Profits Before Patients?

Eileen Marshall Margaret Williams

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The role of the Medical Research Council (MRC) is to fund projects on the basis of expertly written, peer-reviewed and approved proposals. Clearly, therefore, the role of peer-reviewers is of paramount importance as it is they who influence what research the MRC will fund.

In the case of ME/ICD-CFS there are a limited number of peer-reviewers of psychiatric interventions of cognitive behavioural therapy and graded exercise apart from the PACE trial proponents themselves, so the favourable recommendation of the carefully selected peer-reviewers was not unexpected, nor was the decision to fund the trials on "CFS/ME" patients.

The PACE trials involve compulsory aerobic exercise even though the deleterious effects of such exercise on those with ME/ICD-CFS are well documented in the medical literature. It was documented as long ago as 1988 that there was "general agreement that (ME's) distinguishing characteristic is severe muscle fatiguability, **made worse by exercise**. It becomes apparent that any kind of muscle exercise can cause patients to be almost incapacitated (and) the patient is usually confined to bed. What is certain is that it becomes plain that this is an organic illness in which muscle metabolism is severely affected" (see Crit Rev Neurobiol: 1988:4:2:157-178).

The MRC has resolutely refused to heed submitted concerns from the UK ME/ICD-CFS community about the potential dangers of the PACE trials to those with ME/ICD-CFS. Even when sent by Recorded Delivery, these concerns are not acknowledged, let alone addressed. Personal letters (also sent by Recorded Delivery) to Professor Colin Blakemore (Chief Executive) and to Professor Sir Liam Donaldson (Chief Medical Officer at the Department of Health) also go unacknowledged and unanswered. Personal meetings with both these Executives arranged by the Countess of Mar and Earl (Freddie) Howe (Shadow Health Spokesman), at which these same concerns have been raised, have proved fruitless.

The potential danger is not only because exercise – especially aerobic exercise -- is known to cause significant general deterioration and increased pain in ME/ICD-CFS patients: it is because those trials involve graded aerobic exercise in patients who may have serious cardiac problems.

Cardiac problems in ME have been documented in the medical literature for over half a century – the fact that normal loss of blood flow may be persistent in ME was documented by Gilliam in 1938. Other cardiac problems have been consistently in the literature since that time, for example, Wallis (1957); Leon-Sotomayer (1965) and Ramsay (1950s-1980s), and in his 1988 CIBA Foundation lecture, Professor Peter Behan from Glasgow confirmed that he was regularly able to demonstrate micro-capillary perfusion defects in the cardiac muscle of ME patients. Also in 1988 it was noted that "Evidence of cardiac involvement may be seen: palpitations, severe tachycardia with multiple ectopic beats and occasional dyspnoea may occur and are quite distressing. It is of great interest that some patients have evidence of myocarditis" (see Crit Rev Neurobiol 1988:4:2:157-178). In 2001, in her Research Update presentation to the Alison Hunter Memorial Foundation Third International Clinical and Scientific Conference on ME/ICD-CFS held in Sydney, Professor Mina Behan from Glasgow (recently deceased) stated: "Convincing evidence of cardiovascular impairment can be demonstrated".

[For the early references, see "The Clinical and Scientific Basis of ME/CFS" edited by Byron Hyde, Jay Goldstein and Paul Levine, published in 1992 by The Nightingale Research Foundation, Ottawa. See also BMJ 1989:299:1219; Postviral Fatigue Syndrome ed. Rachel Jenkins and James Mowbray, pub. John Wiley & Sons, 1992; Inf Dis Clin Practice 1997:6:327-333; Proc Soc R Coll Physicians Edinb 1998:28:150-163; Hum. Psychopharmacol.Clin.Exp 1999:14:7-17; Clin Physiol 1999:19:2:111-120; JCFS 2001:8:(3-4):107-109].

The difficulty with some of the earlier references is that the documented clinical observations may not have been scientifically evaluated: in the current climate which dictates that "evidence-based medicine" is the only acceptable medicine, such observations are dismissed and ignored because there is no "evidence-based data". In the 21st Century, this is called progress in medicine.

Despite the documented evidence of the potential dangers of graded exercise to those with ME/ICD-CFS, the MRC and its chosen peer-reviewers (with the regrettable approval of certain ME charities) seem determined to support the PACE trials and apparently have little concern for the potential consequences to patients with ME. It seems that the MRC remains committed to its well-known and long-held conviction of its former psychiatrist Board Member (Professor Simon Wessely) that "CFS/ME" is "medically unexplained chronic fatigue" and is therefore a primary psychiatric disorder, and chooses to disregard the evidence that disproves such a conviction. It is also the case that the Government-funded Centres will employ the same psychiatric interventions of cognitive behavioural therapy and compulsory graded exercise.

Consequently there are now ever-louder calls for Judicial Review and for representation to the European Court of Human Rights in Strasbourg, backed by an eminent Queen's Counsel in the House of Lords.

It may seem pointless to bring to attention once again the inherent dangers of graded exercise for those with ME/ICD-CFS, but the recent update of the paper by Carol Sieverling posted on Co-Cure on 10th April 2005 ("The Heart of the Matter: CFS and Cardiac Issues" – a 41 page exposition of Dr Paul Cheney's experience and expertise, from which the following notes are taken and to both of whom grateful acknowledgement is made) has inspired one further attempt.

Cheney's focus is based on the paper by Dr Ben Natelson (neurologist and Professor of Neurology) and Dr Arnold Peckerman (cardiopulmonary physiologist) at New Jersey Medical Centre (ref: "Abnormal Impedance Cardiography Predicts Symptom Severity in Chronic Fatigue Syndrome": Peckerman et al: The American Journal of the Medical Sciences: 2003:326:(2):55-60).

This important paper says that, without exception, every disabled CFIDS (ie. ME/ICD-CFS) patient is in heart failure.

There are two kinds of heart failure: one that any cardiologist can diagnose in about a minute (which CFIDS patients do not have); the other is Compensated Idiopathic Cardiomyopathy (CIM). Given that at least 35% of those with CIM will die within 5 years unless they receive a heart transplant, but given that in 20 years' experience of CFIDS Cheney has never seen one patient go on to transplant, why aren't those with CFIDS-induced CIM not dead? Cheney believes it's because CFIDS itself is protecting patients from a deeper problem that is often missed because it is so well-hidden.

The problem

The New Jersey team looked at many things in CFIDS patients and they found something: a "Q" problem. "Q" stands for *cardiac output in litres per minute*. In CFIDS patients, Q values correlated -- with great precision – with the level of disability. Q was measured using impedance cardiography, a clinically validated and Government agency-recognised algorithm that is not experimental.

Normal people pump 7 litres per minute through their heart, with very little variance, and when they stand up, that output drops to 5 litres per minute (a full 30% drop, but this is normal). Those two litres are rapidly pooled in the lower extremities and capacitance vessels. Normal people do not sense that 30% drop in cardiac output when they stand up because their blood pressure either stays normal or rises when they stand up -- the body will defend blood pressure beyond anything else in order to keep the pulse going. This is critical to understanding what Cheney believes happens in CFIDS patients.

However, what the New Jersey team found in people with CFIDS was astonishing –when disabled CFIDS patients stand up, they are on the edge of organ failure due to extremely low cardiac output as their Q drops to 3.7 litres per minute (a 50% drop from the normal of 7 litres per minute).

The disability level was exactly proportional to the severity of their Q defect, without exception and with scientific precision.

Symptoms

The New Jersey team then looked to see if there were any symptoms that were observable in disabled CFIDS patients but not in others and they found that there was only one such symptom that was seen in patients with a

Q problem: post-exertional fatigue. To quote Cheney: "That is, **when you push yourself physically, you get worse"**.

CFIDS patients have a big Q problem; to quote Cheney again: "**all disabled CFIDS patients, all of whom have post-exertional fatigue, have low Q and are in heart failure"**.

Post-exertional fatigue (long documented as the cardinal feature of ME/ICD-CFS but not of other, non-specific, states of chronic fatigue) is the one symptom that correlates with Q. Among disabled CFIDS patients, 80% had muscle pain; 75% had joint pain; 72% had memory and concentration problems; 70% had unrefreshing sleep; 68% had fever and chills; 62% had generalised weakness; 60% had headaches, but 100% had post-exertional fatigue.

In Cheney's model, symptoms in CFIDS reflect the interaction between Q and how the body compensates for too low a Q, so depending on the nature of the compensation (which is individually distinct), there is an array of symptoms that is individually determined and which will arise out of factors unique to each person.

Cheney posits that when faced with a low Q, the body sacrifices tissue perfusion in order to maintain blood pressure: ie. microcirculation to the tissues of the body is sacrificed to maintain blood pressure so that the person does not die in the face of too a low Q (Q being cardiac output in litres per minute). This compensation is what is going on in the CFIDS patient.

In the Peckerman study, the data on the disabled CFIDS patients reveals that even when they are lying down, their Q is only 5 litres per minute (not 7 as in normals). When disabled CFIDS patients stand up, the Q of 5 litres per minute drops to 3.7 litres per minute, so these patients do not have adequate Q to function. The lower the Q, the more time the patient will spend lying down because lying down is the only time they come close to having sufficient cardiac output to survive.

Compensated Idiopathic Cardiomyopathy

Cheney states that it is important to note that the body does not sacrifice tissue perfusion equally across all organ systems: instead, it prioritises the order of sacrifice and one can observe the progression of ME/ICD-CFS by noting this prioritisation.

Two organ systems in particular have a protective mechanism (the Renin Angiotensin System, or RAS) against restricted tissue perfusion: the lung and the kidneys. These organs can sustain the greatest degree of Q problems because of this extra protection. Additionally, the heart and the brain also have this extra protection, even in the face of an extremely low Q. Therefore the lung, the brain, the kidneys and the heart are a bit more protected than the liver, the gut, the muscles and the skin from a drop in Q.

In what order is tissue perfusion sacrificed, and what are the consequences? Certainly, Cheney's submission seems to tally with the experience of long-term ME sufferers.

The first is the skin: if the microcirculation of the skin is compromised, several problems can arise. One is that without adequate microcirculation to the skin, the body cannot thermoregulate anymore: the patient cannot stand heat or cold and if the core temperature rises, the patient will not be able to sleep and the immune system will be activated. In order to regulate that problem, the body will kick in thyroid regulation which will down-regulate in order to keep the body temperature from going too high. The result of this is that the patient develops compensatory hypothyroidism, which means that now the patient will have trouble with feeling cold. Also, the body will not be able to eliminate VOCs (volatile organic compounds), which are shed in the skin's oil ducts, so VOCs build up in the body's fat stores and the patient becomes progressively chemically poisoned by whatever is present in the environment -- in other words, the patient develops Multiple Chemical Sensitivity.

The second effect: if things get worse, the next microcirculation to be sacrificed is that to the muscles and the patient will have exercise intolerance and s/he cannot go upstairs. If things get still worse, the patient begins to get fibromyalgic pain in the muscles. Cheney posits that if microcirculation to the joints becomes compromised, it may precipitate pyrophosphoric acid and uric acid crystals and the patient starts to have arthralgia linked to this circulatory defect.

The next system to be compromised is the liver and gut. One of the first things the patient may notice in this stage of disease progression is that there are fewer and fewer foods s/he will be able to tolerate, partly because microcirculation is necessary for proper digestion. Also the body will not secrete digestive juices so whatever food is tolerated will not be digested: if food cannot be digested, there will be peptides that are only partially digested and therefore are highly immune-reactive; they will leak out of the gut into the bloodstream, resulting in food allergies and / or sensitivities. The body will be unable to detoxify the gut ecology, so the gut will begin to poison the patient, who will feel a sense of toxic malaise, with diarrhoea, constipation, flatulence and all kinds of gut problems. If this gets worse, a malabsorption syndrome will develop, resulting in increasing toxicity in which the patient feels "yucky" and which can manifest as a variety of skin disturbances (for instance, a rash), as well as problems in the brain.

The fourth affected system is the brain: Cheney posits that there is a devastating effect in the brain as a result of liver / gut dysfunction, which can quickly toxify the brain, resulting in disturbances of memory and of processing speed. Also, the hypothalamus begins to destabilise the patient from the autonomic nervous system perspective. In all probability, the brain and heart suffer simultaneous compromise, but patients usually notice the brain being affected much earlier than the heart – this is because heart muscle cells have the greatest mitochondrial content of any tissue in the body, so when the mitochondria are impaired, the heart muscle has the greatest reserve. Even if the patient is sedentary with not too much demand on the heart, s/he can still think and make great demands on the brain, and energy is energy, whether it is being used physically or cognitively.

The fifth affected system is the heart: Cheney posits that the effect of compromised microcirculation upon the heart has an "a" part and a "b" part: part "a" is the manifestation of microcirculation impairment and part "b" is "the event horizon".

Part "a": manfestation of microcirculation impairment: the initial manifestation of microcirculatory impairment of the heart is arrhythmia with exercise intolerance: when the patient goes upstairs, more cardiac output is needed but the patient cannot sustain it. As it gets worse, there will be mitral valve prolapse (MVP) because of inadequate capillary function. Finally, when there are even more severe microcirculatory problems, the patient starts to get chest pain as the myocardial cells die because they cannot get adequate oxygen.

Part "b": the event horizon: (once this line is passed, there is no going back): Cheney's view is that the "event horizon" with respect to the heart is this: when the microcirculation defect within the heart itself begins to impact Q itself, a vicious circle begins – microcirculation impairment reduces the Q, which produces more microcirculation impairment, which produces even more Q problems, so down goes the patient into the next phase of cardiac failure, which is the lung.

The sixth affected system is the lung and kidney: cardiac failure in the lung produces Congestive Heart Failure (CHF) and pulmonary oedema, then the kidney is affected (the kidney is the last to go because it has the RAS back-up system). Combined with liver impairment, this stage is known as hepatorenal failure, which is the requisite cause of death due to Compensated Idiopathic Cardiomyopathy.

For some interesting reason, there is something about CFIDS that keeps patients from progressing across the final event horizon, although Peckerman believes that a certain percentage of CFIDS patients are heading that way. How will a patient know if s/he eventually loses the ability to compensate? They will know it if when they lie down, they are short of breath.

The cause of the cardiac output problem

Cheney's view is that cardiac muscle has lost power because the mitochondria are dysfunctional due to a redox-state problem. Redox is a reversible chemical reaction in which one reaction is an oxidation and the reverse is a reduction.

What causes the redox-state problem? Cheney does not know, but he does know that in CFIDS, like MCS and Gulf War Syndrome, there is a redox-state problem. There is, however, something unique in CFIDS, which is that the redox-state problem seems centred on the heart. In Cheney's model, candidates include viruses and heavy metals in an interaction with allergies and toxins.

Cheney then discusses Martin Pall's work and theories relating to the pathophysiology at the cellular level that he believes underpins this pathophysiological state (ie. the role of peroxynitrite). Cheney describes it in simple terms: nitric oxide + superoxide = peroxynitrite, which is highly damaging. Nitric oxide and superoxide have to be generated because they are essential for life and are necessary for energy generation. In health, nitric oxide is found *outside* the mitochondria and superoxide is found *inside* the mitochondria. In CFIDS, however, superoxide is out of control, so there are few limits to the formation of peroxynitrite. Using Pall's model, Cheney accepts that if a person is immune-activated (either from a virus, or from bacteria, or from toxin exposure), then that person is generating an excess amount of nitric oxide. Superoxide is produced by the act of making energy (ATP). If the person is also making a significant amount of ATP, it can result in superoxide, which then binds to the nitric oxide to produce large amounts of peroxynitrite, resulting in major problems with oxygen transport, microcirculatory impairment and lack of tissue perfusion. To protect the body from going down the death spiral, it stops making energy, which results in significant reduction of superoxide and thus of peroxynitrite.

Cheney discusses various methods of blocking peroxynitrite, including pharmacological interventions (for example, the blocking of NMDA reduces nitric oxide) and more basic methods such as increasing carbon dioxide by re-breathing (carbon dioxide is a primary scavenger of peroxynitrite). Uric acid is also a powerful scavenger of peroxynitrite; Cheney has measured uric acid levels in CFIDS patients and has found them to be amongst the lowest levels he has ever measured in his entire medical career.

Cheney notes that the best endogenous scavenger of nitric oxide is haemoglobin (a protein that transports oxygen from the lungs to the tissues) but that when haemoglobin scavenges nitric oxide, the nitric oxide bends the haemoglobin, causing the red blood cells to deform. Dr Les Simpson in New Zealand found that the red blood cells of patients with CFIDS were deformed and when deformed, they cannot get through the capillary bed and so cause pain. An indication of such deformity is a drop in the sedimentation rate (SED, or ESR) and Cheney has observed that when measured in a laboratory, CFIDS patients' sedimentation rate is the lowest he has ever recorded, which confirms to Cheney that CFIDS patients have an induced haemoglobinopathy. He believes that the CFIDS patients with the lowest sedimentation rate may have the greatest degree of pain. The more deformed the red blood cells, the more pain may be experienced. Some CFIDS patients have a problem similar to that of sickle cell anaemia in this regard, and sickle cell patients have unbelievable pain. Cheney emphasises that it's bad enough when patients do not perfuse their muscles and joints (because of poor microcirculation) but it's even worse when red blood cells are so deformed that they can barely get through the capillaries or are blocked entirely.

Cheney notes that in the Laboratory Textbook of Medicine, there are only three diseases that lower the sedimentation rate to that level: one is sickle cell anaemia (a genetic haemoglobinopathy); the second is ME/ICD-CFS (an acquired haemoglobinopathy) and the third is idiopathic cardiomyopathy.

Cheney observes that in order to improve cardiac output in CFIDS, patients need to lie down, as this increases the cardiac output by 2 litres per minute. He notes that some patients need to lie down all the time to augment their blood volume in order to survive. He has found increasing the intake of potassium to be helpful (potassium induces aldosterone, a hormone that significantly increases blood volume), and that magnesium is beneficial as it is a vasodilator and helps reduce the resistance the blood encounters.

Cheney is at pains to emphasise that none of these measures is a cure ---they are simply means to help patients disabled with CFIDS remain as functional as possible.

In the UK, the question has to be asked: how can forced aerobic exercise help such patients remain as functional as possible?

In the light of the Peckerman et al paper that was published in 2003, are the psychiatrists and their peer reviewers at the MRC who approved the PACE trial protocol still convinced that these trials (and the exercise regimes to be meted out by the new Centres) pose no harm for those with ME/ICD-CFS, or are they content to rely on the certainty that they themselves can never be held accountable for any harm to any patient because all participants must sign a compulsory waiver which means that no participant can ever pursue any claim for medical negligence or damages?

Another question needs to be asked and urgently answered: would it not more effectively advance medical and scientific understanding of this increasingly prevalent and devastating disorder if the MRC were at last to let it be known that they would look favourably upon applications for research funding submitted by those in disciplines other than psychiatry?

Considering the rapidly increasing weight of available published data on organic pathology in ME/ICD-CFS (little of which is published in the UK medical literature), the MRC will inevitably have its hand forced eventually, as the time will come when such evidence can no longer continue to be ignored, but currently this seems to remain a forlorn hope.

Is this because the biomedical issues that have been shown by internationally respected researchers to underpin ME/ICD-CFS are deemed inconvenient in the UK as they do not accord with Government's preferred policy of off-loading as cheaply as possible the ever-increasing hordes of chronically sick who have no commercial value to the State but who cost it far too much money?

Surely this is a short-sighted policy, because it is well recognised that those who are correctly diagnosed and permitted to rest adequately in the initial stages are the ones who have hope of some recovery; moreover, if relevant research were to be instituted, it would lead to patients being investigated competently and treated correctly, thus offering the prospect of ME/ICD-CFS patients being able to return to an economically productive life.