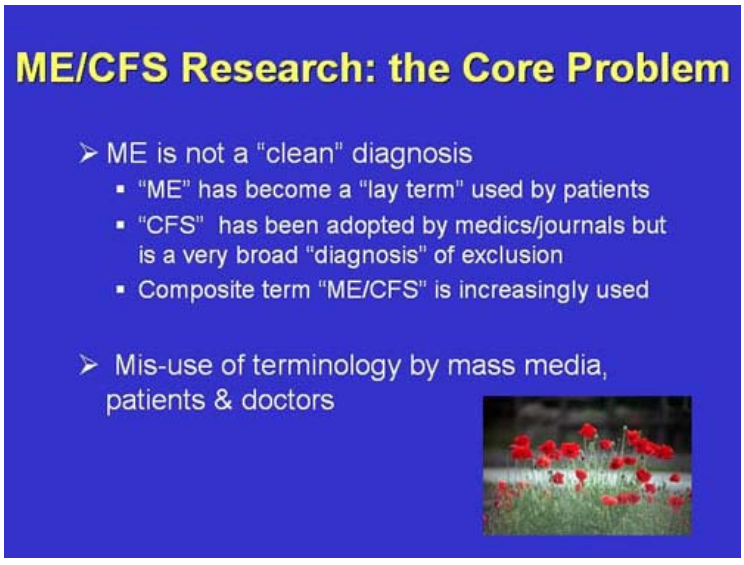
Biomedical research in ME/CFS: issues and challenges

by Dr Vance Spence, Chairman of MERGE

Following the excellent presentation by Linda McLean on her experiences as a carer of a young person with ME, and Dr Gregor Purdie on the need for a centre of excellence, my role is to give a brief 10-minute overview of the challenges surrounding biomedical research into the illness.

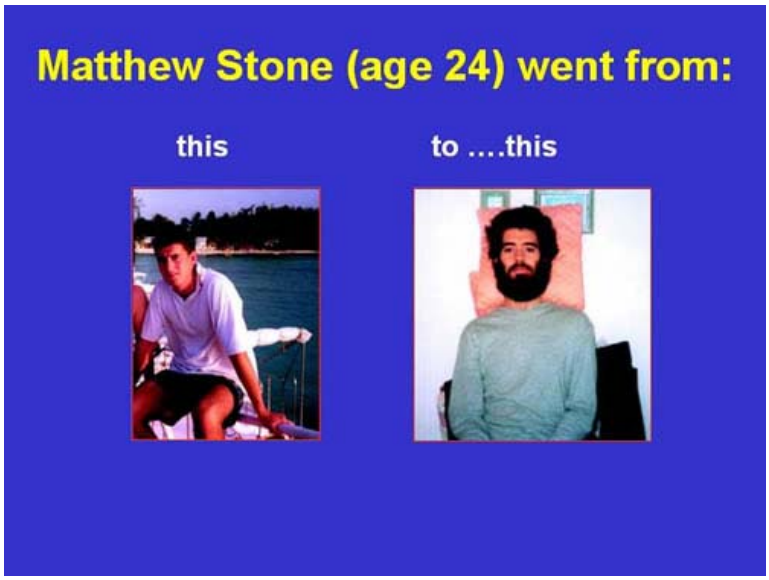
This has a personal aspect for me — it is 25 years this month that I became ill with an infection, the beginning of my own journey into ME. Little did I know that, a quarter of a century later, I would be sitting before a room full of Parliamentarians and patients and carers talking about the need for funding of biomedical research for thousands of patients like myself. Yet, here we are. It is bizarre, but here we are.

The elements that I wish to discuss concern the core problem, the funding and the future. Let's begin with what I think is the core problem, since it is the one that colours all debate on ME, yet rather like the whiteness of a wall it is often not recognised as a colour as all. It concerns the fact that ME/CFS is not a 'clean' diagnosis.



Although the term myalgic encephalomyelitis (ME) — involving an infectious onset, specific neuro-muscular symptoms and signs, and a unique post-exercise component — has a scientific history involving epidemic and sporadic forms, 'ME' at the start of the 21st century has come to be seen as

little more than a 'lay term' used by patients and patient organisations, while chronic fatigue syndrome (CFS) has been adopted by the doctors and scientific journals. Today, the composite term ME/CFS represents the uneasy, not to say stormy, marriage of these two strange beasts. In addition, we find ourselves in a situation where misuse of terminology by mass media, patients and doctors is widespread, as three examples illustrate.



First, in 'Now' magazine, September 2004, there appeared a story — 'ME Stole 6 years of my life' — about a person ill for 6 years who had recovered after thyroxine treatment; second, a newspaper in May 2003 reported that a woman, ill for 25 years, had made a spectacular recovery after several sessions of a simple quasi-psychological technique costing some £500; last, there is the appalling case of Matt, a once-healthy young man diagnosed with ME, who is now bedbound and whose constant care costs his family £2000 per month.

Now, it turns out that in the first case, the person has not actually recovered, and that in the second case the ground-level reports for the particular technique are far less impressive than is claimed in the press. But that's not my point. My point is that the term 'ME' or 'CFS' is used in popular culture to describe a whole bag of widely differing cases (do the three people cited really all have the same illness?), which almost certainly represent different conditions — anything from post-viral states, to psychological illness, to frank severe disease as yet undiagnosed.

The core cause of this confusion is probably the fact that CFS is a diagnosis of exclusion, consisting of (in one reseacher's words) a "ragbag of common non-specific symptoms with many causes, mistakenly labelled as a syndrome". Nevertheless, for the patient on the ground who needs somehow to get out of this 'diagnostic dustbin' into the specific clinic where she/he belongs, the end result can be a Kafkaesque nightmare involving physical illness compounded by the scepticism of healthcare

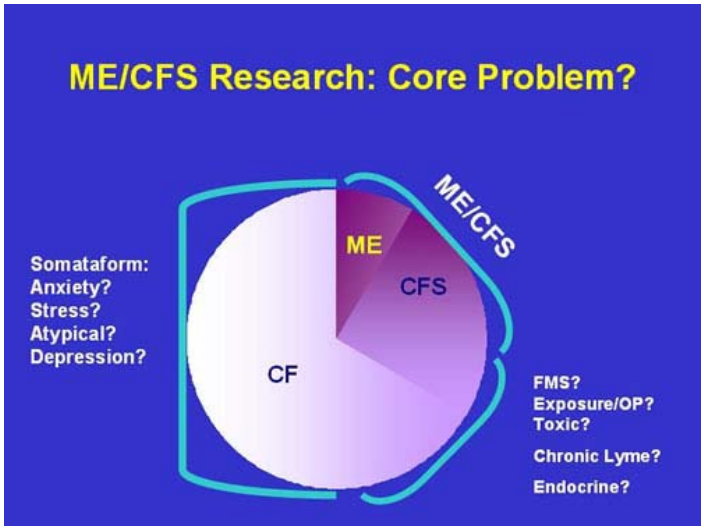
professionals and the disbelief of family and friends. And life at the bottom can be a long, cruel journey — two separate recent reviews have concluded that, "…patients exhibit severe, long-term functional impairment. Substantial improvement is uncommon and is less than 6%" (Anderson et al. 2004); and, "Full recovery... is rare" (Cairns & Hotopf, 2005). Crucially, this confusion about the diagnosis (though not about the personal suffering, which is not in doubt) also complicates biomedical research.

Let me give an example. In the ideal experiment using a theoretical outcome measure, what we wish to see at the end are two distinct groups — with the patients (whatever their illness) clearly distinct from age and sex-matched control subjects (left graph).

In ME/CFS, what we see over and over again, is the graph on the right (which shows real data points from a real biochemical experiment on ME/CFS patients) — with the controls nicely tightly packed, and the 'CFS' patient measurements much more widely scattered. There is clearly something going on since the patients have higher values than the controls on average, yet the scatter is problematic, and researchers scratch their heads when they see it. Why is this happening? Well, if the broad diagnostic net 'CFS' really catches all different kinds of fish, this is what we *would* see, isn't it?

The slide below (ME/CFS research: Core Problem?) attempts to show this problem graphically. While the greatest portion of the circle represents the 'set' of patients with chronic fatigue (CF); i.e., with at least some of the non-specific symptoms including the F-word 'fatigue' (and this set may represent between 1 and 4% of the population), you can see that the set of patients with CFS (i.e., those with 'fatigue' plus 4 symptoms) is much smaller (estimated to be 0.2 to 0.4% of the population in the CMO report of 2002), while those with ME as described in the older scientific literature might represent a subset of CFS itself, since post-exercise 'fatigue' is a key element in their illness (population estimates are unavailable for this subset since healthcare professionals no longer diagnose ME per se). The important point is that

the each slice melds into the next, and that — in the absence of a full clinical assessment — the popular press, healthcare professionals and medical researchers may easily be deceived about the placing of a particular patient (i.e., experimental subject) in a particular diagnostic category.



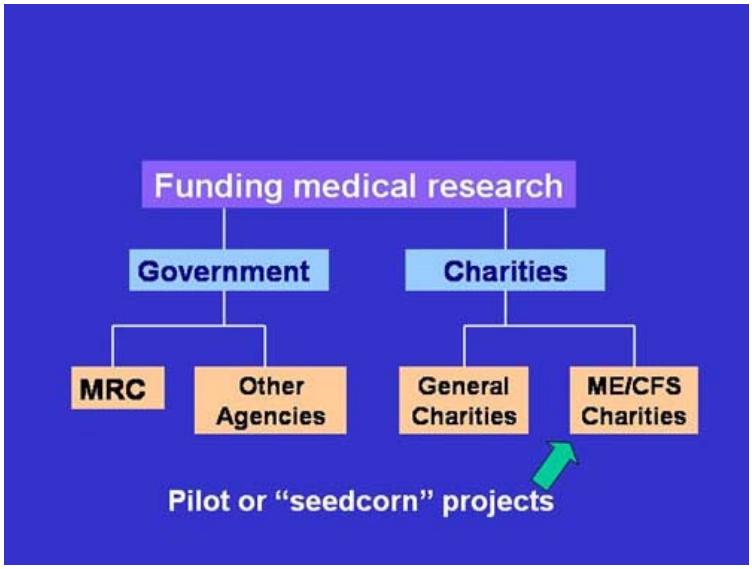
It is also important to recognise that this is only a scheme, a way of seeing, and that the problem may be more or less complex in reality. However, Dr Charles Shepherd of the ME Association put the situation very well in a recent letter (British Medical Journal, December 2004; 329: 1405): "The medical profession has only itself to blame for the awful mess that currently surrounds ME/CFS. It has created an illness that covers a wide variety of fatigue state clinical presentations, with or without psychiatric co-morbidity, and almost certainly an equally diverse range of possible pathological and physiological explanations. Doctors who deal with patients suffering from unexplained abdominal pain, arthralgia or headaches do not work on the basis that they all have the same pathoaetiology and will therefore respond to the same form of treatment. So why apply this form of flawed logic to ME/CFS?"

While this is a central problem, it is not insurmountable. The key point, however, is that the patients selected for biomedical research studies must be well-categorised; i.e., have a full clinical examination (and there is good reason to believe that neuromuscular weakness can be found in patients if such assessments are made), and, ideally, be subsetted according to particular criteria — and the subgroups specified by the Canadian definition of ME/CFS devised in 2003 may come to be seen as a useful starting point for such work.

For there is clearly something different about these patients. Indeed, there is substantial evidence that, despite the apparent heterogeneity of the patient group, biomedical researchers can uncover a range of interesting anomalies, as described in Advances in Biomedical Research. Indeed, fascinating results continue to be published by research groups worldwide: these include reduction of brain serotonin

transporters (Yamamoto, 2003), delayed gastric emptying (Burnett, 2004), and altered muscle excitability in response to exercise (Jammes, 2005).

But how does such biomedical research get funded? The diagram below gives a very basic outline of the origins of medical research funding. On the left, we see the larger national agencies, such as the Medical Research Council (MRC), the Chief Scientist Office (CSO), and NHS rsearch and development. On the whole, these allocate funds to established research groups with a track record of success in a certain area, on the basis of a reasonable scientific hypothesis. In recent years, these agencies have given millions of pounds to internationally-recognised groups of psychiatrists/psychologists to investigate the effect of psychosocial interventions on the management of the symptoms of ME/CFS.

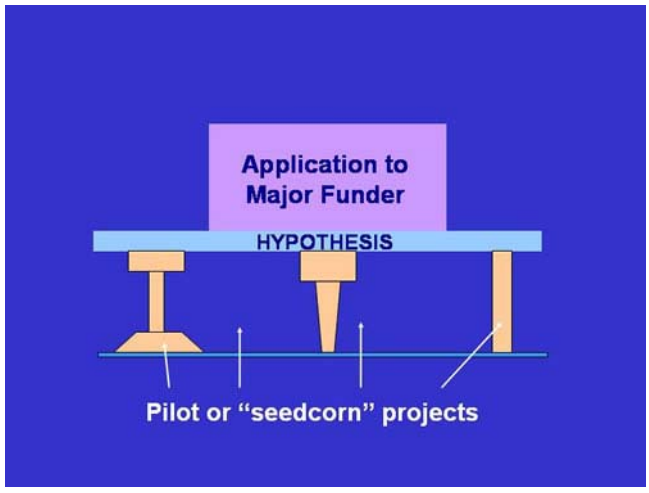


In the same diagram, we see charity-funded research. Interestingly, in most diseases (cancer included) charity-funded research predominates — more than 80% of cancer research funding in the UK comes from charitable sources, for example. However, in ME/CFS, charities funding biomedical investigation are small and rare: the CFS Research Foundation, MERGE itself and the research fund of the ME Association. In effect, patients, carers and friends are having to fundraise at ground level to pay for research into the illness that affects their own lives. Yet, bizarrely, because research is so expensive to mount, the aggregated annual income of all three would barely pay for one medium-sized randomised controlled trial for one year. It's worth thinking about.

It is difficult to overestimate the anger among ME patients at this state of affairs, and it is well to remember that there are some 20,000 members of ME support groups in the UK alone, and that 28,000 people signed the petition in 2004 calling for urgent government-funded research into the physical causes of ME/CFS. There are two problems as they see it. First, the volume of overall research is paltry compared with that going on in other comparable illnesses; and, second, there is an apparent selective

allocation of funding for non-curative psychological management strategies — particularly cognitive behavioural therapy and graded exercise — without corresponding resources going to find the cause of the illness. The situation is particularly galling given the fact that the large-scale review of patient feedback submitted for the CMO report of 2002 showed that only 7% of people with ME/CFS found cognitive behavioural therapy to be "helpful", and that around 50% of people reported that graded exercise had made their condition "worse", and given the fact that ME and CFS are both classified as neurological disorders by the World Health Organisation in section G93.3 of their 10th revision of the International Classification of Diseases. The cartoon (by Trish Campbell of the Warwickshire Network for ME) illustrates what many patients say, that if healthcare professionals — GPs, psychiatrists, psychologists and opinion formers at the national agencies — contracted ME/CFS themselves, funding for biomedical research would not be long in coming.

For the future, then, what we should like to see is central (e.g., MRC, CSO, and NHS research and development) funding allocated for biomedical research to pump-prime the process, through a form of ring-fencing. Until that day dawns, the ME/CFS research charities have three tasks. First, to encourage established research groups into the field. Second, to spend their presently limited resources on novel clinical and biomedical studies that help to unravel the biology of the illness — innovative pilot studies or seedcorn projects are particularly important since they can give rise to the supporting data on which future applications to major funding bodies will have to be based (see diagram above). Last, we need to collaborate with anyone anywhere, particularly other ME/CFS organisations, who can help us to get these projects off the ground.



Twenty-five years is a long time to be ill, but strangely I feel more confident of a breakthrough now than at any other time, and look forward to the day when (like in the cartoon below by Trish Campbell) committees of major funding bodies rejoice at the chance to fund the quest for the cause and cure of ME/CFS.