

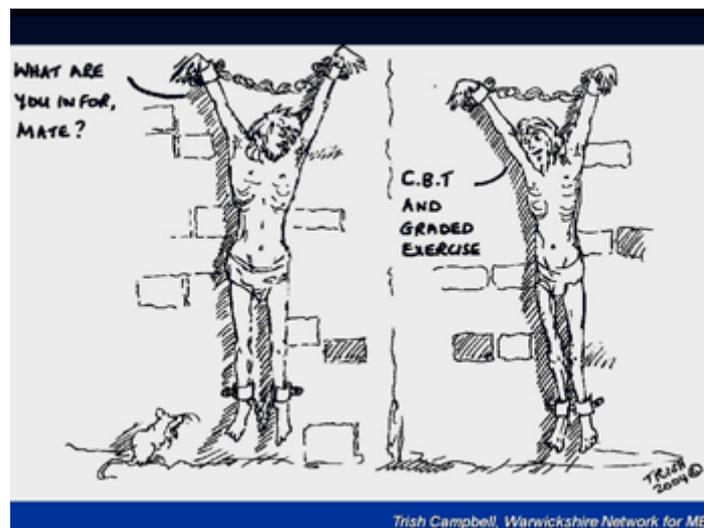
ME/CFS Research: What do patients want? Why isn't it happening?

This is an expanded version of a talk given by Dr Neil Abbot (Operations Director of ME Research UK) at the Royal Society of Medicine conference "Medicine and me: ME and CFS — Hearing the patient's voice" on Saturday 11th July 2009.

Introduction

In 2008, the Royal Society of Medicine hosted a full-day meeting on Chronic Fatigue Syndrome, that focused mainly on biopsychosocial aspects of the condition, so it is a delight to see a meeting in the 2009 "Medicine and ME" series of events designed to "bring together professionals and patients" to explain and explore some aspects of the illness. It would be marvellous if this led on to a larger RSM-hosted meeting in future years centring on biomedical aspects of the illness and attracting experts from around the world.

The title we were given was "ME/CFS Research: What do patients want? Why isn't it happening?" — a big tent of a topic for a 15-minute presentation.



Cartoon by Trish Campbell

There's no apology for starting with the wonderful cartoon by Trish Campbell (Warwickshire Network for ME) since it illustrates the situation many patients find themselves in: a Kafkaesque nightmare involving physical illness compounded by the scepticism of healthcare professionals and the disbelief of family and friends. These two prisoners haven't been out to the GP for years, they certainly haven't been properly physically examined for a long, long time, and their quality of life is poor, illustrating what two separate recent reviews have concluded, namely that "*patients exhibit severe, long-term functional impairment. Substantial improvement is uncommon and is less than 6%*" (1); and "*Full recovery... is rare*" (2).

But the cartoon also indicates that the management strategies making up the bulk of the 'treatments' on offer by the National Health Service in the UK — "CBT and Graded Exercise" as the hanging prisoner says — seem absurd to patients and carers given the problem on the ground. Which brings us to the first suggested answer to the question, "ME/CFS Research: what do patients want?"

ME/CFS Research: What do patients want?

a) *Less emphasis on psychosocial aspects*

It's not surprising that in an 'orphan' illness like ME/CFS there are several hypotheses and proposals to explain how it might be caused or maintained. One of these is the 'biopsychosocial model' of ME/CFS, described in the Chief Medical Officer's report of 2002 as, "*The biopsychosocial model of pathophysiology, applicable to all disease, suggests that once an illness has started its expression is affected by beliefs, coping styles, and behaviours, while consequential physiological and psychological effects act in some ways to maintain and/or modify the disease process*" (3).

The limitations of this model, and the evidence base for its use in ME/CFS, have been comprehensively discussed elsewhere (e.g. "The NICE Clinical Guideline: convincing evidence?"), but it's important to point out that the strategies which it used — cognitive behavioural therapy (CBT) and graded exercise therapy (GET) — are applicable to all illnesses and are therefore not specific to ME/CFS; are used to 'manage' symptoms but are not generally thought to be curative *per se*; and that while the 'biopsychosocial' side dominates treatment and research in the UK, its influence is considerably less in the USA where research interest is most intense. As far as research is concerned, most effort in Britain and most if not all Class 1 funding from sources such as the Medical Research Council has gone towards research into the usefulness of CBT and GET.

Interestingly, a recent meta-analysis of the effect of CBT for ME/CFS showed that, overall, the outcomes of the intervention were mild to moderate (effect size 0.4) (4). Indeed, a large body of both professional and lay opinion considers that these are essentially adjunctive techniques, and have little more to offer than good medical care. As Carruthers *et al* have pointed out in their superb review (5), "*The question arises whether a formal CBT or GET program adds anything to what is available in the ordinary medical setting. A well informed physician empowers the patient by respecting their experiences, counsels the patients in coping strategies, and helps them achieve optimal exercise and activity levels within their limits in a commonsense, non-ideological manner, which is not tied to deadlines or other hidden agenda.*"

The scientific literature also contains concerns about many of the 'shibboleths' surrounding the influence of psychological factors of various kinds in the development or maintenance of ME/CFS. Two examples suffice.

The first concerns 'somatisation', a term occasionally used to describe ME/CFS or other groups of patients said to focus irrationally on their bodily (somatic) symptoms; these patients, it is said, "*experience and communicate somatic distress and symptoms unaccounted for by pathological findings... attribute them to physical illness... and seek medical help for them*". However, a recent review (6) of patients seeking treatment for pain (a symptom reported by 79% of ME/CFS patients in one large survey, and by 87% of 2,073 consecutive ME/CFS patients in one published study (7)) concluded, "*We recommend that researchers... do not use the term somatisation but use the term multiple physical symptoms instead... Making sense of physical symptoms that cannot be explained by current medical models may easily lead to a psychologisation of illness.*" This paper strikes a particular chord since many patients on the ground do indeed feel shunted towards a psychological explanation for their symptoms early in the assessment

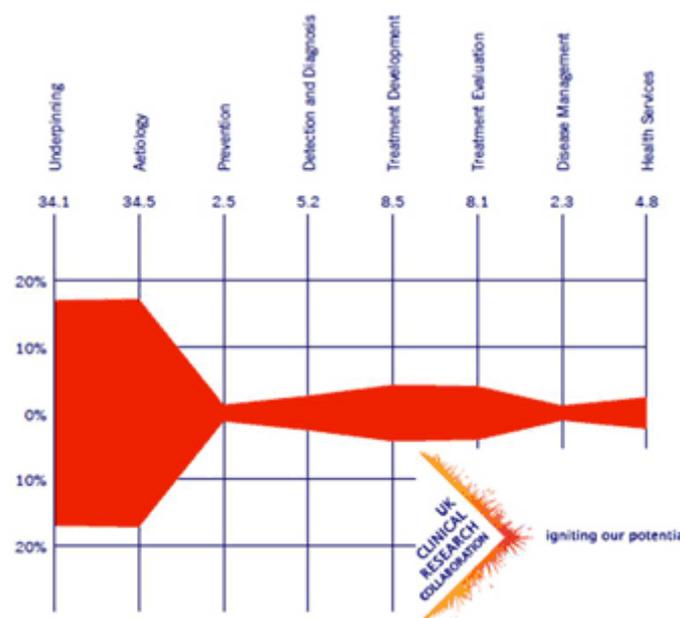
process, when a biomedical investigation for the causes of their pain or other symptoms would be most appropriate.

A second example concerns ‘personality’ and its apparent role in the illness, with some reports claiming rates of personality disorders as high as 40% among patients — some of these claimed personality disorders go under exotic, rather enthralling names, such as alexithymia (emotional deficiency), action-proneness, learned helplessness, and histrionic states. However, Belgian investigators (8) recently evaluated the prevalence of ‘DSM-IV-TR personality disorders’ in a sample of 50 women with ME/CFS and, importantly, in two matched control samples.

The results showed a striking similarity between the ME/CFS sample and the Flemish healthy control group on various measures, including the prevalence rates of an Axis II disorder (defined as “*underlying pervasive or personality conditions, as well as mental retardation*”) which were 12% in both the healthy Flemish and ME/CFS groups compared with 54% in the psychiatric sample. As the researchers say, “*The results of the present study are unambiguous and straightforward... a person diagnosed with CFS is as (un)likely to have a personality disorder as a subject without CFS.*”

b) Far more emphasis on Biomedical Research

The corollary of a decreased emphasis on psychosocial research is that focus will turn to biomedical model-based research, in which ME/CFS is seen as “*a condition like many other medical conditions where illness results from a specific pathological defect in physiological functioning, mediated at organ, tissue, cellular and/or molecular level, by as yet undefined mechanisms. It... implies that a primary disease entity exists and that the biopsychosocial aspects are consequential*” (3).



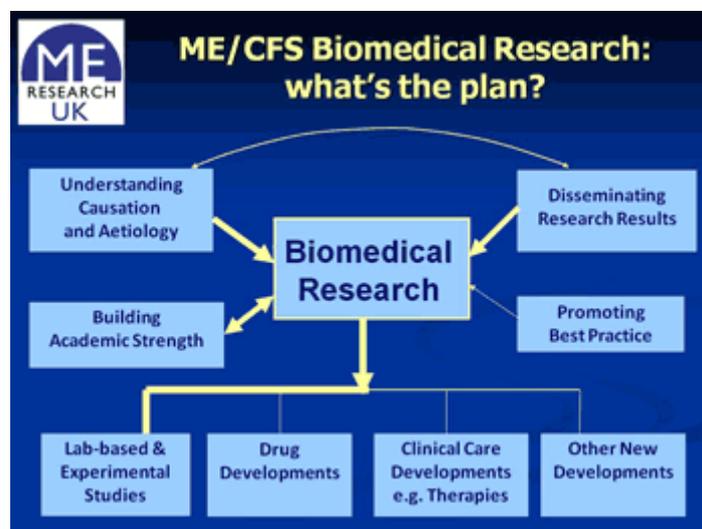
Research funding in the UK

Interestingly, from the UK Clinical Research Collaboration’s document, “UK Health Research Analysis (2006)”, we have a map of the distribution of total funding spend by research activity in UK, so we know

what the pattern of spending looks like in other illnesses and across all illness as a whole (9). The Kite diagram shows the proportion of total spend by research activity (indicated at the top of the kite diagram), with data from the 11 largest government and charity funders of health research in the UK.

The first important point to note is that the great bulk (68.4%) of all grant spend for all illnesses is to the left of the Kite, i.e. is spent on 'aetiology' (research into the risk or cause and development of ill health and diseases) or 'underpinning' (research into understanding normal processes and functioning, forming the basis for subsequent investigations) — so the type and distribution of funding that ME/CFS patients want to see is actually the norm looking at the global spend in the UK.

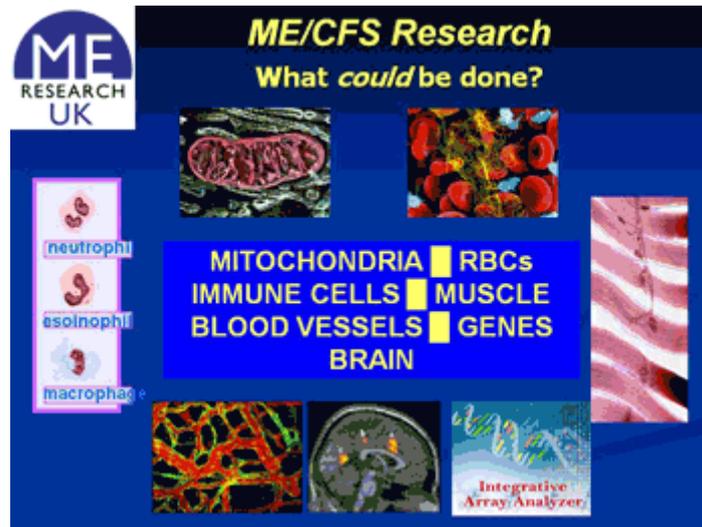
The second point is that the red areas on this diagram represent many hundreds of millions of pounds, spent across all illnesses — if the actual UK grant spend in ME/CFS from all sources, charitable included, was drawn on it, it would be a very thin red line indeed (and almost invisible!).



The plan for ME/CFS biomedical research

There is no doubt about the areas of biomedical investigation that need to be targeted — the diagram flags up 'understanding causation and aetiology' and 'lab-based and experimental studies' as the most vital initial steps. And everyone agrees that a Centre of Excellence — a single point of reference to which ME/CFS patients could be referred for biomedical assessment and investigation — would be invaluable. Ideally, operating hand-in-glove with the Centre (providing a ready source of properly diagnosed patients) would be a national ME/CFS Research Centre.

There are many templates on which such an entity could be modelled; one example is the BHF Glasgow Cardiovascular Research Centre (GCRC), a joint venture between charity and University set up in 2005 with the specific aim of providing a multidisciplinary research environment for their investigation of cardiovascular illnesses.



ME/CFS — What could be done?

And there are so many tantalising areas of ME/CFS biomedical research that could be fruitfully explored further. For example:

i) Mitochondria: As ME/CFS is characterised by a profound, generalised post-exertional loss of muscle power, it seems reasonable to suggest that mitochondrial dysfunction may be involved; indeed, over the years, there have been a number of (necessarily small, given the high cost) investigations exploring this aspect and reporting the presence of anomalies. There is indeed a sense that not all is well with mitochondria, and that intriguing findings might well be uncovered from a battery of validated mitochondrial tests from a larger sample of well-characterised ME/CFS patients (and controls) and their extended families.

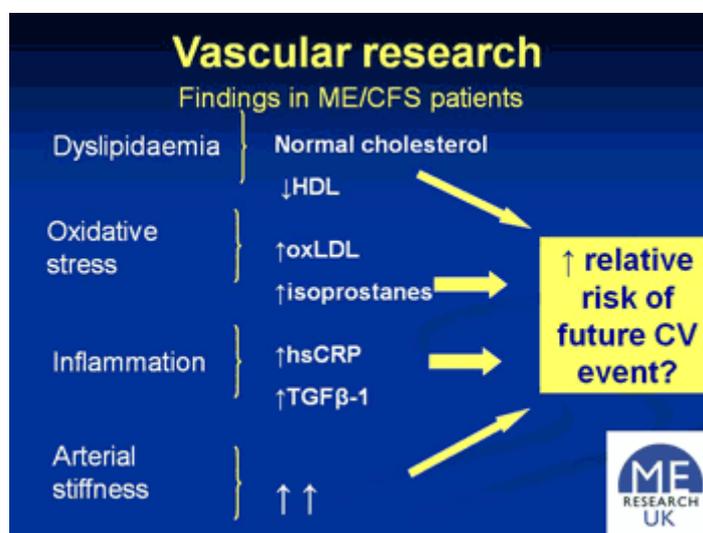
ii) Infection and immunity: ME/CFS cases are commonly triggered by a viral infection, and the burning question is why an initial infection persists in some people — with serious consequences that can last a lifetime — but not in others. Chronic immune activation has long been thought to be a component of ME/CFS, and there is much diverse evidence (reviewed by Klimas and Koneru) (10) that could form the basis of further intense investigation.

iii) Brain and CNS: In historical publications on epidemics of ME, symptoms consistent with central nervous system pathology were reported with regularity, and were as characteristic as the post-exercise malaise, myalgia or the range of other symptoms that patients experienced. It has not yet been established for certain what causes the prominent cognitive dysfunctions in the illness, but factors which might contribute include vascular insufficiency, metabolic dysregulation or an ongoing infectious process. A range of structural and functional studies to date have had positive findings that in any other illness would have been explored further.

One of the most recent is a report from Cornell University in New York (11) showing average lateral ventricular lactate concentrations to be increased almost three-fold in ME/CFS patients compared with generalised anxiety patients, and 3.5-fold compared with healthy volunteers (both $p < 0.001$), even after

controlling for ventricular volume, raising the possibility of a decreased regional cerebral blood flow with consequent increases in brain lactate.

iv) Vascular: Reports of vascular anomalies have appeared regularly in the scientific literature on ME/CFS over the years. Most recently, the Vascular and Inflammatory Diseases Research Unit, University of Dundee, which has received several grants from ME Research UK since 2001, has uncovered unusual sensitivity of the 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 ME/CFS patients. On balance, with the observed dyslipidaemia, oxidative stress and inflammation, ME/CFS patients have a lipid profile and oxidant biology that is consistent with, but not necessarily accompanied by, increased cardiovascular risk. It is surely important that these results are expanded and reproduced by others.



Vascular findings in ME/CFS

The point of listing the above is to show the plethora of areas in which further biomedical investigation is warranted. What patients want to see is a general advance across a broad range of scientific fronts.

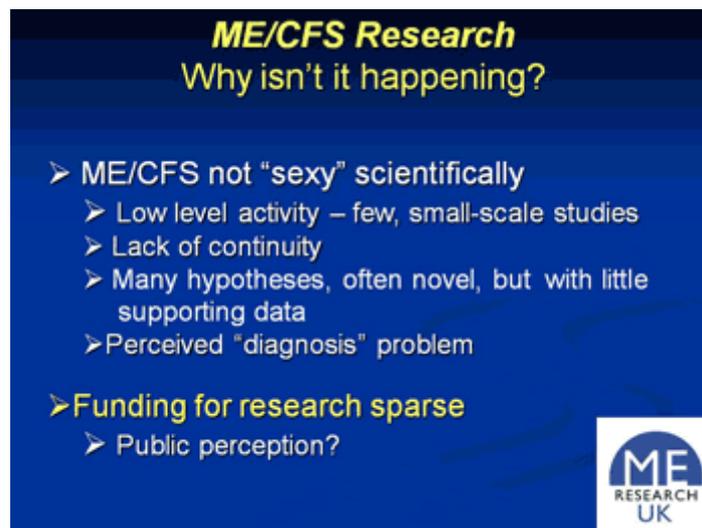
ME/CFS Research: Why ‘what people want to see’ isn’t happening

(i) ME/CFS not ‘sexy’

ME/CFS biomedical research is not ‘sexy’ in scientific terms. 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, one of the biggest challenges lies in encouraging established researchers into the field (and attracting fresh young investigators).

Interest in researching the illness is increasing (ME Research UK now provides funding to the Universities of Newcastle, Dundee, Strathclyde, Brussels, London (St George’s and Hammersmith), Glasgow and Calgary), yet much more has to be done. In fact, ME/CFS biomedical research really is a fertile field for new

discovery, and a fresh exciting challenge — and this has to be conveyed to and recognised by the wider scientific community.



ME/CFS Research
Why isn't it happening?

- ME/CFS not “sexy” scientifically
 - Low level activity – few, small-scale studies
 - Lack of continuity
 - Many hypotheses, often novel, but with little supporting data
 - Perceived “diagnosis” problem
- Funding for research sparse
 - Public perception?



Why isn't ME/CFS research happening

ii) Scientific/biomedical activity is low-level

One of the striking things about the ME/CFS scientific literature — across all disciplines and models of the illness — is just how small it actually is. To give an example, the absolute number of MEDLINE-listed articles over the past 10 years for the broad subject area ‘schizophrenia’ is approximately 32,800; for ‘rheumatoid arthritis’ 32,000; for ‘multiple sclerosis’ 20,000 — and for ME and CFS together 2,500.

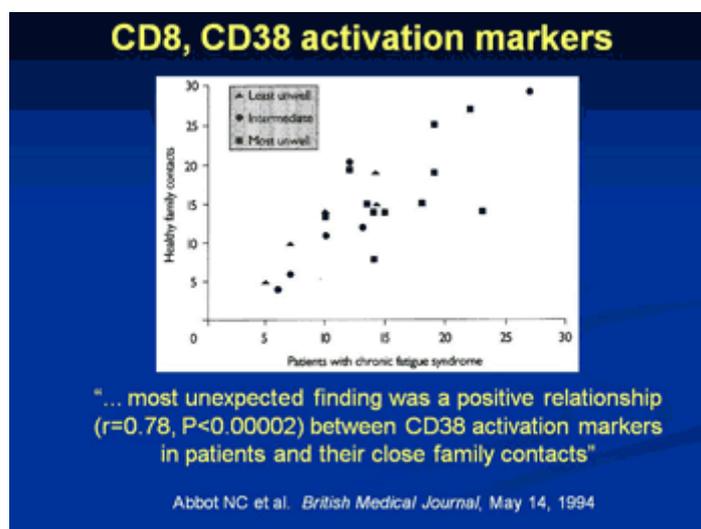
The discrepancy between the size of the scientific literatures on multiple sclerosis and ME/CFS is even more striking when you consider that the prevalence of multiple sclerosis is between one third and one half that of ME/CFS. Put another way, if ME/CFS elicited the same level of scientific interest as multiple sclerosis, there would have been around 30,000 to 40,000 MEDLINE-listed articles in the past decade instead of the 2,500 in actuality. This is what we mean when we say that scientific activity is at a low level in ME/CFS, and so long as this continues the illness will be disadvantaged. In reality, for breakthroughs to occur, there have to be many, many groups around the world 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.

iii) Lack of continuity

One consequence of the lack of profile of ME/CFS as an illness is that whatever research is, in fact, done tends to be piecemeal and discontinuous. Two simple examples, from the early 1990s, illustrate the point. In the first (12), blood flow at the brain stem of 43 ME/CFS patients was found to be significantly lower than in healthy controls ($p < 0.0001$) and patients with major depression ($p < 0.005$); a fascinating result which might have clinical significance, but which has never been reproduced with equivalent methodology.

In the second (13), ME/CFS patients were found to have higher blood levels of CD8, CD38 T cells (markers of immune activation) than controls, and (unexpectedly) there was a strongly positive relationship between

activation markers from patients and their close family contacts. Could it be that an infectious agent affects both patients and household contacts but causes symptoms only in patients, or is the relationship entirely innocent? No-one knows, since follow-on work by independent groups has never been done.



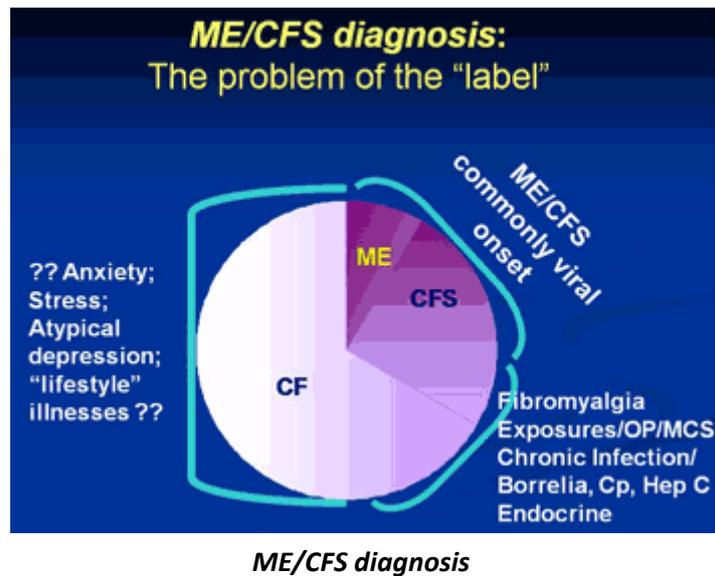
CD8, CD38 activation markers

Funding smallish pilot studies 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 and Inflammatory Diseases Research Unit, University of Dundee, which in a step-by-step progression has uncovered a range of anomalies, but such a progression, following progressive funding, is rare indeed.

iv) Diagnosis: the clinical problem

ME, CFS, CFS/ME and ME/CFS mean different things to different people, whether members of the public, patients, clinicians or researchers. This problem colours all debate on ME/CFS, yet rather like the whiteness of a wall it is often not recognised as a colour at all. The problem has been alluded to many times, but the central point for this discussion is that diagnostic difficulties queer the pitch both at the clinic and in the research lab, and hinders the progress everyone wants to see.

The slide below is our attempt to describe the problem graphically — though we must be aware that this is only schematic, a way of visualising the problem which may be more or less complex in reality. While the greatest portion of the circle represents the set of patients with chronic fatigue (CF) — which might represent between 1 and 4% of the population — you can see that the set of patients with CFS (i.e., those with 6-months fatigue plus 4 symptoms) is much smaller (estimated to be 0.2 to 0.4% of the population in the Chief Medical Officer's 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 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 in a particular diagnostic category.

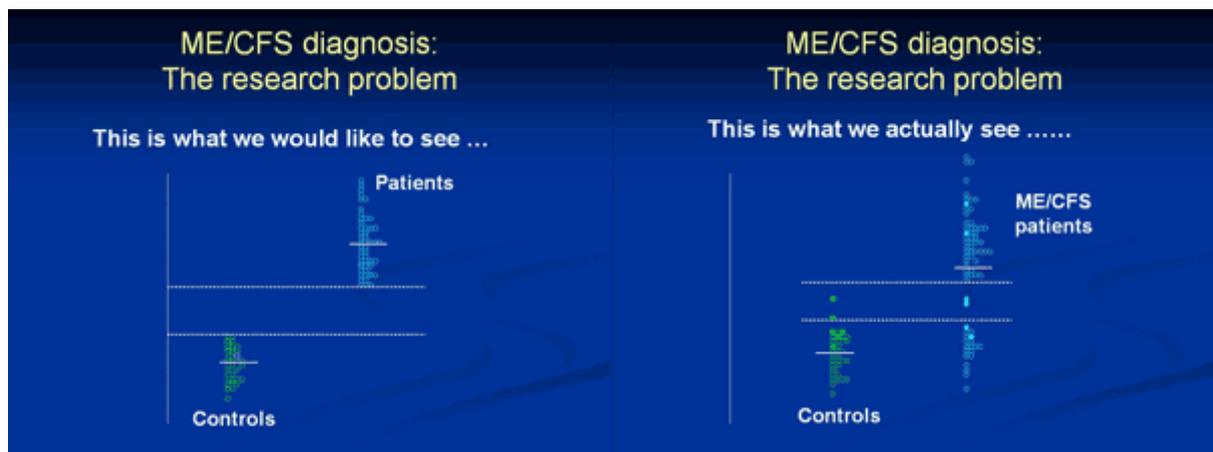
Fortunately, we have two real examples which illustrate the problems that can arise if investigations to exclude other conditions are not performed before the “diagnosis of exclusion” ME/CFS is given. The first was an audit of 100 consecutive outpatients with CFS in the University of Dundee in 1993: of these patients, 21% were found to have other organic illnesses (e.g., muscle, connective tissue, endocrine disorders); 12% had psychiatric disorder alone; and 7% fibromyalgia. The second was an audit of service in 2007 after 3 years at the CFS/ME CNCC in Newcastle: CFS was confirmed in 56% of referrals, but alternative diagnoses were provided in 28%, sleep apnoea was diagnosed in 9%, and depression and anxiety in 7%. Thus, it can be seen that in around 40% of patients referred from primary care with a diagnosis of ME/CFS, alternative exclusionary diagnoses can be found after investigation at a specialist clinic.

For clinicians presented with a heterogeneous group of patients referred from primary care with a diagnosis of ME/CFS, the problem can be acute, and was prettily expressed in a recent article by Fischer et al in 2008 (14). Describing a clinic seeing patients with fatigue, exercise intolerance and weakness (very like ME/CFS patients), the authors say, *“Sometimes in our clinic, we feel as if we’re wandering through a herd of zebras... Not all the ‘stripes’ on the animals are the same, and not every animal in the herd is actually a zebra... Navigating through clinical complexities is difficult, and we’re still learning how to best diagnose and manage our patients.”*

v) Diagnosis: the research problem

In a biomedical world which prizes homogeneous groups of patients — those with a confirmed diagnosis, sharing similar signs and symptoms and fulfilling strict criteria (such as males aged 30 to 50 with confirmed HIV infection and a white blood cell count less than 400 CD4/mm³) — the diagnostic mess that is ME/CFS is a real complication. In ME/CFS what we see over and over again are the graphs below (the upper, an ideal

scenario; the lower from a real biochemical experiment on ME/CFS patients), with the controls nicely tightly packed, and the 'CFS' patient measurements much more widely scattered.



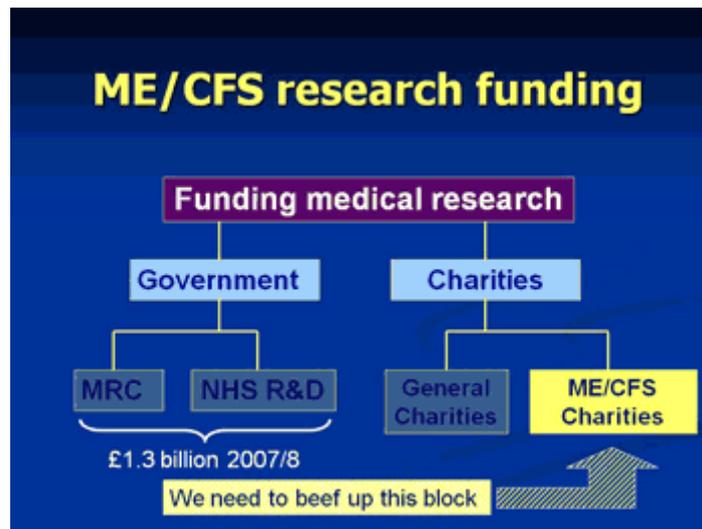
The research problem

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. It is therefore important to select for biomedical research studies patients that are well-categorised; i.e., have a full clinical examination (and there is good reason to believe that neuromuscular signs 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.

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, so 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.

vi) Funding for biomedical research in ME/CFS is sparse

According to its financial statement of 31st March 2008, Cancer Research UK had an income of £476,559,000. In approximately the same period, ME Research UK's income was £264,862. Indeed, if all potential charitable sources of funds in the UK were included, the total available charitable spend would not exceed £400,000, a figure which barely covers the cost of one medium-sized clinical trial (which might in fact have an inconclusive result). This is a core problem, and the major reason why the biomedical research patients want to see is not happening.



Big money will be needed to unravel the causes and find cures for ME/CFS. As the diagram shows, some medical research funding in the UK comes from 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. But getting monies from these larger funders is very difficult, and 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. As most research funding for many, if not all, illnesses comes from charitable sources, i.e. directly or indirectly from public donations, we have to beef up our efforts, increasing funding by a factor of 10 to 100, and attracting new blood and fresh ideas into the field.

ME/CFS Biomedical Research: Quo Vadis?

- ↑ Funding (by a factor of 10—100)
 - MRC Expert Group on ME/CFS
 - *Ground-level fundraising*
- ↑ Number of research groups
 - Step by step continuous progress
 - Critical mass of data
- ↑ Fresh ideas, New blood



Quo vadis?

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