ME Research: Making the Breakthrough

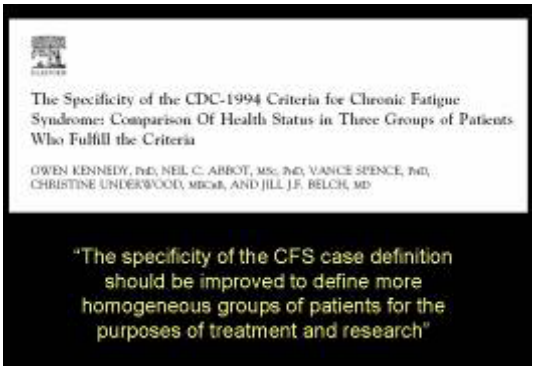
A presentation by MERGE Chairman Dr Vance Spence
on 12 November 2005 at the Oak Tree Court Conference Centre, Coventry,
at the invitation of the Warwickshire Network for ME

Let me thank the Warwickshire Network for ME — a sterling group which actively supports biological research into ME, and campaigns for appropriate services for people with the illness (http://www.meresearch.org.uk/friends/group.html#warwick) — for the invitation to this lovely conference centre, home of the Coventry Chamber of Commerce. I'm told there are people in the audience from as far away as Dawlish in Devon and Stowmarket in Suffolk — illustrating the intense interest in ME/CFS research and the pressing need for action to get to the bottom of this illness. As many of you know, I have been ill with ME myself for many years — I was forced to retire early on health grounds 15 years ago — and I am presently a Senior Research Fellow (honorary) in the University of Dundee, as well as being Chairman of MERGE. With the help of Roger Jefcoate CBE, who is in the audience today, and the Countess of Mar, MERGE was created with the principal aim of energising research into this neglected illness.

First, I propose to deal briefly with some of the problems we face in trying to execute ME/CFS research, as there are particular problems specific to this illness which impact on "making a breakthrough". Then, I shall briefly describe some of the current research projects and areas of interest.

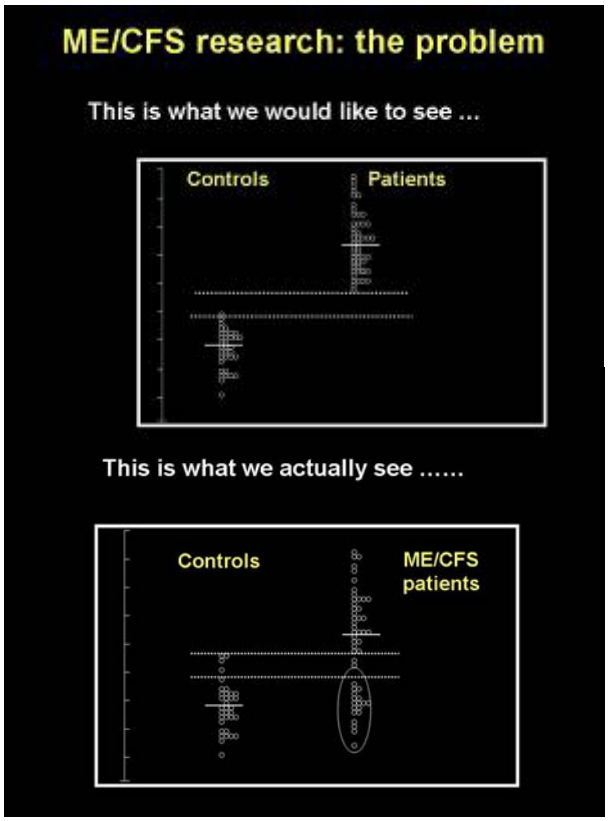
The first problem — perhaps the principal problem — is that ME/CFS is not a "clean" diagnosis. Indeed, the terms ME and CFS mean different things to different people. As I say over and over again, this problem colours all debate on ME, yet rather like the whiteness of a wall it is often not recognised as a colour at all. Much of the background was described in a talk (http://www.meresearch.org.uk/information/publications/workshop/spencetalk1.html) I gave to the RSE/Wellcome conference in 2003, but the essential point is that although the term myalgic encephalomyelitis (ME) — involving an infectious onset, specific neuromuscular symptoms and signs, and a unique post-exercise component — has a scientific history (http://www.meresearch.org.uk/information/keypubs/index.html#epidemics) involving epidemic and sporadic forms, "ME" today has come to be seen as a "lay term" used by patient organisations and patients themselves, while chronic fatigue syndrome (CFS) has been adopted by medical journals and healthcare professionals. At present, the composite term ME/CFS is used, though in fact it represents the uneasy union of two strange bedfellows (http://www.meresearch.org.uk/information/publications/parliament/parliamentpres2.html), as

discussed recently at the Scottish Parliament. In addition, we find ourselves in a situation where misuse of terminology by the mass media is common; a recent article in the UK's Daily Telegraph (daily circulation, approximately one million) gives an example. It describes the travails of Olympic rower Anna Hemmings. As the article says, *"For Anna Hemmings, the Sydney and Athens Olympics tell two very different stories. In 2000, the professional canoeist was a member of the British team, but just four years later Hemmings was suffering from CFS and was so exhausted that she slept for 15 hours a night and was sometimes too tired to wash her hair."* It goes on to describe how Anna was greatly helped by a psychological therapy, and seems to be on the mend, which is heartening. The question is: what illness did she have? Many people have "chronic fatigue" (between 1 and 4% of the population), and many medical conditions, such as cancer and diabetes, have fatigue as a central complaint. Indeed, athletes at Olympic standard like Anna Hemmings may have "burnout" due to over-training; however, recent research (Mommersteeg et al, 2005) shows that the "burnout" experienced by athletes differs from CFS, and is certainly not ME as described in earlier literature. This is just one example of many media stories — thrown out into the public arena — which have an uncertain meaning in the context of ME/CFS.

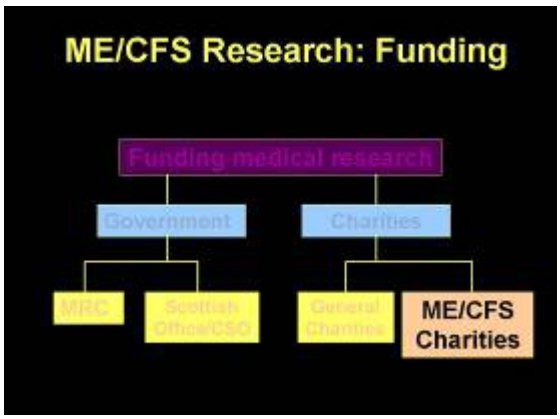


The diagnostic mess that is ME/CFS is illustrated by our own research on three groups of patients with quite different onsets to their illness: "sporadic" ME/CFS cases (i.e., most of the patients in ME/CFS support groups); people who developed illness after services in Gulf War 1; and people who developed illness after apparent contact with organophosphates. While all these patients were classified as having CFS (because they fulfilled the CDC 1994 criteria for the illness), distinct psychological and biological differences could be found between them. As this paper (Kennedy et al, 2004) says, *"The specificity of the CFS case definition should be improved to define more homogeneous groups of patients for the purposes of treatment and research."* This view was echoed by Professor Leonard Jason who published in 2004 an excellent review on the need for subgrouping of the over-broad "diagnostic category" CFS which can catch widely different groups of patients in its net. As he said, *"This review suggests that there is a need for greater diagnostic clarity and that this might be accomplished by subgroups that integrate multiple variables including genetic, neurological, psychological and biological domains."* At present, what patients are left with is a "devalued" diagnosis consisting of (in one researcher's words) a *"...ragbag of common non-specific symptoms with many causes, mistakenly labelled as a syndrome"*. In this respect it is worth recalling what Dr Dean of the National Institutes of Health in the USA said in a recent debate about ME/CFS in the USA: *"There is a significant stigma attached to it... The medical community bears some of the responsibility for invalidating ME/CFS as a real condition"*; and what Professor Anthony Komaroff stated: *"None of the participants in*

creating the 1988 CFS case definition and name ever expressed any concern that it might trivialize the illness. We were insensitive to that possibility, and we were wrong."



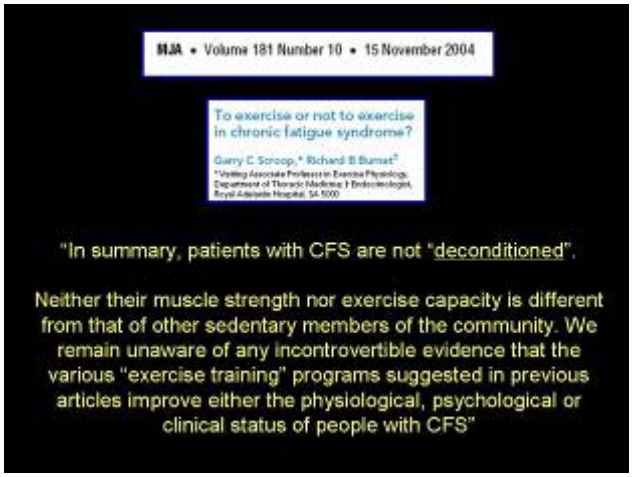
The problem with the definition carries over into research studies, of course. In ME/CFS, what we see over and over again are the graphs on the right (the upper, an ideal scenario; the lower from a real biochemical experiment on ME/CFS patients), with the controls nicely tightly packed, and the "CFS" patient measurements much more widely scattered. 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 (http://www.co-cure.org/cccd.htm) 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 their apparent heterogeneity, biomedical researchers can uncover a range of interesting anomalies (http://www.meresearch.org.uk/information/publications/advances.html), as described in a recent article. Furthermore, fascinating results covering many of the prominent symptoms of ME/CFS continue to be published by research groups worldwide. These include reduction of brain serotonin transporters in relation to pain (Yamamoto et al, 2003), delayed gastric emptying (Burnett et al, 2004), and altered muscle excitability in response to exercise (Jammes et al, 2005).



The second obstacle standing in the way of "making the breakthrough" is funding. The diagram on the left gives a very basic outline of the origins of medical research funding, from (on the left) larger national agencies, such as the Medical Research Council (MRC), 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. However, it is not generally recognised that medical research into most if not all illness is funded overwhelmingly from charitable sources. Take cancer: the income of Cancer Research UK in 2003–4 was around £384,000,000, and this is only one of the many charities raising money for cancer. Take away the first digit and the three noughts at the end and you are left with MERGE's approximate income for the same period. As I've said before, the three main charitable sources of ME/CFS research funds in the UK — the CFS Research Foundation (http://www.cfsrf.com/), the ME Association (http://www.meassociation.org.uk/) and MERGE (http://www.meresearch.org.uk) — would struggle to fund between them one medium-sized clinical trial from their aggregated annual income.

The third problem is the predominance of the biopsychosocial model of the illness — a model defined in the Chief Medical Officer's report of 2002 as a *"...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"* (http://www.dh.gov.uk/assetRoot/04/05/95/06/04059506.pdf). An example is the recent editorial in the Medical Journal of Australia which stated *"...one can safely conclude from these studies that graded physical exercise should become a cornerstone of the management approach for patients with CFS"*, stimulating a number of letters to the MJA, including one from Garry Scroop, visiting Professor of Exercise Physiology who stated, *"In summary, patients with CFS are not 'deconditioned'. Neither their muscle strength nor exercise capacity is different from that of other sedentary members of the community. We remain unaware of any incontrovertible evidence that the various 'exercise training' programs suggested in previous articles improve either the physiological, psychological or clinical status of people with CFS."*



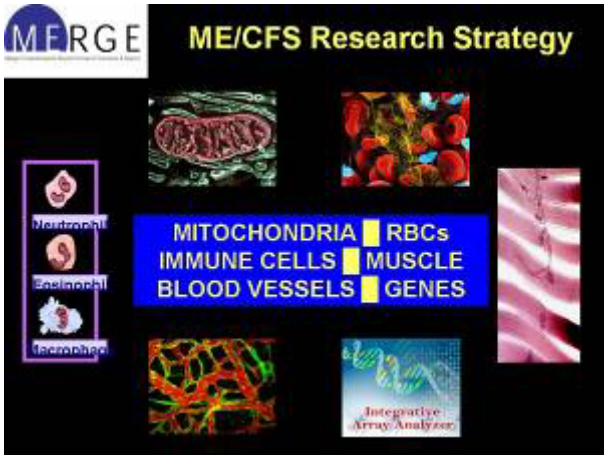
This model colours the perception of the illness across the board — from official reports, such as the report to the Chief Medical Officer's report mentioned above, to government agencies such as the Department of Work and Pensions which is producing its new electronic guidelines in 2005, to research funding bodies such as the Medical Research Council. The recent large trials funded by the Medical Research Council — the FINE Trial (designed to increase activity and challenge dysfunctional illness beliefs) costing £1,147,000, and the PACE (Pacing, Activity, and Cognitive behaviour therapy) trial costing £3,101,792 — are examples of the resources found for proponents of the biopsychosocial model. Given that biopsychosocial therapies are not cures for ME/CFS, people are suggesting that the total

spend of £4,248,792 be given directly to the patients on the trials (£4425.82 each) so that they can challenge their own "dysfunctional illness beliefs" in their own way. The issue was well put in an editorial called "The discomfort of patient power" in the British Medical Journal in 2002: *"Many patients have tried cognitive behavioural therapy and report that thinking differently does not make their disease go away, though it can ameliorate some of the sense of privation which these illnesses often engender. Even so, there is a consensus among patients that if resources were allocated towards rigorous material empirical biochemical research it would be more likely to produce a helpful insight into the nature of these diseases, which would be preferable in their eyes to promulgating an…incomplete paradigm as though it were a cure."*

Finally, the fourth problem is that high quality biomedical research gets ignored (http://www.meresearch.org.uk/information/publications/advances.html) particularly when it conflicts with the prevailing paradigm. To continue the example of graded exercise therapy mentioned above — widely touted as a proven management strategy for ME/CFS patients — a recent paper from Snell et al (2005) reported, *"These results implicate abnormal immune activity in the pathology of exercise intolerance in CFS and are consistent with a channelopathy involving oxidative stress and nitric oxide-related toxicity."* Another recent paper has shown that exercise provokes pro-inflammatory and anti-inflammatory cytokines in CFS patients (White et al, 2005), and another report has described that after exercise there is a particular gene expression in CFS patients that is not found in normal healthy people. Add to this the patients' own reports that most are not helped by cognitive behavioural therapy (Action for ME survey, and the 25% ME Group survey), and one would think healthcare professionals and would be rushing to read and implement the latest biomedical research findings. Not on your Nellie. Yet there is indeed a growing evidence base supporting the biomedical model of the illness, as illustrated by the comments of Professor Anthony Komaroff in a recent newspaper article, *"For years, many doctors and others dismissed people with CFS as depressed, lazy, or just plain malingerers… Analysis of 2,000 research papers suggests that CFS is not a psychiatric illness, but a nasty mix of neurological, immunological and hormonal abnormalities…"*

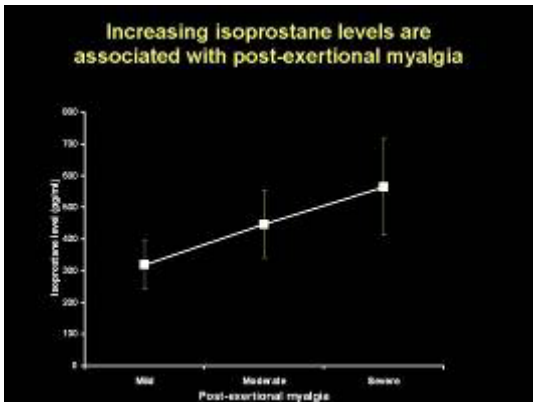
Now, let us pause there. I can think of no other illnesses for which a talk on biomedical research would need a half-hour preamble on the obstacles — diagnosis, funding, competing models and ignoring of biomedical data — standing in the way of "making the breakthrough". However, this is where we patients find ourselves (for some it feels like going round in circles, as the cartoon by

Trish Campbell of the Warwickshire Network for ME illustrates), and yet it is the base camp from which research charities such as MERGE have to march forward. Of course, the ideal is for central (e.g., MRC and NHS R&D) funding of biomedical research to be provided through a form of ring-fencing. Until then, however, we have to spend our 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 — and encourage larger established research groups into the field.



In MERGE, to date we have had a several-pronged research strategy based on the potential importance of mitochondria, immune cells, muscle, blood vessels and genes (http://www.meresearch.org.uk/research/sponsored/index.html) in the development and maintenance of ME/CFS. It is probably simplest if I describe the strategy from the viewpoint of oxidative stress, though in reality there are many ways to approach the body of work that is being undertaken.

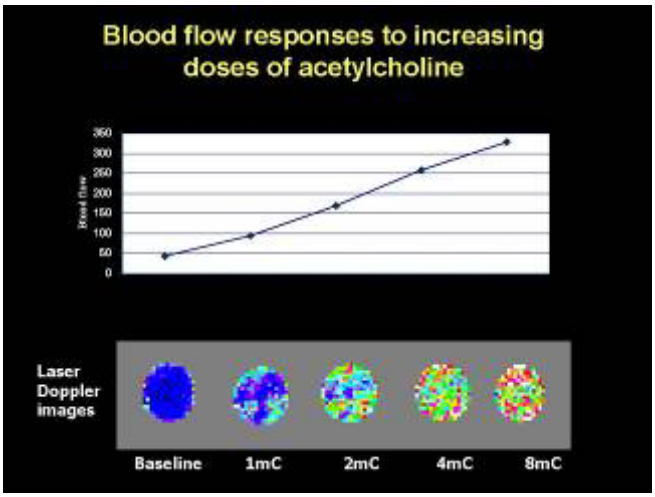
Let me begin with our recently published paper (Kennedy et al, 2005) which showed high levels of isoprostanes in ME/CFS patients, and the fact that these were correlated with symptoms (http://www.meresearch.org.uk/research/sponsored/oxidative_stress.html). There have now been around 12 papers from several research groups showing raised markers of oxidative stress in these patients, but this investigation was the first to measures isoprostanes, which are now recognised as one of the most reliable approaches to assessing in vivo oxidative stress. It must also be stressed that current evidence suggests that isoprostanes represent a biomarker that has the potential to be of great importance in the assessment of human atherosclerotic cardiovascular disease. There are several possible sources for these oxidants, including muscle, blood vessel endothelium and inflammatory/immune cells.



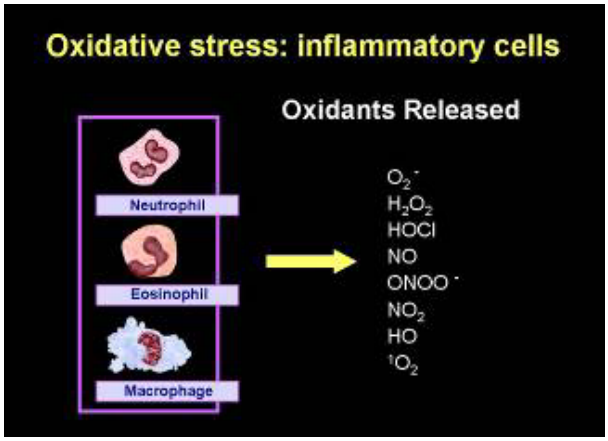
Looking at muscle, there is no question that muscle tissue is a source of free radical generation — indeed, McArdle et al (2005) used an intracellular probe to examine free radicals within the myotubules of muscle before, during and after exercise. In 2005, a report from the Jammes group in France (http://www.meresearch.org.uk/archive/muscle.html)

showed increased M-wave duration in the 30-minute period after an exercise challenge in ME/CFS patients. Jammes concluded that, *"This accentuated response by CFS patients to incremental exercise was a result of oxidative stress together with marked alterations of the muscle membrane excitability."* This research was so important that we have funded Dr Wood and Dr Paul of Caledonian University to replicate and extend these findings looking at M-wave and H-wave durations in patients and healthy matched controls up to 4 hours after exercise. In addition, we have been interested in the interaction between muscle and the immune system and have funded a research group at University of Strathclyde to consider the cytokine IL-6, its receptor, and a neutralising protein, since previous research (Arnold et al, 2002) had shown that if IL-6 was injected into CFS patients, *"they experienced an increase in somatic symptoms (e.g., aches and fatigue) whereas matched controls did not experience any symptoms in the first 6 hours after IL-6 administration"*. The Strathclyde group is interested in the relationship between IL-6 and neutralising proteins up to 24 hours after an exercise challenge.

The blood vessel endothelium is an area that we have been interested in ever since the publication of several papers in the early 1990s on brain blood flow imaging and orthostatic intolerance with vascular pooling in the extremities. The cells that line all blood vessels — endothelial cells — are a potential source of reactive oxygen species generation via several pathways. SPECT imaging studies by Schwartz et al (1994) showed areas of low blood flow in the various brain regions of people with ME/CFS, and the authors postulated that these regions of hypoperfusion were a result of a focal infection of small cerebral blood vessels. Around the same time, Dr Peter Rowe, Dr David Bell and others demonstrated that ME/CFS patients had significant cardiovascular responses to standing upright, manifested by changes in vascular volume/heart rate/blood pressure. Some psychiatrists suggested that the cardiovascular changes to upright tilt were simply cardiovascular deconditioning, but nothing could be further from the truth. In an article in The Biologist in 2004, Professor Julian Stewart and I outlined some of the "physical" arguments surrounding this aspect of the illness (http://www.meresearch.org.uk/information/publications/standing.html). The first thing to recognise is that the blood pressure in most ME/CFS patients is maintained by a significant increase in heart rate, at least in the early stages of upright posture. Professor Stewart has published some interesting data on what happens to ME/CFS patients when they are upright, and it shows that there is a group of patients whose leg blood is low when lying down and it *increases* when upright, a wholly abnormal response and indicative of a shift of vascular volume towards the legs. Might there be a problem with peripheral blood vessels in ME/CFS patients? Well, since 2000 we have been looking at how skin blood vessels respond to the



endothelium-dependent vasodilator, acetylcholine. To do this we use a novel instrument, a laser Doppler scanner which images blood flow in the skin. In ME/CFS patients, blood vessels are sensitive to acetylcholine driven through the skin; i.e., the skin blood vessels dilate more than expected, a novel if not unique finding (i.e., most diseases show the opposite response to acetylcholine, which is a blunted or decreased blood flow). Our series of experiments on this aspect of vascular biology at the Vascular Diseases Research Unit in the University of Dundee was the subject of a review (http://www.meresearch.org.uk/research/sponsored/ach_review.html) in 2004, and we have continued to research this aspect of ME/CFS patients given its importance to understanding some of the unusual vascular phenomena which characterise ME/CFS. In this respect we recently awarded a further grant to Dr Faisel Khan and colleagues at the University of Dundee to continue work on acetylcholine-mediated vasodilatation in ME/CFS patients, and especially to look at the role of nitric oxide, prostacyclin and endothelium-derived hyperpolarising factor (EDHF) in promoting acetylcholine sensitivity.



Inflammatory/immune cells also generate large numbers of free radicals — superoxide, H_2O_2, hypochlorous acid, NO, ONOO, etc. — especially during an infection and when cells are undergoing apoptosis or necrosis, etc. Indeed, neutrophils kill microbes like bacteria or fungi by releasing huge amounts of H_2O_2. To date, we have funded work — mentioned in the British Medical Journal in August 2004 (http://bmj.bmjjournals.com/cgi/content/full/329/7463/468?eaf) — showing that neutrophils in ME/CFS patients undergo early cell death (apoptosis), significantly more so than in healthy controls (http://www.meresearch.org.uk/research/sponsored/neutrophil.html). As part of further research in this area, in 2004 in conjunction with the Tymes Trust (http://www.youngactiononline.com/) and Search ME (http://www.search-me.org.uk/), we awarded a grant entitled, "An Investigation into biochemical and blood flow aspects of ME/CFS in children" to Dr Gwen Kennedy and Professor Jill Belch, and part of this investigation involves examining neutrophil apoptosis at both intra and extracellular domains in children. Intriguingly, the significant developments in gene expression in ME/CFS patients which have occurred recently — from Dr Jonathon Kerr and Dr John Gow in the UK (http://www.meresearch.org.uk/research/sponsored/genesig.html) — are consistent with the

thrust of this, particularly increased cell membrane prostaglandin-endoperoxidase synthase activity with downstream changes in O_2 transport, increased macrophage activation, and cellular apoptotic pathway activation, and we were delighted to be able to contribute to Dr Gow's research with a project on the characterisation of differential gene expression in ME/CFS.

Looking at our findings overall we see dyslipidaemia, oxidative stress and inflammation. On balance, ME/CFS patients have a lipid profile and oxidant biology that is consistent with cardiovascular risk, findings that may explain some of the symptoms of the disease such as the brain symptoms (http://www.meresearch.org.uk/archive/graymatter.html) that characterise many ME/CFS patients and some of the peripheral vascular consequences of being upright. There is a long way to go, but progress has begun and the body of biomedical evidence is slowly accumulating. Of course, in this talk I have discussed only the projects for which we have been able to action funding. A further group of projects are at the negotiation stage, and there are some on the table that we should like to do if funding becomes available and if researchers can be found to take on the work.

It is not generally realised that things have moved on considerably since Darwin and Mendel in the 19th century. The age of the lady and gentleman scientist has gone forever, and modern researchers follow funding as hummingbirds follow nectar-bearing blossoms. A highly successful fundraiser for cancer research told me that in the 1960s, when she began, the word "cancer" could barely be whispered. But over years, thanks to the efforts of people like her, there was a sea change in awareness, and contributions began to flow in (from well people, not only patients and their families) reaching the hundreds of millions of pounds raised today. We have to do the same — it is ground-level backbreaking work, but only with data, data, data will be able to answer our critics AND solve the enigma of ME/CFS.