

## **New Research Directions for CFS/ME**

### **Summary of a report from the Medical Research Council's CFS/ME Research Advisory Group**

#### **Towards a new research strategy**

This report summarises the work of a group of independent scientists brought together by the Medical Research Council to develop a strategy for taking forward research on the complex and debilitating condition – or range of conditions - known as Chronic Fatigue Syndrome(CFS)/ME.

This Research Advisory Group was set up following a report by the Chief Medical Officer, which acknowledged the severity of suffering associated with CFS/ME and called for research into all aspects of the condition.

The Group's conclusions were reached in the light of consultation with current and former patients, carers, charity representatives, clinicians and researchers, who were also invited to comment on a draft of the strategy.

The final version of the research strategy aims to provide a framework for improving understanding and treatment of CFS/ME. It sets out the key priorities for future investigation, offers guidance on research methods and emphasises the importance of the continuing involvement of people with CFS/ME, their carers and the groups representing them.

#### **Working methods**

Members of the Research Advisory Group were drawn from a range of scientific disciplines associated with CFS/ME, including immunology, muscle physiology, virology, clinical trials and psychology. There were also two consumer representatives.

They set out to consider the areas of future research most likely to bring benefits for patients in the light of recent reviews, patient experiences and current knowledge

In addition to their own formal meetings held between September 2002 and March 2003, members of the Group met with ME charities, CFS/ME patients and their carers to gain a better understanding of their perspectives on the condition.

They also gave careful consideration to the results of two rounds of a public consultation exercise which drew more than 200 responses from, people with CFS/ME and people who have recovered, carers, researchers, clinicians and specialists, and relevant voluntary organisations.

They did *not*, however, undertake a full review of all the literature on CFS/ME, examine health care provision or decide how their recommendations should be implemented.

### Responses to consultation

Responses to the public consultation exercise drew attention to the following perceived problems:

- *Problems with definition/understanding*

There are many shades of opinion – and seemingly little agreement – on what constitutes and is meant by CFS/ME. The tensions and frustrations surrounding this issue stand in the way of effective management and treatment of patients, as well as useful research;

- *Problems with communication*

People with experience of CFS/ME complain of sceptical, unhelpful and unsupportive health professionals and are critical of the way psychiatric issues seem to dominate research. While recognising the validity of some of these concerns, researchers and clinicians often feel under attack from patient organisations;

- *Problems with research*

Research hasn't yet reached agreement on *defining* the condition, let alone established its causes, symptoms, prevalence and impact. What research there is has been short-term, poorly-co-ordinated and lacking in patient involvement;

- *Obstacles to research*

Respondents complained of the low status of research into CFS/ME and an associated shortage of funding and resources. Effective research is also hampered by lack of knowledge about people with CFS/ME and lack of suitable measurements for symptoms like fatigue.

Key ways forward arising out of the consultation included:

- More research funding, properly directed;
- More co-operation and collaboration between researchers, care providers and patients, including those who are severely ill;
- Getting the priorities right – which for many means a shift from psychological to biological and medical research;
- An open debate on meanings and definitions;

Many of those who responded saw the development of a research strategy as an opportunity to improve communication and make a real difference to the lives of those affected by CFS/ME.

### What's in a name?

Disagreements over terminology are symptomatic of the lack of consensus over most aspects of CFS/ME. Chronic Fatigue Syndrome (CFS) and Myalgic encephalomyelitis or encephalopathy (ME) are the terms that have been used most often to describe patients with a combination of variable symptoms, always including disabling fatigue.

The consultation elicited widely different views on how these symptoms should be described, defined and classified. But the Research Advisory Group decided to adopt the 'umbrella term' of CFS/ME, used in the CMO report, rather than reconsider the terminology in depth.

It emphasises, though, that this term does not refer to a specific diagnosis and that they hold no particular position on whether CFS/ME is one condition with a variety of causes and presentations or a number of similar conditions with different characteristics.

Although many patients and groups prefer to identify with the term ME rather than CFS, the Group believes that research will be best served by an 'inclusive approach'. They accept, however, that as knowledge and understanding increase there may come a time when this umbrella term may no longer be appropriate.

### The way ahead

In considering the best ways to advance research on CFS/ME, the Research Advisory Group identified a number of important considerations, including:

- *Variability*. Research must take account of the wide variation in the intensity and nature of symptoms and the potential overlap with other disorders. It must also encompass a large variation in the age range of people affected, posing additional issues about the ethics of research on children;
- *Inclusiveness*. Given this variability, research studies need to be as inclusive as possible in terms of range of participants, including the most severely ill, with sample sizes large enough to allow for different 'subgroup' effects;
- *Integration*. The group recommends an integrated approach to studying CFS/ME, with experience and expertise from a variety of appropriate disciplines brought together as part of a holistic approach;
- *Scientific rigour*. New findings must be subjected to rigorous scientific analysis, published in peer-reviewed journals and confirmed through independent replication in other centres.

## Key research priorities

The Research Advisory Group defined a number of important areas for research, as follows:

### 1. Case definition

Understanding of CFS/ME has been hampered by the use of numerous different definitions of the disorder, linked to a lack of universally agreed diagnostic criteria. Standardised case definition is clearly fundamental to studying the prevalence, presentation, causation and management of any illness. And thus the development and validation of appropriate 'tools' for case definition is a research priority. Nevertheless, the Group believes that studies into other aspects of CFS/ME should not be held up while awaiting these tools, as long as they include a broad and clearly-defined range of participants;

### 2. Population studies (epidemiology)

Population-based studies are important for answering questions about the prevalence and incidence of specific conditions and their relationship to time, place and people within populations. They are also crucial to testing theories about causation, particularly for establishing the respective roles of genetic and environmental influences. The group highlighted three types of epidemiological studies for CFS/ME:

- *Descriptive studies* on the incidence and prevalence of the condition and its nature, duration and severity;
- *Studies of causation* (aetiology), examining potential causes and triggers of the disease. Such studies are considered of primary importance by many patients and support group. But, while the Group acknowledges their importance, members believe such studies may not have the same immediate benefits for patients as studies on symptoms and management, which should not be delayed while awaiting confirmation of causation;
- *Outcome studies*, looking at patterns of recovery and the various factors involved.

### 3. Disease development (pathophysiology)

A wide variety of factors have been suggested as factors in the development of CFS/ME, but the evidence for each has been weak, contradictory or unconfirmed. Areas discussed by the Group are as follows:

- *Infections*. Some people are known to develop prolonged fatigue following certain infections. Although no single infectious cause of CFS/ME has been identified, infection may well be a factor in a proportion of cases, and recent advances

- in virology and bacteriology make it easier to study its potential role in the development of the disease;
- *Neurology*. Abnormal neurological signs are not consistently reported in most patients with CFS/ME, and initial reports of inflammation of the brain, spinal cord or muscles have not been confirmed. New imaging techniques might help to shed more light on this aspect of the disease;
  - *Muscle fatigue/weakness*. These symptoms are very common in people with CFS/ME, but it is not clear whether these problems arise in the central nervous system or the muscles themselves;
  - *Immunology*. Although there have been many reports of immune system changes in people with CFS/ME, there is no consensus on the nature and extent of these changes and their potential role in the development of the disease;
  - *Neuroendocrinology*. Abnormalities in the levels of brain hormones, such as cortisol, have been found in some CFS/ME patients although it is not clear whether these are causes or consequences of the disease;
  - *Central nervous system (CNS) function*. Fatigue, intellectual impairment and sleep disturbances are all symptoms of CFS/ME associated with CNS dysfunction, but again it is not clear whether these are causes or consequences of the illness. 'Longitudinal' studies of people throughout the course of their illness may help to resolve this issue, while modern imaging techniques could be used to study the underlying brain pathways of these and other symptoms, including chronic pain;
  - *Cognitive (intellectual) performance*. Although most studies to date have shown little change in overall intellectual functioning, there is evidence of attention, memory and concentration problems in CFS/ME, which are hard to pin down and cannot be entirely explained by mood variations;
  - *Psychological factors*. This is a controversial area because many people with ME feel that researchers have tended to focus on psychological causes of CFS/ME at the expense of physical factors. However, the Group points out that psychological factors, including personality, coping mechanisms and social support, play a role in the manifestations of *all* illnesses, however well established their physical causes. A key problem with CFS/ME is that it is not clear at what point in the illness psychological factors might play a part.

On this key point of the potential role of psychological and psychiatric factors in CFS/ME, the Group makes the following very clear statement:

*'It is the firmly held belief of the Group that psychiatric illnesses are no less real or debilitating than neurological illnesses.'*

### The search for useful treatments

A variety of interventions (treatments) have been considered for CFS/ME, but research so far has identified only two which consistently appear to offer potential benefits: graded exercise therapy (GET) and cognitive behavioural therapy (CBT).

Focusing on how the evidence base for potentially effective treatments can be strengthened, the Group draws attention to the fundamental importance of objective, sensitive and consistent 'outcome measures' (signs of clinically important effects), which can be used to test the effectiveness of individual treatments and to make comparisons between treatments.

Trial procedures should be made as objective as possible by randomising participants to either active or placebo (dummy) treatment and masking them to which treatment they are receiving where possible. Trials should be large enough to detect clinically useful effects, last long enough to achieve benefit and follow up all participants for long enough to determine whether effects are sustained.

*Crucially, the Group believes it is not necessary to wait for a full understanding of the causes and development of CFSME before exploring potential treatments. The cause of diabetes, for example, remains unknown, but knowledge of the underlying manifestations of the disease has allowed effective treatment to be developed and rigorously tested.*

The Group calls for rigorous assessment of interventions – suggestions include:

#### 1. Musculoskeletal-based interventions (rehabilitation)

There appears to be considerable confusion and disagreement about the best approach to physical rehabilitation of people with CFS/ME, not helped by the fact that some people improve and others deteriorate with treatment, leading to a high degree of scepticism among patients. The CMO's report agreed that rehabilitation was important but stressed that it should be graded, tailored to individual needs and start from a low baseline. The Group believes that an integrated package of care, including a variety of therapies – both physical and psychological - is likely to be most beneficial;

#### 2. Psychologically-based interventions

The Group believes that cognitive behaviour therapy (CBT) *can* play an important role in the management of many illnesses, particularly chronic ones, and that this treatment, together with GET, deserves further study. However, many studies to date have focused on less severe cases of CFS/ME and further research should aim to focus on the effects of these treatments across the spectrum of the condition.

### **Delivering the best health care**

Health services research is a specific branch of research, examining the best, most cost-effective ways of organising and delivering effective care. But the Group acknowledges that this type of research needs to wait on more basic findings about the incidence and prevalence of CFS/ME and the value of individual treatments.

Once this information becomes available, further research will be needed to establish:

- Which groups of patients are likely to benefit from which types of treatment;
- How the appropriate care services are distributed and accessed;
- Cost-effectiveness, appropriateness and acceptability of various 'technologies', or treatments;
- How services should be organised and delivered, including staff training and the relative role of general and specialist centres.

### **Collaboration in research**

The Group sees a need to attract high-quality researchers from basic science and specialised clinical disciplines to undertake research into CFS/ME and is keen to promote multidisciplinary collaboration, including allied health professionals, around shared research goals.

Such research teams will need strong links with the health service in order to recruit and gain access to trial participants – particularly those most severely affected by the disease.

### **Patient and public involvement**

The participation of patients, carers and support organisations has enriched the process of developing this research strategy, and their continuing involvement in research offers important two-way benefits:

- Researchers can gain access to user perspectives, which will help them both frame their research questions appropriately and work towards the most relevant outcomes;
- Patients and support groups can help to set the research agenda as well as gaining access to scientific expertise.

In terms of involvement with specific research studies, the Group believes consumers have several important roles to play:

- Getting involved at an early stage so that multiple perspectives can be taken into account in the design and interpretation of individual studies;
- Liaising with broader groups to raise awareness of research studies and ensuring their results are widely disseminated and recommendations implemented;

- Helping to identify potential study participants – particularly those who are severely ill – and involve them in research.

### Next steps

The MRC CFS/ME research strategy was published on May 1 2003, and the full document is available on the MRC website ([www.mrc.ac.uk](http://www.mrc.ac.uk)). Future grant applications to fund research into any aspects of this condition are likely to be judged according to how well they fit within the proposed framework in addition to their scientific quality.

When announcing the completion of the strategy, the Chair of the Research Advisory Group, Professor Nancy Rothwell, said:

*'Improving health and quality of life for those who are ill with CFS/ME is clearly very important. We've made our recommendations based on what is attainable in the short term, and what has to be developed over a longer period.'*

*'We recognise that there are many varied views about research needs and priorities and it has been our job to strike a balance. Our recommendations will be a stimulus for research, and the field will then evolve naturally as more is done and other possibilities present themselves.'*

ENDS