INFORMATION FOR THE MRC "CFS/ME" RESEARCH ADVISORY GROUP
BROUGHT TO THEIR ATTENTION BY HOOPER et al 8th February 2003

Malcolm Hooper[1], Eileen Marshall[2] and Margaret Williams[2] wish to draw attention to this current document and therefore invite members of the ME community to bring it to the notice of their Members of Parliament and particularly to the Chairman of The Select Committee on Health at The House of Commons, London SW1A 0AA, whose Sixth Report (Volume I) includes an inquiry into the way patients with ME are treated [Procedures Related to Adverse Clinical Incidents and Outcomes in Medical Care published by The Stationery Office, October 1999]. Amongst many other concerns, The Health Committee included in its Report submissions from at least eight sources about problems experienced by people with ME at the hands of Government bodies.

The Medical Research Council (MRC) "CFS/ME" Research Advisory Group (RAG) draft document dated 17th December 2002 states that it "*fully endorses the conclusions of the Report of the CMO's Independent Working Group…that CFS/ME is a real, serious and debilitating condition".* So, indeed, are many psychiatric disorders, but in apparent acquiescence to the ruthless psychiatric lobby and the insurance industry who are intent on claiming the disorder as a primary psychiatric condition (for example, the contribution of Wessely et al to the WHO Guide to Mental Health in Primary Care, which asserts that ME is a mental health problem), the MRC draft document fails to make clear that the "ME" component of the ambiguous, unclassified and unrecognised term "CFS/ME" is not a psychiatric condition but a legitimate neurological disorder.

[It is perhaps worth noting that, although having been involved with the process, Simon Wessely and his colleagues refused to sign the final version of the two Reports launched on 15th January 2003 by Richard Sykes (formerly Director of the ME charity Westcare) at the Royal College of Physicians in London because Sykes is adamant that Chronic Fatigue Syndrome / ME is a physical disorder (but with psychological co-morbidity in *some* patients): the press release states categorically that *"It is important that research is pursued on the physical basis of CFS/ME and on physical treatments for it"*. From this, it is clear that Wessely and his followers continue to be uninfluenced by any of the abundant evidence which does not accord with their own beliefs and aims].

The MRC "CFS/ME" RAG draft document also states: *"A strategy is proposed which…aims to provide a rational framework for advancing the understanding of the illness and its management"*. We therefore once again submit that unless the issue of sub-grouping is comprehensively addressed by the MRC RAG, then confusion, misdiagnosis and inappropriate management such as compulsory psychotherapy are all likely to continue: we remain concerned that in relation to the vital issue of sub-grouping, the MRC RAG document states only that "*It is acknowledged that, as our understanding of the area increases, such an umbrella term as CFS/ME may no longer be appropriate. However, at the present time it is considered that an inclusive approach is beneficial in the development of a research strategy".*
In our opinion, if the MRC forthcoming research strategy fails to address the issue of sub-grouping, it would simply reinforce the view of Wessely et al which underpins the internationally criticised 1996 Joint Royal Colleges' Report on CFS, which actually advised that laboratory confirmed abnormalities "*should not deflect the clinician from the (psychiatric) approach endorsed below, and should not focus attention towards a search for an 'organic' cause" (ref: Chronic Fatigue Syndrome: Report of a joint working group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners; October 1996 / CR54; RCP Publications Unit).*

Rather than merely accepting the regrettably ill-informed views about the need for sub-grouping contained in the CMO's Report of January 2002, we urge that in their deliberations concerning the formulation of a strategy for the direction of future research into "CFS/ME", all members of the MRC

"CFS/ME" RAG inform themselves of and base their decisions on accurate international scientific and clinical opinion provided by those who are expert and experienced in the field.

We ourselves consistently drew the published views of world experts concerning the urgent need for sub-grouping to the attention of all members of the Key Group of the CMO's Working Group but the evidence submitted was comprehensively disregarded.

We therefore again publicly draw the issue to the attention of the MRC "CFS/ME" RAG.

The four-page extract below is taken from a document entitled "**Matters of continuing concern submitted by the 25% ME Group for the Severely Affected 9th March 2001**" which was submitted to the CMO's Working Group on "CFS/ME". It was compiled in response to the various drafts of the CMO's Report and to a document dated 2nd December 2000 written personally by Professor Anthony Pinching (Deputy Chair of the CMO's Working Group): Pinching advised the Working Group that sub-grouping of "CFS" was unnecessary: the drafts of the CMO's report stated *"It seems appropriate to regard CFS/ME as a single clinical entity…on present evidence (the question of sub-groups) may be considered a matter of semantics and personal philosophy…"*. The present authors believe it is relevant to the deliberations of the MRC "CFS/ME" RAG that this same position statement remains in the final version of the CMO's Report (Annexe 4: General concepts and philosophy of disease"), a document claimed as informing the understanding of the MRC "CFS/ME" Research Advisory Group.

"Where is the evidence that there is a need for careful sub-grouping within "CFS"?

There is now an unmistakable recognition that sound research has strengthened the need for consideration of subgroups. [1][2][3][4][5][6][7][8]

A recent Editorial in the Journal of Chronic Fatigue Syndrome [9] makes the point that *"the sorting of patients into subpopulations….is helping in the design and interpretation of clinical trials for therapeutic interventions aimed at particular disease manifestations".*

The 1994 CDC criteria for CFS (whilst referring only to CFS) themselves recommend that researchers use stratification techniques to identify subgroups of patients. [10]

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[1] A Subgroup Analysis of Cognitive Behavioural Treatment Studies. Fred Friedberg. *JCFS 1999:5:3-4:149-159*

[2] Estimating rates of chronic fatigue syndrome from a community-based sample: a pilot study. Jason LA et al. *Am J Community Psychol 1995:23(4):557-568*

[3] Politics, Science and the Emergence of a New Disease. The case of Chronic Fatigue Syndrome. Jason LA et al. *Am Psychol 1997:52:9:973-983*

[4] Chronic fatigue syndrome, Fibromyalgia and Multiple Chemical Sensitivities in a community-based sample of chronic fatigue syndrome - like symptoms. Jason LA et al. *Psychsom Med 2000:62(5):655-663*

[5] Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. John DeLuca, Benjamin H Natelson et al. *J Neurol Sciences 1999:171:3-7*

[6] Fatigue 2000 Conference Proceedings. The National ME Centre in conjunction with The Essex Neurosciences Unit. 23-25 April 1999

[7] Severe and very severe patients with chronic fatigue syndrome: perceived outcome following an inpatient programme. DL Cox LJ Findley. *JCFS 2000:7(3):33-47*

[8] Symptom patterns in long-duration chronic fatigue syndrome. Fred Friedberg et al. J *Psychsom Res 2000:48:59-68*

[9] Editoral. Roberto Patarca-Montero. *JCFS 2000:7(4):1*

[10] The Chronic Fatigue Syndrome: A Comprehensive Approach to its Definition and Study. Keiji Kukuda, Michael C Sharpe, Simon Wessely et al. *Ann Int Med 1994:121:12:953-9*

One clear message which emerged from the National Institutes of Health (NIH) State of the Science Conference on CFS held on 23-24 October 2000 in Arlington, Vancouver was that CFS is heterogeneous and researchers ***must*** subgroup patients by features including chronicity, immunology and neuroendocrinology. [11] Conference participants included Dr David Bell, Professor Dedra Buchwald and Professor Nancy Klimas, all world-renowned experts on CFS.

Roberto Patarca-Montero, Assistant Professor of Medicine and Director of the Laboratory of Clinical Immunology, University of Miami School of Medicine (as well as Editor of The Journal of Chronic Fatigue Syndrome) emphasises the importance of subsets of patients in his paper "Directions in Immunotherapy". [12]

Experienced researchers and clinicians presented evidence at the Fifth International AACFS Conference held in Seattle, 27-29 January 2001 about the need for subgrouping. Some examples include the following:

--- Professor Leonard Jason from De Paul University, Chicago, concluded that *"Subtype differences detected may account for some of the inconsistencies in findings across prior studies that have grouped CFS patients into one category. Subtyping patients according to more homogeneous groups may result in more consistent findings which can then be used to more appropriately and sensitively treat the wide range of illness experience reported by different types of individuals with CFS"* [13]
--- Professor Kenny de Meirleir from Brussels compared immunological profiles in three different subgroups of CFS patients; he found significant differences between the groups. [14]

--- Dr Pascale de Becker from Brussels presented evidence that there is a need to assess the homogeneity of a large CFS population in order to establish those symptoms which can improve differentiation of CFS patients. [15]

--- Dr Paul Levine from Washington demonstrated that factor analysis is an important tool for separating subgroups of CFS; he showed that it should be utilised in future attempts to develop case definitions for CFS to identify discrete patient groups, which may have different pathogeneses and responses to treatment. [16]

--- Dr Katherine Rowe from Australia presented evidence showing that at least three distinct subgroups can be identified within the CFS syndrome. [17]

--- A large international multicentre study of autoimmunity was presented by E.Tan
(with, amongst others, participants from The Scripps Research Institute, La Jolla,
California; the University of Washington; Harvard Medical School, Boston; State University of New York and George Washington University,Washington DC.
Of interest is that another participant was Simon Wessely from Kings College, London).

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[11] Conference calls for Serious Research. T.Lupton. *CFIDS Chronicle 2001:14:1:12-13*
[12] Directions in Immunotherapy. Roberto Patarca-Montero. *The CFS Research Review 2001:2:1*
[13] Subtyping patients with Chronic Fatigue Syndrome in a Community Based Sample. Leonard A Jason et al. Presented at AACFS, January 2001 # 011
[14] Cytokine Levels in CFS Patients with a Different Immunological Profile. Kenny De Meirleir et al. Presented at AACFS, January 2001 # 017
[15] A Definition Based Analysis of Symptoms in a Large Cohort of Patients with Chronic Fatigue Syndrome. Pascale De Becker et al. Presented at AACFS January 2001 # 019
[16] Use of Factor Analysis in Detecting Subgroups (of CFS patients). Paul H Levine et al Presented at AACFS January 2001 # 052
[17] Symptoms Patterns of CFS in Adolescents. Katherine Rowe et al. AACFS Jan 2001 # 064

This large study reflected the heterogeneity from one CFS centre to another; it emphasised the importance of subcategorising CFS studies. [18]

In the light of current awareness of the overriding need for consideration of subgroups within CFS (including that which has emerged from Seattle), there is concern that if some of the content of chapter 3 of the present draft is incorporated into the final version, then the UK CMO's Report may be immediately dismissed and be held in derision by well-informed clinicians and patients alike.

The various views of the CMO's Working Group on the need for subgroups

> ***"It has been argued by many that not only can ME be differentiated from CFS by biological markers, but that its clinical features also differ"***

Under "Priority Areas for Research", the author concludes *"Certain areas for research have been identified as being important in enabling the Working* In February 1999 a member of the CMO's Key Group (Dr Derek Pheby of The Unit of Applied Epidemiology, Frenchay Campus, Bristol) produced a discussion document [19] for the Working Group to consider. In that document, the author is unequivocal about the need for attention to be given to the existence of subgroups and he quotes from the Report of the UK National Task Force on CFS / PVFS / ME. [20] The Task Force Report states unequivocally that ***"Although both the terms "CFS" and "ME" have a range of applications, they do not represent the same populations".***

It is a matter of record that those who favour a psychiatric aetiology (and who wish to eradicate the classification and even the existence of ME [21]) were unhappy about the Report from the Task Force; indeed, the Report itself acknowledges this, stating *" People who gave us their much-valued help are not necessarily in agreement with the opinions expressed".* Being known to be in disagreement with the Report from the National Task Force (which did not have a psychiatric bias), the proponents of the psychiatric view responded to the Task Force Report by producing their own report (that of the Joint Royal Colleges' mentioned above, in the Preface to which it confirms that the authors of the Joint Royal Colleges' Report are not in agreement with all the findings of the National Task Force report).

In his discussion document for the CMO's Working Group [19] Pheby explicitly states (emphasis added):

> *"The National Task Force recommended that five main sets of issues should be addressed, i.e.* ***Clarify the difference between the various chronic fatigue syndromes…*** *areas where in the view of the Task Force research needed to be encouraged included:* ***clear definition of the various chronic fatigue syndromes"***
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> *" CFS is a* ***spectrum*** *of disease"* [i.e. not a disease entity in itself (quoting Levine) [22] who is emphatic that *"It is clear that CFS is not a single entity"*]

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[18] A multicenter study of autoimmunity in CFS. K.Sugiura, D Buchwald, A Komaroff, P Levine, S Wessely, EM Tan et al. Presented at AACFS 2001 # 037

[19] Discussion Document: an overview of the recent research literature. Dr Derek Pheby.Feb 1999

[20] Report from The National Task Force on Chronic Fatigue Syndrome, Postviral Fatigue Syndrome, Myalgic Encephalomyelitis. Westcare, Bristol 1994

[21] Eradicating ME. Report of a lecture given by Simon Wessely on 15 April 1992 at Belfast Castle,Belfast. Pfizer / Invicta Pharmaceuticals 1992: 4-5

[22] Epidemiologic advances in chronic fatigue syndrome. Levine PH. *Journal of Psychiatric Research 1997:31:1:7-18*

"Variations in prognosis may be attributable once again to the heterogeneity of the condition, ***with different subgroups having different prognoses"***

"The heterogeneity of CFS has made it very difficult to interpret research results from different studies which may have been conducted in very dissimilar populations"

"If progress is to be made, it is necessary to consider…the possible existence of subgroups within the population of patients with CFS / ME"

"The increasing knowledge of pathological processes occurring in CFS / ME has led to a belief that it should be possible to define subgroups on the basis of biomarkers and thus to draw a distinction between CFS and ME"

Group to achieve its objectives. These include…systematic reviews to consider ***subgroups****"*

On 24th August 2000 Helen Wiggins of the NHS Executive (who co-compiled chapters 1 and 2 of version 6) e-mailed a correspondent as follows:

" I would also like to assure you that the CFS/ME Working Group is aware that treatment that works for one person does not necessarily work for another. Hence the fact that the team undertaking the Systematic Review will look at evidence that subgroups of patients respond differently to treatment"

On 18th August 2000 Professor Pinching wrote to Mrs Anne Crocker of Okehampton as follows:

"…. there is no doubt in my mind that the CMO's Group is well aware of the heterogeneity of CFS/ME….obviously "one size" will not fit all….I hope very much that the final product will adequately address these issues".

In an e-mail to a correspondent dated 11th December 2000 Professor Pinching wrote:

" I am all too well aware of the fact that current treatment options are unsatisfactory and that there is a significant group of patients where our current very limited armamentarium is either ineffective or worse".

On 11th January 2001 he e-mailed a correspondent as follows:

" It may be that we can define subgroups that are useful and I would have no problem with the concept (I have done this on other disease entities (when) subgrouping has also been helpful)"

<u>The apparent change of mind by the authors of chapter 3 of the CMO draft report regarding the need for subgroups</u>

Chapter 3 was compiled by Dr Derek Pheby, Professor Anthony Pinching and

Dr Tim Chambers. From what had earlier been made known of the WG's intentions (examples of which are set out above), many people were hopeful that the matter of sub-groups would be addressed, especially given their importance in relation to the implications for treatment outcomes.

Seemingly this is not to be.**"**

However, the present authors note that this need has been fully recognised in the "Recommendations of the Name Change Workgroup Presented to the US Department of Health and Human Services (available on Co-Cure Archives, 23rd January 2003)

This important document states:

> "Unfortunately, uncontrolled patient heterogeneity in empirical studies is a consequence of ignoring the issue of sub-classification. When unique patient groups are combined, any distinctions pertaining to specific subtypes of CFS become blurred. Researcher have begun to determine the validity of an approach that involves subdividing their patients into groups. This proposal will lead investigators to make efforts in future studies to sub-group samples and thus might help identify more consistent pathophysiological markers and therapeutic interventions for this illness. We believe that our proposed term (Neuroendocrineimmune Dysfunction Syndrome or NDS) will accommodate research-driven subtyping. Under the Neuroendocrineimmune Dysfunction Syndrome, we recommend the following subtypes
>
> A. Myalgic Encephalomyelitis B. Fukuda et al (1994) criteria
> C. Canadian clinical criteria D. Gulf War Syndrome
>
> We believe that evidence-based research must drive the development of these sub-groups (and) we believe that the subtypes or sub-categories will aid appreciably in identifying biomarkers of the syndrome and provide a practical working construct for clinicians and biomedical researchers from a wide variety of disciplines.
>
> The name CFS will no longer be used."

The present authors recommend that the MRC "CFS/ME" Research Advisory Group members fully acquaint themselves with the evidence before committing themselves to a strategy which they may rest assured will be most rigorously scrutinised by the ME community.

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