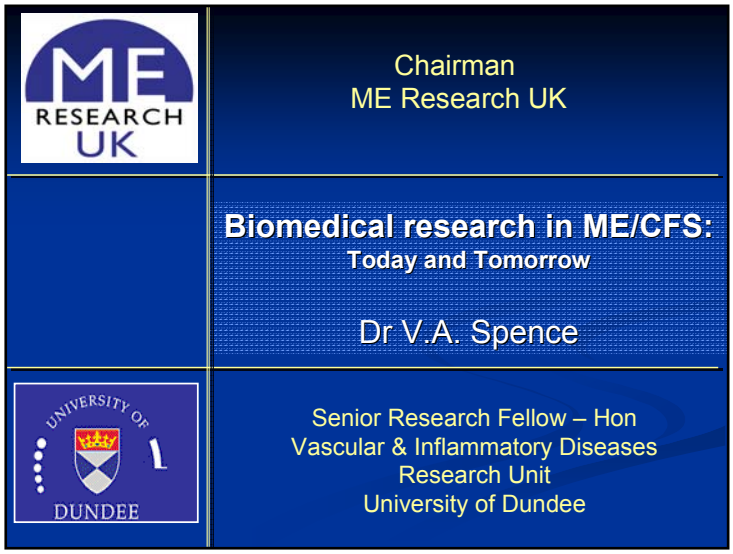
Sheffield ME Group

Open Meeting by Dr Vance Spence

Saturday 09 October 2010

Saturday October 9th 2010 was the Annual Conference of the Sheffield ME Group (www.sheffieldmegroup.co.uk) at the Circle in Rockingham Lane, Sheffield, and the guest speaker was Dr Vance Spence, Chairman of ME Research UK who gave an hour-long talk entitled "ME/CFS research — today and tomorrow" which included recent developments across a range of investigations from XMRV to apoptosis to disorders of the autonomic nervous system.

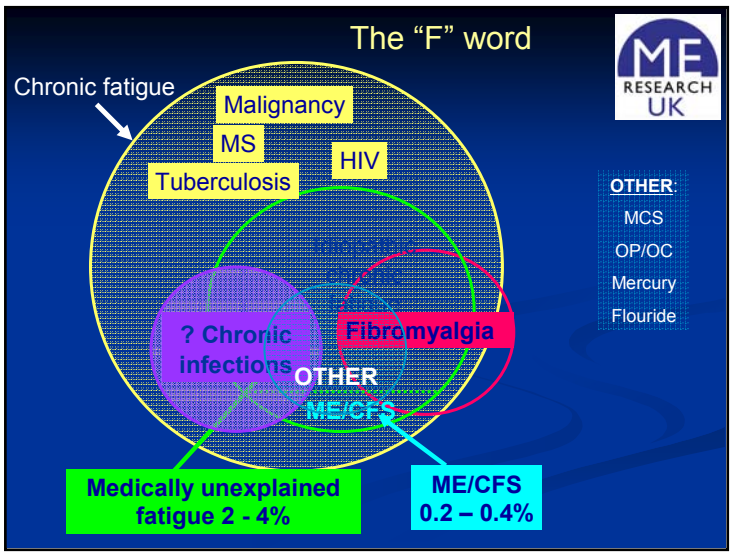
Background and ME Research UK



Vance explained that he had been ill for almost 30 years with an illness which people call "ME" or "CFS", but without appropriate tests who could tell? He realised there was a burning need for biomedical research, hence the charity ME Research UK (website www.meresearch.org.uk) of which he is Chairman, and which celebrates its 10th anniversary this year. Dr Spence reminded the audience that he was not a medical practitioner but a clinical scientist; before contracting ME, he was a Principal Clinical Scientist in Vascular Disease and Director of Vascular Research at the University of Dundee. He explained how the charity operates and how it fulfils its main role - of commissioning and funding scientific (biomedical) investigation into the causes, consequences and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). In the past decade, the charity has grown in size and respect, punching above its weight in a variety of spheres. For instance, it has funded 29 specific investigations, most in the past six years in Britain and abroad – that's more specific research projects on ME/CFS than any other single organisation in the world outside the American continent.

Diagnosis

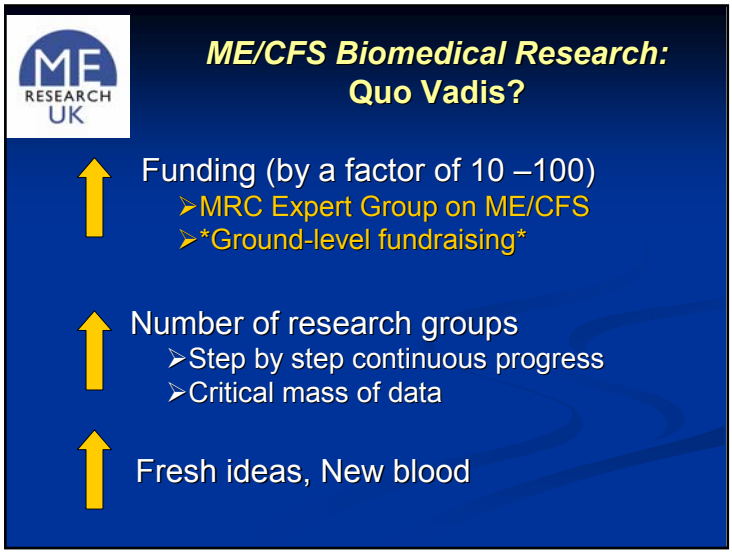
Vance spent a long time discussing ME, "CFS", fatigue and the complexity of diagnosis nowadays. He described how patients today are diagnosed with ME/CFS – a diagnostic mess in a variety of ways (as the slide shows). Originally, the label Myalgic Encephalomyelitis (ME) was used for an illness that had been found to occur in epidemic and sporadic forms, believed to be caused by a continuing or persisting viral infection. Its characteristics were a profound, generalised post-exertional loss of muscle power (fatigability); muscle pain that could include tenderness and swelling; neurological signs; and a proneness to relapses, which could take the form of recurrences of the original systemic illness. But, as there was no specific diagnostic test for ME, and since post-exercise "fatigue" was one of its prominent symptoms, people with ME began in the 1990s to be diagnosed with "Chronic Fatigue Syndrome" (CFS), or the compromise diagnosis ME/CFS, which is based on a collection of vague non-specific symptoms (fatigue, sleep disturbance, sore throat etc) shared with other illnesses. The upshot is that today ME is not a diagnosis recognised by doctors or scientists, nor is it taught in medical schools (though until recently Vance gave voluntary lectures for medical students).



So what do the people today diagnosed with ME/CFS actually have wrong with them? A good question, and at least 2 studies have tried to tease this out. First, some people with a diagnosis of ME/CFS when examined at the University of Dundee were found to have other organic illnesses (e.g. muscle, connective tissue, endocrine disorders 21%), while 12% had a potentially treatable psychiatric disorder that could account for their symptoms, and 7% had fibromyalgia. In the second, 44% of ME/CFS patients in Newcastle were found to have other diagnoses, e.g., sleep apnoea or depression and anxiety, to account for their symptoms.

So, it seems that around 40% of patients given a diagnosis of ME/CFS might, in fact, have other things wrong with them. The slide illustrates what might be under there – somatoform disorders, fibromyalgia syndrome, a variety of infections e.g. Lyme (tick-borne), rickettsia, mycoplasmal diseases, etc. So, the key is for people to get a thorough medical examination initially to exclude other more treatable conditions, and only then to be given a diagnosis of ME/CFS. One new "complication" is potential XMRV infection, and if this virus is found to be at the root of at least some cases of ME it might be possible to reclassify patients on the basis of whether they have virus or not, arriving at objective diagnostic criteria based on state-of-the-art methodology.In fact, the WPI group has already suggested that a new disease entity — X associated neuro-immune disease, or XAND.

Funding crisis



Vance mentioned that while these diagnostic problems caused problems for clinicians like GPs, they also complicated research studies because volunteers had to be screened and categorised by medical examination before they could be enrolled into studies – raising the costs of medical research substantially. And he explained that the funding available for ME/CFS research was small; for instance, Cancer Research UK's income 2008/9 was £498,221,000, compared with ME Research UK's income of £264,862 for the same period. Funding is the core problem, and the major reason why the biomedical research that patients want to see is not happening. 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. Only then can we being to see a large number of research groups

undertaking the large number of studies we all want to see, attracting new blood and fresh ideas into the field of ME/CFS research, as the slide suggests.

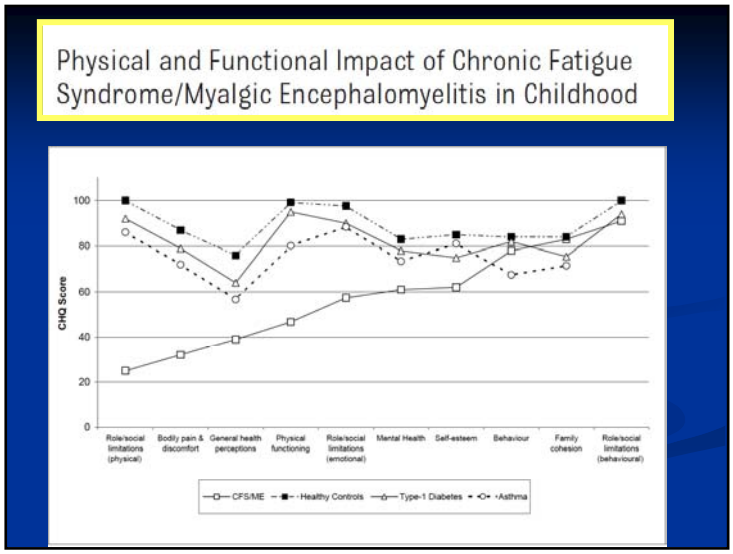
Research projects

He then went on to describe some ongoing research that ME Research UK is funding:

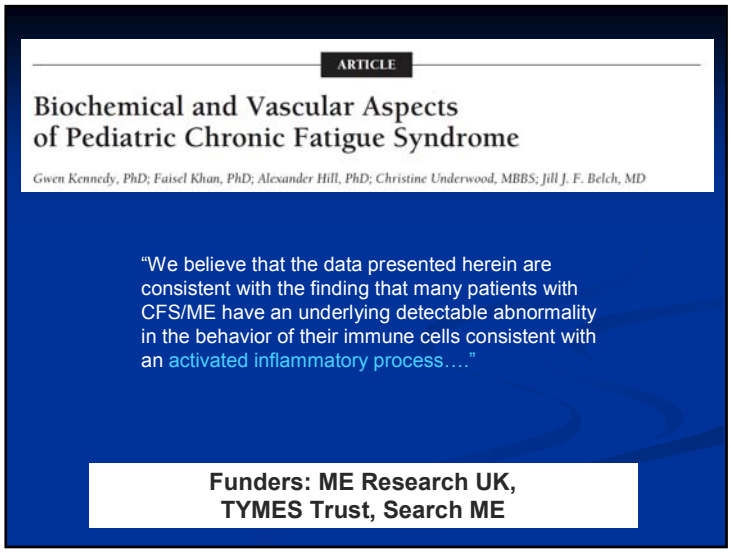
a) Studies at the University of Dundee

(i) Inflammation and apoptosis – children and adults

With funding from ME Research UK, researchers at the Vascular and Inflammatory Diseases Research Unit, University of Dundee, have uncovered a range of potentially important cardiovascular findings in ME/CFS patients, including **increased oxidative stress** (these toxic molecules can, amongst other things, damage blood vessels), **abnormal metabolism of acetylcholine** (an important neurotransmitter and dilator of blood vessels), and increased **early death of white blood cells** (which may indicate active inflammation). All this has provided accumulating evidence of a compromised cardiovascular system in patients with ME/CFS, and of the potential importance of inflammation in this disease process. And the most recent finding – of similar abnormalities in children with ME/CFS – also points in this direction.



In 2010, Dr Gwen Kennedy and her colleagues in University of Dundee have published results on children with ME/CFS, to see whether the abnormalities found in adult patients are also present in children with ME/CFS. But another aim was to investigate objectively the quality of life of children with ME/CFS (see slide). Her main finding of the study (funded by ME Research UK, the Tymes Trust, and Search ME) was that children with ME/CFS scored significantly lower than the healthy children in 10 out of 14 areas covered by the Child Health Questionnaire. The slide shows that They had particularly low scores for global health (21.4 compared with 84.1 in the healthy children) and for social limitations due to physical health (24.9 compared with 100). Self-esteem, mental health, body pain and discomfort, and the effect of the child's health on family activities were also significantly worse for children with ME/CFS. However, there were no differences between children with ME/CFS and healthy children in how well the family got along, or in the children's perception of their own behaviour. Importantly, the illness had started with an infection in 88% of the children, which confirms the known association between initial infection and subsequent development of illness. Also, a significant proportion of children in the study had interrupted schooling, and only 1 of 25 children was able to attend school full-time, a finding which accords with other studies on the interruption of education in children with ME/CFS. Fortunately, just over half of the children who participated felt that their symptoms were improving, and the prognosis for children with ME/CFS is generally thought to be better than for adults, although no long-term studies have been conducted. Overall, Dr Kennedy's findings confirm that ME/CFS does have a serious impact on children's quality of life, and she comments: "This experience of illness occurs at a particularly vulnerable time of life when disruption to education and family has the severest consequences… it is important that the condition be recognised and diagnosed so that the consequences on quality of life can be attenuated."



Coming to the biochemical measurements, compared with healthy control children, the young people with ME/CFS had:

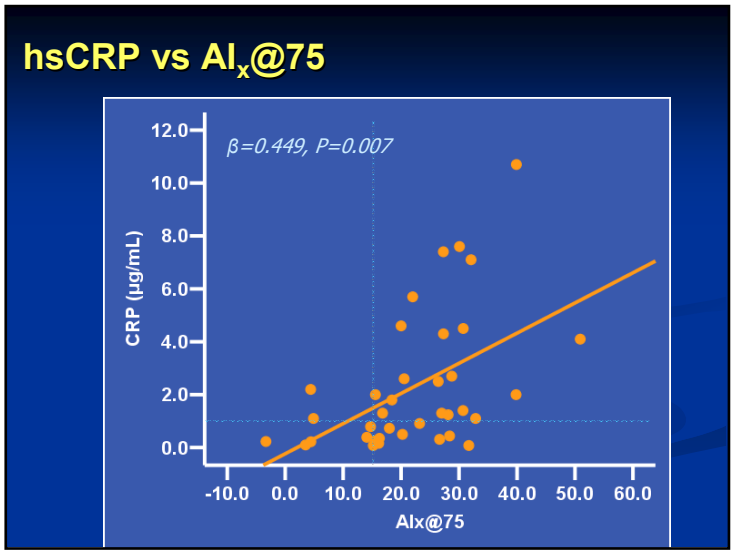
1.Higher levels of oxidative stress, manifested as elevated levels of isoprostanes

2.Reduced levels of vitamins C and E

3.A greater percentage of white blood cells undergoing apoptosis

The increased apoptosis (or programmed cell death) may be caused by a number of factors, including a persistent viral infection or toxic agent, or an abnormal immunological response (slide). This finding is particularly intriguing given that many patients, including most children in this study, report that their disease started following a viral infection of some kind. At present, however, there is insufficient evidence to make a causal link between infection and increased apoptosis, though the finding is tantalising.

(ii) Arterial stiffness



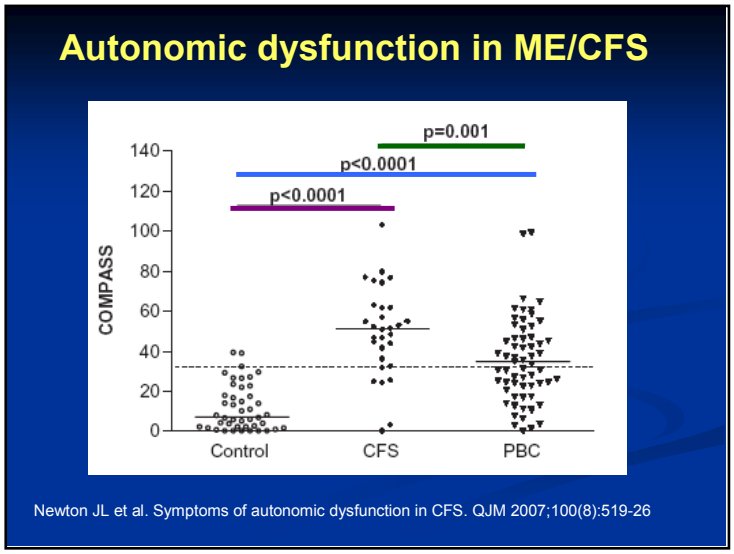
Coming to adults with ME/CFS, Dr Faisel Khan in Dundee found that patients with ME/CFS had significantly stiffer arteries than healthy, age-matched control subjects, and they also had higher levels of C-reactive protein, indicating significant inflammation and oxidative stress. Furthermore, there was evidence of a relationship between arterial stiffness (Alx@75), and inflammation (CRP) and oxidation (slide). The cause of increased arterial stiffness in ME/CFS is still unknown. While lifestyle characteristics such as smoking, obesity and physical fitness also play a role in its development, the patients in this study were no different from the control subjects in this regard. Dr Khan is, however, careful to emphasise that this is an association only and that the current his results do not prove cause and effect.

Do these results mean that people with ME/CFS are at an increased risk of developing cardiovascular problems such as heart disease? At the moment, no-one knows but the work does raise the possibility that suppressing inflammation in carefully selected patients may lead to an improvement in arterial stiffness and a reduction in long-term cardiovascular problems, something already achieved in patients with rheumatoid arthritis using the anti-TNFα drug, etanercept. Clinical trials are unfortunately very expensive so conducting a similar trial on ME/CFS patients would need the sort of investment that only pharmaceutical companies can deliver. However, further research is needed before this can be answered definitively.

b) Studies at the University of Newcastle

(i) Autonomic nervous system (ANS), including heart

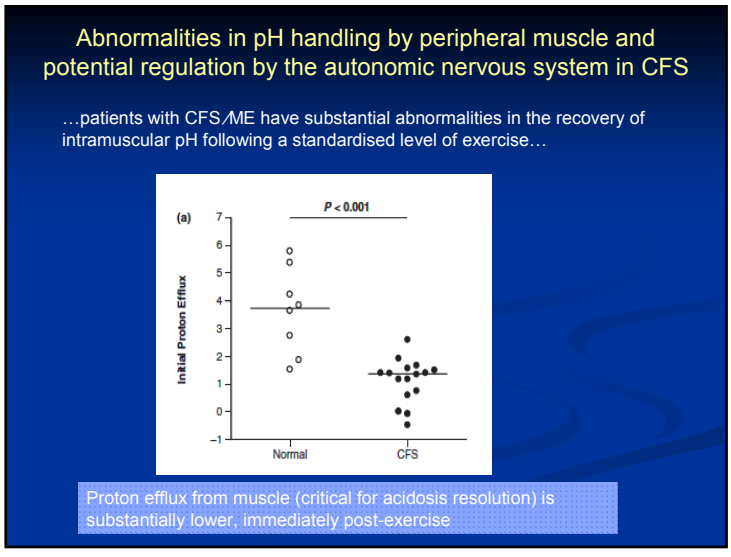
The autonomic nervous system (ANS) controls cardiovascular, digestive and respiratory functions, and has a range of other important roles. When it goes wrong, the consequences can be severe. Since one of the key difficulties that ME/CFS patients face is standing, most especially standing still, without experiencing symptoms such as dizziness, altered vision, nausea, fatigue etc, the possibility exists that there could be a problem with the autonomic nervous system. Professor Julia Newton of the School of Clinical Medical Sciences, University of Newcastle, has been looking at the ANS in ME/CFS patients since 2006 with funding from ME Research UK. Vance mentioned that Julia Newton gets her patients from the NHS CFS clinic in Newcastle, and that it might be possible for some people to obtain a referral there, though of course all referrals must come via a GP, since they are the front line access points to secondary care.



In a series of fascinating scientific papers, Prof Newton and colleagues have shown that autonomic dysfunction is present in three-quarters of the patients – a most unexpected finding (slide). Furthermore, she has also shown that a simple-to-measure assessment of the heart rate response to standing was abnormal in nearly 90% of patients. Because of this, MERUK has given its largest ever research award of £130,000 to Professor Newton for a two-year study of autonomic nervous system (ANS) dysfunction at the University of Newcastle, funding provided in conjunction with the John Richardson Research Group and the Irish ME Trust. Vance described how this award was intended to extend and explore some of the mechanisms behind these autonomic problems in ME/CFS patients.

In separate studies, Prof Newton is also looking at ways patients can deal with the symptoms of ANS dysfunction, and there are some drugs available, as well as non-drug methods, such as tilt-training! After initial training, patients at home (with another person there for safety) lean against a wall with their feet 15 cm away, increasing the length of time to 30 minutes over days to weeks (evidence suggests that such once-daily tilt training can be effective in preventing the recurrence of fainting).

(ii) Muscle



The autonomic nervous system also plays a part in regulating events in the exercising muscle, however, and the Prof Newton and colleagues researchers hypothesised that might be involved in the exercise-induced symptoms so characteristic of ME/CFS. To examine this, they enlisted the help of phosphorus magnetic resonance spectroscopy (MRS), a marvellous tool which allows assessment of acid (pH) handling inside the muscle where the problems

might lie. The results published in Journal of Internal Medicine (2010) show significant impairment of proton excretion in recovery phase following exercise – in simple terms, ME/CFS patients recovered substantially more slowly compared with controls (slide). Could simple deconditioning be the cause? Probably not since both maximum voluntary contraction measurements and muscle volume were similar in patients and in the sedentary controls. Rather, the researchers think it more likely that impaired acid handing could be one of the mechanisms through which autonomic abnormalities act to produce post-exercise symptoms and fatigue, given the role played by the autonomic nervous system in regulation of acid transporter pathways and vascular flow in muscle.

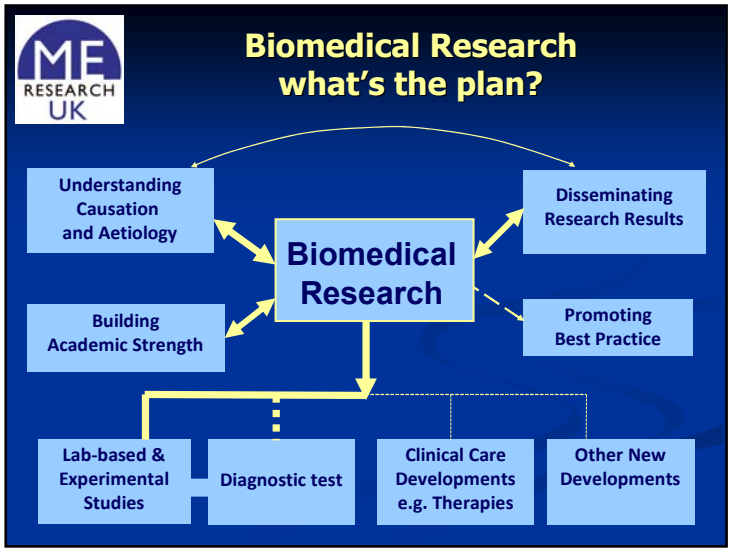
Despite the key role of post-exercise symptoms in the illness, there has actually been very little scientific investigation into muscle physiology during exercise in ME/CFS – a fact that makes these novel findings so important. Based on these results, ME Research UK has now actioned funding for the next step, and examination of the function of an energy-generating enzyme which might be under-performing in people with ME/CFS.

c) Studies on XMRV

Vance discussed some recent developments on the XMRV viral link to ME/CFS, reported in a scientific paper in Science last year. Given that the presence of infectious virus in white blood cells of patients could account for some of the known features of this chronic illness, e.g. neurological symptoms and immune dysfunction, the finding is certainly appealing, and a study in Sweden which MERUK is funding with the Irish ME Trust is ongoing.

However, in the year following the initial report, 7 other studies have been published and all but one have been "negative" for the presence of virus in a range of patients across the world. There might be several reasons for differences between studies. Intriguingly, one of these reports from Dr Harvey Alter of the National Institutes of Health published a report in Proceedings of the National Academy of Sciences recently found a more diverse group of closely related viruses, but not XMRV itself, in patients – so this story is far from over and viruses might indeed have a critical role in ME/CFS. In the US, the Blood XMRV Scientific Research Working Group formed by the NIH in July 2010 is trying to arrive at a standard "gold standard" protocol for XMRV/MLV testing, and Vance awaits its results keenly.

Conclusion



Vance ended by pointing to the basic plan for funding research adopted by ME Research UK (slide). Given the few resources available, the focus has to be on "lab-based and experimental studies". However, the real problem is funding. Modern researchers follow funding, and we have to be like the larger cancer charities which raise money from the population at large year-on-year so that contributions begin to flow in (from well people, not only patients and their families). Only then will the ME world have the data, data, data to answer its critics AND solve the enigma of ME/CFS.