THE FAILURE OF NICE TO ADDRESS ITS REMIT re: "CFS/ME"

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On 22nd August 2007 the UK National Institute for Health and Clinical Excellence (NICE) published its Clinical Guideline 53: "Chronic fatigue syndrome / myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children"

As can be seen from the title of the Guideline, the remit for NICE specifically included the production of guidance not only on the management but on the diagnosis of ME/CFS, which Government Departments -- including the so-called "independent" NICE (which is not in fact independent as it is funded by and accountable to the Department of Health) refer to as "CFS/ME" on the advice of their Wessely School (psychiatric) advisers.

In defiance of its remit, NICE failed to provide appropriate guidance on the diagnosis of the disorder. In its Guideline, NICE also expressly proscribed certain laboratory tests that unequivocally aid in the diagnosis of the disorder.

It is submitted that in so doing, NICE has been perverse and irrational and has failed in its duty of care to the patients and clinicians whom the Guideline was intended to assist.

It is also submitted that, in clear breach of the AGREE Instrument to which it is party, NICE failed even to identify correctly the disorder ME/CFS by failing to distinguish ME/CFS from "chronic fatigue".

Despite the vast amount of information demonstrating the biomedical basis of ME/CFS that was provided during the consultation period, NICE chose to ignore it.

A perverse policy decision by NICE?

In the preparation of its Guideline, it seems that a policy decision was taken by NICE not to consider the evidence that demonstrates the many biomedical abnormalities that occur in ME/CFS, knowledge of which would greatly assist in correct diagnosis of the disorder and easily distinguishing it from the somatisation (behavioural) disorder that Wessely School psychiatrists assert it to be.

The Guideline states that consideration of the aetiology of "CFS/ME" (and thus the biomedical evidence in relation to ME/CFS) was "*outside the scope of the guideline and therefore a systematic search of the area was not carried out"* and did not come within

its remit. Specifically, the Guideline does not recommend study of this evidence-base, stating: "*the GDG has not made a research recommendation about the causes of CFS/ME"* (see the 52 page version of the Guideline, section 4, page 39).

Since its remit was to produce guidance on diagnosis, for NICE not to consider the available literature on the disorder in question that demonstrates the clear biomedical aetiology of that disorder (and even to advise against future study of this evidence-base) was perverse, irrational and detrimental to those for whom the Guideline was intended.

The difference between ME/CFS and "CFS/ME"

The distinction between ME/CFS and "CFS/ME" has immense significance in that ME/CFS refers to a specific nosological entity classified since 1969 as a neurological disorder by the World Health Organisation at section G93.3 in its International Classification of Disease ICD-10, a disorder for which there is a significant body of over 4,000 published papers demonstrating serious organic pathology.
In contrast, "CFS/ME" is not so classified. By design and definition, "CFS/ME" encompasses all forms of "medically unexplained" fatigue or chronic tiredness, and specifically includes psychiatric disorders. Crucially, Wessely School members do not consider psychiatric disorders to be exclusionary for a diagnosis of "CFS/ME". The Wessely School selects patients according to its own criteria (the Oxford 1991 criteria, which specifically include patients with "chronic fatigue" and specifically exclude those with neurological disorders). The Wessely School defines ME as a "myth" and assert it is an "aberrant illness belief" that can be ameliorated by psychotherapy and exercise.

Although the term "CFS/ME" purports to refer to the discrete disease ME, in reality it refers to on-going tiredness and associated symptoms such as aches and pains and insomnia. Where such symptoms have no obvious explanation, the Wessely School refers to them as "chronic fatigue syndrome" (which they deem is synonymous with ME) and for which they assert there is only one solution: cognitive behavioural therapy (CBT) combined with graded exercise therapy (GET) -- see, for example, "Coping with Chronic Fatigue" by Trudie Chalder, Sheldon Press, 1995. Trudie Chalder is a tireless Wessely School activist and a frequent co-author with Simon Wessely; she is a former Registered Mental Nurse who is now Professor of Cognitive Behavioural Psychotherapy at King's College and The Institute of Psychiatry, London, and is an ardent believer in the curative properties of CBT/GET, even though her own published studies show it is ineffective.

Core issues

The core issues that the NICE Guideline failed to address adequately in its guidance on diagnosis include:

- the heterogeneity of "CFS/ME": this comes down to the confusion by Wessely School psychiatrists of chronic fatigue with ME, whether it be case definition;

criteria; management; service provision; misinformation supplied to the media etc, and their failure to accept that the hall-mark of ME (incapacitating post-exertional exhaustion and intense malaise) is not the same as "chronic tiredness" or "de-conditioning". Just concentrating on "unexplained fatigue", and ignoring or dismissing the many other well-documented symptoms of ME defies reality. Those symptoms include vertigo and balance problems; severe myalgia; neuromuscular incoordination; cardio-pulmonary problems; liver problems; pancreatic dysfunction; gastro-intestinal symptoms, with loss of bowel control; frequency of micturition with nocturia; hair loss; mouth ulcers; and the invariably present parasympathetic neuropathy which is such a cardinal part of the disorder. None of these symptoms are described by Wessely School psychiatrists looking at "CFS/ME": indeed, those psychiatrists actively deny the existence of these symptoms (see, for example, the submission to NICE during the consultation period sent by Professor Peter White's Unit at St Bartholomew's Hospital)

- the unreasonable rejection by the Establishment, including NICE, of the significant body of published scientific literature on ME/CFS that disproves the Wessely School's belief that "CFS/ME" is a behavioural disorder that is amenable to CBT/GET

- the relentless dismissal and denigration by the Wessely School of the significant body of international research that shows ME/CFS to be an organic disorder

- the total refusal of the accountable authorities even to consider this robust biomedical research (because it does not fit with current policy that "CFS/ME" is to be managed as a behavioural disorder as recommended by the Wessely School psychiatrists). When this robust biomedical evidence was passed to Government Ministers by the Countess of Mar (with a request for a detailed response), the answer came in a written response: it had been decided at Ministerial level that the evidence should be ignored and no action should be taken

- the rigorous refusal to allow patients with ME/CFS to be suitably investigated and accurately diagnosed (for example, NICE advised against the use of the 2003 Canadian Criteria, which are internationally acknowledged to be the best available to diagnose ME/CFS)

- the manipulation of the scientific process: for example, patients in the Medical Research Council (MRC) current PACE trials (run by Wessely School psychiatrists) are selected by means of the psychiatrists' own criteria (Oxford 1991); the MRC claims to be looking at patients with "CFS/ME" when – as mentioned above -- in reality the Oxford criteria select patients with chronic fatigue and expressly exclude patients with neurological disorders such as ME, yet the trial investigators claim they are studying people with "CFS/ME", so where does this leave patients with ICD-classified G93.3 ME? NICE has failed to address this matter.

ME has been documented in the medical literature since 1938 (AJ Gilliam, US Public Health Bulletin No: 240; 1938), and in 1957 AL Wallis meticulously documented over 200 cases of ME (Doctoral Thesis; University of Edinburgh, 1957). Throughout the 1990s in the UK, there was convincing published evidence of enteroviral infection in people with well-defined ME. Enteroviruses are related to the poliovirus and display tropism for muscle, pancreas, heart and brain tissue. Autopsy results dating back to 1956 have apparently revealed the presence of enterovirus in cases of ME. The rise to dominance of the Wessely School psychiatric lobby caused this important research to be ignored. Evidence of enteroviral infection in ME/CFS continues to be published internationally (see, for example "The Role of Enterovirus in Chronic Fatigue Syndrome". JK Chia; J Clin Path 2005:58:1126-1132, which demonstrates the importance of enteroviruses in ME/CFS and substantiates the 1990s work of Archard et al in the UK). More recently, indisputable evidence of persistent enteroviral infection has again emerged and has been demonstrated in the US by Chia and Chia ("Chronic fatigue syndrome is associated with chronic enteroviral infection of the stomach". J Clin Path: September 2007). This earlier evidence was available to NICE, yet NICE chose to ignore it. There is no evidence of on-going enteroviral infection found in people with "chronic fatigue" (i.e. "CFS/ME").

Whilst ME has been documented in the medical literature for at least 70 years, there is evidence that since the 1980s it is rapidly increasing in both incidence (new cases of a condition) and prevalence (refers to all cases in the country).

It has been shown that in ME/CFS, the immune system is dysfunctional in specific ways, and that this damage may have been caused by a virus. It has now been demonstrated that there is central nervous system hypomyelination in ME/CFS, which the authors note is associated with organophosphates and with chemical warfare agents ("Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome". N. Kaushik, SCM Richards, ST Holgate, JR Kerr et al. J Clin Path 2005:58:826-832). This evidence was also available to NICE.

If environmental toxins such as organophosphates and biowarfare agents (such as mycoplasma / borreliosis) and other intra-cellular pathogens, as well as viruses, are implicated in the rising incidence of ME/CFS by virtue of acquired damage to certain genes, it may explain the Government's policy to deny the existence of ME/CFS, since it was the Government who granted the product licences for those environmental toxins; equally, if biowarfare agents are implicated, the Government is just as culpable so, as in Gulf War Syndrome, this may be why the Government continues to deny the very existence of these life-wrecking disorders.

<u>Abnormal pathology seen in ME/CFS that was ignored by NICE</u>

The abnormal pathology that has been repeatedly demonstrated in ME/CFS, but not in "CFS/ME", includes evidence of an over-activated immune system; abnormal

dysregulation of the 2-5A synthetase / RNASE L pathway (a critical anti-viral pathway and part of the body's essential natural antiviral defences: in ME/CFS a protein that in healthy controls weighs 80 kDa [kiloDalton] uniquely weighs only 37kDa); low NK cell function (these latter two being specific markers of the disease).

Other significant abnormalities have been demonstrated on nuclear imaging such as MRI (looking at structure), *f*MRI (looking at brain function), MRS (looking at the chemistry of the brain), SPECT (looking at bloodflow in the brain) and PET (looking at brain metabolism) scans. It is notable that MRS scans of patients with ME/CFS have revealed free choline, which is indicative of active viral infection in the brain, with damage to the nerve cell membranes. These nuclear imaging scans have also revealed abnormalities in cerebral white matter and decreases in blood flow throughout the brain. The NICE Guideline specifically proscribes such scans to assist in the diagnosis of patients with "CFS/ME".

It has long been shown that in ME/CFS there is dysfunction of the autonomic nervous system (adversely affecting temperature control, respiration; bladder and bowel control; heart rate; blood pressure control, with neurally-mediated hypotension [NMH] and postural orthostatic tachycardia syndrome [POTS] etc). Yet more biomedical abnormalities have been shown to include low levels of cortisol; problems with fluid balance; abnormal thyroid function; muscle abnormalities; impaired oxygen delivery to muscles; cardiac dysfunction, and abnormal EEG profiles.

Unique vascular abnormalities have been demonstrated in ME/CFS, with markers of oxidative stress (oxidative stress is caused by highly reactive molecules known as free radicals circulating in the bloodstream of people with ME/CFS and results in cell injury; research has shown that many patients with ME/CFS could have an inflammatory condition and be in a 'pro-oxidant' state; exercising muscle is a prime contender for excessive free radical generation).

There is convincing research from Belgium which demonstrates that an intracellular inflammatory response in the white blood cells plays an important role in the pathophsyiology of ME/CFS and that patients' symptoms reflect a genuine inflammatory response (Maes M et al. Neuro Endocrinol Lett 2007:28(4)).

Research from Australia has demonstrated that patients with ME/CFS have a broad and variable spectrum of signs and symptoms, with alterations in standard blood parameters and in urinary excretion profiles. These alterations include a significant decrease in red cell distribution width and increases in mean platelet volume, neutrophil counts, and the neutrophil / lymphocyte ratio. The urinary abnormalities include a reduced rate of amino acid excretion, with significant decreases in asparagine, phenylalanine and succinic acid, as well as increases in 3-methylhistidine and tyrosine. The authors conclude that this data supports the existence of alterations in physiologic homeostasis in ME/CFS patients (Haematologic and urinary excretion anomalies in patients with chronic fatigue syndrome. Niblett SH, Dunstan RH, McGregor NR et al. Exp Biol Med 2007:232(8):1041-1049). This group has identified amino acids and their derivatives as

indicators of disturbed metabolic pathways which reflect the clinical features of ME/CFS: excreted 3-methylhistidine is an established marker of active breakdown of muscle.

These abnormalities have not been seen in "chronic fatigue" (i.e. "CFS/ME").

In view of the fact that the peer-reviewed research data supports the organic abnormalities in ME/CFS, on what rational grounds can NICE recommend only behavioural modification for such a devastating disorder? In summary, NICE has ignored the following:

- evidence of disrupted biology at cell membrane level
- evidence of abnormal brain metabolism
- evidence of widespread cerebral hypoperfusion
- evidence of central nervous system immune dysfunction
- evidence of central nervous system inflammation and demyelination
- evidence of hypomyelination
- evidence that ME/CFS is a complex, serious multi-system autoimmune disorder (in Belgium, the disorder has now been placed between MS and lupus)
- evidence of significant neutrophil apoptosis
- evidence that the immune system is chronically activated (eg. the CD4:CD8 ratio may be grossly elevated)
- evidence that NK cell activity is impaired (ie. diminished)
- evidence of hair loss in ME/CFS
- evidence that the vascular biology is abnormal, with disrupted endothelial function
- novel evidence of significantly elevated levels of isoprostanes
- evidence of cardiac insufficiency and that patients are in a form of cardiac failure
- evidence of autonomic dysfunction (especially thermodysregulation; frequency of micturition with nocturia; labile blood pressure; pooling of blood in the lower limbs; reduced blood volume (with orthostatic tachycardia and orthostatic hypotension)
- evidence of respiratory dysfunction, with reduced lung function in all parameters tested
- evidence of neuroendocrine dysfunction (notably HPA axis dysfunction)
- evidence of recovery rates for oxygen saturation that are 60% lower than those in normal controls
- evidence of delayed recovery of muscles after exercise (note: there is no evidence of deconditioning)
- evidence of a sensitive marker of muscle inflammation
- evidence that the size of the adrenal glands is reduced by 50%, with reduced cortisol levels
- evidence that up to 92% of ME/CFS patients also have irritable bowel syndrome (IBS)

- evidence of at least 35 abnormal genes (acquired, not hereditary), specifically those that are important in energy metabolism; **there are more abnormal genes in ME/CFS than there are in cancer**
- evidence of serious cognitive impairment (worse than occurs in AIDS dementia)
- evidence of adverse reactions to medicinal drugs, especially those acting on the central nervous system, such as anaesthetics
- evidence that symptoms fluctuate from day to day and even from hour to hour
- there is no evidence that ME/CFS is a psychiatric or behavioural disorder.

For references, see:

(i) "Illustrations of Clinical Observations and International Research Findings from 1955 to 2005 that demonstrate the organic aetiology of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome" by Professor Malcolm Hooper, Eileen Marshall and Margaret Williams, 12th December 2005 (submitted to the Gibson Parliamentary Inquiry into ME). 174 pages.
Available online: http://www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm

(ii) "What the Experts say about ME/CFS" by Margaret Williams, 28th March 2006.
Available online: http://www.meactionuk.org.uk/What_the_Experts_say_about_ME.htm

For NICE deliberately to decline to consider this extensive literature on the disorder in question when the internationally documented abnormalities would aid diagnosis is perverse.

For NICE to proscribe the tests that reveal these abnormalities is equally perverse.

It is akin to telling patients presenting with symptoms of cancer, or multiple sclerosis, or Parkinson's Disease, or motor neurone disease, that they cannot have investigations that would confirm their disease but instead, they are only to be given a form of brain-washing that will convince them that they are not physically ill, together with a programme of "rehabilitation" that will restore them to health and productivity, if only the patient will allow that to happen and not persist in their abnormal illness beliefs.

Promotion of the flawed NICE Guideline by The Royal Society of Medicine

The NICE Guideline 53 is heavily flawed in numerous key areas; notwithstanding, on 28th April 2008, The Royal Society of Medicine is to host a "scientific conference" to take a "broad look" at chronic fatigue syndrome at which the NICE Guideline will be promoted; those taking part are almost exclusively members of the Wessely School (Professor Peter White; Dr Anthony Cleare; Professor Simon Wessely; Professor Matthew Hotopf; Professor Rona Moss-Morris; Professor Richard Baker, Chair of the Guideline Development Group, and Sir Peter Spencer, CEO of the patients' charity Action for ME [AfME] that has aligned itself with the psychiatric lobby).

It seems that no amount of evidence will make the slightest impression on this powerful group of psychiatrists who control UK Government policy on "CFS/ME" on the basis of their own opinion (which they elevate to the status of "evidence-based" medicine).

In 1999, Leonard Jason, Professor of Psychology at DePaul University, Chicago, wrote: "*Unfortunately, some uninformed physicians continue to believe that (ME)CFS (is) primarily psychiatric in nature. Biases such as these have been filtered through to the media (which) compromises patient-doctor relationships and medical care for patients"* (LISTSERV.NODAK.EDU 18th March 1999).

Most importantly, these same psychiatrists know and concede that the management regime recommended by NICE is ineffective (and therefore cannot be cost effective) for people with ME/CFS. That CBT/GET is a poor treatment for patients with "CFS/ME" has long been recognised: it is a matter of record that observed gains may be transient (Deale, Chalder & Wessely, Am J Psychiat 2001:158:2038-2042); that the beneficial effects of CBT/GET may be illusory (CRD Systematic Review: JAMA 2001:286:11:1360-1368), and that many patients with "CFS/ME" do not benefit from these interventions (Huibers & Wessely, Psychological Medicine 2006:36: (7):895-900).

A recent Australian meta-analysis of the efficacy of CBT in treating chronic fatigue syndrome found that it was only moderately effective and that it had a drop-out rate of up to 42% ("Efficacy of cognitive behavioural therapy for chronic fatigue syndrome: A meta-analysis". John Malouff et al. Clinical Psychology Review: Nov 2007: Epub).

Of significance is the fact that the authors of this Australian meta-analysis refused to include one of the studies of CBT upon which NICE relied, about which NICE had been given proof that the study in question was corrupted, so no reliable conclusions could be drawn from it. Malouff et al agreed and excluded it from their meta-analysis.

Notwithstanding the evidence that its favoured management regime is ineffective, this regime is the only one recommended by NICE for the management (as distinct from the treatment) of the unidentified disorder "CFS/ME".

The NICE Guideline makes binding recommendations for tens of thousand of UK patients with ME/CFS on the basis of a wholly inadequate evidence-base consisting of only 777 patients in total (the RCTs recruited 959 patients initially, but a total of 182 dropped out) and it is not known how many of the 777 (if any) actually had genuine ME. The drop-out rate was high, averaging 18.5%. There was little lasting benefit at follow-up, yet NICE maintains that it is the best available evidence.

Since NICE has demonstrably failed to fulfil its remit, it is reasonable to mount a challenge in the form of Judicial Review.

Appendices

For more detailed information on signs and symptoms and on demonstrated organic abnormalities in ME/CFS that NICE chose to ignore, see Appendix I below.

APPENDIX I

The NICE Guideline says that there are no abnormal signs in "CFS/ME", but in ME/CFS there are abnormal signs, for example:

labile B/P (this is a cardinal sign)
nystagmus and vestibular disurbance
sluggish visual accomodation
fasciculation
hand tremor
incoordination
cogwheel movement of the leg on testing
muscular weakness
marked facial pallor
POTS
positive Romberg
abnormal tandem or augmented tandem stance
abnormal gait
vascular signs such as demarcation that can cross dermatomes
evidence of Raynaud's syndrome and vasculitis
mouth ulcers
hair loss
flattened or even inverted T-waves on 24 hour Holter monitoring
singular reduction in lung function tests
abnormal glucose tolerance curves

enlarged liver (not usually looked for by psychiatrists)

SYMPTOMS of ME/CFS (most of which NICE chose to ignore) include:

extreme malaise; abdominal pain and diarrhoea; post-exertional exhaustion almost to the point of collapse; inability to stand unsupported for more than a few moments – this is absolutely diagnostic of ME; sometimes too weak to walk (different from deconditioning); inability to walk upstairs or to maintain sustained muscle strength, as in repeated brushing of hair with arms elevated, or inability to carry a shopping bag, or dry oneself after a bath, peel vegetables or prepare a meal; neuromuscular incoordination, not only of fine finger movement with clumsiness and inability to control a pen and to write legibly, but also of the larynx and oesophagus -- a frequent complaint is the need to swallow carefully to avoid choking; oesophageal spasm and pain; dysequilibrium ie. loss of balance; staggering gait (ataxia); bouts of dizziness and frank vertigo; difficulty with voice production, especially if speaking is sustained; aphasia (inability to find the right word); muscle cramps, spasms and twitching; black-outs and seizure-like episodes; spasmodic trembling of arms, legs and hands; episodes of angor animi (brought about by abrupt vasomotor changes that cause the sufferer to have uncontrollable shaking, like a rigor, and to think they are at the point of death) – it is essential to understand the terror that such attacks induce in a patient, and no patient can fake them; photophobia; difficulty focusing and in visual accommodation, with rapid changes in visual acuity; blurred and double vision, with loss of peripheral vision; eye pain; swollen and painful eyelids, with inability to keep eyelid open; tinnitus; hyperacusis, for example the noise of a lawnmower can cause acute distress and nausea; heightened sensory perception (for example, acute sensitivity to being patted on the back; inability to tolerate lights, noise, echoes, smells, movement and confusion such as found in a shopping mall or supermarket without being reduced to near-collapse); frequency of micturition, including nocturia; peripheral neuropathy; numbness in face; altered sleep patterns, with hypersonmia (in the early stages) and insomnia (in the later stages); alternate sweats and shivers; temperature dysregulation, with intolerance of heat and cold; parasthesias; sleep paralysis; intermittent palindromic nerve pains; tightness of the chest alternating with moist chest; muscle tenderness and myalgia, sometimes burning or vice-like; typically shoulder and pelvic girdle pain, with neck pain and sometimes an inability to hold head up; orthostatic tachycardia; orthostatic hypotension, and symptoms of hypovolaemia, with blood pooling in the legs and feeling faint due to insufficient blood supply to the brain; labile blood pressure; intermittent chest pain akin to myocardial infarct; segmental chest wall pain; subcostal pain; vasculitic spasms, including headaches; cold and discoloured extremities, with secondary Raynaud's; easy bruising; peri-articular bleeds, especially in the fingers; shortness of breath on minimal exertion; the need to sleep upright because of weakness of the intercostal muscles; pancreatic exocrine dysfunction leading to malabsorption; rashes (sometimes vasculitic in nature); flushing of one side of the face; ovarian-uterine dysfunction; prostatitis; hair loss and mouth ulcers that make speaking and eating difficult. The notable point about symptoms in ME/ICD-CFS is their variability.

All the above symptoms and more are documented in the literature; they bear little resemblance to "chronic fatigue" or to a "continuum of on-going tiredness" or to "CFS/ME".

DOCUMENTED ABNORMALITIES (most of which NICE chose to ignore) include the following:

- abnormalities of the central nervous system include abnormalities of brain cognition, brain perfusion, brain metabolism and brain chemistry; there is evidence of low blood flow in multiple areas of the brain; neuro-imaging has revealed lesions in the brain of approximately 80% of those tested and according to the researchers, these lesions are probably caused by inflammation: there is a correlation between the areas involved and the symptoms experienced; abnormalities on SPECT scans provide objective evidence of central nervous system dysfunction; there is evidence of a chronic inflammatory process of the CNS, with oedema or demyelination in 78% of patients tested; there is evidence of a significant and irreversible reduction in grey matter volume (especially in Brodmann's area 9) which is related to physical impairment and may indicate major trauma to the brain (which could also explain the low recovery rate); there is evidence of seizures; a positive Romberg is frequently seen in authentic ME/CFS patients

- abnormalities of the autonomic and peripheral nervous systems: there is evidence of dysautonomia in ME/CFS patients – see, for example, "Standing up for ME" by Spence and Stewart: Biologist 2004:51(2):65-70; according to Goldstein, ME/CFS represents the final common pathway for a multi-factorial disorder causing autonomic dysfunction

- cardiovascular dysfunction: there is evidence of haemodynamic instability and aberrations of cardiovascular reactivity (an expression of autonomic function); there is evidence of diastolic cardiomyopathy; there is evidence of endothelial dysfunction; there is evidence of peripheral vascular dysfunction with low oxygenation levels and poor perfusion and pulsatilities; there is evidence of abnormal heart rate variability and evidence of abnormal orthostasis; there is evidence of abnormally inverted T-waves and of a shortened QT interval, with electrophysiological aberrancy; there is evidence of abnormal oscillating T-waves and of abnormal cardiac wall motion (at rest and on stress); there are indications of dilatation of the left ventricle and of segmental wall motion abnormalities; there is evidence that the left ventricle ejection fraction – at rest and with exercise – is as low as 30%; there is evidence of reduced stroke volume

- respiratory system dysfunction: there is evidence of significant reduction in many lung function parameters including a significant decrease in vital capacity; there is evidence of bronchial hyper-responsiveness

- a disrupted immune system: there is evidence of an unusual and inappropriate immune response: there is evidence of very low levels of NK cell cytotoxicty; there is evidence of low levels of autoantibodies (especially antinuclear and smooth muscle); there is evidence of abnormalities of immunoglobulins, especially SIgA and $IgG_{3,}$ (the latter having a known linkage with gastrointestinal tract disorders); there is evidence of circulating immune complexes; there is evidence of a Th1 to Th2 cytokine shift; there is evidence of abnormally diminished levels of intracellular perforin; there is evidence of abnormal levels of interferons and interleukins; there is evidence of increased white blood cell apoptosis, and there is evidence of the indisputable existence of allergies and hypersensitivities and positive mast cells, among many other anomalies, with an adverse reaction to pharmacological substances being virtually pathognomonic

- virological abnormalities: there is evidence of persistent enterovirus RNA in ME/CFS patients; there is evidence of abnormalities in the 2-5 synthetase / RNase L antiviral pathway, with novel evidence of a 37 kDa binding protein not reported in healthy subjects or in other diseases; there is evidence of reverse transcriptase, an enzyme produced by retrovirus activity, with retroviruses being the most powerful producers of interferon; there is evidence of the presence of HHV-6, HHV-8, EBV, CMV, Mycoplasma species, Chlamydia species and Coxsackie virus in the spinal fluid of some ME/CFS patients, the authors commenting that it was surprising to find such a high yield of infectious agents on cell free specimens of spinal fluid that had not been centrifuged

- evidence of muscle pathology: this includes laboratory evidence of delayed muscle recovery from fatiguing exercise and evidence of damage to muscle tissue; there is evidence of impaired aerobic muscle metabolism; there is evidence of impaired oxygen delivery to muscles, with recovery rates for oxygen saturation being 60% lower than in normal controls; there is evidence of prolonged EMG jitter in 80% of ME/CFS patients tested; there is evidence of greater utilisation of energy stores; there is evidence that total body potassium (TBK) is significantly lower in ME/CFS patients (and abnormal potassium handling by muscle in the context of low overall body potassium may contribute to muscle fatigue in ME/CFS); there is evidence that creatine (a sensitive marker of muscle inflammation) is excreted in significant amounts in the urine of ME/CFS patients, as well as choline and glycine; there is evidence of type II fibre predominance, of scattered muscle fibre necrosis and of mitochondrial abnormalities

- neuroendocrine abnormalities: there is evidence of HPA axis dysfunction, with all the concomitant implications; there is evidence of abnormality of adrenal function, with the size of the glands being reduced by 50% in some cases; there is evidence of low pancreatic exocrine function; there is evidence of an abnormal response to buspirone challenge, with a significant increase in prolactin release that is not found in healthy controls or in depressives; there is evidence of abnormal arginine – vasopressin release during standard water-loading test; there is evidence of a profound loss of growth hormone; even when the patient is

euthyroid on basic screening, there may be thyroid antibodies and evidence of failure to convert T4 (thyroxine) to T3 (tri-iodothyronine), which in turn is dependant upon the liver enzymes glutathione peroxidase and iodothyronine deiodinase, which are dependant upon adequate selenium in the form of selenocysteine (which may be inactivated by environmental toxins)

- defects in gene expression profiling: there is evidence of reproducible alterations in gene regulation, with an expression profile grouped according to immune, neuronal, mitochondrial and other functions, the neuronal component being associated with CNS hypomyelination

- abnormalities in HLA antigen expression: Teraski from UCLA found evidence that 46% of ME/CFS patients tested were HLA-DR4 positive, suggesting an antigen presentation

- disturbances in oxidative stress levels: there is mounting evidence that oxidative stress and lipid peroxidation contribute to the disease process in ME/CFS: circulating in the bloodstream are free radicals which if not neutralised can cause damage to the cells of the body, a process called oxidative stress: in ME/CFS there is evidence of increased oxidative stress and of a novel finding of increased isoprostanes not seen in any other disorder; these raised levels of isoprostanes precisely correlate with patients' symptoms (isoprostanes being abnormal prostaglandin metabolites that are highly noxious by-products of the abnormal cell membrane metabolism); there is evidence that incremental exercise challenge (as in graded exercise regimes) induces a prolonged and accentuated oxidative stress; there is evidence of low GSH-PX (glutathione peroxidase, an enzyme that is part of the antioxidant pathway: if defective, it causes leakage of magnesium and potassium from cells)

- gastro-intestinal dysfunction: there is evidence of objective changes, with delays in gastric emptying and abnormalities of gut motility; there is evidence of swallowing difficulties and nocturnal diarrhoea; there is evidence going back to 1977 of hepatomegaly, with fatty infiltrates: on administration of the copper response test, there is evidence of post-viral liver impairment -- an increase of at least 200 in the copper level is the expected response, but in some severely affected ME/CFS patients the response is zero; there is evidence of infiltration of splenic sinuses by atypical lymphoid cells, with reduction in white pulp, suggesting a chronic inflammatory process; there is evidence that abdominal pain is due to unilateral segmental neuropathy (Gastrointestinal Manifestations of Chronic Fatigue Syndrome: H Hyman, Thomas Wasser: JCFS 1998:4(1):43-52); Maes et al in Belgium have found significant evidence that people with ME/CFS have increased serum levels of IgA and IgM against the LPS of gram-negative enterobacteria, indicating the presence of an increased gut permeability resulting in the autoimmmunity seen in many ME/CFS patients; this indicates that the symptoms of irritable bowel seen in ME/CFS reflect a disorder of gut permeability rather than psychological stress as most psychiatrists believe (gastro-

intestinal problems are a serious concern in ME/CFS, and 70% of the body's immune cells are located in the GI tract)

- reproductive system: there is clinical evidence that some female patients have an autoimmune oophoritis; there is evidence of endometriosis; there is evidence of polycystic ovary syndrome; in men with ME/CFS, prostatitis is not uncommon

- visual dysfunction: there is evidence of latency in accommodation, of reduced range of accommodation and of decreased range of duction (ME patients being down to 60% of the full range of eye mobility); there is evidence of nystagmus; there is evidence of reduced tracking; there is evidence of problems with peripheral vision; there is evidence that the ocular system is very much affected by, and in turn affects, this systemic condition.

The above list is by no means comprehensive but merely gives an overview of documented abnormalities seen in ME/CFS that can be accessed in the literature, as well as in the abstracts and reports of international Clinical and Research Conferences.

Individual references can be accessed at http://www.meactionuk.org.uk/SUBJECT_INDEX.htm