CONCERNS ABOUT THE FORTHCOMING UK CHIEF MEDICAL OFFICER'S REPORT ON MYALGIC ENCEPHALOMYELITIS (ME) AND CHRONIC FATIGUE SYNDROME (CFS), NOTABLY THE INTENTION TO ADVISE CLINICIANS THAT ONLY LIMITED INVESTIGATIONS ARE NECESSARY

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FOREWORD

I am happy to be associated with this challenging document written out of the "white heat" of the suffering and neglect that is so often the lot of people with ME, 25% of whom are severely affected and wheelchair, house or bed bound.

The need for good science is emphasised throughout the document; this provides a sound basis for the diagnosis of ME, which is a multi-faceted condition. These studies need to be kept in the forefront of the minds of decision makers who are responsible for advice that will affect the care and management of ME sufferers. It is notable that some of these studies are supported by funds provided by the UK ME Association (1) and must therefore have been approved by the Medical Director.

It is essential to address ME holistically. The growing body of scientific literature clearly shows that there are profound disturbances of and damage to the neuro-endocrine-immune systems which must be understood as inter-connected systems that share many common messenger molecules.

Functional Medicine provides an essential paradigm that identifies the need not only to determine blood or urine levels of significant marker molecules but also to understand the functional efficiency of the systems with which they are associated. The paradox of euthyroid levels of thyroid hormones associated with reduced thyroid function raises difficult and demanding questions. It is not enough simply to measure certain parameters. Such measurements must be allied to understanding how the whole system is integrated into the functioning of the whole person. (2)

Overlapping syndromes which share many common symptoms together with an emerging pattern of biochemical dysfunction (3) are providing new insights into "syndromes of uncertain origin" which require non-routine tests for their identification. (4) These include myalgic encephalomyelitis, chronic fatigue syndrome, Gulf War Syndrome, Fibromyalgia, Multiple Chemical Sensitivity and pesticide (OP) poisoning.

Treatment needs to be prioritised and structured. This requires a holistic understanding which considers support structures including the environment, nutrition and nutritional supplements, particularly as drug therapy in these patients is often precluded by serious adverse reactions.

References

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Malcolm Hooper, May 2001

Concerns about the forthcoming UK Chief Medical Officer's Report on ME and

CFS, notably the intention to advise clinicians that only limited investigations are necessary

1st May 2001

In addition to the matters raised in our April 2001 observations entitled *Information on Cognitive Behavioural Therapy, Professor Simon Wessely and PRISMA*, there are further matters of continuing concern relating to the UK Chief Medical Officer's forthcoming Report on ME/CFS which are so important that we believe they should be in the public domain.

We are aware that it is quite probable that some members of the Key Group (the "inner circle" of the CMO's Working Group on ME/CFS) intend to recommend that the CMO's Report should advise clinicians that *only limited investigations are necessary* for ME/CFS patients. Our understanding is that this specific advice comes from the Medical Director of the UK ME Association (Dr Charles Shepherd) and from those members of the Key Group who are known adherents of the "Wessely School". Such advice is merely repeating the message of the 1996 report on CFS of the UK Joint Royal Colleges, which states unequivocally that no investigations should be done to confirm the diagnosis of ME/CFS. (1) That Report was psychiatrically biased (half of the 256 cited references were by the same or associated group of authors, with 10% of the references being by Professor Simon Wessely himself; nine had not been published or reviewed); it was deficient in mention of references to the organic basis of ME/CFS and it was heavily criticised on both sides of the Atlantic. (2, 3, 4, 5, 6, 7)

We are unable to agree with advice to clinicians that only limited investigations are necessary or appropriate for ME/CFS sufferers and believe that such a view is medically and scientifically untenable; hence we believe there is a legitimate case for making this known in advance of the Report being issued. In our opinion, it is entirely unacceptable to advise clinicians that investigations on ME/CFS patients should be limited to a minimal basic routine screen, especially as basic screening is known to be often normal in ME/CFS.

Dr Shepherd is Medical Director of the ME Association; in this role, he is charged with representing the medical interests of Association members.

The approach which Dr Shepherd takes to the diagnosis and treatment of ME in respect of the ME Association is entirely a matter for him and the members of that Association. Dr Shepherd has over the years shown himself to be committed to the cause of ME. We, however, are of the opinion that any Government review of this disorder should advise the setting up of research units and specialist clinics within the NHS. We also believe that the best interests of patients are not served by following a psychiatric or behavioural model of evaluation which suggests that only

limited investigations are necessary for such patients. As mentioned in the original paper (reference 58), UK researchers looked at the common neuroendocrine tests for ME/CFS patients and concluded that the tests were inadequate for ME/CFS patients. We are strengthened in out belief by the fact that in July 2001 the American Medical Association issues a statement explaining that 90% of CFS/ME patients show normal test results on basic investigations and that studies designed for specific subgroups are needed. Professor Komaroff stated "*Researchers are already using imaging technology to measure brain hormones and are examining the function of the immune system. There is considerable evidence already that the immune system is in a state of chronic activation in many patients with CFS.*"
(ref: AMA, Co-Cure, 17 July 2001).

As we will show in this paper, it is clear that best clinical practice in this area is increasingly being understood to involve a comprehensive battery of sophsticated tests to facilitate a better understanding of this complex disorder. US Professors Fred Friedberg and Leonard Jason make the point in their recent book (8), noting that *"Some physicians make the odd assumption that we know all we need to know about these illnesses, thus obviating the need for further research and greater understanding of these patients".*

We find it difficult to overcome our concern about the fact that the most influential members of the CMO's Working Group are members of Healthwatch; **as officially recorded in Hansard (ref *Hansard (Lords) 28 April 1993:364-382* and *Hansard (Lords) 10 May 1995:66-68*),** Healthwatch **has in the past been** funded by drug companies and in its literature, its clearly-stated aims are to promote the use of pharmacological interventions and to oppose *"Diagnoses…that may encourage unnecessary treatment for non-existent diseases"*. Specifically, Healthwatch members are opposed to the use of non-pharmacological interventions such as homoeopathy, acupuncture, dietary modulation or vitamin supplementation and they are vociferously opposed to all practitioners of alternative or complementary medicine. Membership of Healthwatch **has in the past been refused to those who do not** promote the pharmacological industry (9). Notably, the Medical Adviser to the UK ME Association (Dr Charles Shepherd) is a member of Healthwatch, and the involvement of both Professor Anthony Pinching (Deputy Chair of the CMO's Working Group) and Professor Simon Wessely (a very influential member of the Reference Group to the CMO's Working Group) has long been known. (9) Wessely has had connections with Healthwatch since its inception in 1989 (9) and he unceasingly promotes his view that ME is a non-existent disease and that CFS is a psychiatric disorder which is amenable to antidepressants and psychotherapy. *(For a comprehensive referenced review of Wessely's published works on ME / CFS and related subjects (eg. Gulf War Syndrome), see Denigration by Design? E.Marshall & M Williams. Volume I (1987-1996) and Volume II (1996-1999), pp 488. Available at cost price from (UK) 0208-554-3832).*

We believe that investigation is the only way forward towards understanding these complex disorders and we regret that the CMO's Report is intending to amalgamate ME

with CFS as a single disorder despite having had it clearly pointed out that ME and CFS have differing case definitions: by virtue of the current CFS case definitions (Oxford 1991 and CDC 1994), CFS has no physical signs whatever, which is certainly not the case in ME. Our belief and experience is that only by looking will we learn**.**

To put this important issue in context, we briefly list some of the findings which were presented at the American Association of Chronic Fatigue Syndrome (AACFS) Fifth International Research and Clinical Conference held in Seattle in January 2001, which indicate just how essential it is for such patients to be comprehensively investigated.

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

It is perhaps worth reiterating that the American term "CFS" usually reflects patients who are likely to have ME / "core" CFS rather than psychiatric disorder as facilitated by the Oxford 1991 CFS case definition (still widely used by UK psychiatrists of the Wessely School who were participants in its formulation): this situation is one which requires immediate international input to end what is obviously a most confusing and unsatisfactory situation for all involved.

Brain studies / Neurology

Different neurobiological profiles are found in CFS patients compared with healthy controls. Using assays which measured hormones and cytokines with a potential for affecting the central nervous system (cortisol, prolactin, oestrogen, progesteron, CRP, neopterin, TNFalpha, TGFbeta, DHEA-s), significant differences were found in CFS patients compared with controls. (10)

Both baseline heart rate and plasma epinephrine were increased in CFS patients, suggesting an activated sympathoadrenal state. (11)

Sympathetic nervous system dysfunction is integral to CFS pathology. (12)

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

CFS patients showed reduced activation of medial/basal frontal regions but a greater activation of dorsolateral frontal and temporal lobes than controls. This MRI study showed unique features of cognitive impairment, demonstrating that more areas of brain activity were used in task solving than in controls ie. CFS patients are working harder than controls to solve the same problem and use more brain areas than controls. (13)

A quantitative volumetric study suggests that some CFS patients show a lateral ventricular enlargement, which may be associated with white matter loss in the frontal as well as the parietal lobes. (14)

Psychopathology

CFS patients do not display the same improvement with treatment as seen in depressed patients. Little overall change is seen in CFS patients on either physical or mental scores after antidepressant treatment. (15)

Findings from one of the largest well-studied patient groups in the world which used a factor analysis (done by computer, which eliminates all bias by the researcher) suggests that psychiatric disorder is not a core aspect of CFS and that this is a strong argument against CFS being a psychosomatic or "functional somatic" disorder. (16)

Whilst significant neuropsychological impairment was found in CFS patients, no subject performed in the range suggesting lack of effort or feigned impairment. (17)

The often-proposed hypothesis that CFS is a form of somatisation disorder was tested.
It is apparent that there is no relationship between the number of medically unexplained symptoms and psychiatric diagnosis. CFS has no relation to somatisation disorder. (18)

Visual processing disabilities

Investigation of the biological basis of visual processing disability in CFS showed that alteration in visual processing response is associated with evidence of altered connective tissue turnover. (19)

Biochemistry

Symptom expression is associated with changes in serum lipid levels. Significant changes in glucose, amino acid and inflammatory mediating fatty acids may be involved in symptom expression. Increases in levels of polyunsaturated fatty acids had the highest correlation with both fatigue and muscle pain scores. (20)

Objective examination of skeletal muscle tissue in CFS patients (biopsy of the vastus lateralis muscle) showed that activity of all skeletal muscle anti-oxidative enzymes was significantly increased in CFS patients compared with controls. Lipid analysis showed fatty acid modifications in patients but not in controls. Fluorescence polarisation showed a significant decrease of membrane rigidity with a consequent increase in membrane fluidity.
There is evidence of a dengenerative process of the muscle tissue in CFS patients, as typically occurs in mitochondrial myopathies. This may contribute to muscle fatiguability and it supports an organic origin for CFS. (21)

Virology

CFS patients with active HHV6 infection (viraemia) have activation of coagulation and are hypercoagulable. Since HHV6 is known to infect endothelial cells, there may be a resultant endothelial cell dysfunction triggering the coagulation system. (22)

Genetic abnormalities

Recent studies have demonstrated circulating plasma RNA in Gulf War Syndrome patients. A study was therefore conducted to determine the presence or absence of RNA in CFS patients and to determine if the amplified sequences of RNA were similar to or different from those found in GWS. All chronic illnesses studied (including GWS, CFS, AIDS and multiple myeloma) show prominent RNA not observed in normal controls. Prominent RNA bands so far sequenced show homology with human genes which are noted for their tendency for gene rearrangement under severe physiologic stress. The most amplified sequences appear to be disease specific. (23)

Dr N.Afari, Associate Director of the University of Washington CFS Research Centre said that genetic abnormalities may team up with environmental influences to produce CFS. Environmental influences which worldwide researchers are investigating include the frequent pairing of CFS with food and chemical sensitivities. (24)

Microbiology

The dysregulation of the important anti-viral 2-5 RNase L pathway in CFS is a potential biomarker for the disorder. The RNase L pathway is a series of enzymatic reactions which go on inside white blood cells when they perceive themselves to be challenged by viruses and possibly also by some toxic exposure. Elevated levels of RNase L are associated with reduced maximal oxygen consumption (VO_2max) and exercise duration in patients with CFS. Both abnormal RNase L activity and low oxygen consumption were observed in most patients with CFS. These findings demonstrate that patients' extremely low tolerance for physical activity is likely to be linked to abnormal oxidative metabolism, perhaps resulting from defective interferon responses. (25)

Much of the Belgian work focused on the abnormal enzyme pathways found in CFS. In healthy people, the enzyme breaks down viral RNA and destroys the infected cell. Instead of the normal size 80kDa (kiloDalton) enzyme, those with CFS show only a 37 kDa size enzyme. This 37 kDa low molecular weight (LMW) RNase L fragment found in CFS patients is produced by calpain (an apoptotic enzyme) cleavage, and the whole process affects the calcium and potassium channel mechanisms. The channelopathy will lead to low body potassium. Testing the ratio of the 37kDa and 80kDa enzymes has revealed that a high ratio is associated with more severe clinical symptoms. The 37kDa RNaseL is associated with incomplete cell death, which means that the cell constituents cannot be recycled for use by other cells. (26)

Patients suffering from CFS present many symptoms, including pain, which are likely to reflect dysregulation in cellular ion transport. Fragments released by a pathological protein cleavage result in dysregulation of sodium channels, which play a major role in the generation of pain and hyperalgesia in peripheral neurons, with a resultant shift in the pain sensitivity threshold as well as causing (if occurring in epithelial cells) drenching sweats. An improper function of the sulfonylurea receptor (SUR1) could lead to an extreme loss of cellular potassium. ATP is the main energy releasing source of the cell: improper function of ATP binding cassette (ABC) transporters leads to serious neurological dysfunction. Common symptoms of CFS could be due to a malfunction of various ABC transporters. (27)

Immunology

Increased apoptosis (programmed cell death) in peripheral blood mononuclear cells (PBMC) of patients with CFS has been suggested to contribute to the symptomatology. RNase L activation has been directly linked to the induction of apoptosis. This study showed that the activation of RNase L in the PBMC of CFS patients upregulates apoptotic activity in these cells. This suggests that the peturbed apoptotic process may play a role in the altered immunologic functions in CFS. (28)

A large number of CFS patients have an abnormal immunological profile which can result in the production of immunologic mediators such as interferon, interleukin and other cytokines. The upregulation of the 2-5A Synthetase /Rnase L pathway shown in CFS patients indicates an activated immune state. According to their immunologic profile, CFS patients were divided into three groups. The results show that the presence of an increased amount of LMW RNase L correlates with higher levels of interferon gamma. (29)

Autoimmunity in CFS was reviewed. Low titres of antinuclear antibodies have been found in CFS patients. A major multi-centre study looked at the presence of autoantibodies to a cellular protein expressed primarily in nerve cells (microtubule-associated protein 2 or MAP2). Initial studies with immunohistochemistry showed a high percentage of CFS sera reactive to centrosomes. Preliminary evidence shows that other proteins beside MAP2 might also be target antigens in CFS autoimmunity. Of interest is the high frequency of reactors in lupus and rheumatoid arthritis as well as in CFS patients. (30)

The intracellular content of the Natural Killer (NK) cell is perforin, a cell lytic protein common in many cells of the immune system which correlates with the cytolytic potential of the cell. In CFS, this chemical is reduced in NK cells. This finding substantiates claims of an NK associated defect in CFS and suggest a molecular basis for the reduced cytotoxicity (immune system killer cell function). This defect may not be NK specific but may encompass the cytotoxic T cell subset as well. Mice which were genetically engineered to have low or absent levels of perforin show the same immune abnormalities as CFS. Other abnormalities found include activated lymphocytes in various subsets,

elevated levels of immunoglobulins (IgG in particular) and increased levels of immune molecules called pro-inflammatory cytokines. Also found was a reduced activity of delayed hypersensitivity. (31)

Overlapping symptomatologies between CFS and Gulf War Syndrome have been observed by different investigators. It was therefore of great importance to verify whether various immunologic abnormalities found in CFS are also found in GWS. Overall differences between the two groups were not significant. The results indicate that, as in the case of CFS, Gulf War veterans are suffering from neuroimmunological disorder. Importantly, it was shown that basic laboratory testing is not sufficient for these groups of patients and that advanced immunological tests including immune function and antibodies to the neurological system are needed. (32)

This should be compared with the recommendations in the UK 1996 Joint Royal Colleges' Report on CFS (1), which specifically state that no investigations should be performed to confirm the diagnosis *(page 45)* and that immunological abnormalities should not "*deflect the clinician from the biopsychosocial approach….and should not focus attention….towards a search for an 'organic' cause*" *(page 13).*

It may also be salutary to reflect on the opinion expressed by Professor Pinching (deputy Chair of the CMO's Working Group) in his article on CFS in Prescribers' Journal ie. that *"over-investigation can (cause patients) to seek abnormal test results to validate their illness"*. (33) Prescribers' Journal was a publication of the UK Department of Health but is no longer produced.

In our opinion, when taken in consideration of all that is already known about the biomarkers of ME/CFS, the evidence of serious pathology presented at Seattle emphasises the unacceptability of advising that such pathology should not be fully investigated. It also underlines the fallaciousness of advising that such substantial pathology can be satisfactorily treated by cognitive behavioural therapy or graded exercise; thus we believe it is imperative for people to be aware that the most influential members of the CMO's Working Group are apparently still determined to proceed along such avenues despite all the evidence which has been put before them.

Advice from Members of the CMO's Working Group about Testing for RNase L and urinary markers in ME / CFS

RNase L in ME/CFS

We are particularly concerned about the advice which may be issued in the CMO's Report that tests for RNase L and tests for urinary markers should not be performed on UK patients: we understand this is because the Medical Director of the UK ME Association (Dr Charles Shepherd) regards them as (*quote)* "unnecessary and

unproven". We understand he is further advising that tests for viral antibody titres are also unnecessary and unproven.

We understand that in a forthcoming edition of *Perspectives* (the magazine of the UK ME Association), Dr Shepherd intends to inform readers that his view of the well-conducted international work on RNase L is that it " *may involve what I and many of my colleagues regard as over-investigation for highly speculative abnormalities in antiviral pathway activity"*.

We compare the personal opinion about the significance of RNase L of the Medical Director of the UK ME Association not only with the evidence demonstrated in the Seattle presentations outlined above but also with what Professor Anthony Komaroff wrote about the work on RNase L of De Meirleir et al in an Editorial in The American Journal of Medicine: *"What is this research telling us? It is another piece of evidence that the immune system is affected in chronic fatigue syndrome and it reproduces and extends the work of another investigator (Professor Suhadolnik), lending credibility to the result".* (34) We further compare Dr Shepherd's view with that of Shetzline and Suhadolnik, who in a detailed study of the RNase L enzyme have not only identified the 37kDa form of the enzyme as being part of the underlying pathology of ME/CFS, but with sophisticated labelling techniques have shown that there is an increased rate of RNA hydrolysis by this enzyme and that the low molecular weight enzyme (37 kDa instead of the normal 80 kDa weight) is hydrolysing three times faster than the normal 80 kDA enzyme. Significantly, the researchers have used a specific probe which unequivocally identifies the faulty enzyme. (35)

We note that those with ME/CFS show both an upregulation of the antiviral pathway and an abnormal version of the RNase L enzyme (ie a low molecular weight of 37 kDa); patients who express this abnormal RNase L enzyme suffer an even greater depletion of ATP reserves and an inhibition of protein synthesis (ie. when the various protein kinase enzymes become activated and elevated, protein synthesis is inhibited).

Expression of this low molecular weight RNase L can cause problems with enzymatic detoxification pathways, particularly in the liver *(see below).* Measurements of protein kinase 1 are very important in studying mechanisms of interference with signal transduction in lymphocytes, and **distinct abnormalities are seen in ME / CFS**.

Concerning the issue of testing for RNase L and urinary markers in ME/CFS, accumulating evidence (of which the CMO's Working Group ought to be aware) dictates that such investigations are essential if this serious disorder is ever to be understood.

In a letter dated 17 July 2001 which he wrote to the Chief Medical Officer, Shepherd offers an explanation for his advice that no such tests should be carried out on UK patients with ME/CFS; he wrote

" I acknowledge that I have opposed the inclusion of testing for RNase L

> **(an antiviral marker) and CFS urinary markers (a test which is advocated by a group of Australian researchers…..One of the major problems with both of these tests is that all the published information so far comes from researchers who have a financial interest in their promotion -- a situation which involves a clear conflict of interests."**

Possibly of relevance to Dr Shepherd's advice are the significant findings by Professor Vojdani and Dr Charles Lapp, namely their discovery that this same antiviral pathway can be damaged by *chemicals.* (36) This work relates to the findings of Dr Howard Urnovitz from the Chronic Illness Research Foundation at Berkeley, California, whose work has been published in the Journal of the American Society for Microbiology and in Clinical Microbiology Reviews; he has demonstrated a fundamental breakthrough linking toxic exposure with chronic diseases such as ME/CFS and other autoimmune disorders; (37) he and others suggest that the huge increase in chemical usage is chronically stimulating the immune system. Clearly, such findings might be unpalatable to members of Healthwatch and to the chemical and pharmacological giants whose interests Healthwatch was set up to serve (**9**).

Urinary markers in ME/CFS

Another area where we disagree with Dr Shepherd's advice to the CMO's Key Group concerns his recommendation that there should be no investigation of urinary markers in ME/CFS. We believe several urinary markers are important and that where certain markers are positive, dietary modulation can result in alleviation of distressing gastro-intestinal symptoms. Given that the remit of the CMO's Working Group is to assess treatment and management of these patients, assessment of something which can deliver any relief should surely be a priority.

We make particular mention of just three urinary markers which in our view merit inclusion in the assessment of patients suspected of having ME/CFS:

(i) CFSUM1 (Chronic fatigue syndrome urinary marker 1). In February 1995 Dr Neil McGregor of the University of Newcastle (Australia) CFS research team presented information at a CFS Conference in Sydney about the nature of the novel chemical which his team had found in the urine of people with ME/CFS; the urine concentration appeared to correlate strongly with a number of ME/CFS symptoms. The chemical name for this marker is amino-hydroxy-N-methyl-pyrrolidine. The base structure of this compound is similar to the base structure of many pesticides. This team went on to characterise more markers: at the Brussels World Congress in September 1999, another member of the Newcastle team (Dr Hugh Dunstan) presented evidence of UM 27 (urinary metabolite 27); this marker molecule was elevated in ME/CFS and there was a positive correlation with elevation and symptomatology.

(ii) IAG TESTING (*trans*-indol-3-ylacrolglyciney, a tryptophan metabolite). This is a test for urinary markers which is almost 100% positive in ME/CFS. It is inexpensive and is available at a British university. We believe that screening for allergies and hypersensitivities should be mandatory in these patients, as the cost is minimal and the benefit is considerable; thus the cost-benefit ratio is eminently justified. It is our opinion that specific advice should be given in the CMO's report about the very real value of elimination diets in cases of ME/CFS where there is reproducible and reliable evidence of a leaky gut, in which high levels of small peptides cross the damaged gut membrane, leading to changes in brain chemistry which have behavioural, cognitive, neurological, endocrinological and immunological consequences. The well-validated IAG urine test is a test for an aberrant metabolite of tryptophan and if positive, is indicative of a malfunctioning and leaky gut; it indicates a compromised digestive process which in turn leads to opioid excess as a result of mal-digestion and uptake of opioid peptides derived from dietary sources. The main culprits are well-known as being the opioid precursor peptides gluten and casein, with casein from cows milk causing more problems than casein from sheeps milk; they are broken down in the gut to opioid peptides, namely gliadomorphin and casomorphin and it is these which readily cross the damaged gut membrane and give rise to a cascade of multi-systemic problems. These "escaped" peptides are scientifically measurable in urinary peptide profiles. (38) Significantly, if the *gut* is leaky, the same factors also cause the *blood brain barrier* to be leaky, with resultant effects of opioids on the central nervous system; this causes not only a local, but also a systemic, reaction. Studies show that this is not a genetic phenomenon but an acquired one. On this same aspect, we note that Wessely himself (perhaps the archetype non-investigator) is now recommending that all ME/CFS patients be routinely screened for undiagnosed coeliac disease, stating *"there is now evidence from primary care of a surprisingly high frequency of unsuspected EMA tests* (endomysial antibodies) *in people with non-specific symptoms….we now suggest that screening for CD* (coeliac disease) *should be added to the relatively short list of mandatory investigations in cases of suspected CFS".* (39) Both these factors may relate to the increased incidence of irritable bowel syndrome in ME/CFS, which is high: 73% as opposed to 22% in the general population. (40)

(iii) Urinary creatine test At the British Society of Rheumatologists' Conference in Edinburgh, April 2001, evidence was presented which showed that patients with ME/CFS are excreting in their urine significant levels of creatine and other muscle related metabolites including choline and glycine. (53% of ME/CFS patients were positive compared with 0% of healthy controls). This may well represent evidence of on-going muscle damage in ME/CFS. Creatine has previously been shown to be a sensitive marker of muscle inflammation. (41)

General observations

Whilst it is true that there is as yet no single, definitive laboratory test for ME/CFS, there is a spectrum of abnormalities which, if positive, enable a diagnosis to be made with reasonable certainty; if minimal routine investigations are to be carried out on UK sufferers, then no progress will be made in the medical understanding of ME/CFS and unnecessary suffering will continue. In our view, that is unacceptable.

Immunological testing

The immune abnormalities documented in ME/CFS follow a recongisable, reproducible and consistent pattern, with clear evidence of an immune activation state. In our view, screening for NK levels and function *per cell* (and not just gross killing) is mandatory, as is measurement of the CD4-CD8 ratio; other immunological tests should routinely include testing for ANAs (antinuclear antibodies), IgGs, including IgG3, CICs (circulating immune complexes), IL2; IL4 (interleukin 2 + 4), measurement of Th1 - Th2 response and mitogen stimulation tests. In particular, tests should be performed for thyroid antibodies (*see below).* It has been demonstrated that in ME/CFS, changes in different immunological parameters correlate with particular aspects of disease symptomatology and with measures of disease severity. (42). Further consolidation of the correlation between ME/CFS symptomatology and evidence of immune dysfunction is to be found in the convincing work of Natelson et al who have demonstrated the link between IL4 and a type 2 cytokine pattern in ME/CFS; a preponderance of a Th2 response is consistent with autoimmunity. (43, 44).

In particular, we suggest that ME/CFS patients should be screened for evidence of autoimmunity. There is increasing evidence of antilamin antibodies in ME/CFS: specifically, antilamin antibodies have been found in the blood of ME/CFS patients (antibodies against this protein are proof of autoimmunity and of damage to brain cells). It has been demonstrated that 52% of patients with ME/CFS develop autoantibodies to components of the nuclear envelope (NE), suggesting that in addition to the other disturbances of the immune system, humoral autoimmunity against polypeptides of the NE is a prominent immune derangement in ME/CFS. The occurrence of autoantibodies to an intracellular protein like lamin B 1 provides **laboratory evidence** for an autoimmune component in ME/CFS. No patients with depression or atopy showed reactivity to NE proteins. Autoantibodies to NE proteins are relatively infrequent in routine ANA serology and most of these fall into the broad category of an unusual connective tissue disease subset which is characterised by brain or skin vasculitis. (45,46) As mentioned above, results of a multicentre study looking at autoimmunity in ME/CFS presented at the AACFS Fifth International Research and Clinical Conference at Seattle in January 2001 looked at the presence of autoantibodies to a cellular protein expressed primarily in neuronal cells (MAP2). Immunohistochemistry results showed a high reactivity in ME/CFS patients, as also in patients diagnosed with lupus and rheumatoid arthritis. (30) Mindful of the serious and costly consequences (both human and financial) flowing from undiagnosed AI (autoimmune disease) and bearing in mind the present body of evidence,

we fail to understand the re-emergence in the UK of advice that such investigations are "unnecessary" and "inappropriate".

Virological screening

We again point out the importance of screening for viral antibodies as early in the diagnostic process as possible: it is imperative to ascertain any viral trigger but antiviral antibody levels fall off after three months. It is crucial to look for viral markers because management interventions must *always* refrain from doing harm and the enforcement of unvalidated exercise regimes upon such patients could, in our opinion, result in indefensible legal action. There is a body of published, competent medical opinion which supports the involvement of CBV (Coxsackie B virus) in at least a subgroup of ME/core CFS, especially those with cardiac, pancreatic and gut dysfunction (47, 48, 49, 50, 51); this being so, the CMO's guidelines on ME/CFS management cannot afford to ignore or dismiss it. We believe that this aspect should be brought to the specific attention of clinicians.

Endocrine testing

We also suggest that detailed endocrine function studies be included in the recommendations to clinicians. The endocrine system is uniquely disrupted in ME/CFS. (52,53,54) A key feature is the demonstrated defect in HPA axis function (55, 56) and patients are severely limited by the loss of dynamic hormone responses. There is an abnormality of adrenal function and CT scans have shown that both the right and left adrenal glands are reduced by 50% when compared with controls. (57) In one of the larger studies, Lucinda Scott MB, MRCPsych (part of the Scott / Dinan team of ME researchers) looked at the common neuroendocrine tests (which are often normal in ME/CFS) **and concluded the tests were inadequate for ME/CFS patients.** (58)

Specifically, we believe that thyroid function needs careful evaluation in ME/CFS: it has long been noted by practitioners that ME/core CFS patients are often clinically hypothyroid even though biochemically euthyroid. Evidence suggests that such patients may not really be euthyroid, especially at the tissue level. (59) Abnormal thyroid hormone levels have been described in autoimmune disease. (60) In our opinion, particular attention needs to be paid to investigating the bioavailablity of T3. In ME/core CFS, T3 levels are often low (or at the low end of the normal range). We therefore suggest that selenium levels be investigated in patients with ME/core CFS who have reduced T3 levels: this is because selenium (as selenocysteine) is an integral component of two important enzymes, glutathione peroxidase and iodothryonine deiodinase; it is expressed in the liver and it regulates the conversion of thyroxine (T4) to the active and more potent T3. Individuals who have a deficiency of 5' deiodinase cannot produce T3 from T4 (61), thus it is advisable to establish baseline levels of selenium in ME/CFS patients whose T3 levels are low. Additionally, recent evidence demonstrates a lymphoctyic thyroiditis in chronic fatigue. (62)

Central, autonomic and peripheral nervous system testing

There is a universally acknowledged dysfunction of all nervous systems in ME/core CFS. (63) Testing for Rombergism and nystagmus is mandatory in ME/CFS but often overlooked. Nystagmus is jelly-like and variable: a patient examined in the morning might have nystagmus, which would disappear at midday, recur later, disappear and recur the next day (64); thus a once-only cursory examination could be misleading.

Given what is now known, we believe that tests for sympathetic over-activity and for orthostatic hypotension in ME/CFS should not be omitted. (65)

Nuclear imaging

There is objective evidence of brain impairment in the majority of patients with ME/CFS (66, 67, 68, 69); such patients show a particular pattern of hypoperfusion of the brain stem and this brain perfusion impairment provides objective evidence of central nervous system dysfunction. Brain magnetic resonance imaging (MRI) data have demonstrated that the presence of brain abnormalities in ME/CFS are significantly related to subjective reports of physical function ie. ME/CFS patients with MRI brain abnormalities are more physically impaired than those without MRI brain abnormalities. (70)

Tests for hypercoagulability and vascular dysfunction

There is increasing evidence of hypercoagulability in ME/CFS. Researchers in Phoenix, Arizona have demonstrated a model of coagulation activation in ME/CFS; using five tests (fibrinogen, prothrombin fragment 1+2, thrombin / anti-thrombin complexes, soluble fibrin monomer and platelet activation by flow cytometry), they have shown that ME/CFS can be classified as a type of antiphospholipid antibody syndrome. (71) Phospholipids are constituents of all tissues and organs, especially the brain; they are synthesised in the liver and small intestine and are involved in many of the body's metabolic processes. An antiphospholipid antibody syndrome is a clinical disorder with recurrent arterial and venous thrombotic events; the heart, central nervous system and skin may be affected. This is significant because in ME/CFS, vascular problems are well-documented: at the World Congress on ME/CFS in Brussels 1999, it was stated that vasculitic patterns are identical to those in HIV patients. (72) Scientists in Dundee, Scotland have demonstrated the presence of a defect in peripheral cholinergic activity within the vascular endothelium; this abnormality affecting the blood vessels may provide an explanation for some of the vascular features seen in ME/CFS. (73) In addition, increased sensitivity to glucocorticoids in peripheral blood mononuclear cells has been demonstrated (74), which is important evidence of a biological marker in ME/CFS.

Lung function testing

Tests have shown that compared with controls, patients with ME/CFS showed a significant reduction in all lung function parameters. (75) There is repeated reference to respiratory problems throughout the ME/CFS related literature. (76, 77)

Tests of exercise capacity

Investigation of exercise capacity (VO_2 max) ie. measurement of maximal oxygen uptake and investigation of oxygen delivery to muscle are essential in patients with ME/CFS; oxidative metabolism is known to be reduced in ME/CFS. (78) This could affect patients' physical abilities to a severe degree. ME/CFS patients have recovery rates for oxygen saturation that are 60% lower than normal controls. (79) It is imperative to ascertain oxygen delivery status before insisting on inappropriate interventions eg. CBT / graded exercise.

Tests for cardiac anomalies

Cardiac anomalies are well-documented in the ME literature. (80, 81, 82) In our opinion, such anomalies should always be looked for in ME/CFS patients.

Tests for liver dysfunction

Given the evidence of hepatic dysfunction in ME/CFS, we suggest that liver involvement should always be assessed. (83, 84, 85). In our experience, this rarely happens.

Ocular tests

Ocular problems are common in ME/CFS (86, 87,88) and we believe ocular testing should be carried out on ME/CFS patients.

Conclusion

We acknowledge that this summary discusses international research findings which have been carried out in centres of excellence, and that it is unrealistic to expect all tests mentioned to be readily available at all hospitals throughout the country. Nevertheless, we believe that the need for specialist ME/CFS units (providing both complex investigative and assessment facilities, together with the necessary care provision) are long overdue, and that advice contained in the forthcoming CMO's Report should reflect this need.

This summary is merely an outline of just some of the abnormalities which are known to be present in ME/CFS; it is by no means a comprehensive list (for example, it does not include reference to neuropsychological assessment in ME/CFS patients, which is known to produce a distinctive pattern of abnormalities).

It is hoped that it might serve to motivate people into contacting their Member of Parliament, their legal advisers and the media about the continuing exclusion of patients with ME/CFS from NHS provision and delivery of care as at present, and about the apparent determination of some members of the CMO's Key Group to advise in the forthcoming Chief Medical Officer's Report on CFS/ME that for such patients, *"only a limited set of investigations are necessary"*. Given the extent of the evidence of such complex underlying pathology, we believe such advice is indefensible.

Finally, we again draw attention to the factual evidence set out in our observations on claims by psychiatrists of the Wessely School that CBT is the evidence-based treatment of choice for ME/CFS (*Information on Cognitive Behaviour Therapy, Professor Simon Wessely and PRISMA, April 2001)* and in this respect we would draw attention to the mounting evidence that cognitive behavioural therapy has been shown to be of no long-term benefit in disorders other than ME/CFS: in a multi-centre study, researchers from the Department of Psychiatry and Behavioural Sciences at The Royal Free and University College Medical School, London, have found that there are no differences in clinical outcomes between cognitive behavioural therapy and the usual general practitioner care at 12 month follow-up for patients suffering from depression and from depression with co-existing anxiety. (89). Members of the CMO's Working Group may wish to take note.

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