Observations on Charles Shepherd's Comments on CMO's Draft /11 April 2001
(on chapters 4& 5)
submitted on behalf of The 25% ME Group for the Severely Affected

21 April 2001

In general, we support and appreciate Charles Shepherd's comments, especially those relating to CBT and graded exercise. We do not, however, agree with all his recommendations and wish to make formal representation of our concerns as follows:

Chapter 4

page 1 ASSESSMENT We are unable to agree with Charles Shepherd's recommendation that *"only a limited set of investigations are necessary"* (he substituted the word "necessary" for the word "appropriate" which was in the draft document). As pointed out in our own Submission on chapters 4 +5 (dated 9 April 2001) and as made plain in our earlier Submission on chapters 1-3 (dated 9 March 2001), this is merely repeating the message of the heavily criticised and biased joint Royal Colleges' 1996 Report, which stated unequivocally that no investigations should be done to confirm the diagnosis. **Specifically, in our opinion such a view is medically and scientifically untenable, especially in the light of the clear message coming from the AACFS International Conference in Seattle in January 2001, ie. that basic laboratory testing IS NOT SUFFICIENT FOR THESE PATIENTS AND THAT ADVANCED IMMUNOLOGICAL TESTS ARE NEEDED.** 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, IgGs, CICs, IL 2 and mitogen stimulation tests.

In particular, we urge the recommendation that patients should be screened for evidence of autoimmunity in ME/core CFS. 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. Results of a multicentre study looking at autoimmunity in ME/CFS presented at the AACFS International 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 in patients diagnosed with lupus and rheumatoid arthritis). 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 of advice that such investigations are "unnecessary".

References include the following:

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

A multicentre study of autoimmunity in CFS. K Sigiura et al. *AACFS January 2001 # 037*

Anti-nuclear envelope antibodies: Clinical associations. Nesher G, Margalit R, Ashkenazi YJ. *Semin Arthritis Rheum 2001:Apr 30 (5):313-320*

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). No matter how keenly some other members of the Key Group would prefer to ignore the existence of at least a subgroup who have unequivocal evidence of enteroviral protein in their blood (usually Coxsackie B), the evidence is well-known and will not be suppressed. For such patients, it is crucial to look for viral markers because management interventions must *always* refrain from doing harm and the enforcement of contra-indicated exercise regimes upon such patients could, in our opinion, result in indefensible legal action. There is such a large body of published, competent medical opinion which supports the involvement of CBV in at least a subgroup of ME/core CFS (especially those with cardiac, pancreatic and gut dysfunction) that the CMO's guidelines cannot afford to ignore or dismiss it. We believe that this aspect should be brought to the specific attention of GPs.

We also urge that detailed endocrine function studies be included in the recommendations to GPs. In one of the larger studies, Dr 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.** (The role of the HPA axis in chronic fatigue syndrome. LV Scott. PhD Thesis. *British Library, 1997*). Specifically, the effect of ME/CFS on thyroid function needs careful evaluation: it has long been noted that ME/core CFS patients are often clinically hypothyroid but biochemically euthyroid; evidence suggests that these patients may not really be euthyroid, especially at the tissue level. Abnormal thyroid hormone levels have been described in autoimmune disease. 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 urge

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 (which is expressed in the liver and which 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, thus it is imperative to establish baseline levels of selenium. Additionally, recent evidence demonstrates a lymphoctyic thyroiditis in chronic fatigue. (Fine needle aspiration cytology of the thyroid in chronic fatigue B.Wickland et al. *Lancet 2001:357:956-957*). Further, investigation of adrenal function in ME/CFS patients should be mandatory: end-organ hypofunctioning is known to occur in ME/CFS, which is probably due to a deficiency of ACTH.

Tests for sympathetic over-activity and for orthostatic hypotension should not be omitted, nor should tests for **hypercoagulability.**

Equally, investigation of exercise capacity (VO_2 max) and investigation of oxygen delivery to muscle are essential in patients with ME/CFS --- oxydative metabolism is known to be reduced in ME/CFS and it is imperative to ascertain oxygen delivery status before insisting on inappropriate interventions (eg. CBT / graded exercise).

Of some interest is the fact that Wessely himself (the archetype of non-investigators) now advises routine screening of ME/CFS patients for undiagnosed coeliac disease, stating *"…there is now evidence from primary care of a surprisingly high frequency of unsuspected positive 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 suspected cases of CFS".*
(High prevalence of serum markers of coeliac disease in patients with chronic fatigue syndrome. A Skowera, S.Wessely et al. *Journal of Clinical Pathology 2001:54:335-336*).
[this is also relevant to the section below on irritable bowel symptomatology and to the significance of testing for the tryptophan metabolite indolylacroylglycine --- see below].

We again point out that patients are exceedingly well informed about findings and advice emanating from ME/CFS conferences and they will not acquiesce with recommendations for which there can be no medical justification. The cost implications cannot be permitted to over-ride the clinical implications of non-investigation; moreover, correct and timely investigations could well prove cost-effective in the long-term. INVESTIGATION IS THE ONLY WAY FORWARD TOWARDS UNDERSTANDING THIS COMPLEX DISORDER : only by **looking** will we **learn**. In our view, it is wholly unacceptable to advise that investigations in ME/CFS be limited to a minimal and basic routine screen (especially as basic screening is known to be often normal in ME/CFS).

Page 2 CONSISTENT SYMPTOMS. Irritable bowel syndrome

Charles Shepherd recommends removing digestive disturbances from ME/CFS core symptomatology: he suggests incorporating them in *"overlapping disorders".* We recall that in his own book Living with M.E. (first edition, Cedar / Heinemann 1989) Charles Shepherd acknowledges (pp 52-55) that *"ME patients… have a lot of problems with their digestion and bowels…..food sensitivity or allergy may be a problem.."* He consistently refers to these gut problems prevalent in ME as *"irritable bowel".* We are thus unable to understand his present recommendation to exclude these gut symptoms from the proposed list of core symptomatology, particularly in the light of the known link between CBV and gut symptomatology.

At the last meeting of the Key Group, Tony Pinching noted that IBS symptoms are a prominent feature of ME/CFS. The evidence (published and clinical) supports Professor Pinching's view. Some illustrations include the following:

1. Ramsay Description (ME Association, November 1981)
2. ANZMES 1985 (Gorringe diagnostic criteria, New Zealand)
3. Information for Doctors (Action for ME)
4. CFIDS Association: A Patient's Guide (1989)
5. Understanding M.E. Dr David Smith (written when he was medical adviser to The ME Association. Robinson Publishing, London 1989)
6. Diagnostic & Clinical Guidelines for Doctors (Professor Behan / ME Assn 1991)
7. Postviral Fatigue Syndrome (ed Jenkins & Mowbray, John Wiley & Sons 1991)
8. The Disease of a Thousand Names (Dr David Bell, Pollard Publications 1991)
9. The Clinical & Scientific Basis of ME/CFS (ed Hyde et al, 1992)
10. Guidelines for the care of patients (Dr Charles Shepherd / ME Assn 1994+ 2nd edition)
11. Gastrointestinal Manifestations of Chronic Fatigue Syndrome (CFS): Symptom Perceptions and Quality of Life. Herbert Hyman, Thomas Wasser. *JCFS 1998:4: (1): 43-52* **This study evaluated not only functional GI complaints but also other abdominal complaints in ME/CFS, particularly neurological. It also discusses the fact that the gut mucosa contain immunologically active lymphoid tissue and it explores the pathophysiological and clinical implications. This study demonstrated three primary findings, one of which being that ME/CFS patients showed significantly more GI symptoms than those with FBD (functional bowel disease) only.**
12. Prevalence of irritable bowel syndrome in chronic fatigue. Gomborone JE et al *JRCP Lond 1996:30:5:512-513* **The purpose of this study was to determine the prevalence of irritable bowel syndrome in ME/CFS sufferers.A questionnaire was sent out to 4,500 members of Action for ME; respondents reported more bowel symptoms (including the Manning criteria) than the general population: 73% qualified for the diagnosis of IBS, which greatly exceeds estimates of IBS prevalence of up to 22% in the general population.**

We particularly request that IBS symptoms should be included in the list of "Consistent Symptoms"; in our view, omitting such core symptoms of ME/CFS does not accord with good medical practice.

Page 2 CONSISTENT SYMPTOMS. Omission of adverse drug and chemical reactions/ multiple chemical sensitivity (MCS)

In our opinion, there is evidence which cannot be ignored that those with ME/CFS suffer from adverse drug and chemical reactions. There is a very extensive literature on this prominent feature of ME/CFS which *cannot* credibly be ignored. **A representative reference list of this literature on the existence of allergies and multiple chemical sensitivity (MCS) in ME/CFS has already been supplied to the CMO's Working Group and also directly to Rachel Richardson of the Systematic ReviewTeam at the Centre for Reviews and Dissemination at York.** Charles Shepherd himself makes brief mention of "allergies" on page 8 of his comments in his section on IMPORTANT OMISSIONS, but we believe that this adverse drug and chemical reaction should be listed as a core symptom. An increasing sensitivity and adverse reaction to many drugs / therapeutic substances is virtually pathognomonic of ME/core CFS and was described in such terms by Professor Charles Poser (of the Department of Neurology, Harvard Medical School and the Neurological Unit, Beth Israel Hospital, Boston, Massachusetts) at the Dublin International Meeting on ME/CFS in May 1994. This meeting was convened under the auspices of The World Federation of Neurology. Moreover, it is an important consideration in the light of (a) the clearly demonstrated findings that the RNase L antiviral pathway is also affected **by chemicals** (Interferon-induced proteins are elevated in blood samples of patients with chemically or virally induced chronic fatigue syndrome. Vojdani A, Lapp CW. *Immunopharmacol Immunotoxicol 1999:21(2):175-202*)
and (b) the fact that MCS is now officially recognised in ICD 10 and its prevalence in ME /CFS is now widely acknowledged (Comparison of patients with chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivity. D Buchwald, D Garrity. *Arch Intern Med 1994:154:2049-2053).* The continued ignoring of this evidence by some members of the Key Group in the hope of strengthening their own preferred beliefs will not be tolerated by such a well- informed patient community nor by scientists and clinicians who are aware of the relevant literature, nor indeed by many Members of Parliament who support them.

page 3 UNNECESSARY AND UNPROVEN TESTS (ie. tests for Coxsackie and other types of viral antibody titres…….RNase L and urinary markers)

Our comments above on **ASSESSMENT** apply here also. We would specifically disagree with Charles Shepherd when he states that tests for urinary markers and for RNase L should not be done.

Urine testing for IAG (indolylacrolylyglycine) has already been found to be of practical benefit (see below in the section on diet and nutrition omissions).

As for RNase L testing, Nancy Klimas (Professor of Immunology at The University of Miami and a world expert on ME/CFS) believes this is important. Those with ME/CFS show both an **up-regulation** of this anti-viral pathway and an **abnormal** version of the RNase L enzyme (ie. a low molecular weight of 37kDa). Patients who express this abnormal RNase L enzyme suffer an even greater depletion of ATP reserves (the main energy releasing source of the cell) and 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. In the US, Professor Vojdani recommends measurements of RNase L inhibitor and of protein kinases as these can be used to show a viral aetiology and to monitor relapses. Measurements of protein kinase 1 are very important in studying mechanisms of interference with signal transduction in lymphoctyes, and **distinct abnormalities are seen in ME/core CFS patients.**

In our opinion (which is based on the published evidence of Professors de Meirleir, Komaroff and Suhadolnick), to advise that no RNase L investigations are necessary defies reason. Accumulating evidence dictates that such investigations are essential if this devastating disorder is ever to be understood.

Chapter 5

Management

We are in firm agreement with Charles Shepherd in his comments on the dangers of inappropriate CBT and graded exercise in ME/CFS. The message being conveyed in the present draft of chapter 5 is indeed as noted by Charles Shepherd ie. that the majority of people with ME/core CFS have a psychosomatic illness involving abnormal illness beliefs and behaviour and that the principal perpetuating factor involves simply a vicious cycle of reduced activity and excessive rest followed by bursts of activity followed by over-attention to bodily sensations.

Such a view reveals an alarming lack of awareness of the published evidence of organic pathology in ME/CFS. In our view, the aims and desires of any treatment in any medical disorder should be improvement of the patient's morbidity, not simply the imposition of the therapists' own beliefs about one particularly favoured intervention for which there is no proven justification (because the patients on whom supposedly supportive studies were carried out do not suffer from either virally induced or chemically induced ME but from on-going fatigue as defined by the Oxford 1991 criteria).

We note with relief that Charles Shepherd draws particular attention to the failure by the author(s) of chapter 5 to make any attempt at a balanced over-view of *all* the published evidence on CBT/graded exercise, including the many studies which found it to be either ineffective or to have caused significant and sustained relapse.

Interventions for which there is insufficient evidence of effectiveness

We welcome and support Charles Shepherd's suggestion that homoeopathy be put forward as something which may be tried if patients so desire. We note, however, that recent findings refute his claim that there is a lack of objective scientific evidence that homoeopathy can be efficacious: the stringently controlled and blinded work of Professor Madeleine Ennis from Queen's University, Belfast, together with a consortium of independent pan- European research laboratories in France, Italy, Belgium and Holland (led by Professor M. Roberfroid from the Catholic University in Brussels) which is shortly to be published in Inflammation Research has demonstrated that --- contrary to all scientific expectation---homoeopathy is effective. *(Thanks for the memory. Lionel Milgrom. Guardian,15.03.01).* As Charles Shepherd observes, many patients with ME/CFS do find it helpful.

IMPORTANT OMISSIONS FROM C5

Alternative and Complementary

We do not support Charles Shepherd's view (page 7) that "*there is no link between ME/CFS and the so-called candida hypersensitivity syndrome"*; in our opinion (and in the opinion of Professor Jonathan Brostoff, until recently Professor of Immunology at UCL) a disordered immune system *can and does* result in candida and there is considerable anecdotal evidence that it occurs in ME/CFS; it may be amenable to anti-fungal treatment prescribed by the GP.

Whilst we entirely support Charles Shepherd in his concern about *"weird diets"* and "*bogus (allergy) testing",* we nevertheless believe that screening for allergies / hypersensitivities is essential (not only classical IgE reactions but especially non-classical IgG reactions which detect bacterial toxins resulting from a compromised or "leaky" gut). We believe 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, endocrine and immunological consequences The well-validated IAG test (indolylacrolylglycine) is a test for an aberrant metabolite of tryptophan and if positive, is indicative of a malfunctioning and leaky gut and of compromised digestive processes which in turn lead 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 (casein from cows' milk causes more problems than casein from sheeps milk), which are broken down in the gut to opioid peptides, namely gliadomorphins and casomorphins. It is these which readily cross the damaged gut membrane, giving rise to the "leaky gut" syndrome. These "escaped" peptides are scientifically measurable in urinary peptide profiles. We therefore strongly disagree with Charles Shepherd's recommendation that in ME/CFS patients there should

be no investigation of urinary markers: 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. Studies show that this is not a genetic phenomenon but an acquired one. This is an area in which GPs are particularly well-placed to offer practical management advice in ME/CFS, so the CMO's report ought to make sure this is adequately addressed, as the relief experienced by patients can be considerable and there are almost no cost implications since patients are responsible for their own dietary modulation. (Rapid Analysis of Low Levels of Indolylacrolyglycine in Human Urine. Shattock P et al. *J Chromatography 1998:**B**:712:51-58*).