

IGNORING THE EVIDENCE? A response to the final version of the MRCCFS/ME Research Advisory Group Strategy of 1st May 2003

Malcolm Hooper¹ Eileen Marshall² Margaret Williams²

5 May 2003

Having read the report, we conclude that it is like the proverbial curate's egg: "good in parts". However, in terms of demonstrating an understanding of ME/ICD-CFS and a grasp of the issues (and thus of providing hope of real progress to those whose life is blighted by it), the bad parts seem to outweigh the good: essentially the report is, as widely predicted, simply "more of the same" from a Government agency which is under the nominal political control of the Labour Science Minister Lord (David) Sainsbury (whose Linbury Trust has for so long financially supported those UK psychiatrists of the "Wessely School" who claim that ME does not exist and that "CFS" is a mental disorder which must be managed by cognitive behavioural therapy and graded exercise).

Membership and remit of the Research Advisory Group (RAG)

Annex 1 to the RAG report lists the membership of the Group, whilst Annex 2 is the previously released Summary Report dated November 2002 prepared on the 187 responses to the MRC Consultation Questionnaire of August 2002 by Kate Saffin and Annette Hackett of the NHS Public Health Resource Unit, Oxford.

The RAG report states that the remit of the MRC RAG was not to review the existing body of scientific knowledge about the disorder, but "in the light of the Report of the CMO's Independent Working Group on CFS/ME (including its recommendations for research)" to "propose a research strategy". However, the summary states that the MRC RAG has not provided a detailed plan for the science, nor has it set out an agenda of research projects but has merely provided a "framework" which focuses on "strategic themes", one of which is "interventions". It makes the point that the MRC CFS/ME RAG considers it appropriate to explore potential interventions in the absence of knowledge of causation. On interventions, it states that future trials could be used "to evaluate interventions which have been shown in one or more trials to have a benefit".

The ME community will at once recall that the only trials which the CMO's report claimed to have benefit are of cognitive behavioural therapy and graded exercise, whereas there is mounting evidence that other interventions are effective in some cases: these include dietary modification; nutritional supplements (including essential fatty acids) and detoxification support (see Hooper, Engaging with Myalgic Encephalomyelitis: towards understanding, diagnosis and treatment 2003, available from the author. A copy was supplied to the MRC for consideration by the RAG).

Analysis of input by the public

At paragraph 31, the RAG report states that 145 responses were received to the preliminary draft report released for public consultation on 17th December 2002, (our detailed response to which can be viewed at www.meactionuk.org.uk/Initial_Comments.htm). Certainly, respondents hoped and requested that their comments, together with the evidence from the mainstream literature which they supplied, would be seen and properly considered by the members of the RAG themselves, but it seems that no member of the RAG saw any of the submitted responses or the supportive evidence: what the Group members saw was an “independent qualitative analysis” of the responses prepared for their consideration by the NHS Public Health Resource Unit, Oxford. Naturally, people wondered about this “analysis” and if, in the interests of transparency, they were to be allowed to see it. Questions which immediately arose included asking if the 145 responses had been effectively “vetted” to remove anything which did not accord with a pre-set management agenda; who had carried out this “independent qualitative analysis” of the submitted responses; what are their qualifications; what experience of understanding and interpreting complex medical literature have they got, and who advised the team which carried out this analysis of the submitted evidence? No names are provided in the RAG report.

However, it has now been ascertained that all responses and the data provided were carefully studied, paragraph by paragraph, by the designated Team Leader at the NHS Public Health Resource Unit and a very detailed and comprehensive document which diligently summarised all the submitted responses (even naming the respondents) was provided for the MRC RAG. It has also been established that the decision was taken by the MRC not to include this detailed analysis of the responses as an annex to the RAG report; instead, the MRC has requested from the Public Health Resource Unit a short summary of the detailed analysis, which will be on the MRC website in the near future.

Without this knowledge and without seeing the analysis, it was unclear if members of the MRC RAG were made aware of the calibre of the evidence supplied for their use, since the content, conclusions and recommendations of the RAG report seem to raise serious doubt about this. We are satisfied that no failure lies with the Public Health Resource Unit as it has been established that RAG members *were* aware of the submitted evidence. We are thus compelled to conclude that RAG members have been deliberately selective and that such selectivity is likely to be in accordance with a pre-set agenda as so relentlessly promulgated by the “Wessely School”, about which we have publicly raised legitimate concerns for the last decade.

Specific concerns

Para 10 + 11: (“The RAG considers that...it is not essential to identify causal pathways (but) it is appropriate to explore interventions in the absence of knowledge of causation or pathogenesis”)

We note with concern that the MRC RAG considers that studies investigating causal pathways and mechanisms would not have “immediate impact on increasing understanding of CFS/ME” and that “it is not an essential prerequisite to identify triggers or causal pathways in order to undertake research on CFS/ME”. In our response to the MRC RAG draft document referred to above, we pointed out that such a view seems to echo the Linbury Trust view (written by Simon Wessely) that *“It is usual to try to discover the cause of an illness before thinking about treatment (but) some illnesses are treated without knowledge of the cause...examples include chronic fatigue syndrome”*(New Research Ideas in Chronic Fatigue. Edited by Richard Frackowiak and Simon Wessely for The Linbury Trust; published by the Royal Society of Medicine Press, 2000). On 2nd May 2003 the Financial Times reported Professor Nancy Rothwell, Chair of the MRC CFS/ME RAG, as saying it was important to recognise that important advances in healthcare could be made without knowing the underlying causes of an illness. We again ask why should ME/ICD-CFS be excluded from what Wessely himself says is the “usual” approach, and on what rational grounds is it acceptable not even to **try** to find the cause of such a devastating and increasingly common illness?

Para 17 + 52 + 59: (“In considering ways to advance research on CFS/ME, the RAG has focused on...the topics outlined in the research recommendations of the report of the CMO’s Independent Working Group...(these include) case definition”)

We are pleased that the MRC RAG recognises the need for an accurate, standardised case definition, but we have on-going concerns that any such case definition might be constructed in the UK in such a way as to achieve the desired outcome of future studies. In the formulation of a case definition, we hope that proper attention will be paid to the recent Canadian case definition as set out in “Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols on ME/CFS” by BM Carruthers, De Meirleir KL, Klimas NG et al (JCFs 2003;11(1):7-116): we note that this case definition merits only a meagre mention at paragraph 57.

We are particularly concerned that the RAG considers it possible that research studies can be undertaken without reaching a case definition consensus. We draw attention to the fact that it was the identification of a case definition, presented by Professor Robert Haley at the House of Lords on 19th June 2002, that led to the recent much clearer understanding of Gulf War Syndrome and the revelation of definite clinical evidence of neurological damage to deep brain structures.

Para 18 + 25: (“The RAG has not undertaken a full literature or systematic review of the published literature on CFS/ME”)

We remain deeply concerned by the admission that the RAG did not undertake a full or systematic review of the published literature on ME/CFS, their given reason being that it would have been “a substantial undertaking that would have taken a significant length of time”. Instead, the report states that the RAG wished to capitalise on the recommendations of the “CMO’s Independent Working Group” which is “in line with the request from the Department of Health” to “take forward the research recommendations of that Group”, so the RAG chose only to “provide a framework in the context of recent reviews”. We note from the cited references that one such “recent review” upon which the RAG has relied is the one on cognitive behavioural therapy by Whiting et al (the “York Review” to which psychiatrist Simon Wessely was an adviser; it is the case that Wessely was a member of the MRC Research Boards; it is also the case that the RAG report states that the preliminary draft was considered by the MRC Research Boards). Other cited references include the much criticised and discredited Joint Royal Colleges’ Report on CFS (RCP CR54, 1996) and the equally criticised and discredited Clinical Practice Guidelines produced by the Royal Australasian College of Physicians, 2002 (both widely acknowledged to be pervasively biased). In our opinion, there is undue reliance upon the Australasian report throughout the RAG report: given the justified international criticism it evoked, such a discredited document ought not to have been relied upon in a supposedly unbiased MRC research strategy proposal. It is particularly problematic that RAG members who have produced that strategy have ignored such elementary rules of procedure as the prerequisite awareness of knowledge of what has already been established about the disorder in question. We remain baffled but unsurprised that the MRC has allowed such a potentially biased research strategy to be entertained.

Para 32/33: (“The CMO’s Independent Working Group report discussed at length the issues surrounding nomenclature and the RAG did not consider this topic in detail (but) agreed with the CMO’s Independent Working Group and used the term “CFS/ME”)

Given that the MRC report states “It was evident from the responses to the draft research strategy that the topic of nomenclature was one of concern to many respondees”, we remain disappointed that the RAG saw no need to assist future research projects by clarifying nomenclature, agreeing instead not to address the issue of terminology. We believe that until this is resolved, confusion will continue to abound; scientific research will continue to be hindered and patients will continue to be

wrongly labeled and thus mismanaged, especially given the RAG report's acknowledgement that the term "CFS/ME" does not refer to a specific diagnosis. We are puzzled as to how the MRC's stated aim ("To stimulate high quality research proposals") can be achieved with such uncorrected obfuscation.

Para 37: ("The RAG has noted the concerns of many respondents to both consultation exercises over neurological and psychiatric aspects of CFS/ME")

We are especially concerned that the RAG failed to use the opportunity to clarify

the differences between ME / ICD-CFS and the "CFS" which certain psychiatrists equate with "chronic fatigue", and that the RAG report failed to point out that since 1969, the WHO classifies ME / ICD-CFS as a neurological disorder at G 93.3 but that it classifies quite separately (under mental and behavioural disorders at F 48.0) the state of medically unexplained "chronic fatigue". From the standpoints of both future research and of management strategies this difference is important, but we note that the RAG endorses the continued use of the composite term "CFS/ME" without clarifying (for the benefit of potential researchers) that "CFS" means one thing to the international research community (ie. the internationally used term "CFS" equates with ME in the International Classification of Diseases) but that the identical term "CFS" has been highjacked by certain UK psychiatrists to mean somatisation disorder. To add to the confusion, the RAG report states: "It is the firmly held belief of the Group that psychiatric illnesses are no less real or debilitating than neurological illnesses". No-one denies the reality of psychiatric illness, nor the debility such psychiatric illness may cause, but what is at issue here is **accuracy of case definition**, which in our view has not been helped by this report: whereas psychiatric illness is amenable to psychotherapeutic interventions, complex neuro-immune disorders are not.

Para 42 + 43: ("There are many potentially important comparisons to be made between severely affected patients, who tend to have a poor prognosis, and those individuals who recover...Such comparisons may help to identify subgroups....The RAG recommends that research studies should aim to be as inclusive as possible in terms of recruitment of participants")

We have long argued the need for sub-groups and are pleased that this is now accepted by the RAG. We wholeheartedly agree that future research should include the most severely affected. However, we are concerned at the RAG's recommendation that future research studies should be as "inclusive as possible in terms of the recruitment of participants", since in our view, such a broad canvas would inevitably dilute the requisite homogeneity, since such an approach would include not only the severely affected but also those with on-going fatigue and psychiatric disorder. Any conclusions

would thus be skewed, as happened with the 1991 Oxford criteria and also with the 1994 CDC criteria, leading to international calls for a revised case definition with the addition of common and significant symptoms such as respiratory problems, palpitations, dizziness, nausea, incoordination, gut problems, allergies, skin (vasculitic) lesions, loss of hair, chest pain etc that are currently excluded --- see Chronic Fatigue Syndrome: Evaluation of a 30-Criteria Score and Correlation with Immune Activation. A Hilgers, J Frank JCFS 1996:2(4):35-47.

Para 47: (“Many reported findings in the area of pathophysiology are not published in the peer-reviewed literature...as indicated by the reviews of the Royal Australasian College of Physicians....”)

We are once again baffled by the RAG’s assertion that “Many reported findings in the area of pathophysiology are not published in the peer-reviewed literature, or are not well-described, as indicated by the reviews of the Royal Australasian College of Physicians (2002), Whiting et al (2001)”. In our response to the MRC RAG draft document of 17th December 2002, we listed 92 prestigious mainstream journals which had published such findings. We find it incomprehensible that the RAG states “Furthermore, it is important that new research findings are considered within the context of existing relevant data”. This seems an attempt to curtail the advancement of medical science and to preserve the status quo, which in our view would be contrary to the long-established aims of the MRC.

Para 70: (“There would appear to be little evidence about which patients recover, or what factors pre-dispose to recovery”)

The RAG states that “very few studies have looked at patterns of recovery, which the MRC CFS/ME RAG considers to be a potentially fruitful area of research”. We are puzzled at the apparent ignoring by the RAG of the evidence on “recovery”: Annex 2 to the CMO’s report (upon which the RAG has relied) is quite clear: “Much of the evidence is anecdotal, but such evidence is the product of much clinical experience and is in line with the research evidence that is available....A systematic review published in 1997 demonstrated that, even when patients say they have recovered, very few return to their level of functioning before the illness. The authors reviewed five studies in adults and found that, in terms of functional capacity, fewer than 10% returned to premorbid levels of activity, the majority remaining significantly impaired”. Why has the MRC RAG chosen also to ignore the evidence provided for them that 80% of those with ME do not recover (Presentation before the Scottish Parliament by Dr A. Chaudhuri, Senior Clinical Lecturer in Neurology, University of Glasgow on 4th April 2001), and also the CDC evidence that only 4% of patients had full remission (not recovery) at 24 months? (US

CDC CFS Programme Update, August 2001). To be so selective indicates that the RAG's intention is to study non-ME patients, but those with chronic fatigue, who can and do make significant recovery with psychological interventions.

Para 72 – 122: (“Developing hypotheses about pathophysiology”)

In order to avoid repetition of our documented concerns about the misinformation contained in the RAG draft document of 17th December 2002 and the evidence upon which we relied in support of those concerns, we again draw attention to our response to the draft document (which can be viewed at www.meactionuk.org.uk/Initial_Comments.htm) because in our opinion, misinformation remains in the RAG final report. In our document we addressed the areas of virology, neurology, muscle pathology, immunology, neuroendocrinology, cognitive impairment, personality factors and the advances in understanding obtained from nuclear imaging techniques in ME/ICD-CFS in which we disagree with the RAG's beliefs.

One additional comment we would make, however, is in relation to “central fatigue” (para 91). Central fatigue simply cannot explain all the features of patients with ME/ICD-CFS, as quite clearly there are unequivocal peripheral factors involved in the generation of muscle fatigue --- see, for example,

(i) Impaired oxygen delivery to muscle in Chronic Fatigue Syndrome.

KK McCully, BH Natelson et al Clin Sci 1999;97:603-608

(ii) Exercise capacity in Chronic Fatigue Syndrome

Pascale de Becker, Kenny de Meirleir, Neil McGregor et al

Arch Int Med 2000;160:3270-3277

(iii) Specific oxidative alterations in vastus lateralis muscle of patients with a diagnosis of Chronic Fatigue Syndrome

Fulle S et al Free Radical Biol Med 2000;29:1252-1259

To quote from “Unhelpful Counsel” (provided by the charity MERGE and available at www.mereseach.org.uk):

“As the CFIDS Association of America makes clear, although the aetiology of the illness remains elusive, numerous biological abnormalities have been reported in:

- Immune function --- in the form of cytokine overproduction or poor cellular function (Patarca-Montero et al 2000; Patarca-Montero et al 2001)
- Brain and CNS ---with possible involvement of the basal ganglia (Chaudhuri et al 2000) or functioning of the blood-brain barrier (Bested et al 2001)
- Muscle --- in the form of post-exertional deficits (Lane, 2000; Paul et al 1999)
- Autonomic functioning --- as neurally-mediated hypotension (Bou-Holaigah et al 1995)
- Hormonal function --- most prominently at the HPA axis (Scott et al 1999)
- Cardiovascular integrity ---endothelial sensitivity to acetylcholine (Spence et al 2000)
- Neuropsychological functioning --- including impaired working memory and information processing unrelated to psychiatric illness (Review by Michiels et al 2001).

We are most concerned that much misinformation remains in the final report of the RAG research strategy for “CFS/ME”.

Para 126: (“Interventions”)

In the section on Interventions, we are concerned to note the report states that the RAG has not considered in detail the information in the York systematic review but instead has “chosen to consider how the evidence-base for potentially effective management options can be strengthened”. This clearly refers to CBT and graded exercise regimes: it seems to indicate a narrowness of approach which we find disturbing and not in patients’ best interests, given the amount of documented information setting out how patients have been actively harmed by CBT and graded exercise regimes.

Para 137: (“The optimum approach to the rehabilitation of people with CFS/ME...Parallels could be drawn between patients with CFS/ME and patients with chronic low back pain of non-specific origin”)

This paragraph refers to the findings of the Joint Royal Colleges' 1996 Report that the greater the fatigability and chronicity, the stronger the association with a psychological component, whilst paragraph 138 goes on to repeat the party line: "inactivity results in a decline into a 'vicious spiral of immobility' (and) it is very difficult to break into this downward cycle and the key to any effective rehabilitation programme should be to support the patient through this process". In our view, this represents either a negligent lack of knowledge of the published literature on ME/ ICD-CFS or a deliberate strategy of denial of that evidence. The RAG report suggests that parallels could be drawn between patients with "CFS/ME" and those with chronic low back pain of non-specific origin. Whilst not wishing to denigrate patients with chronic low back pain or to minimise the suffering it undoubtedly causes, we find such a comparison deeply insulting to patients with ME/ICD-CFS. People with ME are not only disabled and in pain, they are severely and systemically sick with multi-organ and multi-system involvement, quite often with features of autoimmune overlap disorder. Indeed, as long ago as 1994, Paul Levine (Professor of Viral Epidemiology, Division of Cancer Aetiology, National Cancer Institute, Bethesda, Maryland, USA) stated:

"the spectrum of illnesses associated with a dysregulated immune system must now include CFS" (ref: [Summary and Perspective: Epidemiology of Chronic Fatigue Syndrome](#). Paul H Levine. Clinical Infectious Diseases 1994: 18 (Suppl 1):S57-S60).

To equate the management of such patients with those having low back pain is, in our view, iniquitous and demonstrates dereliction of duty to patients. We recall that it was the CMO who, on 11th January 2002, put himself on the record saying that this disorder should be classed as a chronic condition with long-term effects on health, alongside other illnesses such as multiple sclerosis and motor neurone disease.(ref: BBC News, 11.01.02)

Para 166: ("Lay participation")

Whilst lip-service is paid to the value of lay participation, the bottom line seems evident from the statement that the MRC CFS/ME RAG "believes that patient organisations can play an important role in involving participants in research"; this could be interpreted as meaning that the nurturing of a relationship between researchers, funders and lay people will ensure a ready supply of "guinea pigs" for psychiatric studies. Any other interpretation is difficult, since the RAG report has been skilfully crafted so as to list and note the valid concerns and research proposals of patients whilst proceeding to disregard most of them.

Conclusion

The crux of the whole document lies in its recommendations for the direction of future research into the management of those with “CFS/ME”; those recommendations are for CBT and graded exercise to be delivered across the entire spectrum of the disorder (ie. it is recommended for the least sick and the most severely sick alike).

The Press Release of 1st May 2003 for the RAG report states “To encourage research proposals MRC has today issued a highlight notice to the research community welcoming high quality proposals across the entire spectrum of CFS/ME research...into basic treatments. MRC highlight notices are a mechanism for alerting the research community to areas in which MRC would be particularly keen to see quality applications. This is the usual method for flagging an area deemed a current research priority”. However, it then states “All proposals received under this initiative will compete for funding according to normal criteria”, which can be translated as confirming that no funds will be ring-fenced for ME research.

Given the excoriating criticism levelled at the MRC in the recent report of the House of Commons Select Committee on Science and Technology (ref: The Work of The Medical Research Council / HC 132, March 2003), it will be interesting to see if the £2.6 million already lined up by the MRC for psychiatrists Simon Wessely, Michael Sharpe, Peter White and colleagues for yet more studies on cognitive behavioural therapy and graded exercise in “CFS” over a four year period (which is in addition to the Linbury Trust funding of over £4 million and is irrespective of any RAG proposals) will be forthcoming. One thing is certain: the ME community will be watching diligently and they will ensure that so will their Members of Parliament.

Malcolm Hooper ¹

Emeritus Professor of Medicinal Chemistry

Department of Life Sciences

University of Sunderland

Sunderland

SR2 7EE, UK

Eileen Marshall ²

Margaret Williams ²

ME Research (UK)

c/o The British Library

Science Reference & Information Service

Boston Spa, Wetherby

West Yorkshire

LS23 7QB, UK

5th May 2003