starts to get chest pain as the myocardial cells die because they cannot get adequate oxygen.**

Part "b": the event horizon: (once this line is passed, there is no going back): Cheney's view is that the "event horizon" with respect to the heart is this: when the microcirculation defect within the heart itself begins to impact Q itself, a vicious circle begins – microcirculation impairment reduces the Q, which produces more microcirculation impairment, which produces even more Q problems, so **down goes the patient into the next phase of cardiac failure, which is the lung.**

The sixth affected system is the lung and kidney: **cardiac failure in the lung produces congestive heart failure (CHF) and pulmonary oedema, then the kidney is affected (the kidney is the last to go because it has the RAS back-up system). Combined with liver impairment, this stage is known as hepatorenal failure, which is the requisite cause of death due to Compensated Idiopathic Cardiomyopathy.**

For some reason, there is something about ME/CFS that keeps patients from progressing across the final event horizon, although Peckerman believes that a certain percentage of CFIDS patients are heading that way. **How will a patient know if s/he eventually loses the ability to compensate? They will know it if when they lie down, they are short of breath.**

The cause of the cardiac output problem

Cheney's view is that the cardiac muscle has lost power because the mitochondria are dysfunctional due to a redox-state problem. Redox is a reversible chemical reaction in which one reaction is an oxidation and the reverse is a reduction.

What causes the redox-state problem? Cheney does not know, but he does know that in ME/CFS, like MCS and Gulf War Syndrome, there is a redox-state problem. There is, however, something unique in ME/CFS, which is that the redox-state problem seems centred on the heart. In Cheney's model, candidates include viruses in an interaction with toxins.

Cheney comments on Professor Martin Pall's work on the role of peroxynitrite in ME/CFS. Uric acid is a powerful scavenger of peroxynitrite, as is uric acid. Cheney has measured uric acid levels in ME/CFS patients and has found them to be amongst the lowest levels he has ever measured in his entire medical career.

Cheney notes that Dr Les Simpson in New Zealand found that the red blood cells of patients with ME/CFS were deformed and when deformed, they cannot get through the capillary bed and so cause pain. An indication of such deformity is a drop in the sedimentation rate (SED, or ESR) and **Cheney has observed that when measured in a laboratory, ME/CFS patients' sedimentation rate is the lowest he has ever recorded, which confirms to Cheney that ME/CFS patients have an induced haemoglobinopathy. He believes that the ME/CFS patients with the lowest sedimentation rate may have the greatest degree of pain.** The more deformed the red blood cells, the more pain may be experienced. **Some ME/CFS patients have a problem similar to that of sickle cell anaemia in this regard, and sickle cell patients have unbelievable pain.** Cheney emphasises that it is bad enough when patients do not perfuse their muscles and joints (because of poor microcirculation) but it is even worse when red blood cells are so deformed that they can barely get through the capillaries or are blocked entirely.

Cheney notes that in the Laboratory Textbook of Medicine, there are only three diseases that lower the sedimentation rate to that level: one is sickle cell anaemia (a genetic haemoglobinopathy); the second is ME/CFS (an acquired haemoglobinopathy) and the third is idiopathic cardiomyopathy.

Cheney observes that in order to improve cardiac output in ME/CFS, patients need to lie down, as this increases the cardiac output by 2 litres per minute. **He notes that some ME/CFS patients need to lie down all the time to augment their blood volume in order to survive.** He has found increasing the intake of potassium to be helpful (potassium induces aldosterone, a hormone that significantly increases blood volume), and that magnesium is beneficial as it is a vasodilator and helps reduce the resistance the blood encounters.

Cheney is at pains to emphasise that none of these measures is a cure ---they are simply means to help patients disabled with ME/CFS remain as functional as possible.

Cheney's credentials include more than two decades' experience treating over 5,000 ME/CFS patients in 15 countries; research positions relevant to ME/CFS with the US Centres for Disease Control; Emory University and the University of Pennsylvania, and numerous journal articles. He was a founding director of the International Association of Chronic Fatigue Syndrome, an association of scientists and clinicians.

2005

"There is mounting evidence that oxidative stress and lipid peroxidation contribute to the disease process and to some of the symptoms (in ME/CFS). *While free radicals may generate tissue injury, it is also evident that other oxidative by-products, especially isoprostanes, can exert potent biological activity and act as a powerful vasoconstrictor of the peripheral vasculature. Such biological effects may be instrumental in the development of some of the vascular features that characterise patients with ME/CFS.* ***The novel findings of 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 potent biological effects associated with increased cell permeability. They have also been shown to be powerfully vasoconstricting and are involved in endothelial injury.* ***Exercising muscle is a prime contender for excessive free radical generation, with recent evidence pointing to good correlations between muscle pain thresholds and fatigue with various blood markers of oxidative injury in ME/CFS patients, and further evidence of viral persistence in muscle tissue in some patients with the illness. Research evidence has demonstrated that incremental exercise challenge potentiates a prolonged and accentuated oxidative stress that might well account for post-exercise symptoms in ME/CFS patients.*** *It could be suggested that ME/CFS is an inflammatory condition with many patients in a pro-oxidant states, and this could explain many of the pathological manifestations that underlie the illness"* (G Kennedy, VA Spence et al. Free Radical Biology & Medicine 2005:39:584-589).

2005

Researchers at the US centres for Disease Control (CDC) reported that patients with ME/CFS exhibited scores on assessment tools that quantify impairment and symptoms occurrence, duration and severity and were able to be identified with precision. **The authors reported that the ME/CFS patient exhibited scores similar to patients with congestive heart failure** (WC Reeves et al. BioMed Central Medicine, 15th December 2005).

2006

Researchers used serial cardiopulmonary exercise tests to support a diagnosis of ME/CFS. The authors noted: *"In the absence of a second exercise test, the lack of any significant differences would appear to suggest no functional impairment in ME/CFS patients. However, the results from the second test indicate*

the presence of an ME/CFS related post-exertional malaise. It might be concluded that a single exercise test is insufficient to demonstrate functional impairment in ME/CFS patients. A second test may be necessary to document the atypical recovery response and protected malaise unique to ME/CFS" (VanNess MJ et al. Medicine & Science in Sports & Exercise 2006:38:5: Suppl: S85).

2006

In his September 2006 seminar (available on a two-DVD boxed set from videos@dfwcfids.org), Professor Paul Cheney again warned that aerobic exercise may kill the patient with ME/CFS. As before, Cheney acknowledges his debt to the work of Peckerman. Cheney noted that there is an objective database in key medical literature that includes evidence of diastolic dysfunction and heart failure in ME/CFS.

There are two types of heart failure: systolic (which is a failure to eject) and diastolic (which is not a failure to eject, but a failure to fill properly). Diastolic heart failure was first described in the 1980s but there was no significant literature until the 1990s, and no significant way to measure it until 2001.

Whilst there has been little recognition of the existence of diastolic dysfunction by some cardiologists (considered a relative rarity in 1986), in 2006 an article entitled "Diastolic heart failure – a common and lethal condition by any name" was published by Gerard Aurigemma, who concluded that: "*the development of specific, effective management approaches for diastolic heart failure must become a high priority"* (NEJM 2006:355:3:308-310). The NEJM carried a significant paper on more than 4,500 patients studied with diastolic heart failure; this increase is unexplained, but is accelerating, and Cheney wonders if it is in fact an explosion of ME/CFS.

A simplistic summary of Cheney's seminar is as follows:

The evolution of ME/CFS

There are four phases:

1. the onset, or trigger phase
2. the triad phase
3. the dynamic dysfunction phase (although the fatigue and pain and brain dysfunction are a little better, patients in this phase can do less than when they were more sick)
4. DNA phenotype adaptation phase (there is a phenotypic adaptation that locks this in at gene level)

Key scientific articles

Phase 1: (immune activation: fever, swollen glands, sore throat, malaise: general indications of immune activation)

- Suhadolnick et al (Temple University, USA)
- Komaroff et al (Harvard, USA)
- Klimas et al (Miami, USA)

Phase 2: (the centre of gravity of this illness: fatigue, brain problems and pain; xenobiotic toxicity coming from the gut and the environment)

- McGregor et al (Newcastle University, Australia)
- Pimental (UCLA, USA)

Phase 3: (the brain and heart components)

- Demitrack et al (NIH, USA)
- Moorkens et al (Antwerp, Belgium)
- Schwartz et al (Harvard, USA)
- Peckerman et al (NMJ & D, USA)
- Drexler et al (Hanover, Germany)

Phase 4: (phenotypic and genotypic adapatation → oxidative stress)

- Vernon et al (CDC, USA)
- Kerr et al (London, UK)
- Urowitz et al (Berkeley, USA)
- Pall (WSU, USA)
- Kennedy et al *(Cheney's overhead stated "USA", but if he means Kennedy and Spence, it should be Dundee, Scotland)*

Oxidative stress links ME/CFS to fibromyalgia, multiple chemical sensitivity and Gulf War Syndrome.

Do people recover from (ME)CFS?

Functional recovery *is* seen: one's ability to do things can improve, but it can go the other way, or there may be no change over time. Komaroff's data from Harvard is that after 10 years of illness, there is only a 30% chance of any functional recovery.

The Physical Examination

In phase 1: (immune activation) one sees

- lymphyodynia (seen in 80-90%)
- crimson crescents bilaterally on soft palate (seen in 80%)
- sub-normal temperature

In phase 2: one sees

- evidence of subcortical brain injury
- vestibular dysfunction (seen in 94%)
- hyper-reflexia, especially of the knees and ankles (seen in 70%)

In phases 3 and 4: the most interesting are the metabolic disturbances:

- there is shortened breath-holding capacity (seen in 60%)
- there is very poor oxygen transport (seen in 90%): pulse oximetry readings measuring saturation of haemoglobin show a significant inhibition to desaturate
- there is finger-print destruction (seen in 50%): cross-hatching occurs, with degradation of the ridges; punch biopsies found perivascular lymphoid infiltrates ie. an inflammatory cuffing exactly as seen in lupus, which signifies a non-specific immune activation issue (so the finger-print changes could be reflecting much more than just loss of finger-prints and may represent a vasculopathy)
- there is sub-normal temperature (seen in 80%)
- there is low systolic blood pressure (in 50% of patients it is less than 100mmHg)

- there is orthostatic B/P or pulse changes (seen in 70%)

These findings portend significant physiological issues, chief of which is that oxygen is being prevented from getting into the cell, and if there is no oxygen, there is no energy.

Magnetic Resonance Spectroscopy

- 70% of patients show elevated lactate levels in the ventricular system (the lactate elevation is not normal and indicates a defect in energy in the brain: ME/CFS patients have significantly elevated lactate levels and the fatigue correlated significantly with the level of lactate)
- 10% have evidence of neuronal destruction and elevated choline peaks, typically in the perivascular areas

Magnetic Resonance Imaging

- 78% of patients have punctate lesions which are most consistent with small strokes and there is evidence to support this

Mixed venous blood gas picture

- P_vO_2 is 25 (it should be 40)
- P_vCO_2 is 55 (it should be 45)

This is a differential hypoxia with hypercarbia. There are only two diseases where this is seen: one is pulmonary hypertension; the other is ME/CFS.

Where does the oxygen go? It's being transported somewhere, but not to the mitochondria. ME/CFS patients have been shown to have increased pooling of extra-cellular fluid in the belly, pelvis and legs which might contain this dissolved oxygen, but it is more likely being consumed by the oxidative pathway to create superoxide in massive amounts. Superoxide is the progenitor of all free radicals. The consequences are increased intra-cellular oxdidative stress.

ME/CFS as cellular metabolic dysfunction

There are problems at cell level in energy production, and because of this degraded energy problem, patients suffer a defect in the ability to detoxify toxins, especially in the portal circulation (giving rise to gut toxicity as seen in phase 2). Gene alterations (seen in phase 4) generate a massive disturbance in the development of energy at the cell level. If you lose energy, you lose glutathione, but the more glutathione you give, the more you just create oxidised glutathione, which generates loss of citrate, causing a left shift on oxyhaemoglobin desaturation. Citrate also binds to magnesium, so over time the patient will develop a severe magnesium depletion syndrome. When that happens, you've had your last good night's sleep: when you lose magnesium, you can't sleep any more.

In ME/CFS, these serious issues are a big problem, especially in the brain, the heart and in muscle. ME/CFS is a compensatory response to down-regulate energy production and oxygen transport in order to reduce tissue damage.

Attempts to push beyond energy limits will cause injury.

Prolonged energy deficits can cause semi-permanent DNA phenotype adaptations and complications can occur, especially within energy-sensitive systems such as the heart, the brain and the muscles.

In ME/CFS, catalase is deficient in the heart, lungs and liver (catalase is the most protective enzyme in the body against the ravages of superoxide), and Cheney noted that electromagnetic fields [EMFs] "*screw up*" superoxide dismutase (SOD), which is a major anti-oxidant scavenger.

Is there an ME/CFS-associated cardiomyopathy?

According to Cheney, a subset of "CFS" patients suffers from diastolic dysfunction.

Cheney reports that echocardiograms (sonograms of the heart) indicate that as many as 99% of his ME/CFS patients test positive for some level of diastolic dysfunction.

ME/CFS patients have a high heart rate but a low cardiac output. In ME/CFS there is a cardiac dimension that is independent of (but not excluding) autonomic function or blood volume.

82% of patients have abnormal cardiac impedence.

Cheney says that at least half of patients exhibited atrial cavitation, and that when these patients stood up, in 80% the filling volume collapsed. He tested this with magnesium and the results were significant: magnesium restored 12% of energy in one minute. Magnesium affects the intracellular energetics, proving that patients have a "tremendous" energy problem that is very sensitive to magnesium. (The reason magnesium is so important is that without it, ATP cannot be converted to ADP for the production of energy).

Cheney says that ME/CFS patients "*squeeze the hell"* out of their left ventricle, resulting in a "*whopping"* 70% increase in left ventricular wall motion thickness. The reason why patients are squeezing so hard is because they do not have enough energy to fill the chambers of the heart properly so they are trying to compensate by squeezing a lot harder (ie. the way patients are compensating for this loss of cardiac output is by squeezing the left ventricle much harder).

There are significant consequences of this. One consequence is that ME/CFS patients become asynchronised (i.e. the heart can be filling and ejecting at the same time).

If out of synchrony, the ventricle cannot cope, so cardiac output is severely degraded.

A second consequence is that patients develop a strain pattern, which is an indication of ischaemia. Cheney has seen ischaemic changes in the inner ventricular wall because of the increased squeezing.

Cheney has demonstrated that, because of the increased left ventricular strain, the communication between the right and left sides of the heart that closed at birth (the foramen ovale) opens up and becomes patent (Patent Foramen Ovale / PFO). This hole in the heart produces a right to left shunt of unoxygenated blood full of carbon dioxide as well as products of liver metabolism – the liver is literally draining into the right heart and the blood is being shot straight to the brain. **This was demonstrated on the DVD by means of Trans Cranial Doppler bubbles.** It results in significant oxygen toxicity.

It is increasingly clear that in ME/CFS, a diminished threshold for oxygen toxicity exists, and that each patient will have a unique threshold. These findings have a significant negative effect on Accident & Emergency and operating theatre uses of oxygen during surgery, because an ME/CFS patient could be given too much oxygen and be killed on the operating table.

The complications of PFO include:

- cerebral aneurysm
- multiple mini-strokes
- cerebral hypoperfusion produces pressure headaches, migraine, cognitive impairment and a lower seizure threshold

- venous hypoxia complications are fundamentally linked to intracellular acidosis which depletes electron buffers
- depleted acid buffers leads to increased sensitivity to diet, drugs and the environment.

PFOs cause significant instability.

There is a difference between diastolic dysfunction and diastolic failure: in diastolic dysfunction there is a filling problem but the body is compensating for it and achieving enough cardiac output to match metabolic demand.

Diastolic failure begins when the body can no longer compensate and there is a reduction in cardiac output. Cheney repeated that this is seen in 80% of ME/CFS patients.

If patients draw down their lifestyle to live within the means of the reduced cardiac output, then progression into congestive cardiac failure (CCF) is slowed down, but if things continue to progress, a point will be reached where there is no adequate cardiac output, and dyspnoea will develop, with ankle oedema and other signs of congestive cardiac failure.

The message from Cheney is clear: in order to stay relatively stable, it is essential for the ME/CFS patient not to create metabolic demand that the low cardiac output cannot match.

According to Cheney, it is difficult to talk about a low cardiac output without talking about the involvement of the brain and the adrenal glands.

If the cardiac output goes down, in order not to die, there is a rise in noradrenergic tone (also involving the adrenal glands) to bring the output back up. In ME/CFS, this is a serious problem, because when the adrenals are exhausted, there will be low cardiac output.

There is no such thing as an ME/CFS patient who is NOT hypothyroid: this has nothing to do with thyroid failure, but everything to do with matching metabolic demand and cardiac output.

A mismatch between metabolic demand and cardiac output, even very briefly, will kill.

A major cause of death in ME/CFS is heart failure.

2007

The 8th International Association of Chronic Fatigue Syndrome (IACFS) Conference was held at Fort Lauderdale, Florida, from 10th-14th January 2007. The following extracts are taken from "Facts from Florida" (http://www.meactionuk.org.uk/Facts_from_Florida.htm).

- The conference was attended by over 250 clinicians and researchers from 28 different countries and there was a strong sense that they were all co-operating to build on the science. **It is the science that has freed the world from any doubt that ME/CFS is a legitimate disease with an aetiology that is not rooted in the psyche -- Japanese and Swedish research teams collaborated in a comprehensive study of a neuro-molecular mechanism and concluded that ME/CFS is an organic disorder. It was described as "this miserable illness".**

- The latest figures (January 2007) on the economic impact of ME/CFS in the US are between $22 billion and $28.6 billion annually; in Japan, the figure is over $10 billion annually. The Japanese Government recognises ME/CFS as a real threat not only medically but also economically and has initiated a large research programme into causation and treatment.

- **One of the most striking elements was the convergence of research findings: the three areas that came up again and again were inflammation, mitochondrial abnormalities, and vascular problems.**

- **Three separate research teams found evidence of microvascular problems in ME/CFS.**

- **The significant confluence of findings on elastase (a protease enzyme, i.e. it digests and degrades a number of proteins, including elastin, a substance that supports the structural framework of the lungs and other organs); vascular problems; apoptosis (programmed cell death); free radical production (highly damaging to DNA, to cell membranes and to proteins) and inflammation was undeniable**.

- Research findings addressed many areas and provided yet more evidence that cognitive processing differs in ME/CFS compared with controls; there is evidence of distinctive chemical and molecular differences in ME/CFS patients; **there is evidence of the role of specific viral agents, and there is confirmation that differences in gene expression exist between ME/CFS patients and healthy controls, as well as between subgroups of "CFS".**

- **The importance of sub-typing was recognised and emphasised.**

- Dr Ellie Stein from Alberta, Canada, pointed out that suicide is the third leading cause of death in ME/CFS (the others being cancer and heart disease).

- In ME/CFS, testing for elastase, RNase-L, C-reactive protein, selected cytokines and NK cell activity are recommended because they are objective markers of pathophysiology and severity. In addition, **an exercise test/re-test of cardiopulmonary function is necessary because it is 100% objective and confirms reduced functional capacity as well as post-exertional malaise for disability purposes.** Further, lipid abnormalities and evidence of metabolic syndrome should be looked for.

<u>Cardiovascular system</u>

- Researchers are developing methods to measure cardiovascular and cardiopulmonary health in ME/CFS patients, which relates to oxygen consumption.

- ME/CFS patients' ability to work is impaired, as shown by an abnormal exercise stress test. Margaret Ciccolella and Christopher Snell et al from Stockton, CA, demonstrated that patients show extreme abnormalities in a next-day/second session of exercise. They do not recover in 24 hours. In one study, only one patient had recovered to baseline within 48 hours. These changes in serial testing point to a significant and confirmable physical abnormality, verifying the cardinal symptom of post-exertional malaise. **This test/retest exercise test is 100% objective and can prove to the disability companies that ME/CFS is neither malingering nor faking. In ME/CFS patients, the measurements declined by about 25%, far more than in other significant diseases such as COPD and even heart failure.**

- **Post-exertional malaise following exercise challenge results in fatigue, light-headedness, vertigo, joint pain, muscle pain, cognitive dysfunction, headache, nausea, trembling, instability, and sore glands**.

- I**n ME/CFS patients, there is cellular hypoxia — oxygen is delivered to the cells of the heart, brain, skeletal muscle and other organs, but the process of turning oxygen into energy is derailed.**

- **Graded exercise therapy is ill-advised — if a patient has abnormal oxygen consumption, muscles will not have enough oxygen and exercise will result in relapse.**

- A US NIH-funded trial by Professor Barry Hurwitz, a colleague of Professor Nancy Klimas at the University of Miami, found that 70% of ME/CFS patients have a low red blood cell volume.

Treatment to increase blood volume was ineffective in respect of exercise tolerance and fatigue.

- One of the highlights of the conference was the presentation of Dr Vance Spence's work (University of Dundee) on inflammation and arterial stiffness in patients with ME/CFS – **arterial stiffness is rarely found in adolescents, but in ME/CFS these young patients had higher levels of arterial stiffness than diabetic patients. This work looked at inflammatory factors (free radical by-products and C-reactive protein, an inflammatory marker) and found abnormally high levels of free radical by-products and C-reactive protein in patients but not in controls. C-reactive protein levels were significantly correlated with increased arterial stiffness.** A likely cause is elastase. Elastase is a central factor in Professor Kenny de Meirleir's RNase-L paradigm (see below), and Dr Baraniuk's cerebrospinal fluid proteome study suggests elastase is implicated in blood vessel problems in the brain of ME/CFS patients. The logical consequences of increased arterial stiffness are exercise intolerance and diastolic (cardiac) dysfunction. The circulatory problems seen in ME/CFS may originate in endothelial cells lining all blood vessels. These cells are involved not only in opening and closing blood vessels but in the immune response as well, and they are often attacked by pathogens.

- Professor Paul Cheney presented evidence of diastolic (cardiac) dysfunction in ME/CFS, with evidence of another cardiac abnormality (patent foramen ovale, or PFO). This results in hypoxia (low oxygen levels relative to metabolic needs).

- **Cheney stated that the cardiac index of ME/CFS patients is so severe that it falls between the value of patients with myocardial infarction (heart attack) and those in shock.**

- Professor Mark van Ness from the University of the Pacific found that maximum aerobic capacity (VO_2 peak) is reduced in ME/CFS compared with sedentary controls.

- Van Ness found that oxygen capacity at the anaerobic threshold is reduced in ME/CFS.

- Van Ness also found that serum lactate is elevated, suggesting an abnormally early shift to anaerobic metabolism.

- In a subset of patients, Martin Lerner (Wayne State University, Detroit) described persistent EBV and/or CMV in ME/CFS patients: in addition to having high titres, all 37 patients studied had an elevated heart rate at rest, recurrent T-wave inversion on Holter monitoring, cardiac abnormalities and/or biopsy-proven cardiomyopathy. Symptoms included not only tachycardia but chest pain and syncope.

- **According to Lerner, all ME/CFS patients have abnormal T waves; inversion is seen in 96%; there is resting tachycardia. Cardiac biopsies show fibrosis, myofibre disarray and fatty infiltrates.**

Other key areas of ME/CFS research reported in "Facts from Florida" include Nuclear Medicine (showing some of the abnormalities in functioning that patients with ME/CFS experience on a daily basis); Proteomics (the study of proteins made in the cell, including evidence of unique markers in the cerebrospinal fluid of ME/CFS patients that are completely absent in controls and which were described as *"unbelievable"*); Virology (showing evidence of viral persistence in ME/CFS patients); Gastrointestinal dysfunction (evidence was presented of enterovirus in stomach biopsies of 80% of ME/CFS patients, compared with none in controls); Sleep disruption (due to a lack of parasympathetic activity during attempted sleep periods); Pain (described as a major feature in many aspects of ME/CFS); Cognitive impairment (evidence was presented suggesting that the central nervous system correlates of cognitive dysfunction in ME/CFS have an inflammatory basis); Immunology (evidence of activated CD8 cells; poorly functioning NK cells; novel findings – seen only in ME/CFS – of abnormalities of the 2-5A pathway [RNase-L ratio]; cytokine abnormalities [pro-inflammatory dysregulation]; increased TGF, and 27 times

more circulating immune complexes than in controls; Neuroendocrine dysfunction (evidence of neurobiological distinctions between 'pure' ME/CFS and CFS/ME with psychiatric morbidity -- further evidence that ME/CFS is not psychiatric in origin); Genomics (the study of the function and interactions of genetic material, including interactions with environmental factors which play a significant role in ME/CFS) and Paediatrics (with the presentation of new paediatric diagnostic criteria from Professor Leonard Jason et al, which means there is now a science-based instrument to correctly diagnose children and adolescents with ME/CFS).

In summary, this international conference demonstrated the difference between science and psychiatry.

All the above evidence was available to the GDG but they were directed not to consider it (J Inf 2007:55:6:569-571) and instead chose to refer to "*perceived exertion",* even stipulating that: "*signs and symptoms of cardiorespiratory disease* ***should not be attributed to CFS/ME****"* (52 page version, 15:1.2.1.4).

Evidence of cardiovascular dysfunction continues to mount

Following publication of the Guideline, papers which confirm and add to the existing body of knowledge about cardiovascular dysfunction in ME/CFS continue to be published. For example:

- a team from the US CDC produced evidence of higher heart rate and reduced heart rate variability during sleep in ME/CFS (Autonomic Neuroscience, 2007)

- a Belgian team published evidence of a genuine intracellular inflammatory response in the white blood cells in ME/CFS patients (Neuro Endocrinol Lett, 2007)

- a Norwegian team demonstrated that adolescents with ME/CFS have a sympathetic predominance of cardiovascular regulation with hypovolaemia and abnormalities of the reflex mechanisms during even very mild orthostatic stress (Clin Physiol Funct Imaging, 2007)

- a Japanese team published evidence from echocardiographic examination demonstrating significant differences in ME/CFS patients and controls --smaller values of both left ventricular end-diastolic dimensions and end-systolic, as well as stroke volume and cardiac indices, with evidence that a considerable number of ME/CFS patients have a small heart compared with controls (Clin Cardiol 2008)

- a Scottish team noted that as long ago as 1997, markers of inflammation were demonstrated in some patients with ME/CFS, and that in 2005, vascular stiffness was shown to have an impact on resting and exercise-induced haemodynamics; aware of the accumulating evidence that the cardiovascular system is compromised in many patients with ME/CFS, this team investigated the relationship between inflammation and arterial stiffness in ME/CFS patients. (If arteries become stiff, the heart has to work harder and, ultimately, blood pressure becomes higher. Stiff arteries have been linked to kidney problems and heart disease, and may contribute to the orthostatic problems (dizziness on standing) experienced by some ME/CFS patients). This study demonstrated that the augmentation index (a measure of arterial stiffness) was significantly greater in patients with ME/CFS than in controls and concluded: "*The results of this study have shown that patients with ME/CFS have high serum CRP levels* (C-reactive protein, a sensitive biochemical marker of inflammation) *indicative of chronic inflammation*. *The combination of increased arterial wave reflection, inflammation and oxidative stress may result in unfavourable haemodynamics and an increased risk of a future cardiovascular event in these patients"* (VA Spence et al. Clinical Science 2008:114:561-566).

Undue influence of the Wessely School on the NICE Guideline

The GDG claims that the Guideline *"offers best practice advice on the care of people with CFS/ME"* (52 page version, page 6) and that it is "*evidence-based*", even though little of it actually is evidence-based, because (i) many of the RCTs on which the GDG relies for its management recommendations specifically exclude those with ME/CFS, and (ii) the GDG was directed to disregard the existing international evidence-base, focusing only on the Wessely School model of "CFS/ME".

Pertinent questions require urgent answers, for example:

- are the Wessely School psychiatrists who advised NICE via the Systematic Review team at the Centre for Reviews and Dissemination at York (and as Stakeholders) all still convinced that the exercise regimes to be meted out by the "CFS" Centres on the recommendation of the NICE Guideline pose no harm for those with ME/CFS?

- is Professor Anthony Pinching (who, it has been confirmed by NICE, was instrumental in formulating the GDG's remit and who is very supportive of the Wessely School's behavioural model of "CFS/ME", as confirmed in a personal communication of 17th May 2001) also certain that incremental aerobic exercise is safe for every ME/CFS patient as recommended in the Guideline?

- are the peer reviewers at the MRC who approved the PACE trial protocol still certain that the incremental exercise component poses no harm for people with ME/CFS?

- have all MRC trial participants been screened for cardiac anomalies before starting the trial, or are the Principal Investigators (psychiatrists Peter White and Michael Sharpe, assisted by Simon Wessely) content to rely on the certainty that they themselves can never be held accountable for any harm to any patient, since all participants must sign a compulsory waiver, which means that no participant can ever pursue any claim for medical negligence or damages?

Problems with delivery of the NICE Guideline's recommendations

The NICE Guideline states that participation in graded exercise should be a co-operation between the therapist and the patient, but in practice the evidence is that this simply does not happen.

Apart from the concern recorded in the Gibson Inquiry Report of 2006 about his commercial conflicts of interests arising from his involvement with and his work for the medical insurance industry (http://www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf), there are other equally disturbing matters that seem to involve psychiatrist Professor Peter White.

It is a matter of record that the Royal Free (Hampstead) NHS Trust Fatigue Service – a very large Centre -- was coercing "CFS/ME" patients into signing up to participate in CBT and graded exercise on pain of being refused access to a physician unless they agreed to do so (i.e. it was being made clear to patients that they would have access to a physician for medical advice at the Centre only if they agreed to participate in CBT and graded exercise therapy regimes; if patients declined to enter into a contract to participate in such regimes, they would be discharged and would have no access to a physician at the Centre).

In the absence of the part-time Clinical Lead at the Royal Free Fatigue Services Centre, Dr Gabrielle Murphy, the person in overall charge is Professor Peter White.

It is understood that Professor White has been recruiting patients attending the Royal Free Fatigue Services Centre to the MRC "CFS/ME" trials (of which he is a Principal Investigator), which raises the possibility that he is recruiting only CBT/GET-compliant patients to his trials, which would decrease the number of trial drop-outs at a stroke. Staff at the Royal Free Fatigue Services Centre (Nathan Butler and Karen Levy,

a graded exercise therapist and an occupational therapist respectively) are team members on the MRC PACE trial.

Written evidence exists that, less than one month after publication of the NICE Guideline on "CFS/ME" on 22nd August 2007, the Royal Free Fatigue Services Centre policy (that patients believed denied them access to a physician unless they agreed to take part in a regime that is already known to be harmful in 50% of participants) would seem to have been in breach of the assurances contained in the Guideline.

The NICE Guideline is unambiguous and states in ten places that if a CFS/ME patient refuses CBT and GET, such refusal should not end the treatment contract with the doctor and it stipulates that patients may not be discharged from medical care -- see the Full Guideline, pp 28, 31, 116, 130, 158, 178, 214, 259, 283 and 298. For example, page 28 of the Guideline states: "*Healthcare professionals should be aware that – like all people receiving care in the NHS -- people with CFS/ME have the right to refuse or withdraw from any component of their care plan without this affecting other aspects of their care, or future choices about care".* The Guideline is clear that a patient's right to care should not be limited by the personal treatment preferences of an NHS professional: "*Personal views or beliefs are not allowed to impede any individual's access to care and support"* (page 186). Further, on page 213, the Guideline states: "*The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership".*

It has been reported both by patients and by medical consultants that this fundamental principle, enshrined in law and endorsed by NICE, has being actively negated, in letter and in spirit, by NHS practitioners at a leading London CFS/ME Centre (http://www.meactionuk.org.uk/COERCION_AS_CURE.htm).

The NICE Guideline states: "*Objectives of the CBT programme must be agreed with the patient, and they must clearly be willing to take part".* Indeed so, but some Centres have a way of inducing "consent", and patients who hesitated were threatened with having no access at all to a physician (which, apart from any symptomatic medical care, they need in order to support their claim for state benefits).

It has also been established that this same Centre is no longer prepared to support individual patients' applications for Disabled Living Allowance but simply hands patients a pro-forma letter.

This is in clear breach of the Guideline, which states that every person with "CFS/ME" should be offered assistance with negotiating the healthcare, benefits and social care systems (52-page version, section 1.1.3.2).

In his Editorial in the BMJ in which he zealously supported the NICE Guideline's recommendation for "CFS/ME" to be managed by the behaviour-modifying interventions of CBT and graded exercise (BMJ 1st September 2007:335:411-412), White asserted: "*We remain unsure how to classify (CFS/ME)".*

This is in total disregard of the WHO classification of almost 40 years -- an era, as noted in an eBMJ Rapid Response to that Editorial, when great care was taken over detail and documentation in the identification of a disease entity.

Professor White is unremitting in his promotion of the NICE Guideline. On 23rd July 2008 he wrote in the eBMJ: "*Both patients and their family physicians seemed to share uncertainty about either whether CFS existed or how to treat it. Physicians' uncertainty and ignorance cannot be attributed to a lack of available guidance. Fortunately the UK has seen a recent publication of the most authoritative guideline so far; that produced by the National Institute for Health and Clinical Excellence, an independent quasi-governmental organisation responsible for publishing all clinical guidelines for the UK National Health Service. This gives explicit advice regarding diagnosis and management in both primary and specialist care (and) is easily accessible to both patients and healthcare practitioners.* ***The challenge now is to make sure that our scientific understanding is translated into clinical practice****"* (Medical care free of science and based on social networks. Peter D White).

The problem is that the Wessely School's interpretation of "*scientific understanding"* does not accord with the international evidence, which they persistently dismiss or disregard.

It is notable that in June 2004, Peter Denton White was awarded an OBE; the citation was: "*For services to medical education"*. Notices circulating at the time proclaimed him as leading the research into "CFS/ME" and said his OBE was a *"well-deserved honour and acknowledgement of his contribution to work on CFS/ME"*.

For someone to receive such an honour seems surprising if the person so honoured is apparently ignorant of the established facts pertaining to the subject of his research interest for which he was honoured.

Conclusion

The NICE Guideline on "CFS/ME" recommends the national implementation of only behavioural interventions for such patients, yet the GDG is at pains to state that it does not regard those interventions (CBT and GET) as curative or directed at the underlying disease process (Full Guideline, page 252). The GDG is careful to state that it makes no assumptions about aetiology, yet it relies only upon trials which do make such an assumption (i.e. that "CFS/ME" is a behavioural disorder). It is not possible to design any clinical trial without an assumption of aetiology, and the only "evidence" that the GDG relied upon was that of Wessely School psychiatrists whose assumption of "CFS/ME" aetiology is that it is a somatoform disorder and whose model is based on fear avoidance and deconditioning.

For clarification of the precise meaning of the terms "CBT" and "GET", the MRC Trials state: "***CBT will be based on the illness model of fear avoidance"*** and "***GET will be based on the illness model of deconditioning and exercise intolerance"***.

In both instances, the study references claiming to support these statements are exactly those used by NICE to support its recommended management interventions (http://www.biomedcentral.com/1471-2377/7/6).

For an explanation of its recommended therapies, the Guideline refers readers to the Glossary of Terms on page 12, which is clear: CBT is "*an evidence-based psychological therapy"* and GET is "*an evidence-based approach that involves physical goal-setting and education. The duration of the activity is gradually increased (and) is followed by an increase in intensity.* ***The objective is to improve the person's CFS/ME symptoms and functioning, aiming towards recovery"***.

That statement is pivotal, because the GDG could not rationally state that the objective of its recommended interventions is ***"aiming towards recovery***" if it had not made the assumption that "CFS/ME" is a behavioural disorder from which recovery is possible.

To mislead patients and clinicians alike by implying that "***recovery"*** is the objective might be deemed a failure of duty of care, because there is absolutely no evidence that patients with ME/CFS recover with GET (but there is significant evidence that some patients have been actively harmed by it).

This effectively means that NICE is advising healthcare professionals to tell patients that they are recommending something which will aid "***recovery***", **even though it is not directed at the underlying disease process**. This seems to be clear evidence that the GDG believes that "recovery" is in the hands of the patients themselves.

It is the case that psychiatrist Professor Peter White urged the Guideline Development Group to include "recovery" as the goal of intervention (see Stakeholders' Comments on Chapter 6: page 308, line 6.3.6.16: http://www.nice.org.uk/nicemedia/pdf/CFSMECommentsTable6.pdf).

In the light of so much evidence (not hypotheses) of serious heart and vascular problems in a subset of ME/CFS patients (all of which the GDG was directed to disregard), the question has to be asked: how can incremental aerobic exercise as recommended in the NICE Guideline – **which is carefully aimed only at "*those who wish to recover*" and is to be "*undertaken only with informed consent*", thereby placing the onus of "recovery" directly on the patient** -- help such patients remain as functional as possible?

If ME/CFS patients decline to engage with behavioural modification and incremental aerobic exercise regimes, no other intervention is offered to them. They are too often left abandoned, derided, disparaged and denigrated (see http://www.meactionuk.org.uk/Quotable_Quotes_Updated.pdf). By virtue of recommending only behavioural interventions for all patients with "CFS/ME", the NICE Guideline has done nothing to rectify this travesty.

This present document looks at just some of the evidence about one dysfunctional system in ME/CFS, the cardiovascular system, but patients suffer to the same degree with dysfunction in all bodily systems.

ME/CFS is a devastating disorder -- described by the severely affected patients as "a living death" -- but the Guideline does not adequately or accurately reflect the degree of incapacity or severity of illness experienced on a daily basis by those with ME/CFS.

It is essential to ascertain why such an important Guideline was deliberately restricted in its remit; why GDG members were expressly directed not to consider the totality of the existing evidence-base and why only those professionals who support the behavioural model of "CFS/ME" were chosen as GDG members.

A fundamental question remains: **is the Wessely School's refusal to heed the biomedical evidence that has been shown by internationally respected researchers to underpin ME/CFS based on the psychiatrists' personal involvement with the medical insurance industry alone, or is it due to the fact that the biomedical evidence is deemed inconvenient in the UK because it does not accord with Government's current policy of off-loading as cheaply as possible the ever-increasing hordes of chronically sick who have no commercial value to the State but who cost it far too much money?**

If so, this is surely a short-sighted policy, because it is well recognised that patients with ME/CFS who are correctly diagnosed and permitted to rest adequately in the initial stages are the ones who have hope of some recovery. If relevant biomedical research were to be instituted, it would lead to patients being investigated competently and treated correctly, thus offering the ME/CFS patient the prospect of being able to return to an economically productive life, thereby relieving the State of an ever-increasing financial burden.

In 2002, the annual cost of ME/CFS to the nation was said by Lord Clement-Jones to be estimated at £4 billion (Hansard: Lords: 16th April 2002: 898). In May 2003, a statistical analysis carried out by The Survey and Statistical Research Centre at Sheffield Hallam University for the charity Action for ME found that ME/CFS was costing the nation £3.5 billion per annum, which is £9.5 million every day ("Cost to the Nation Report", AfME, 12th May 2003).

The latest figures (January 2007) on the economic impact of ME/CFS in the US are between $22 billion and $28.6 billion annually; in Japan, the figure is over $10 billion annually (http://www.meactionuk.org.uk/Facts_from_Florida.htm).

To deny the nature, reality and impact of ME/CFS is a continuing abuse of sufferers.