RESEARCH CHALLENGES IN ME/CFS

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INTRODUCTION

For Socrates, uncertainty was better than certainty because it presented challenges which, when overcome, resulted in the discovery of the real facts of the world. From this lofty viewpoint, then, ME Research UK should be proud to be working in the field of ME/CFS. Aside from the usual challenges of conventional biomedical science (isolating the cause of the illness, testing therapies and developing treatment programs), there are particular challenges specific to ME which impact on "making a breakthrough".

What are these additional challenges, and how might they be overcome to the benefit of patients, estimated by the 2007 NICE guideline to number over 193,000 in the UK alone (250,000 people with ME according to some charities)?

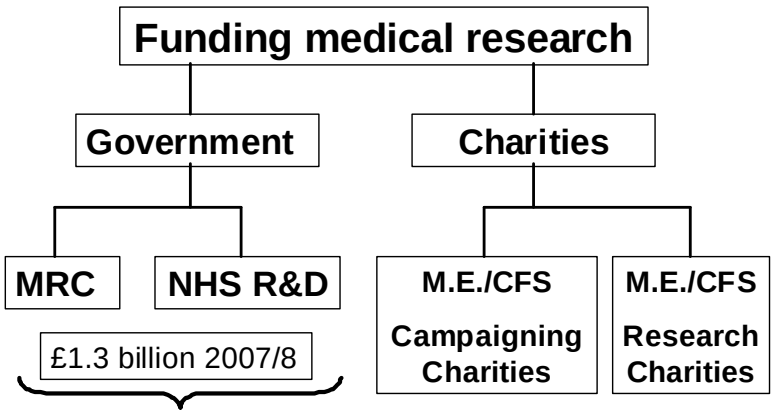
FUNDING CHALLENGE

Money is the platform which supports all biomedical research. But there is a problem: medical research is expensive — one medium-sized clinical trial can cost £300,000 and can possibly have an inconclusive result — so big money will be needed to unravel the causes and find cures for ME/CFS.

The diagram below gives a very basic outline of the origins of medical research funding in the UK. The best-known elements are the larger national agencies (called Class 1 funders), such as the Medical Research Council (MRC) and the NHS Research and Development, which allocate funds to established research groups with a track record of success in a certain area, on the basis of a reasonable scientific hypothesis.

It is very difficult, however, for any researchers in any field to obtain funding from these central sources — the MRC funds only 4 out of every 20 applications, sometimes only after substantial revision — and in any case the money available (some £1.3 billion in the current year, for all types of research across all illnesses) does not go far given the expense of the investigations and many demands made. Even if the biomedical investigation of ME/CFS got its fair share of Class 1 funding — something that many of us are still pressing for — that share would fund only a small part of the biomedical activity that is necessary.

ME/CFS research funding



In fact, a significant proportion of research funding for many, if not all, illnesses comes from charitable sources — the Association of Medical Research Charities estimates that some £791 million was spent on projects in 2006/7 by its members. The beauty of these sources is that unlike government sources they are illness-specific, since donors can give to the cause of their choice: taking cancer as an example, the annual income of Cancer Research UK to 31st March 2007 was £468 million and it is only one of a large number of cancer charities. Much of this income comes directly or indirectly from public donations.

We have to do the same for ME/CFS. As most patients are too ill to fundraise themselves, our strategy has to be to raise awareness of the need for biomedical research into the illness, ensure that our organisations are worthy of the trust and support of patients, carers and fundraisers, and get and keep the research community on-side in the struggle.

DIAGNOSTIC CHALLENGE

CFS is not a 'clean' diagnosis. In 2007, there are at least three different definitions of CFS in use, all non-validated and all based on vague, non-specific symptoms shared with other common illnesses. While it is likely that they overlap, they do not necessarily contain scientifically comparable groups of patients, a fact which complicates the comparison of studies and raises questions about how representative are the findings of any particular study. In a biomedical world which prizes homogeneous groups of patients — those with a confirmed diagnosis, sharing similar signs and symptoms and fulfilling strict criteria — it is a real complication.

What can be done about this? We could return to diagnosing 'classic' myalgic encephalomyelitis (ME), involving an infectious onset, a variety of neuromuscular symptoms and signs, and a post-exercise component. But since there are several different definitions — none recognised by modern medicine or science today — it is hard to see that as a viable option in the short to medium term. One strategy which has a lot of support is to subgroup patients on the basis of symptom clusters — the Canadian definition of 2003 could be the basis for such an attempt — or on the severity of existing symptoms (which might result in the identification of 'classic' ME patients at one end of the spectrum, as suggested in a scientific paper in 2003 (1).

Whatever the eventual resolution, this central problem tends to increase the costs of research studies, because ideally volunteers need to be screened and categorised by medical

examination. Interestingly, however, biomedical anomalies can indeed be found in patients diagnosed with ME/CFS — there are many reports out there which show this; e.g., the report in September 2007 (2) describing the discovery of enterovirus VP1 protein in 135/165 (82%) of stomach biopsy samples of CFS patients compared with only 7/34 (20%) of control samples; or the paper in 2004 which identified, after clinical examination, muscle weakness in the lower limbs, and absent or abnormal reflexes in ME/CFS patients (3). And it may be that careful screening for ME/CFS, with proper exclusion of those with differential diagnoses, is one of the most useful things that can be done.

THE ELEPHANT IN THE ROOM

The 'elephant in the room' — ever-present but rarely alluded to in the media or the mainstream scientific literature — concerns the overarching influence of the psychosocial model of the illness, which emphasises "beliefs, coping styles, and behaviours" (summarised in the Chief Medical Officer's report of 2002). It colours the perception of the illness across the board — from official reports such as the 2007 NICE Guideline, to the policy of government agencies such as the Department of Work and Pensions and NHS Plus. But it also impacts on research. In most illnesses, research on psychosocial aspects is an adjunct to the contemporaneous biomedical research that spearheads the drive towards a cure. Yet, in ME/CFS, psychosocial investigation seems to have hoovered up attention and funding at the expense of hard-core biomedical investigation. Take the Medical Research Council for example: the vast bulk of its £3 million ME/CFS grant-spend since 2002 has gone towards research into psychological management strategies, while around 30 other applications, some from established biomedical research groups with a track record in the field, have been rejected — facts we only know because some stalwart patients have requested the information under the Freedom of Information Act. Moving basic scientific and clinical research centre-stage, into the spotlight presently occupied by psychosocial models in the minds of opinion formers and healthcare professionals, is one of the greatest challenges.

ATTRACTING RESEARCHERS

ME/CFS biomedical research is not 'sexy' in scientific terms — in this respect it resembles leprosy, a field I worked in a decade ago. Because its profile is low and coloured by the emphasis on psychosocial aspects of the illness, and characterised by disparaging labels ("yuppie flu", "all in the mind"), and because researchers looking in would see little chance of high-level funding, encouraging established researchers into the field — and attracting fresh young investigators — is one of the biggest problems we face. However, by advertising inside the NHS, by encouraging applications from our website and hosting conferences (as well as a little personal persuasion), we are convinced that interest is slowly increasing. ME Research UK now provides funding to the Universities of Newcastle, Dundee, Strathclyde, Brussels, London (St George's and Hammersmith), Glasgow and Calgary.

NEED FOR CONSISTENCY

There is also a need for consistent directed work over a broad front. Funding a smallish pilot study is one thing, but real breakthroughs come at the end of a programme of painstaking work by a specialist group of researchers.

One of the few examples in ME/CFS in the world is the work at the Vascular Diseases Research Unit, University of Dundee, which has received several grants from ME Research UK since 2001. In a step-by-step progression involving both adults and young people with the illness, the group has uncovered:

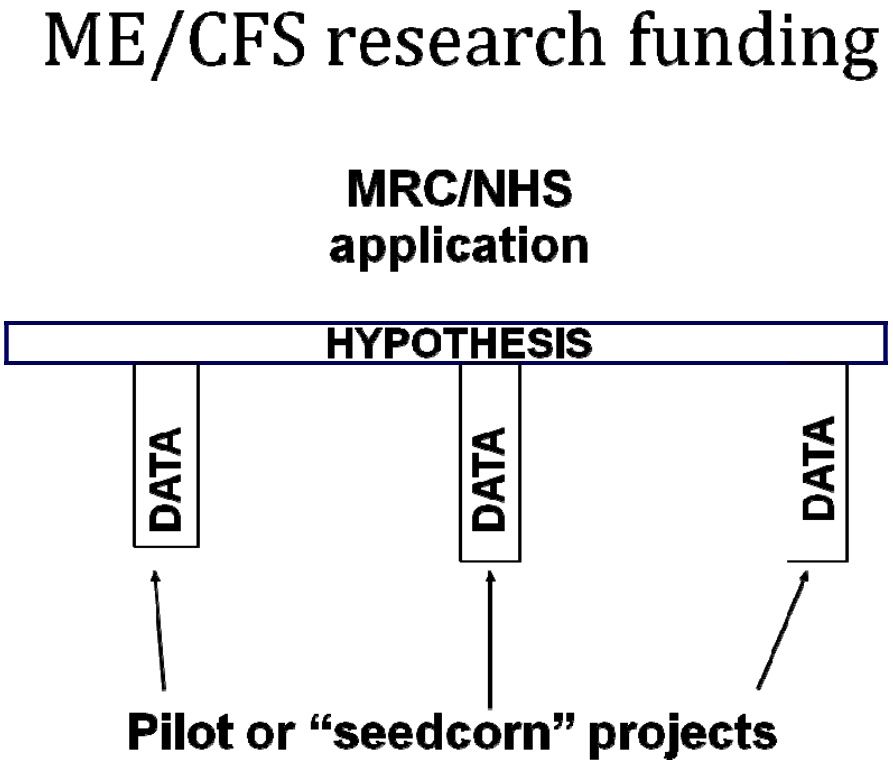
- unusual sensitivity of blood flow responses to acetylcholine (a neurotransmitter),
- increased levels of isoprostanes (a gold standard marker of oxidative stress in the bloodstream),
- an unexpected increase in dying (apoptotic) white blood cells, consistent with an activated inflammatory process or persistent infection, and
- increased cardiovascular risk factors with arterial stiffness in patients.

Such a progression — whether towards positive findings or away from negative ones — is the norm for scientific investigation. The burning need in this illness is for there to be many groups undertaking programmes of research across a range of basic and clinical sciences fields so that a 'critical mass' of investigators can produce a 'critical mass' of biomedical data.

TARGETING SCARCE RESOURCES

Research charities such as Cancer Research UK which raise millions of pounds per annum have the luxury of providing core funding for dedicated research units year-on-year, offering specific researcher awards, and commissioning their own research.

As yet, this has not been possible in ME/CFS, so ME Research UK's short-term strategy has been to provide essentially pilot funding to 'pump prime' work of potential importance. The resulting publications help to build critical mass in the scientific literature and the data obtained can form the basis of researchers' subsequent applications for Class 1 funding. The challenge here is to make the best use of scarce resources.



CONCLUSIONS

There cannot be many other illnesses in which so many unusual challenges stand in the way of 'making the breakthrough'. The ideal scenario would be for central (e.g., MRC and NHS R and D) funding of biomedical research to be provided through a form of ring-fencing, making it much easier to entice good, established biomedical researchers into the field.

But this alone is not the answer. Experience has convinced us that the funding strategy for ME/CFS must mirror that of other illnesses such as cancer research which obtains most of its revenue from private sources and ground-level fundraising. It is a huge task, but much can be achieved by a determined and collaborative ME community.

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