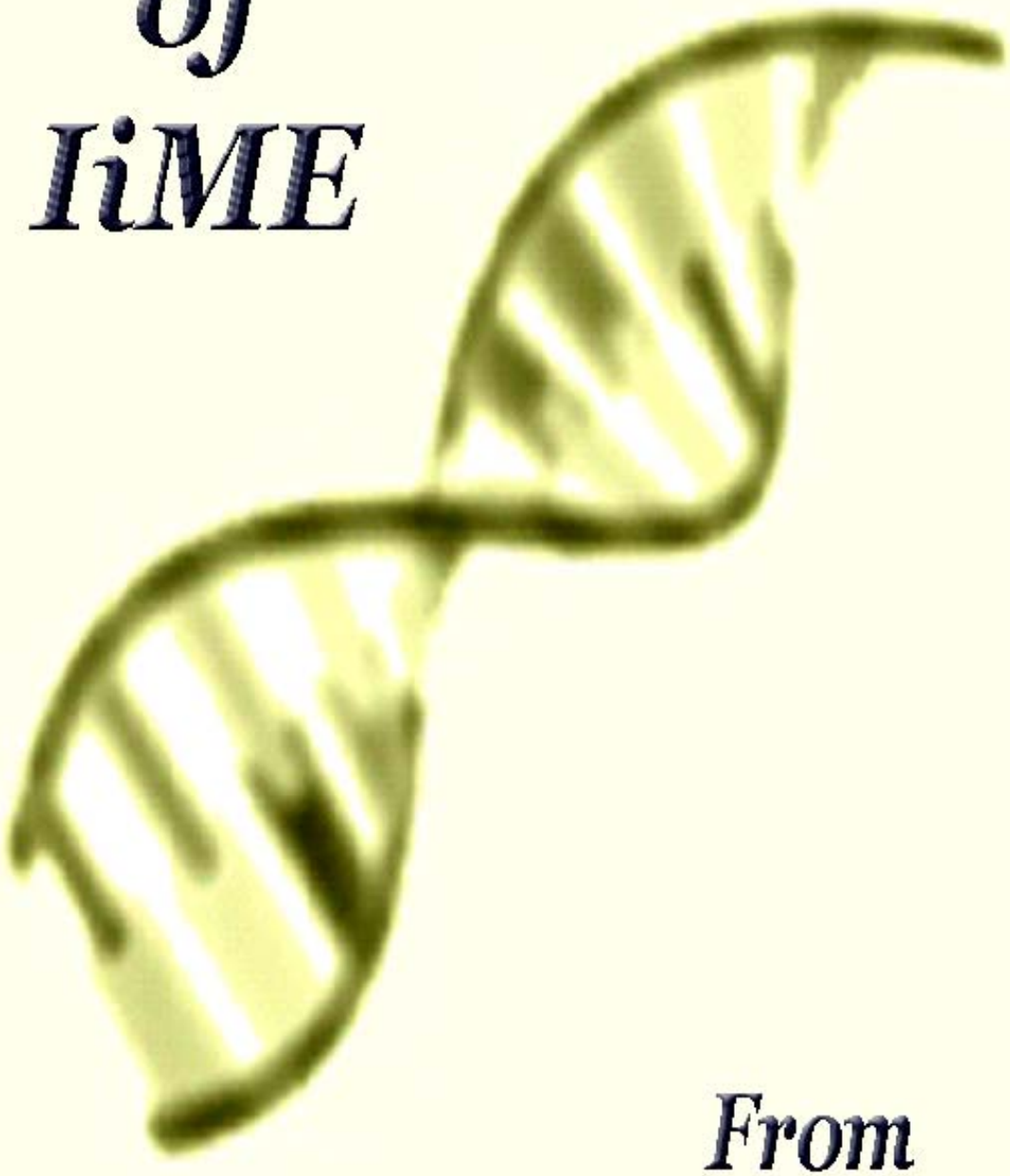
Journal of IiME



From Invest in ME

VOLUME 1 ISSUE 2

Autumn 2007

Facts About ME

In the World Health Organisation International Classification of Diseases -- to which the UK is a signatory and is therefore bound by it – myalgic encephalomyelitis (ME) has been classified as a neurological disorder since 1969. In the 1992 revision (ICD-10) chronic fatigue syndrome (CFS) is listed as a synonymous term for ME and both terms are listed in the neurological diseases section at G93.3, hence the disorder is referred to as ME/CFS.

ME Story

This is not the life I want, to be 31 with no job, living with my parents and other people's ignorant attitudes , "everyone gets tired", "you just need to sleep less" makes me mad. The government's lack of funding into research appalls me and the doctors I have seen know less about M.E than I do

– Vikki

This issue of the Journal continues with the objectives from the first issue – to provide a platform for serious research, appraisal and awareness of the neurological illness Myalgic Encephalomyelitis (ME).

In this issue we have research provided by Dr. Tae H. Park from South Korea. Dr. Park has been involved in treating ME for 10 years and his practice in South Korea has treated thousands of patients.

We also welcome Professor Sakudo from Japan who publishes for the first time his paper on the potential of visible and near-infrared (Vis-NIR) spectroscopy for the diagnosis of CFS using serum samples. Possible diagnostic testing has never been far from the demands of the ME patient community and Dr. Estibaliz Olano from Spain also presents news of another possible diagnostic test.

Invest in ME recently noticed news of mitochondrial research by Dr. Marisol Corral-Debrinski which asked 'Can "molecular addressing" correct mitochondrial diseases?' This seemed of interest, when one considers past research on ME and mitochondrial abnormalities. We asked Dr. Corral-Debrinski to publish articles on her work and she has written a detailed overview of her research. We hope it will provide awareness of wider possibilities relating to ME research.

We also have a paper on links between Q-fever and ME by Dr. Dragan Ledina from the University of Croatia.

Dr. Nigel Speight gave an excellent presentation at the IiME conference in London in May and in this Journal he presents a personal view of ME and Children over the last twenty years.

All of these papers reflect the outcome of the IiME conference in May – that there is an abundance of science available to encourage biomedical research into ME – something IiME and others have been pressing the government to acknowledge and yet something NICE have failed to recognise in their recently published guidelines on CFS/ME.

Both biomedical conferences of ME Awareness Month 2007, in which IiME and MER UK worked together to promote biomedical research, also demonstrated what an exciting field ME can be for potential researchers.

The need for urgent funding of biomedical research into ME is highlighted even further by Margaret Williams' article on the PACE trials – controversial trials claimed by the Medical Research Council to be worthwhile - but denounced by the ME community as being worthless and a waste of scarce funding.

Finally, with most of the ME community objecting to the prominent role psychiatry plays in the diagnosis and treatment of ME we reference a paper from Dr. Marek Marzanski detailing his research on how psychiatry and the Hippocratic Oath co-exist.

The science and the advocacy available for all to see seemingly makes the plight of people with ME, and their families, even more tragic and we continue with stories from patients and carers on their experiences with dealing with this illness – including a harrowing account from one family who have had to deal with their severely ill daughter being apportioned yet another psychiatric diagnostic term – Pervasive Refusal Syndrome.

We believe this further endorses the need for Journal of IiME – a blend of research, science, facts, politics and real life experiences.

Inside This Issue

Email: info@investinme.org

From the Chairman of Invest in ME

Welcome to the second Journal of Invest in ME – a combination of research, information, news, stories and other articles relating to myalgic encephalomyelitis.
Our first version of the Journal appeared in the delegates' conference pack at our International conference in London in May 2007. The conference brought together some of the foremost experts on ME and representatives from ME patient groups from all over the UK and Europe.
We believe that everyone left not only with an enhanced knowledge gained from the conference but also with renewed hope for the future treatment and possible cure for myalgic encephalomyelitis.
As Professor Malcolm Hooper commented in his introduction to the Issue 1 of the Journal - "*achievements, hope, and future actions were brought together in this conference*".

The breadth of knowledge, science and experience regarding ME, as discussed and presented at the conference, was not only impressive but also exciting. There are grounds for hope that a treatment and cure are on their way.
We are glad to see that the many contacts which were established at the conference have continued. To see renowned experts on ME discussing with each other and forming or re-enforcing collaborative efforts was reward enough for hosting the conference. To turn into reality our efforts to form a world alliance of campaigning ME Support organisations was also justification for the conference.
The presentations from our distinguished speakers displayed an amazing amount of knowledge regarding the organic nature of myalgic encephalomyelitis.

Invest in ME made the decision to fund the DVD of the conference in order that we had a permanent record of the events of that day and of the impressive science which exists already. The conference DVDs have been sold in twenty countries and testify to the need for education about ME. They are an educational tool for physicians to learn about ME.

As with many illnesses to which the government gives insufficient attention, and where some existing organisations seemingly fail to represent patients properly, the patients and carers are those who learn most about the illness, out of necessity. It is they who are forced into lobbying for proper attention. Invest in ME was created through such a state of affairs.
Our aim is, where possible, to provide information and educational material either free or at cost price - our recent London conference being an example of that where pwme and their carers could attend for a basic price which covered just food and refreshments.

Lobbying can work. The recent case of the GMC attempting to discipline Dr. Sarah Myhill is, perhaps, a case in point. Lobbying by patient groups and patients has perhaps forced the GMC to rethink their strange tactics. Dr. Myhill's case proves how out of touch an established organisation can be with the needs and welfare of patients and their families.

Similarly NICE has shown itself to be an organisation unwilling to progress the treatment and perception of ME.
Invest in ME have written to the current minister responsible for ME at the DoH, Mrs. Ann Keen, requesting a meeting with representatives from ME patient groups. The reply was the standard template from the DoH showing both ignorance and apathy to the plight of ME patients and

From the Chairman of Invest in ME (continued)

families in this country. IiME was also recently asked by the BBC Radio 4 Programme "You and Yours" to supply information for their series of programs on ME.

So education is still a huge priority and Invest in ME, and other groups, continue to perform work in this area - much of it unpublished - but with the intention of making ME a mainstream illness and deserving of educated and sufficient debate.
We are determined that what happened to Sophia Mirza, who died, "… ***as a result of acute renal failure due to dehydration arising as a result of Chronic Fatigue Syndrome (M.E.)"*** must never be allowed to happen again.
We shall endeavour to continue the campaign to educate and lobby and improve the lives of people with ME and their carers.

Invest in ME has taken over the distribution of the Canadian Guidelines in the UK. Together with both 2007 and 2006 conference DVD sets, and the Quotable Quotes on ME booklet, we have a useful range of educational material for healthcare staff, politicians, media and, of course, ME patient groups and pwme and their carers. Our 52-page response to the NICE guidelines has also been added to our web site.
We hope the Journal of IiME will also continue to assist in this area by providing a platform, as does the IiME conference, for biomedical researchers and clinicians to provide details of their research and work. It will also continue to offer real life experiences from those who have to deal with this illness on a daily basis – a fact to which too many politicians and organisations still remain indifferent.

As IiME plan for the May 2008 conference we look forward to working together with those interested in campaigning for funding of biomedical research into ME – the only sure way to provide a cure for this neurological illness.

We wish everyone a pleasant autumn and hope and believe that progress will continue in providing a future treatment/cure for ME.

Best Wishes *Kathleen McCall*

Articles for the Journal of IiME

Invest in ME welcomes articles for inclusion in the Journal, especially research papers on ME.

Our aim is to provide as much information, fact and science regarding myalgic encephalomyelitis in the hope that it will encourage research, funding and discussion of ME and provide more accurate perception on this illness.

Articles for consideration should preferably be in MS Word.
Please send any articles to jiime@investinme.org and provide a contact number and full address details.

The NICE Guidelines

"By pre-determining the result based on its requirements to view this illness as a broad chronic fatigue illness NICE has failed to grasp the reality, failed to analyse and use proper research, failed to respond to patients' demands and requirements and produced a document that will continue to allow this illness to be blended into a nebulous fatigue syndrome which only benefits psychiatrists interested in funding of their projects and other organisations who depend for their existence on paying members."

- IiME Comment on the NICE Guidelines for CFS/ME (Page 44)

Facts About ME

The textbook used to train NHS clinicians (and which is likely to be on the desk of every GP in the UK - Clinical Medicine: Kumar and Clark) categorises CFS/ME in the mental health section under "Functional or Psychosomatic Disorders" -

despite the fact that the World Health Organisation has recognised ME as a neurological illness and that this recognition is also officially supported by the British government.

Facts About IiME

The IiME website was set up in late 2005. The aim is to provide news, educational material, research information and stories of ME.

The IiME website usage has steadily grown with up to 60,000 visits per month from around the world.

www.investinme.org

COMPREHENSIVE TREATMENTS of CFS/ME WITH IVIG

By Dr. Tae H. Park

CFS/ME Clinic of Seoul, South Korea

PURPOSE OF STUDY:

To see the effectiveness of low dose gammaglobuline treatment in CFS/ME patients with strict control of diet, activities and sleep.

As is commonly known the research into CFS/ME patients is progressing rapidly, but treatments of CFS/ME patients in the clinical frontline is very limited, and most of the treatments are aimed toward the symptomatic relief of CFS/ME.
Here (in South Korea), we have 10 years experience of treating CFS/ME with IVIG, strict diet control, ample hydration and activity or exercise control.

Overall the response rate is 90% with these regimens. Those who responded had returned to work and resumed normal activities.

Contrary to the CDC report that initial symptoms are important for the prognosis of CFS/ME, our study showed that the severity and duration of sx of CFS/ME are not major determinants of prognosis (J.Reeves CDC).

There have been several reports about IV gammaglobuline therapy (K.S.Row, Lloyd) but the cost and adverse effect of IVIG treatments prevent CFS/ME patients to have IVIG tx.

Further more, the results of IVIG tx are not significant enough to recommend for general use for CFS/ME patients
Except Dr.Row's report that 75-80% of children return to normal school activities and 5-6 yr follow-up also showed the significant improvements.

Selection of patients

Among our clinic's 5378 patients, we selected 50 patients who met the 1994 Fukuda criteria in random fashion.

Duration of illness:	from 2 years to 15 years
Ages of patients:	18 to 50
Gender:	male: 28 female:22

Method of treatments

Sleep control:
Sleep before midnight and at least 7 hours sleep.
If there is DIMS (difficulties in initiating and maintaining sleep), used klonopine and (or) prozac (10-20mg) at night.

Dr Tae Park M.D.

Dr.Park runs his own CFS clinic in Seoul, Korea. Dr. Park attended the Invest in ME International ME/CFS Conference in London in May 2007 and has subsequently supplied this and the following articles.

Diet control
Organic foods: rice and vegetables
Avoidance of certain foods: bread, canned food, coffee, chocolate, monosodium glutamate, aspartame and hot peppers, orange juice, carbonated beverages.
A high protein diet (but avoidance of pork).

Ample hydration
2-3 litres of water with 2 tsp of salt.

Strict control of exercise and activities.
No heavy lifting (anything using upper extremities – such as house cleaning) is prohibited.
Walking is allowed if patient improves.
If the patient feels any post-exertional malaise, then reduce the exercise.

IV Gammaglobuline
One gram per week in 500cc of 0.9% normal saline infused over one hour.
Avoid NSAID (non-steroidal anti-inflammatory drugs) medication, and avoid tests using contrast media (like CT-scan, or IVP)

How to have rest
Rest (like monks meditate),
No loud music and no reading books.
In acute stages, absolutely no exercise.
If anyone does exercise they may develop cardiomyopathy or severe cardiac arrhythmia - even death.

Results of treatment
90% of patients who were treated with the above regimens recovered and returned to work, or returned to school.
Showed KS score from 40 to 90.
The fatigue impact scale improved from 120 to 20-40.
Especially, we found improvements in the cognitive functions. We found improvements in concentration and comprehension, but short-term memory is the last to recover.
Most of our CFS/ME patients showed impaired renal functions. They showed reduced GFR (glomerular filtration rate) and when compared with normal controls (Park, presented at Japan CFS/ME conference 2007).

(continued on page 6)

COMPREHENSIVE TREATMENTS of CFS/ME WITH IVIG *(continued)*

In CFS/ME patients, 88% of patients showed GFR below 80ml/min (compared with non-diabetic general populations: 39%), 46% of CFS/ME patients showed GFR below 60ml/min (compared with 19% of general non-diabetic population).
Due to the low GFR nearly all of CFS/ME patients we need to be careful to monitor their renal function on a regular basis (every 3 months to check s-creatinine).

Method of follow up of patients

1. Check quality of sleep: dreams, DIMS, snoring with apnea, refreshing sleep.
2. Check BP: each time of visit, manually checking BP and record correctly. If BP is rising from low BP, then patient's fatigue sx is getting better. If BP is still low with hydration of 2 litres of water with 2 tsp of salts, then add florinef.
3. Nocturia: check how frequently patients experience nocturia. If nocturia reduces, then patient's sx of CFS/ME improves.
5. DIMS (difficulties in initiating and maintaining sleep). If DIMS diminishes then the patient's sx improves.
6. Strict control of exercise and activity. No heavy lifting (anything using upper extremities such as house cleaning is prohibited). Walking is allowed if patient improves. If patient feels post-exertional malaise then reduce the amount of exercise.
7. Check GFR in all CFS/ME patients (nearly 50% of CFS/ME patient's GFR is close to chronic kidney disease range (near GFR of 60 ml/min).
8. Avoid the use of NSAID and contrast media using tests such as CT or IVP.
8. Hunger discomfort (such as sudden weakness, sweating) indicates the patient's liver is enlarged. That means that the patient's activity level is too high or the patient's level of exercise is too great.
10. Check liver and spleen at each consultation. If the liver and (or) spleen became smaller then the patient sx improves. If a patient's liver and (or) spleen are enlarged that means patient's activity level is too high or patient's diet control is poor.

ME Patient's Carer's Story

Some time around May or June I got a letter from social services asking me to contact them. In my innocence I thought it was a follow up to our claim for DLA (Disability Living Allowance), so from the disability team offering support.

Not a bit of it, my sister had reported me for suspected Munchausen's by Proxy.

The fact that she hadn't seen us for two years hadn't held her back. So to add to the difficulties of dealing with the school, the benefits system, a paediatrician from hell and a sick child, I now had to deal with a social services investigation.

- Parents of Emma

Facts About ME

The UK Medical Research Council has a secret file on Myalgic Encephalomyelitis (ME) that contains records and correspondence since at least 1988;

The file is held in the UK Government Archive at Kew and cannot be opened until 2023.

ME Petition to the Prime Minister

The E-petition to the Prime Minister, created by Konstanze Allsopp, to enforce the acceptance of ME as a neurological illness is still open for new signatures.

In fact this petition (at **http://www.investinme.org/E-Petition%202007.htm**) has a closing date of January 2008. One can lend support for this petition, which states -

"We the undersigned petition the Prime Minister to get the Health Service and medical profession to accept the WHO classification of ME/CFS as an organic neurological disorder and not as a psychosocial syndrome."

CFS/ME MAY BE MAJOR CAUSE of CHRONIC KIDNEY DISEASE IN NON-DIABETIC POPULATIONS

By Dr. Tae H. Park

OBJECTIVE OF STUDY:

To prove that CFS/ME is a major cause of chronic kidney disease (CKD) in the general population.

DESIGN:
Cross-sectional study

PATIENTS:
Participants are 20 years of age and older
400 CFS/ME patients
There is a sudden increase in occurrence of non-diabetic, chronic kidney disease patients in the last 3-4 years.
In one report (Class et al), 39% of the non-diabetic population showed GFR below 80ml/min.
Among them 14% showed GFR below 60ml/min.

We collected data from our 400 CFS/ME patients who meet the Fukuda criteria of 1994 and calculated the GFR using the Cockcroft-Gauld formula.
The results which we found in our study are striking.

Among our 400 CFS/ME patients we found 88% of the patients showed GFR below 80ml/in and 46% GFR below 60ml/min.
If we subdivided stage 3 CKD patients (GFR below l60ml/min) then 38.4% showed GFR between 55-60, 33.6% showed GFR 50-54, 29% showed GFR 45-49.

In stage 2 CKD classification (GFR below 90) our study showed 84.7% of CFS/ME patient met stage 2 criteria.
Among stage 2 patients we further subdivided patients.
The result is as follows - GFR 60-65 is 43%, 65-70 is 45%.
Even in stage 2 classification we found 88% of CFS/ME patients were close to CKD.
What this means is that these CFS/ME patients will be CKD patients in the near future without any diabetes or hypertension.
A recent report showed 80% of CFS/ME patients are not diagnosed yet, with only 20% being diagnosed.
If we bear these facts in mind, and if many of CFS/ME patients are misdiagnosed as having a psychiatric disease or as having HIV, then these non-diagnosed CFS/ME patients would contribute to a major risk factor of CKD in general populations.

We suggest that every CFS/ME patient is checked for s-creatinine based GFR and that this is recorded.
Furthermore, one should avoid medication like Non-steroidal anti-inflammatory drugs (NSAIDs) to control pain and most importantly to avoid many tests using contrast media - CT scan, intravenous pyelogram (IVP) especially coronary angiography, even if they have non-specific chest pains.

Facts About ME

"Psychogenesis of these illnesses is based on the shaky foundation of somatoform disorders and somatisation. It is based on emotion-laden phrases, transparent falsehoods, logical flaws, overstated claims, and unsupported or poorly supported opinion".

"It is based on ignoring the existence of a genetic role in these illnesses. It is based on ignoring the long history of false psychogenic attributions of other illnesses"

"It is based on ignoring hundreds of studies documenting real physiological changes in multi-system illnesses".

"It is based on a deliberate ignorance, flaws and quicksand. I do not know how long it will take for the scientific community to realise the demise of the psychogenic view of multi-system illnesses, but it will happen".

"My critique of psychogenesis of multi-system illnesses should not be considered as a critique of psychiatry. It is rather a critique of those who either lack wisdom or who have sold their integrity".

"Whilst the most severe long-term damage created by psychogenic advocates has been to the research prospect for these illnesses, the most severe short-term impact has clearly been to sufferers of these illnesses and their families".

Professor Martin L Pall Professor of Biochemistry and Basic Medical Sciences at Washington State University, (Explaining 'Unexplained Illnesses':; Haworth Press, 2007)

http://www.investinme.org/Documents/PDFdocuments/Martin%20Pall%20Book.pdf

Visible and near-infrared (Vis-NIR) spectroscopy: Introduction and Perspectives for Diagnosis of Chronic Fatigue Syndrome

By Akikazu Sakudo[1]* Yukiko Hakariya[1], Takanori Kobayashi[1], and Kazuyoshi Ikuta[1]

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Summary

Currently, chronic fatigue syndrome (CFS) is diagnosed based on clinical symptoms. Although various information on psychological, endocrinological, and immunological abnormalities in CFS patients has been reported, there is no clear consensus, possibly due to the absence of an objective diagnostic method. One experimental approach is the use of instrumentation for diagnosis. Recently, our research group has shown the potential of visible and near-infrared (Vis-NIR) spectroscopy for the diagnosis of CFS using serum samples. This review will introduce the method and the future perspectives made possible by it.

Keywords:

Chronic fatigue syndrome; myalgia encephalomyelitis; visible and near-infrared spectroscopy; diagnosis

Introduction

Chronic fatigue syndrome (CFS) is a debilitating disorder involving persistent fatigue lasting for more than six months [1]. However, the difference between CFS and CFS-like diseases such as myalgia encephalomyelitis (ME), postviral fatigue syndrome (PVFS), chronic fatigue/immune dysfunction syndrome (CFIDS), and 'Yuppie flu' remains unclear. The symptoms of CFS include fatigue, pain, breathing problems, depression leading to digestive disturbances, low grade fever, difficulty in concentrating, and weakness of the immune system and muscles [1]. The symptoms are not resolved by sufficient rest [1].

The incidence of CFS is 0.4% in the United States and other countries [2] and 0.26% in Japan [3]. Economic losses caused by the disease are estimated at as high as 9.1 billion dollars per year in the United States [4] and 408 billion yen per year in Japan [3]. However, research conducted by the Centers for Disease Control and Prevention (CDC) estimates that less than 20% of CFS patients in the United States have been successfully diagnosed [2, 5], indicating that the number of patients will increase if more reliable diagnostic methods are established. The main barriers to identifying CFS patients are an absence of biophysical and biochemical signs that identify the disease and lack of diagnostic laboratory tests [6]. This may be at least in part due to the heterogeneity of the symptoms of CFS patients [6]. At present, CFS diagnosed based on the presentation of symptoms and exclusion of other medical entities.

Therefore, it relies on symptometology. Most published studies have diagnosed CFS on the basis of CDC criteria [1]. As psychiatric diseases and other treatable conditions are sometimes difficult to distinguish from CFS, the patient's

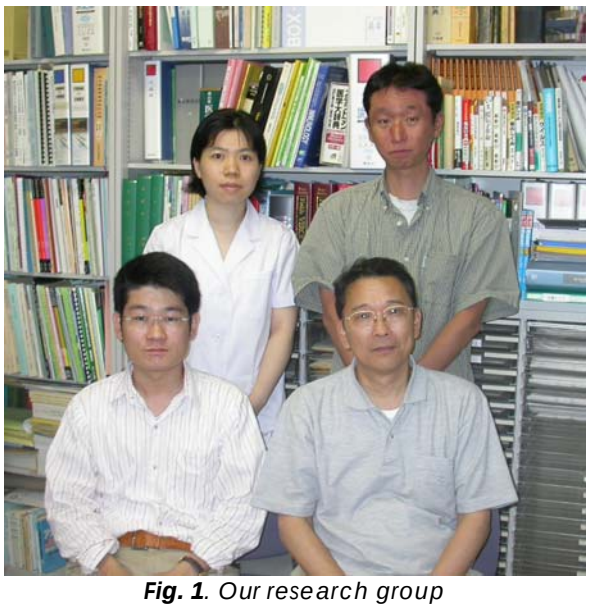

***Fig. 1**. Our research group*

Medical spectroscopy group at Department of Virology, Research Institute for Microbial Diseases, Osaka University was composed of a virologist (Kazuyoshi Ikuta), spectroscopist (Akikazu Sakudo), physician (Yukiko Hakariya), and clinical laboratory technologist (Takanori Kobayashi). Researchers with different backgrounds are studying CFS.

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Visible and near-infrared (Vis-NIR) spectroscopy: Introduction and Perspectives for Diagnosis of CFS

symptoms should carefully be examined. Physicians should, through a careful investigation of the patient's medical history and appropriate testing, rule out other diseases including mononucleosis, Lyme disease, thyroid conditions, diabetes, multiple sclerosis, various cancers, depression and bipolar disorder.

We feel that the main problems in CFS studies can be attributed to the objectivity of diagnosis and absence of biomarkers. Our research group, composed of a virologist, spectroscopist, physician, and clinical laboratory technologist, has been studying visible and near-infrared (Vis-NIR) spectroscopy (Fig. 1). We decided to apply Vis-NIR spectroscopy to the study of CFS. In this review, we introduce the method and its possible uses for CFS research.

Vis-NIR spectroscopy and multivariate analysis

The short wavelength (SW)-NIR region and the red region, the so called "optical window" from 600 to 1,100 nm, are together the most useful region for measuring biological samples [7].

The absorption of hemoglobin and water is extensive in the region below 600 nm and above 1,100 nm, respectively, which limits spectroscopic and microscopic studies [8]. Absorption in the SW-NIR region is due to combinations and overtones of vibration such as the stretching and bending of hydrogen-bearing functional groups including –CH, -OH and –NH [9]. Water, melanin, and bilirubin in animals were absorbed by the radiation of this region [8]. In addition, oxyhemoglobin, deoxyhemoglobin, and oxidized cytochrome c oxidase have characteristic absorption spectra in the SW-NIR region [10]. Recently, biologically important molecules such as albumin [11-13], cholesterol [14, 15], globulin [11-13], glucose [13, 16-24], protein [12, 15, 25-28], urea [12, 13, 27], lipid [15], linoleic acid [15], collagen [15], DNA [15], and a-elastin [15] have also been investigated by Vis-NIR spectroscopy. However, there has been considerable debate as to whether the accuracy and stability of Vis-NIR calibration models for non-invasive transcutaneous monitoring of blood glucose levels in patients with diabetes met criteria for clinical diagnosis [18, 29, 30]. Creatine [27], lactate [22, 31], triacetin [20], triglyceride [13], β-lipoprotein [25], Vibrio cholerae [32], Escherichia coli [33, 34], Yeast [35, 36], Ethanol [36, 37], RNA [28], Acetate [34], Ammonia [22, 34], Glycerol [34], and Glutamine [22] have also been quantitatively determined by Vis-NIR spectroscopy. Representative biomolecules studied by Vis-NIR spectroscopy are listed in Table 1.

Vis-NIR spectroscopy has been recognized as having diagnostic potential ever since Jöbsis first used it to demonstrate oxygenation in cats [38]. Vis-NIR spectroscopy has also been applied in the clinical setting to aging [39, 40], Alzheimer's disease [41], cancer [42-50], chronic fatigue syndrome [51-54], dermatological conditions [43], diabetes [18, 21, 55], epilepsy [56], human immunodeficiency virus (HIV) infection [57], seizure types [58], migraine [59], cervical dysplasia [60], atherosclerotic plaques [61], rheumatoid arthritis [62], hemodynamics [63], glioma [64], intraocular pressure [65], hemorrhagic shock [66], skin moisture [67], brain edema [68], optic neuritis [69], and maternal hypotension [70] (Table 2). The number of diseases studied by Vis-NIR spectroscopy has been increasing, although most studies have focused on the monitoring of oxyhemoglobin and deoxyhemoglobin. At present, the diagnostic application of this method in the medical field is rare.

The development of laboratory instrumentation for Vis-NIR spectroscopy has been well reviewed [71]. Manufacturers and commercially available instrumentation has also been listed [72], and the number of manufacturers has shown further dramatic increase. The range of wavelengths and modes of measurement available must be paid greater attention to select a suitable instrument for analysis.

Cuvettes are sometimes used for measurements. Quartz and polystyrene cuvettes are preferable because much Vis-NIR spectral information on quartz and polystyrene has been reported.

The methods of measurement are divided into four types: transmission, reflection, transflection, and interactance in spectroscopy [73]. In transmission spectroscopy, radiation transmitted through sample is measured. In reflection spectroscopy, radiation reflected on the surface is measured. In transflection spectroscopy, which is a combination of the transmission and reflection methods, radiation is transmitted through the sample and scattered back from a reflector on the opposite side. In interactance spectroscopy, radiation transmitted through the sample is collected in contact with the surface of the sample with the end of a fibre optic probe, which has both a radiator and a detector [74]. The availability of fibre optic probes is one advantage of Vis-NIR spectroscopy. Vis-NIR spectroscopy enables the rapid, non-destructive, accurate, and simultaneous determination of multiple components in both liquid and solid samples [75]. However, it also has disadvantages.

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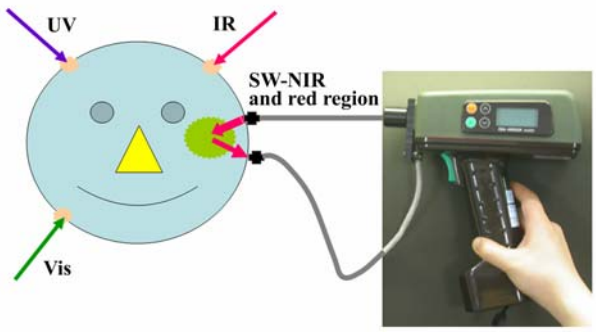

Fig. 2. Characteristics of near-infrared radiation. Ultraviolet (UV), visible (Vis), and infrared (IR) radiation is highly absorbed, whereas near-infrared (NIR) radiation is relatively little absorbed, by water and haemoglobin. Notably, 600-1,100 nm including the red region and short wavelength region of near-infrared (SW-NIR) radiation is called the "optical window", because this region is suitable for biological analysis. Modified from Fig. 1 in Sakudo et al. [103] with permission from Nippon Rinsho Co.

Visible and near-infrared (Vis-NIR) spectroscopy: Introduction and Perspectives for Diagnosis of CFS

Table.1 Representative biomolecules studied by Vis-NIR spectroscopy

Biomolecule	Wavelength [nm]	Algorithm	Reference
Albumin	1300-1850	PLS	[11]
Albumin	400-2500	PLS,MLR	[12]
Albumin	400-2500	PLS,MLR	[13]
Cholesterol	1200-2400	MLR	[14]
Creatine	400-2500	PLS, MLR	[27]
Cytochrome c oxidase	605, 620, 760, 830	None	[87]
Cytochrome c oxidase	700, 730, 750, 805	None	[88]
Cytochrome c oxidase	605, 620, 780, 830	None	[89]
Cytochrome c oxidase	700-865	None	[38]
Globulin	400-2500	PLS,MLR	[12]
Globulin	400-2500	PLS,MLR	[13]
Globulin	1300-1850	PLS	[11]
Glucose	400-2500	PLS,MLR	[13]
Glucose	833-2500	PLS	[16]
Glucose	2000-2500	PLS	[17]
Glucose	400-1700	PLS	[18]
Glucose	2000-2500	PLS	[19]
Glucose	2000-2500	PLS	[20]
Glucose	750-1300	PLS, PCRA	[21]
Hemoglobin	700, 730, 750	None	[90]
Hemoglobin	460-760	Least squares method	[91]
Hemoglobin	700-865	None	[38]
HIV	600-1000	PLS	[57]
Lactate	1000-2500	PLS	[31]
Nitric oxide	470-760	Least squares method	[91]
Prion protein	400-2500	PCA, SIMCA	[92]
Protein	400-2500	PLS,MLR	[12]
Protein	1000-2500	MLR,PCRA,PLS	[25]
Protein	1440-2350	MLR,PCRA,PLS	[26]
Protein	400-2500	PLS, MLR	[27]
RNase A	1250-2500	None	[93]
Triacetin	2000-2500	PLS	[20]
Triglyceride	400-2500	PLS,MLR	[13]
Urea	400-2500	PLS,MLR	[12]
Urea	400-2500	PLS,MLR	[13]
Urea	400-2500	PLS, MLR	[27]
β-lipoprotein	1000-2500	MLR,PCRA,PLS	[25]

Table 1. Representative biomolecules studied by Vis-NIR spectroscopy

HIV: human immunodeficiency virus
MLR: multiple linear regression analysis
PCA: principal component analysis
PCRA: principal component regression analysis
PLS: partial least squares regression analysis
SIMCA: software-independent modeling by class analogy

Vis-NIR spectroscopy is not very sensitive: the limit is only about 0.15% (w/w) for most constituents, and the signal to noise ratio of the instrument is low [less than 10^{-4} optical density (OD)] [76], but is dependent on several factors such as the measurement accessory, spectrometer including detectors, and acquisition time. A large amount of sample is needed for Vis-NIR spectroscopy compared to other methods of chemical analysis [76]. The direct interpretation of spectral absorbance is very difficult for complex mixtures because of broad overlapping and interacting absorption bands [76]. Vis-NIR spectroscopy thus relies on a multivariate analysis to quantify properties or constituents of interest.

A multivariate analysis is an analysis of data with many variables based on statistics and mathematics. It can simplify complicated data and uncover hidden information. The analysis can be qualitative or quantitative. It is based on chemometrics algorithms. Methods of quantitative analysis include the partial least squares regression analysis (PLS) and the principal component regression analysis (PCRA), which are used to develop the regression model for the prediction of the reference value [77, 78]. Methods of qualitative analysis include the principal component analysis (PCA) [79] and the software-independent modeling by class analogy (SIMCA) [80]. PCA is a method for transforming an original variable such as absorbance at various wavelengths into new variables called principal components (PCs). By plotting the data defined by PCs, important relationships in the data (e.g., similarities and differences among objects) can be clearly identified. SIMCA is a recently developed method based on PCA [81]. PCA reduces the amount of data, and SIMCA further extracts discriminant rules among different groups. PCRA is a method for performing PCA on x variables such as wavelength and then regressing y variables on the principal components, whereas PLS

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Visible and near-infrared (Vis-NIR) spectroscopy: Introduction and Perspectives for Diagnosis of CFS

Table.2 Representative clinical applications of Vis-NIR spectroscopy

Clinical application	Sample	Biomolecule	Wavelength [nm]	Algorithm	Reference
Aging	Forehead	HbO2, Hb	775, 825, 850, 904	None	[39]
Alzheimer's disease	Forehead	HbO2, Hb	775, 825, 850, 904	None	[41]
Atherosclerotic occlusive disease	Posterolateral calf	HbO2, Hb	700, 750, 830	None	[94]
Biliary atresia	Feces	Bilirubin, Fat	600-2500	Least squares regression analysis	[95]
Breast cancer	Breast tissue	Not identified	625-1050	PCA	[42]
Chronic fatigue syndrome	Gastrocnemius muscle	HbO2, Hb	760, 850	None	[51]
Chronic fatigue syndrome	Forehead	HbO2, Hb	780, 805, 830	None	[52]
Chronic fatigue syndrome	Leg	HbO2, Hb	760, 850	None	[53, 54]
Epilepsy	Forehead	HbO2, Hb	780, 830	None	[56]
Friedrich's ataxia	Gastrocnemius muscle	HbO2, Hb	760, 850	None	[96]
HIV infection	Plasma	Not identified	600-1000	PLS	[57]
Lung disease	Forehead	HbO2, Hb	775, 810, 850, 910	None	[97]
Metabolic myopathies	Gastrocnemius muscle	HbO2, Hb	760, 850	None	[98]
MELAS and MERRF syndrome	Gastrocnemius muscle	HbO3, Hb	760, 850	None	[99]
Pigmented and non-pigmented skin	Skin	Not identified	400-2500	PCA	[100]
Schizophrenia	Forehead	HbO2, Hb	780, 805, 830	None	[101]
Seizure types	Forehead	HbO2, Hb	730, 810	None	[58]
Skin cancer	Skin	Not identified	400-2500	LDA, Paired t test, Repeated measures analysis of variance	[43, 44]
Type1-diabetes	Finger	Not identified	600-1300	PLS, PCRA	[21]
Type1-diabetes	Thumb	Not identified	400-1700	PLS	[18]
Type2-diabetes	Gastrocnemius muscle	HbO2, Hb	733, 809	None	[55]
Valvular heart disease	Forehead	HbO2, Hb	775, 810, 850, 910	None	[102]

Table 2. Representative clinical applications of Vis-NIR spectroscopy

Hb: deoxyhemoglobin
HbO_2: oxyhemoglobin
HIV: Human immunodeficiency virus
LDA: linear discriminant analysis
MELAS: myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
MERRF: myoclonic epilepsy with ragged red fibers
PCA: principal component analysis
PCRA: principal component regression analysis
PLS: partial least squares regression analysis

gives extra weight to variables that show a high correlation with y variables.
Therefore, PLS is usually more effective for predictions than PCR. Further detailed illustrations and mathematical formulas of algorithms are available in many reports about chemometrics [82, 83].

In a multivariate analysis, the number of PCs is important, because too few or too many PCs distort signals or diminish the signal-to-noise ratio, respectively. To choose the correct number of PCs, a validation step is usually included in the process of modeling [9]. For validation steps, internal validation or external validation is used. Most chemometrics software programs include internal cross validation. In internal cross validation, the sample set is repeatedly divided into two groups. One group is reserved for validation and the other, for calibration. This process is repeated until all groups have been used for validation once. In external validation, sample sets are first separated into calibration samples and test samples, which are subjected to validation and used for assessment of the calibration model. By finding the number of PCs when the model shows a minimum standard error of validation (SECV), the number of PCs can be used to describe the signal in the data.

These results suggest that combining Vis-NIR spectroscopy with chemometrics is a promising way to objectively diagnose CFS. They also suggest that an unknown factor or factors present in the serum of all CFS patients could provide important clues as to the agent causing this debilitating disease.

Recently, commercially available chemometrics software programs such as Pirouette (Infometrics, Woodinville, Washington, USA) and Unscrambler (CAMO Inc., Woodbridge, New Jersey, USA) have been used for Vis-NIR analyse. The number of manufacturers of these software programs is increasing. The programs and their manufacturers are listed in Table 3. The software programs are designed to analyze spectral data, and because pre-processing such as standard normal variate (SNV) [84] and smoothing [85], which minimize differences between spectra caused by baseline shifts and noise, is carried out during the analysis, pre-processing handling, which is time-

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Table 3. Representative chemometrics software and statistical analysis used in Vis-NIR spectroscopy studies

Name	Manufacturer	Statistical algoritum	
		Regression analysis	Classification methods
Unscrambler	CAMO Inc.	MLR, PCR, PLS	PCA, SIMCA
Pirouette	Infometrics	PCR, PLS, CLS	PCA, HCA, KNN, SIMCA
CharmWorks	Process Analysis and Automation Ltd.	PLS	PCA, SIMCA
Extract	Extract Information AB	PLS	PCA
SIMCA-P	Umetrics		SIMCA
PLS Toolbox	Eigenvector Research Inc.	PLS, PCR	SIMCA, KNN
Sirius	Pattern Recognition Systems	PCR, PLS	PCA
Chemometrics Toolbox	The MathWorks	PCR, PLS	PCA

Table 3. Reprentative chemometrics software and statistical analysis used in Vis-NIR spectroscopy studies

MLR:	Mutilinear regression	PCR:	Principal component regression
PLS:	Partial least squares regression	SIMCA:	Soft independent modeling of class analogy
PCA:	Principal component analysis	HCA:	Hierarchical cluster analysis
KNN:	K-nearest neighbors	CLS:	Class least squares

consuming, is not required. Furthermore, cross validation steps are also included, and these reduce the overall handling and risk of error during analysis.

Application of Vis-NIR spectroscopy for CFS research

Several biochemical changes are reported in CFS patients, but there is no clear consensus for any of them. Therefore, the diagnosis of CFS is currently based on clinical symptoms. As this approach relies on experience and skill, CFS can be diagnosed only by limited numbers of medical doctors. To overcome these problems, an additional method using instrumentation to achieve an objective diagnosis is needed. We reasoned that Vis-NIR spectroscopy might provide new insights if patients could be compared with individuals without the disorder. Here, we describe the results obtained when sera from CFS patients as well as healthy volunteers were subjected to Vis-NIR spectroscopy [86]. At the Medical Hospital of Osaka City University, serum samples from 77 CFS patients (33.0 ± 8.8 years old; Male/Female: 29/48), diagnosed on the basis of clinical criteria proposed by CDC were examined [1]. Samples from 71healthy volunteers (41.7 ± 10.4 years old; Male/Female: 33/38) were also used. The sera of the 77 CFS patients and 71 healthy volunteers served as test samples to develop calibration models for PCA and SIMCA. Another 99 determinations [54 in the healthy group (35.9 ± 9.1 years old; Male/Female: 11/7) and 45 in CFS patients (34.9 ± 7.0 years old; Male/Female: 8/7)] were masked and used for predictions. All samples were diluted 10-fold with phosphate-buffered saline and adjusted to a constant volume (2 ml) in a polystyrene cuvette before the Vis-NIR spectroscopic measurements. Three consecutive Vis-NIR spectra were measured at a resolution of 2 nm with an NIRGUN (Japan Fantec Research Institute, Shizuoka, Japan) at 37°C. The spectral data were collected as absorbance values [log(1/*T*)], where *T*= transmittance in the wavelength range from 600 to 1,100 nm. Pirouette software (ver. 3.11; Infometrics) was employed for all data processing. To minimize differences between spectra caused by baseline shifts and noise, prior to calibration, spectral data were mean-centered and transformed by SNV [84] and smoothing based on the Savitsky-Golay algorithm [85]. To identify the predominant absorbance peaks in the spectra, PCA and SIMCA methods were further applied to develop PCA and SIMCA models for CFS diagnosis. A clear difference in the sera of CFS patients from those of healthy donors was seen in PCA scores using the first principal component (PC1) and second principal component (PC2) (Fig. 3A, B). The SIMCA model allowed correct separation of the Vis-NIR spectra of 209 of 213 (98.1%) healthy volunteers and 220 of 231 (95.2%) CFS patients. SIMCA using Coomans plots demonstrated that classes of sera from the volunteers and patients did not share multivariate space, providing validation for the separation (Fig. 4A, C). Furthermore, masked samples were subjected to Vis-NIR spectroscopy, and predictions made with the PCA and SIMCA models. PCA clearly distinguished the masked samples of the healthy volunteers from those of the CFS patients (Fig. 3C). SIMCA correctly predicted 54 of 54 (100%) volunteers and 42 of 45 (93.3%) patients (Fig. 4B, D).

These results suggest that combining Vis-NIR spectroscopy with chemometrics is a promising way to objectively diagnose CFS. They also suggest that an unknown factor or factors present in the serum of all CFS patients could provide important clues as to the agent causing this debilitating disease.

We concede that statistically, the results are not robust enough for clinical use at this time. The PCA and SIMCA model was developed from Vis-NIR

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Visible and near-infrared (Vis-NIR) spectroscopy: Introduction and Perspectives for Diagnosis of CFS (continued)

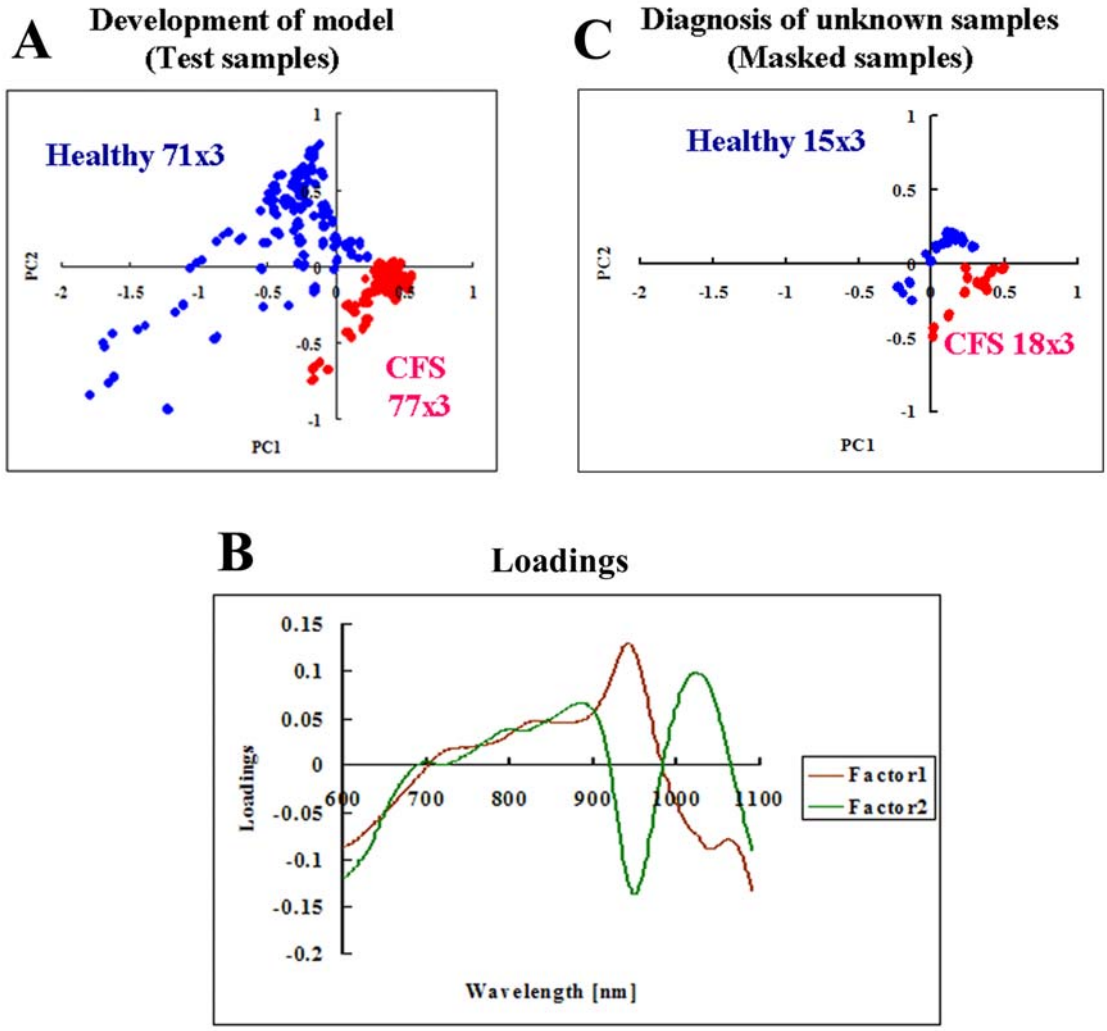

Fig. 3. PCA of Vis-NIR spectra of serum samples for CFS diagnosis

(A-B) Vis-NIR spectra of serum samples from healthy donors (Blue) and CFS patients (Red) were subjected to PCA and the results plotted as PC1 *versus* PC2 to establish a PCA model (A). Loadings show the importance of each wavelength for the PCs indicated by peaks (B). (C) Masked samples, which were not used for development of the model, were subjected to PCA and the results plotted as PC1 *versus* PC2. Modified from Fig. 1 in Sakudo et al. [86] with permission from Elsevier.

spectra of 148 individuals including 77 CFS patients and 71 healthy donors, not a sufficient number for practical use in the clinic. The influences of sex and race, etc. on the results of this diagnostic method remain unclear. To obtain more Vis-NIR spectra, samples for the calibration set should be obtained in a similar way to those that will be analyzed for diagnosis. Furthermore, uniformity of the solvent among samples is very important. For example, in blood samples, identical methods of preparation of serum are necessary.

Stable humidity and temperature should be maintained during the scanning event, because humidity and temperature may affect water absorption in the NIR region. In this study, we used serum samples for Vis-NIR spectroscopy. Therefore, the method is invasive but non-destructive. Vis-NIR spectroscopy can also be applied to non-invasive analyse and we are now approaching the non- invasive diagnosis of CFS (Fig. 5).Hopefully, after these issues are addressed, this diagnostic method might be adopted in the clinic (Fig 6).

The next step in terms of research into the disease, as opposed to diagnosis, is to use this approach together with other evidence to try and identify specific biochemical markers common to CFS. This is the best way to understand the cause of CFS. Our experimental system coupling Vis-NIR spectroscopy with chemometrics may also contribute to this issue.

Finally, we would like to emphasize that international collaboration is important in the development of this method, because CFS is heterogeneous and diagnostic criteria differ slightly among countries. Differences and similarities between CFS and CFS-like diseases such as ME, PVFS, CFIDS, and 'Yuppie flu' would also be made clear by this method.

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Visible and near-infrared (Vis-NIR) spectroscopy: Introduction and Perspectives for Diagnosis of CFS (continued)

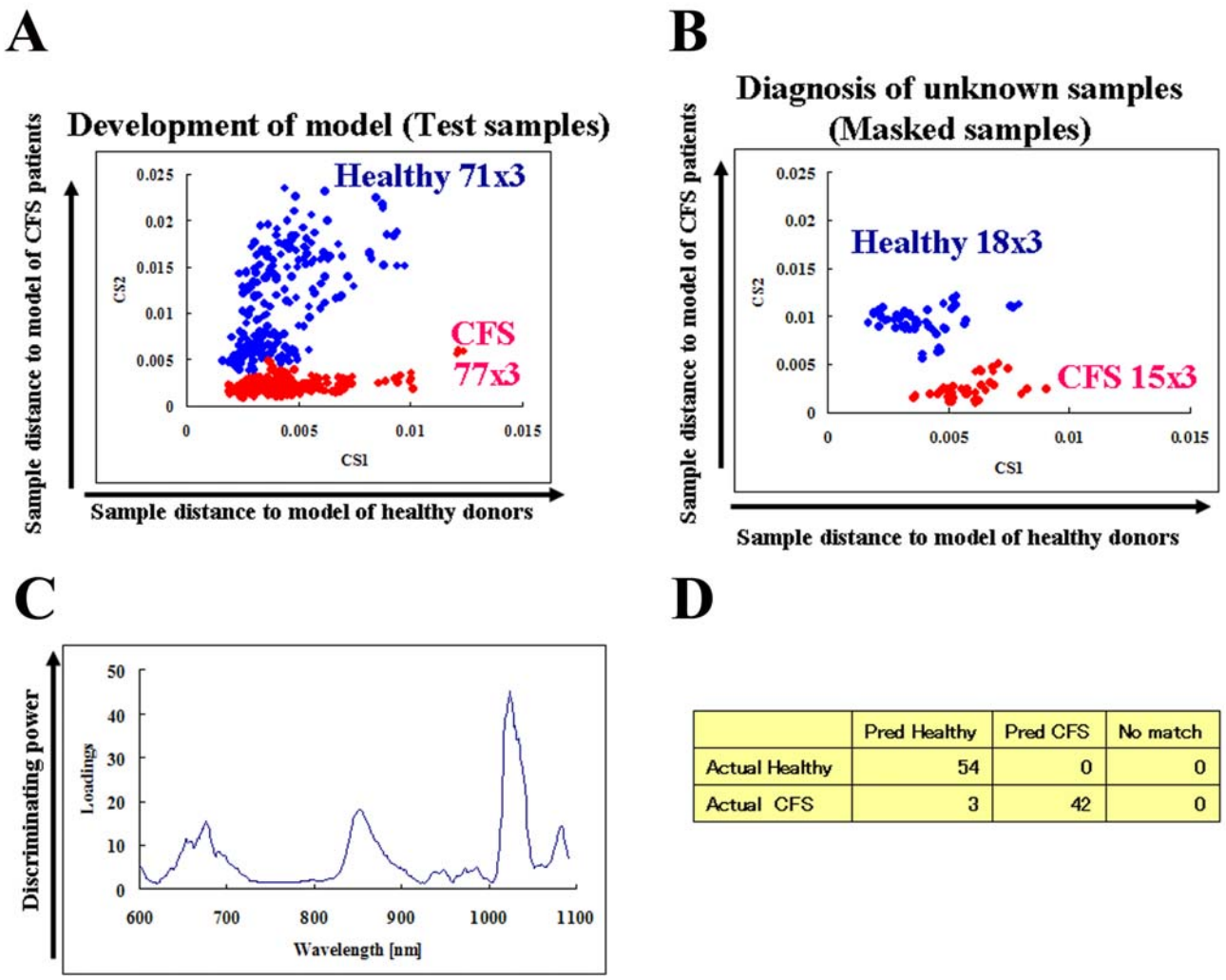

Fig. 4. SIMCA analysis of Vis-NIR spectra of serum samples for CFS diagnosis

(A-B) Vis-NIR spectra of serum samples from healthy donors (Blue) and CFS patients (Red) were subjected to SIMCA. Coomans plots show distances to model of healthy donors *versus* CFS patients to establish a SIMCA model (A). Discriminating power shows the importance of each wavelength for distinguishing healthy donors from CFS patients (B). (C) Masked samples, which were not used for development of the model, were subjected to SIMCA. Coomans plots show distances to model of healthy donors *versus* CFS patients. Modified from Fig. 2 in Sakudo et al. [86] with permission from Elsevier.

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Fig. 5. Plans for non-invasive CFS diagnosis using Vis-NIR spectroscopy

Vis-NIR spectroscopy can be used for non-invasive analyse, because Vis-NIR is highly transmissible into the body. Now, we are trying to study the potential of Vis-NIR spectra collected from the thumb for the diagnosis of CFS. Modified from Fig. 5 in Sakudo et al. [103] with permission from Nippon Rinsho Co.

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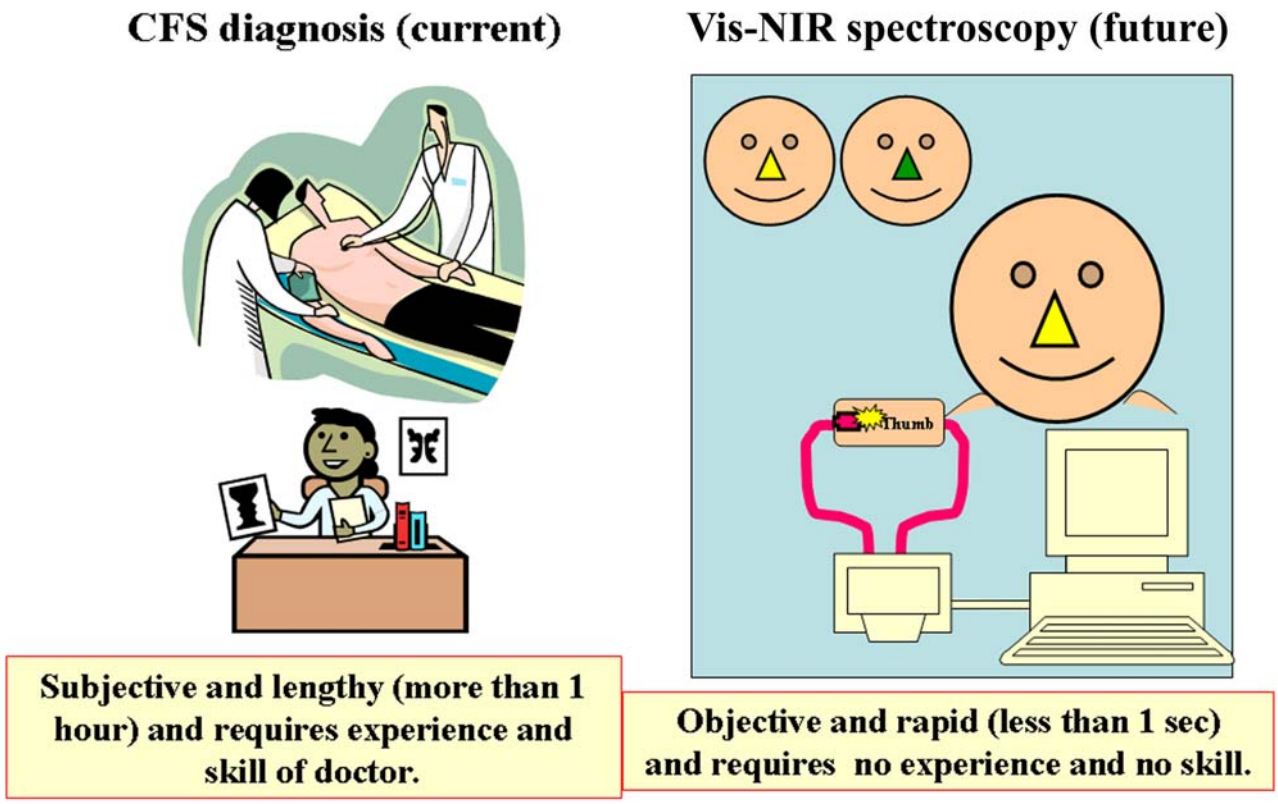

Fig. 6. Comparison of current CFS diagnosis and future Vis-NIR CFS diagnosis
Currently, CFS can only be diagnosed by skilled doctors. The diagnosis requires experience and sophisticated techniques. Furthermore, even with a skilled doctor, it takes long time to reach a final clinical diagnosis. Vis-NIR spectroscopy would enable an objective and rapid diagnosis. Moreover, it would not require experience and skill. Modified from Fig. 2 in Sakudo et al. [103] with permission from Nippon Rinsho Co.

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Identification of Differential Genetic Profiles in Severe Forms of Fibromyalgia and Chronic Fatigue Syndrome in the UK population

by

Estibaliz Olano

Fibromyalgia (FMS) and Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) are two controversial diseases with overlapping symptoms, difficult to distinguish and diagnose properly with clinical criteria. To date there are no biological markers for either condition and are diagnosed using separate but overlapping clinical criteria. All too often the patients concerns are dismissed as imaginary or unimportant and only recently they have started to be recognized and accepted by physicians. Since recent studies have started to point out the genetic background of these diseases, Progenika Biopharma, S.A. has developed a new system of DNA testing for the diagnosis and prognosis in Fibromyalgia and Chronic Fatigue Syndrome.

A multidisciplinary group led by Dr. Ferrán García, Head of Rheumatology (Clínica CIMA, Barcelona), Dr. Joaquim Fernández Solá, Unit of Chronic Fatigue Syndrome (Hospital Clínic, Barcelona) and Dr. Jose Ignacio Lao, Unit of Molecular Genetics (Echevarne Laboratorie) started this research five years ago, by looking at different mutations (SNPs) associated with FM and CFS/ME.

99.8% of the genetic information is homogenous among humans, and only 0.2% is variable. These differences in our DNA can be due insertions or deletions (e.g. familial hypercholesterolemia), repeat sequences (e.g. Huntington disease CAG repeats) or Single nucleotide polymorphisms – SNPs. These SNPs are changes (mutations) of only one of the nucleotides ("building blocks") that forms the DNA, and they account of up to 90% of the variability encountered between humans. Variations in these DNA sequences of humans can affect how we develop diseases, respond to pathogens, chemicals, drugs, etc. Therefore, SNP analysis has the potential for identification of markers for genetic predisposition to disease or even define subtypes within diseases with different prognosis, severity, drug response .....

Some of the results of this ongoing study have been presented in the 8th International IACFS Conference on Chronic Fatigue Syndrome, Fibromyalgia and other Related Illnesses held in Florida and in the ME Research conference held in Edinburgh and are summarised here:

Among the individuals register in the "Fibromyalgia and/or Chronic Fatigue Syndrome patients Record" (www.fundacionfatiga.org/registro_pacientes.htm) 1500 subjects diagnosed with FM, CFS/ME or both were randomly selected and invited to participate in the study. From these, 1371 gave written consent to take part and filled in a questionnaire which included details about their diagnosis, familiar diagnosis of FM or CFS/ME and presence of mental disorders. In addition, those patients were also asked to answer the Fibromyalgia Impact Questionnaire (FIQ) for FM (Burckhardt et al., 1991; Bennett, 2005) and the CDC Symptom Inventory (CSI) for CFS/ME (Wagner et al., 2005) and to provide a blood sample for DNA extraction. Taking into account that there is a recognized gender bias in FIQ (Bennett, 2005), eventually only women were included in the study. Previous treatment for psychiatric disorders was also considered an exclusion criterion. At the end of the selection process the number of recruited subjects was reduced to 403 patients (186 FM patients aged 45-54 years and 217 CFS patients aged 30-39 years). These cases were clinically diagnosed according to the 1990 American College of Rheumatology (ACR) classification for FM (Wolfe et al., 1990) or the US Centres for Disease Control criteria for CFS developed by Fukuda et al.1994 at the Hospital Clinic and Clinica CIMA (Barcelona, Spain). For each sample one hundred and seven SNPs were genotyped by SNPlex™. An independent second association study with 282 women (126 FM / 156 CFS) was used to validate the results. We identified 15 SNPs able to discriminate between FM and CFS patients with a 11·5 Likelihood Ratio (LR+, 95% specificity). The analysis of further SNPs allowed differential genetic profiling between the most aggressive FM phenotype and the mild forms (12·4 LR+) and between a severe CFS phenotype and a milder one (12·4 LR+).

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Dr. Estibaliz Olano

Dr. Olano is a senior scientist at Progenika Biopharma (a biotech company based in Bilbao, Spain). She is responsible for investigating the genetic profiling via SNP analysis by using it as an effective tool to discriminate between the more severe forms of fibromyalgia and chronic fatigue syndrome.

Identification of Differential Genetic Profiles in Severe Forms of Fibromyalgia and Chronic Fatigue Syndrome in the UK population *(continued)*

In this study we prove that genetic profiling via SNP analysis can be a very effective tool to discriminate between the more severe FM and CFS cases. In addition we claim that FM and CFS are two separate diseases with an important genetic component, and we suggest that the severe cases might be different disease subtypes with distinctive genetic profiles.
However this methodology is still dependable of a preliminary reliable diagnose that fulfils all the disease inclusion and exclusion criteria.

These first results of the research carried out so far has lead to the design of "FIBROchip", a DNAchip for the identification of the patient's genetic predisposition to develop the most aggressive forms of Fibromyalgia and Chronic Fatigue Syndrome / Myalgic Encephalomyelitis.

On the genetic profile base, FIBROchip is able to differentiate between the patients with Fibromyalgia and Chronic Fatigue Syndrome. Additionally, being based on the information provided by FIBROchip, the doctor will be able to know if his patient can develop a Fibromyalgia and Chronic Fatigue Syndrome very severe.
The main target of the DNA chip is to identify those patients who have a greater possibility of developing the most aggressive forms of the diseases and this way to apply the most suitable treatment to each patient. The investigation project is in the last phase of clinical validation, and is predicted that their exit to the market is at the end of this year.

Facts About IiME

IiME's May conferences in London have attracted speakers and delegates from all parts of the world. The conference DVDs have sold in twenty countries worldwide.

ME Story

Now at 35 I'm 99% bedridden, I am paralysed down the right hand side and in both legs. I am incontinent and have a supapubic catheter fitted through my stomach into my bladder.

Four years ago, I was forced to go into an old people's Nursing home as we didn't have enough room downstairs for me to have a bedroom where I could be hoisted. Therefore my O.T. involved a man from disability grants who agreed to fund the building of an extension in which I have a ceiling track hoist, as I can't transfer myself at all, that takes me from my small bedroom into an en-suite shower room & Closomat toilet.
I spent 2 years in the nursing home while this was being completed where I deteriorated further,

I have between 35-40 symptoms related to M.E including an immune deficiency. Chemical sensitivity disorder, brain fog etc... I am a member of the 25% M.E group who are the only support group for the one quarter of all M.E sufferers who have severe M.E

Some days I feel so ill that I want to go to sleep and never wake up !!!

-Mattie

Petition to Retain GPs' Rights to Issue Sickness Notes

This E-petition to the Prime Minister, seeks to prevent the application of the return to work legislation that will be overseen by work advisors in surgeries. It will adversely affect chronically ill people like sick Gulf War veterans, ME-CFS sufferers, pesticide poisoned people and MCS sufferers. Text from the petition creator –
The administration is seeking to cut the number of people claiming incapacity benefit but penalising poorly people in need of a sick note is not ethical. Making sick people have to mess around even more is counterproductive. GP's have not complained about issuing sick notes all these years, they are professionally trained, well paid, and should be able to deal with this. I see no reason to change what is a decent scheme.

"We the undersigned petition the Prime Minister to carry on allowing all GPs to issue sick notes to patients and not alter legislation concerning GP's issuing sick notes themselves.."

http://petitions.pm.gov.uk/SickNotesGPs

Can "molecular addressing" correct mitochondrial diseases? Mitochondria are the power plants of the cell and perform most of the chemical reactions that transform sugars into usable energy. Mitochondrial diseases are estimated to affect at least 1 in 5000 people and can lead to a variety of serious diseases. Many of the genes responsible for energy production are made up of mitochondrial DNA, rather than DNA in the cell's nucleus - and an obvious solution to mitochondrial errors would be to introduce a normal copy of the defective gene into the mitochondrial DNA.
Dr. Marisol Corral-Debrinski and her colleagues at the Pierre and Marie Curie University in Paris, France, picked two mitochondrial gene mutations. The team tagged normal versions of these genes with two separate cellular "address codes" and inserted them into the cytoplasm of cells grown in a lab dish. The first code directs the messenger RNA - the molecule that carries the instructions for making a protein - to the surface of the mitochondria, ensuring that the protein gets made at the mitochondrial membrane. The second address code, known as the mitochondrial targeting sequence, tells the protein to enter the mitochondria. These double-tagged genes were able to reverse the effect of both mitochondrial mutations in cell cultures for up to a year. Corral-Debrinski is now planning to test the gene therapy on laboratory mice.
Although not directly affecting ME we felt that Marisol's work on mitochondria might be of interest. Marisol allowed IiME to publish three of her research papers in the Journal but, unfortunately, we have been unable to get the permission to from the publishers to include them here. So instead Marisol has kindly produced the following article describing her work.

Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface

By
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Mitochondrial diseases encompass an extraordinary assemblage of clinical problems, commonly involving tissues that have high energy requirements, such as retina, brain, heart, muscle, and endocrine systems. The clinical presentations range from fatal infantile disease to muscle weakness and most of them are characterized by inexorable progression. Recent epidemiological studies have shown that mitochondrial disorders have a prevalence of at least one in 5000, making them probably the most common form of metabolic disorders. 300 mitochondrial DNA (mtDNA) alterations have been identified as the genetic cause of approximately 30 % of these diseases. Moreover, the spectrum of mitochondrial diseases has been expanded by the recognition that mutations in the genes for nuclear-encoded mitochondrial proteins cause not only a number of neurodegenerative diseases but also haematological and ophthalmological disorders. Hence, finding ways to fight these devastating disorders especially in the case of neuromuscular degeneration is the main objective of many laboratories worldwide. Since almost four years we are using the phenomenon of mRNA localization to the mitochondrial surface aimed at developing a therapeutic strategy for replacing inactive proteins inside the mitochondria. Hence, we have optimized the nuclear expression of *ATP6*, *ND1* and *ND4* genes, originally located in the organelle, by the addition of cis-acting elements which ensures the transport of their transcripts to the mitochondrial surface. The optimization of this approach, known as "allotopic expression" have led to the complete and long-lasting rescue of mitochondrial dysfunction in fibroblasts from patients harboring a deleterious mutation in either *ATP6*, *ND1* or *ND4* genes. Because of their highly sophisticated function in the visual process retinal cells contain a large number of mitochondria. Therefore, any impairment in mitochondrial function leads to retinal cell degeneration that arises from mutations in genes encoding mitochondrial proteins located in either nuclear or mitochondrial genomes, such as neurogenic muscle weakness Ataxia Retinitis Pigmentosa (NARP), Leber Hereditary Optic Neuropathy (LHON) and Dominant Optic Atrophy (DOA). As for the other mitochondrial disorders, no cure is available. Since, the eye is an excellent target organ for gene therapy, given its small size, its relative anatomical isolation and the ease with which vectors can be delivered to retinal cells we have decided to apply our optimized approach as a first step for treating neuromuscular diseases dues to mitochondrial dysfunction. Ultimately, our most important goal is to provide a gene therapy that will impede blindness of adults brutally affected by LHON or DOA, this therapy will subsequently become available for an array of neuromuscular degenerations caused by mutations in both nuclear and mitochondrial DNA genes encoding mitochondrial proteins.

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Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface *(continued)*

A. Introduction

Mitochondria play a central role in intermediary metabolism, energy production, ion homeostasis and apoptosis [1]. Impairment of mitochondrial function is the key pathogenic factor in a growing number of human diseases. Indeed, primary defects in mitochondrial oxidative phosphorylation (OXPHOS) function are implicated in over 130 diseases [2]. Their clinical presentations range from fatal infantile disease to adult muscle weakness and/or nervous system dysfunction. Moreover, mitochondrial impairment can lead to tumor formation and probably play a role in the aging process [3] . Mitochondrial OXPHOS disorders are far more common than was previously anticipated. Recent epidemiological studies have shown that their prevalence is at least one in 5000, making this group of diseases probably the most frequent form of metabolic disorders [4]. Approximately 300 mitochondrial DNA (mtDNA) alterations have been identified as the genetic cause of mitochondrial diseases, one-third of which are located in coding genes for OXPHOS proteins [5]. Despite, more than 70% of human degenerative diseases involving mitochondrial deficiencies remain unravelled at the molecular level; since they are caused by mutations in nuclear-encoded mitochondrial proteins. Hence, only 56 nuclear genes encoding mitochondrial proteins underly clinical mitochondrial disorders [6]. The main obstacle encountered for the identification of disease causing genes is that at least half of the 1500 estimated mitochondrial proteins [7] is not yet discovered; indeed, up until today only 807 are ascribed to the most extensive database of human mitochondrial proteins (http://www.mitop.de:8080/mitop2), [8]. The understanding of the pathogenesis of mitochondrial diseases has improved considerably in the last decade. Nevertheless, the most disappointing area is the lack of efficient treatment for patients with mitochondrial diseases. Indeed, they are still treated with vitamin and cofactor mixtures, harmless but largely inadequate and inefficient.

Ocular involvement is a prevalent feature in mitochondrial diseases, indeed retina cells contain a large number of mitochondria, reflecting their high requirements for OXPHOS [9]. Moreover, mitochondrial impairment may contribute to changes in macular function observed in aging and age-related macular dystrophy [10]. Leber Hereditary Optic Neuropathy (LHON) and Dominant Optic Atrophy (DOA) are both non-syndromic optic neuropathies with a mitochondrial etiology. LHON is associated with point mutations in the mitochondrial genome. The majority of DOA patients harbor mutations in the nuclear-encoded protein OPA1 which is targeted to mitochondria. In both disorders the retinal ganglion cells (RGCs) are specific cellular targets of the degenerative process [11]. Neurogenic muscle weakness, Ataxia, Retinitis Pigmentosa (NARP) syndrome is due to a point mutation in the mitochondrial *ATP6* gene. The most common ocular feature associated with the mutation is retinal dystrophy, with a substantial variability in rod and cone photoreceptor manifestations [9]. As for other visual impairments or mitochondrial disorders, no efficient therapies are available at the present time and current understanding of the cellular and molecular mechanisms underlying retinal cell death due to mitochondrial dysfunction is still quite limited. Remarkably, the eye has a combination of features that make it ideally suited as a target organ for gene therapy. The highly compartmentalized anatomy of the eye facilitates accurate delivery of vectors at target sites within the globe especially at the vicinity of retinal cells, which minimizes systemic dissemination and unwanted systemic effects. The blood retinal barrier and the retinal pigment epithelium (RPE), anatomically protect a wide-spread diffusion of the vectors to the systemic circulation. These barriers also provide a beneficial effect in protecting the retina from the immune response [12]. Retinal function can be easily monitored with non-invasive and quantitative tests such as ophthalmoscopy, electroretinogram (ERG), optical coherence tomography (OCT), and visual evoked potentials (VEP). Moreover, appropriate animal models resembling human retinal abnormalities are available for the development of experimental therapies. Notable successes have been achieved by gene replacement strategies in some of these models. For instance, the Swedish Briand dog is a model for a null mutation in the *RPE65* gene. This gene encodes an RPE-specific visual cycle isomerase involved in the synthesis of 11-cis retinal. Mutations in the *RPE65* gene are responsible of Leber's Congenital Amaurosis (LCA), representing a group of severe early-onset retinal dystrophies [13]. The fact that there are close similarities between human and Briand dogs, in terms of the clinical characteristics of the disease allowed the evaluation of gene replacement therapy. Thus, three independents groups have now reported the restoration of vision in these dogs by the use of recombinant AAV vector-mediated delivery of the *RPE65* gene [14], [15], [16]. These recent advances have enabled the development of proposals for clinical trials of gene therapy for ocular diseases. In May 2007, the first patient, out of 12, has been treated with the rAAV2-*RPE65* vector (Dr. R. Ali, College University, London) at the ophthalmologic hospital of Moorfields in London. This is the first step of phase I/II dose-escalation clinical trial for this severe early-onset retinal degeneration. Dr. F. Rolling (INSERM U 649, Nantes) will conduct a clinical trial in 2009.

Our main objective is to develop in the near future a gene therapy that could be both preventive and curative for retinal dystrophies due to mitochondrial dysfunctions. In this purpose we were mostly interested in the LHON disease. LHON was the first maternally inherited disease to be associated with point mutations in mtDNA and is now considered the most

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Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface *(continued)*

common mitochondrial disorder with an estimated prevalence of 1 in 25,000 in north-east England. The pathology is characterized by selective death of RGCs leading to central vision loss and optic nerve atrophy, prevalently in young males. The age of onset of visual loss ranges from 8 to 60, typically occurs between ages of 15 and 35 years. The course of visual loss is generally acute or subacute, both eyes are involved sequentially. The average time interval between affected eyes is approximately two months, the duration of progression of visual loss in each eye averaged approximately four months [17]. LHON is a devastating disorder with the majority of patients showing no functional improvement and remaining within the legal requirement for blind registration. The three most common pathogenic mutations found in about 95% of LHON's patients are located in *ND1* (G3460A), *ND4* (G11778A) or *ND6* (T14484C) genes. They encoded subunits of the respiratory chain complex I and the mutations have the double effect of lowering ATP synthesis and increasing oxidative stress chronically [17]. Although, extensive studies were conducted since more than 15 years, the pathogenesis of LHON is poorly understood. One recent hypothesis suggests that the pathophysiology of optic neuropathies does not just involve the disorder of ATP production by mitochondria but that the non-maintenance of the sharp mitochondrial gradient at the optic nerve head constitutes the first step in a vicious event cycle that further compromises neuronal respiration and that would eventually lead to profound energy depletion, the increased production of toxic free radicals and neuronal cell death through apoptosis [18, 19]. LHON, as the other mitochondrial diseases, is resistant to treatments with quinone analogs, vitamines or oxygen radical scavengers, which were harmless but very inefficient in most of the cases [20]. Therefore, the allotopic expression (expression of mitochondrial genes transferred to the nucleus) of some of mtDNA genes has been tried in cybrid cells as a possible therapeutic option to cure mitochondrial diseases. However, several attempts failed to obtain a complete and long-lasting rescue of the mitochondrial defect in cells harboring mutations of mtDNA genes [21, 22, 23]. Probably, the highly hydrophobic nature of proteins encoded by the mitochondrial genome represents a physical impediment to mitochondrial import. Therefore, up until today important limitations are found to the allotopic expression as a therapeutic approach for mtDNA-related diseases [24]. In previous studies, we demonstrated that in the yeast *Saccharomyces cerevisiae*, 47% of mRNAs encoding mitochondrialproteins are transported to the organelle surface [25]. This phenomenon represents a key step to ensure the proper import and functionality of the corresponding polypeptides inside the organelle [26] and is conserved in human cells [27]. The delivery of mRNAs to the organelle surface depends on two sequences: the region coding for the mitochondrial targeting sequence (MTS) and the 3' untranslated region (3'UTR) [28].

Thus, we decided to optimize the allotopic expression for mtDNA genes by ensuring the delivery of corresponding mRNAs to the organelle surface. This optimization will prepare the development of an effective treatment for mitochondrial disorders due to mtDNA mutations.
The research project of our team is conducted since 2004 along the following complementary axes:
Optimize the allotopic expression of mtDNA genes.
Rescue of respiratory chain defects in cells harboring different mutations in mtDNA encoded genes.

B. Previous activities of our team: 2004-2007

I. Optimization of the allotopic expression of mtDNA genes (Kaltimbacher *et al.*, *RNA : 12*, 1408-1417 ; 2006)

Recently, we have shown that a protein which is normally encoded by mtDNA was efficiently translocated into the mitochondria of HeLa cells by the use of signals that force its mRNA, transcribed in the nucleus, to localize to the organelle surface. We constructed a nuclear version of the mtDNA-encoded *ATP6* gene flanked by *cis*-acting elements of either *COX10* or *SOD2* mRNAs, which localizes to the mitochondrial surface in HeLa cells [27, 29]. The rationale behind this was that mRNA targeting to the mitochondrial surface will lead to a tight coupling between both translation and translocation processes, which should be required for highly hydrophobic proteins, such as ATP6. Noteworthy, when both the MTS and the 3'UTR of *SOD2* or *COX10* a highly efficient mitochondrial translocation of the ATP6 was observed (Fig.1). Notably, ATP6 protein was insensitive to proteolysis in the presence of detergent, suggesting that it probably was assembled in the complex V of the respiratory chain [30].

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ME Facts

Mitochondrial dysfunction provides a physiological basis for the debilitating and overwhelming fatigue suffered by ME/CFS patients whilst the changes in the NTE (neuropathy target esterase) gene provide an intriguing link with OP poisoning and nerve agent exposure found in GWS.

- Group for Scientific Research into ME 2006 (http://www.erythos.com/gibsonenquiry/Report.html)

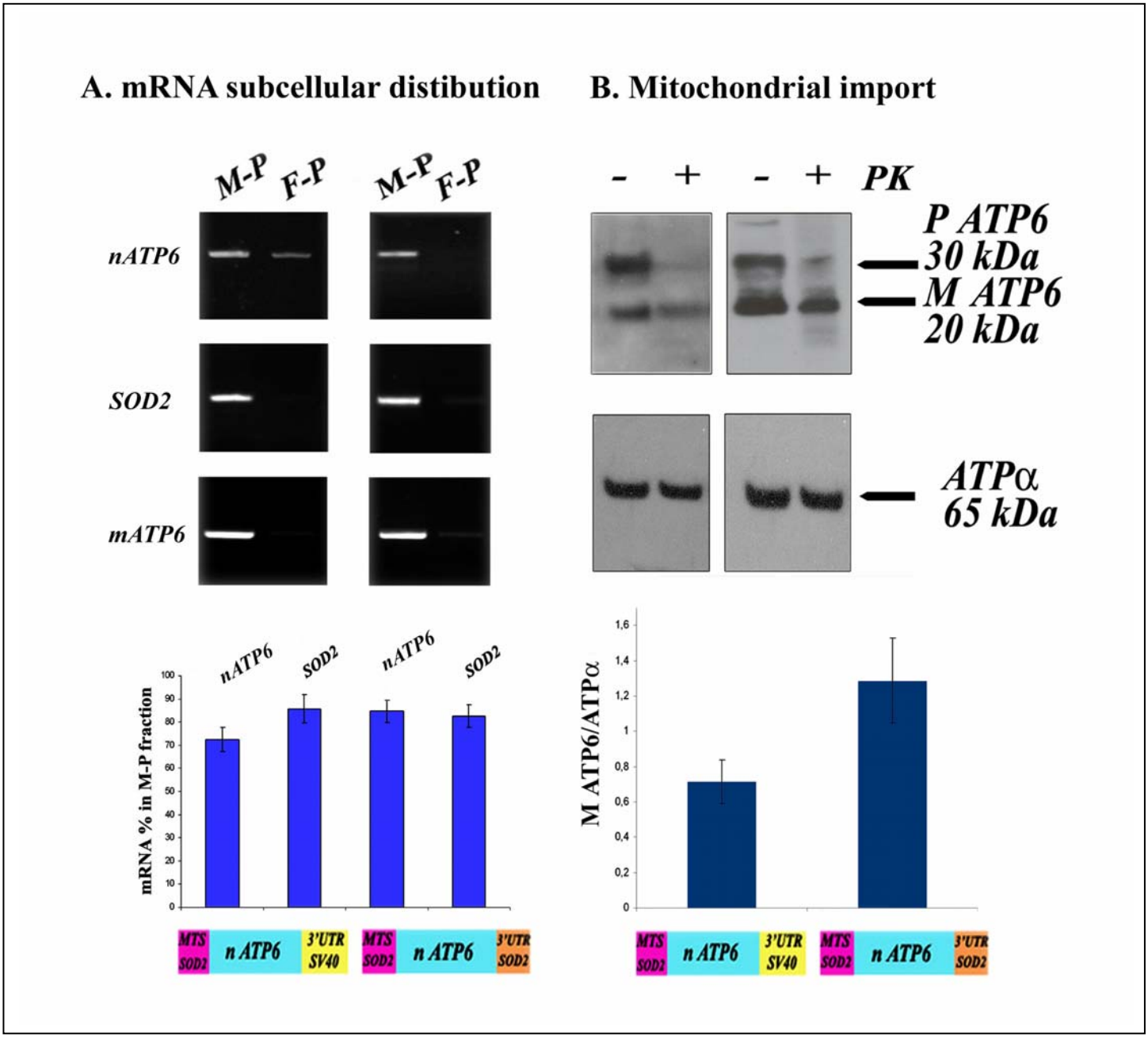
Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface *(continued)*

Figure 1: Enrichment at the mitochondrial surface of the nATP6 mRNA led to an efficient mitochondrial import of the corresponding protein

A. The amount hybrid *nATP6* mRNA was determined by RT-PCR in RNA purifications obtained from free polysomes (FP) and mitochondrion-bound polysomes (MP). The distribution of the endogenous mRNAs *SOD2* and *ATP6* were also examined in both polysome fractions. Four independent experiments were compared, the results obtained are illustrated as bar graphs. The presence of the *SOD2* MTS in the *nATP6* mRNA allowed its enrichment in the MP fraction.
Nevertheless, both the MTS and 3'UTR were required in the hybrid mRNA for allowing its exclusively sorting to the mitochondrial surface.

B. The amount of the chimeric ATP6 protein was evaluated in six independent mitochondrial purifications subjected to Proteinase K (PK) digestion. This amount was compared to the quantity of ATPα protein insensitive to PK proteolysis. When the synthesis of ATP6 was directed by the gene in which both the MTS and 3'UTR of *SOD2* were present, the amount of fully translocated ATP6 protein was not significantly different to the ATPα protein (bar graphs).

(continued on page 25)



Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface

(continued)

II. Rescue of respiratory chain defects in fibroblasts harboring mutations in *ATP6* and *ND4* genes (Bonnet *et al.*, Rejuvenation Research : 10, 128-144 ; 2007)

With the aim of determining whether allotopically expressed mtDNA-encoded genes could rescue mitochondrial dysfunction, we examined human cultured skin fibroblasts harboring either the NARP T8993G *ATP6* mutation or the LHON G11778A *ND4* mutation, allotopically expressing the recoded *ATP6* or *ND4* wild-type genes. Mitochondrial function was evaluated by the measurement of (i) cell ability to grow in galactose medium, which force them to rely on OXPHOS; (ii) *in vitro* ATP synthesis using respiratory chain substrates; (iii) enzymatic activity of respiratory chain complexes I and V [31]. We were able to demonstrate that the allotopic expression of engineered *ATP6* and *ND4* genes in human fibroblasts harboring either of these genes mutated leads to a complete and long-lasting restoration of respiratory chain function [32] (Tables 1 and 2). Notably, we examined a second LHON patient harboring the G3460A substitution in the *ND1* gene. Our optimized allotopic approach significantly rescued respiratory chain I deficiency in these cells. Therefore, our approach for *ND1*, *ND4* and *ATP6* genes ensures the efficient mitochondrial translocation of the corresponding precursors, probably *via* a co-translational pathway. The rescue of mitochondrial dysfunction indicated that the processed polypeptides were fully functional within their respective respiratory chain complexes and, therefore, able to compensate for the endogenous inactive proteins [32], and C.Bonnet, S. Augustin *et al.* (manuscript submitted, 2007) .

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Table 1:

In vitro ATP synthesis rate

	µM ATP/min/10^6 cells		**P value ; n**	
	Complex I substrats	Complex II substratI	Complex I substrats	Complex II substrats
Control	2081.9 ± 138.1	1563.1 ± 214.0		
NARP	805.6 ± 262.4	400.7 ± 221.7		
NARP + *nATP6*	2045.52 ± 428.7	1659.6 ± 522.5	0.0003 ; n = 5	0.0022 ; n = 4
Control	1962.1 ± 352.1	1266.3 ± 62.1		
LHON	793.3 ± 493.7	658.7 ± 185.2		
LHON + *nND4*	1659.4 ± 245.5	1929.7 ± 480.2	0.004 ; n = 5	0.0013 ; n = 4

P values shown in the third column were obtained according to the Student's t test for the pairs NARP/ NARP + *nATP6* or LHON/ LHON + *nND4* for data collected for either complex I or complex II substrates. "n" indicates the number of independent measurements performed. LHON fibroblasts showed a decreased ATP syntesis rate when complexe II substrates were uses. This result suggests a general perturbation of the respiratory chain activity. Notably, this activity was fully restored by the allotopic expression of *ND4*.

Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface *(continued)*

Table 2 :

Complexes I and V activity measurements in NARP and LHON fibroblasts after normalisation with the values obtained in control fibroblasts

	Complexe I	Complexe V	P value ; n
NARP	1	0.6 ± 0,12	
NARP + *nATP6*	1	1.05 ± 0,23	< 0.0001 ; n = 8
LHON	0.47 ± 0.009	1	
LHON + *nND4*	0.97 ± 0.24	1	< 0.0001 ; n = 9

P values shown in the fourth column were obtained according to the Student's t test for the pairs NARP/ NARP + *nATP6* or LHON/ LHON + *nND4*. "n" indicates the number of independent measurements performed. Complex I activity in NARP cells was identical to that measured in control fibroblasts (1). Complex V activiy in LHON fibrolbasts was not different to the one measured in control cells (1). Complex I and V activities were fully restored in LHON and NARP fibroblasts by the optimized allotopic expression of *ND4* and *ATP6* genes respectively.

C. Research Project

We are aware that the optimization of allotopic expression represents a real hope for patients suffering from diseases caused by mutations in mtDNA genes. However, all our efforts will remain unfruitful if the biosafety and the beneficial to mitochondrial function of our vectors are not proved in experimental models for mitochondrial diseases. Since, this proof is the mandatory step required before any attempt to the transfer to clinic, it becomes our highest priority. Unfortunately, only one animal model for mtDNA gene invalidation is available. These mice carry a mutation in the mitochondrial *COXI* gene leading to a decreased cytochome oxydase (COX) activity in several tissues [33]. Even though, they do not have any visual impairment, we will try to rescue their muscle COX deficiency using our strategy. Additionally, we decided to use the optimized allotopic expression approach to create an animal model which will mimic LHON disease. First, we performed *in vitro* mutagenesis of the wild-type engineered human *ND4* gene to obtain a nuclear version harboring the G11778A substitution. This mutation, responsible of 60% of LHON cases, converts a highly conserved arginine to histidine at codon 340 [17]. Each nuclear version of *ND4* was combined with the two mRNA targeting sequences of the *COX10* gene, which ensures the efficient delivery of the polypeptides inside the organelle [32] . We developed an *in vivo* electroporation (ELP) method to introduce either the wild-type or the mutated version of *ND4* into retinal ganglion cells (RGCs) of adult rats, as recently described [34]. If we confirm that the animal model generated share an array of similarities with the clinical manifestations of LHON, we will assess the ability of our vector to protect RGCs. If we can demonstrate the proof-of-principle that our approach results in significant quantifiable improvements of RGC function in the experimental model of LHON that we generated we will open the door to gene therapy for retinal degenerations due to mutations in mtDNA.

Expected consequences for knowledge in the field of medicine and public health

Retinal dystrophies with mitochondrial etiology are inaccessible to curative or pallialtive therapy. Our knowledge on mRNA sorting to mitochondrial surface and its involvement in the organelle biogenesis makes this phenomenon a promising tool to fight these diseases. The transfer to clinic of our gene therapy protocol will undoubtedly represent a major step for the generation of a treatment aimed at improving life conditions of patients suffering for diseases such as LHON or DOA. We can envisage if these trails are successfull that clinical studies on other visual handicaps leading to blindness such as glaucoma [35] and devastating neurodegenerative disorders such as Charcot-Marie Tooth [36] could begin.

(continued on page 27)

Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface *(continued)*

Our position in the international research field

Mitochondrial disorders can not be ignored anymore in most medical areas. They include specific and widespread organ involvement, with tissue degeneration or tumor formation. Primary or secondary actors, mitochondrial dysfunctions are also playing a role in the ageing process. Despite the progresses made in the identification of their molecular bases, nearly all remains to be done as regards therapy. Research dealing with mitochondrial physiology and pathology has almost 20 years of history all over the world. We are involved, as many other laboratories, in the challenge to find ways to fight these diseases. However, our main limitation is the absence of animal models required for both the understanding of the molecular mechanisms underlying the diseases and to evaluate therapeutic strategies. This is especially true for diseases due to mtDNA mutations, an American team has recently described a strategy similar to the one we have developed, to induce retinal ganglion cell degeneration in mice [37]. Nevertheless, their strategy encounters the limitation of the inefficient mitochondrial import of the protein and will not generate a robust experimental model to evaluate putative treatments. If we succeed in creating a long-term animal model for the mitochondrial *ND4* mutation and in confirming that it shares similarities with LHON, it will certainly allow the rapid development of new model systems for studying mtDNA mutations which are to date extremely rare. Most importantly, our protocol of gene replacement therapy for both the rat model and the Harlequin mouse strain will permit the development of clinical trials to treat patients suffering for visual impairment due to mitochondrial dysfunction. These clinical studies will be performed in the Vision Institute, a guarantee of expertise, rigour and thorough. Therefore, we are convinced that we possess a significant advance in comparison to laboratories working in the field worldwide.

Mitochondrial disorders can not be ignored anymore in most medical areas. They include specific and widespread organ involvement, with tissue degeneration or tumor formation. Primary or secondary actors, mitochondrial dysfunctions are also playing a role in the ageing process. Despite the progresses made in the identification of their molecular bases, nearly all remains to be done as regards therapy.

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Additional articles from Marisol's team can be found at the following sites: -

ScienceDirect	**http://www.sciencedirect.com/science/journal/01674889**
RNA Journal	**http://www.rnajournal.org/cgi/content/full/12/7/1408**
Rejuvenation research	**http://www.liebertonline.com/doi/abs/10.1089/rej.2006.0526**

Gene therapy for mitochondrial dysfunctions using optimized mRNA transport to the mitochondrial surface *(continued)*

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ME Story

In a few weeks time it will be the one year anniversary of my gorgeous and funny and talented sister's death. If you knew her before she got ill she was like a force of nature. Talented, funny, generous she had loads of friends and was very much a person who lived her life to the full. She had courage and was original and so much more.

M.E. was the cruellest thing to ever happen to Sophia. I will not go on about how much she suffered because it is an unbelievable amount. To top it all her illness was not recognised as a neurological disease and so there was the added burden of trying to get the authorities to understand the true nature of her illness.

Unfortunately for us all Sophia suffered even more than was necessary.

My amazing sister has paid with her life but she all she wanted was that if only one person was helped by her experience it would all have been worth it for her.

From Sophia Mirza's sister - Roisin Mirza (written in 2006)

Chronic Fatigue Syndrome after Q fever

By
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Summary

Background: Q fever is a common and acute but rare chronic zoonosis caused by *Coxiella burnetii*. Its acute form manifests as atypical pneumonia, flu-like syndrome, or hepatitis. Some authors observed symptoms of chronic fatigue in a small number of patients after the acute phase of Q fever; in many cases serological assay confi rmed the activity of *Coxiella burnetii* infection. The effect of antibiotic therapy on post-Q-fever fatigue syndrome has not been studied in south-east Europe thus far.

Case Reports: Three patients are presented with post-Q-fever fatigue syndrome. All fulfilled the CDC criteria for chronic fatigue syndrome. IgA antibodies to phase I of the growth cycle of *Coxiella burnetii* were positive in two patients and negative in one. Two patients were treated with doxycycline for two weeks in the acute phase of illness and one with a combination of erythromycin and gentamycin.

After 4–12 months they developed post-Q-fever fatigue syndrome and were treated with intracellular active antibiotics (fl uoroquinolones and tetracycline) for 3–12 months. Effi cacy of the treatment was observed in two patients, but in one patient the results were not encouraging.

Conclusions: These results suggest the possibility of the involvement of *Coxiella burnetii* infection in the evolution of chronic fatigue syndrome. This is the fi rst report on post-Q-fever fatigue syndrome in Mediterranean countries. Evidence of IgA antibodies to phase I of the growth cycle of *Coxiella burnetii* is not a prerequisite for establishing a diagnosis of CFS. The recommendation of antibiotic treatment in post-Q-fever fatigue syndrome requires further investigation.

keywords: chronic fatigue syndrome • Coxiella burnetii • post-Q fever fatigue syndrome • antibiotic treatment

BACKGROUND

Q fever is one of the most common anthropozoonoses in southeast Europe. It is caused by *Coxiella burnetii*, an intracellular pathogen whose classifi cation has been changed from the order of *Rickettsiaceae* to the order of *Legionellales* [1]. Human infection develops after inhalation of contaminated aerosol or consumption of unpasteurized milk. It is rarely transmitted by vectors, transfusions of contaminated blood, or transplacentally [2,3]. Recently, a major role in disease spread was attributed to air currents [4]. About 60% of infections caused by *Coxiella burnetii* are asymptomatic [2]. Acute infection usually presents as a febrile state, pneumonia, or hepatitis, while other organs are less commonly affected. *Coxiella burnetii* is endemic in rural, coastal, and non-coastal areas of southern Croatia and is associated with stockbreeding. Acute Q fever in Split-Dalmatia County (470,000 inhabitants) is most commonly presented with both pneumonia and hepatitis (60.0%), followed by pneumonia (25.8%), hepatitis (9%), and nonspecific febrile illnesses (5.2%). During the period from 1985 to 2002, 155 acute Q fever cases were hospitalized at the Split University Hospital, with a mean annual incidence of 1.82/100,000/year. All cases were verifi ed by serologic testing with *C. burnetii* phase II antigen as is routinely done in all patients with clinical syndrome of atypical pneumonia that live in endemic areas [5]. In the northern part of Croatia, *Coxiella burnetii* causes 6.45% of all interstitial pneumonias that are serologically verified [6]. In its chronic form, Q fever mostly presents as endocarditis, infl ammation of intravascular implants, osteoarthritis, and chronic hepatitis [7]. During a follow-up of convalescent patients after acute Q we noticed that some had symptoms that were consistent with chronic fatigue syndrome (CFS). The diagnostic criteria for CFS include fatigue for six months or more together with at least four of the following symptoms: lack of concentration or/and memory that interferes with normal activities, sore throat, tender cervical or axillary lymph nodes, joint pain without swelling, muscle pain, headache, no refreshing sleep, and malaise lasting longer than 24 hours after exertion [8]. CFS is twice as common in females as in males, and it is most common between 25–45 years of age. The cause of CFS is not fully understood. There are three hypotheses about the cause of this impairment: postinfectious, immunological, and depression [9,10]. Penttila and associates found that in Australia, 20% of patients after acute Q fever develop post-Q-fever fatigue syndrome (QFS). Increased concentrations of IL-6 and interferon- as well as lowered concentrations of IL-2 that are found after stimulating peripheral blood mononuclear cells in cultures from these patients are presumed to be implicated in the pathogenesis of QFS [11].

The purpose of this paper is to emphasize the existence of CFS after Q fever in Croatia and its incidence and to show the effects of antimicrobial therapy of patients with QFS. We describe three patients who had QFS. During the period from January 2000 to December 2004, 90 patients with acute Q fever were treated at the Split University Hospital and we observed 3/90 patients with post-Q-fever fatigue syndrome. After the diagnosis of QFS was established, these patients were treated with antibiotics. They were asked to fill out questionnaires assessing their clinical condition before

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Chronic Fatigue Syndrome after Q fever (continued)

and after the treatment. The questionnaire survey included subjective symptoms: fatigue, lack of concentration, no refreshing sleep, sore throat, tender cervical or axillary lymph nodes, joint pain without swelling, muscle pain, headache, and malaise lasting longer than 24 hours after exertion. These symptoms were evaluated according to four grades (0: absent, 1: mild, 2: moderate, 3: severe). If the summed result of the survey was halved after the treatment, the effect of antibiotic therapy was considered favorable (Table 1).

CASE REPORTS

Case 1

A 34-year-old male shopkeeper with atypical pneumonia caused by *Coxiella burnetii* was treated at the Department for Pulmonary Diseases in February 2000. He did not have any serious illness before he caught Q fever. He arrived from a rural area where Q fever is endemic. Laboratory results showed an erythrocyte sedimentation rate (ESR) of 72 mm/hour, while the other hematological and biochemical parameters showed no abnormalities. The patient received a combination of erythromycin 4×500 mg/day p.o. and gentamycin 1×240 mg/day i.v for two weeks. The clinical response was good. A control chest x-ray was normal. The etiology was confirmed by the complement-binding reaction (CBR), which showed a titer for *Coxiella burnetii* of 1:64. A repeat CBR for *Coxiella burnetii* after six weeks was 1:1024.

During follow-up within the year 2000, the patient complained of disrupted sleep, morning fatigue, intense headache, prolonged fatigue lasting more than 24 hours after physical work, muscle pain, and persistent low-grade fever. Transthoracic heart ultrasound was normal. Serology for the phase I and phase II replication cycle of *Coxiella burnetii* did not confirm chronic infection (Table 2). After a one-year duration of symptoms, nine months of treatment with ciprofloxacin (2×500 mg/day p.o.) and doxycycline (2×100 mg/day p.o.) was instituted. The muscle pain and low-grade fever disappeared after this therapy, but the mild headache persisted. Therefore, in January 2002 a lumbar tap was performed. Cytology and biochemistry of CSF showed no abnormalities. The CSF sample was tested for *Coxiella burnetii* using an indirect immunofl uorescence assay and the result was negative. The patient still has low intensity headache and he suffers from fatigue after physical activity, but it disappears after half an hour of rest. He has returned to work, but has changed his job from shopkeeper to watchman. He now suffers from hyperlipidemia and does not show criteria for chronic fatigue syndrome (Table 1).

Case 2

A 32-year-old housewife with pneumonia caused by *Coxiella burnetii* was treated at the Department for Infectious Diseases in February 2003. Laboratory results showed an ESR of 92 mm/hour.

Other hematological and biochemical results, were within physiological limits. She was treated with doxycycline for two weeks with a good clinical response, and her chest x-ray after two weeks confirmed complete regression of pulmonary infiltrations. An indirect immunofluorescence test (IFT) in the acute stage of the disease showed positive IgM (titer: 1:160) and IgG (titer: 1:640) for *Coxiella burnetii*. Repeated serology one month later showed IgM 1:320 and IgG 1:1280. After she had felt well for two months, she started experiencing pain in her neck. Six months later, in August 2003, in addition to the neck pain she began to suffer from insomnia, headache, sweating, and fatigue, which did not resolve after sleep. The symptoms persisted for 12 months.

She was admitted to the Department for Infectious Diseases again in October 2004. Repeated hematological and biochemical results were within physiological values. Electromyography of the upper and lower extremities showed no abnormalities and transthoracic and transesophageal heart ultrasound showed no signs of endocarditis.

Rheumatoid factor, antinuclear antibodies, and antimitochondrial antibodies as well as serology for Epstein-Barr virus, cytomegalovirus, and toxoplasmosis were negative. Anti-HIV and hepatitis B and C markers were also negative, and thyroid hormones were within normal ranges. Paired serum samples in ELISA for *Coxiella burnetii* showed positive phase I IgA and IgG antibodies (Table 2). The therapy included ciprofloxacin (2×500 mg/day p.o.) for two months followed by doxycycline (2×100 mg/day p.o.) for four months. The result of the six months of treatment was regression of symptoms, with only a minor headache persisting. She is now capable of doing all her housework and does not fulfill the criteria for CFS (Table 1).

Case 3

A 30-year-old male professional soldier with interstitial pneumonia was treated at the Department for Pulmonary Diseases of the Clinical Hospital of Split in February 2004.

In the acute phase of illness his ESR was 46 mm/hour, while other hematological test results were normal. Blood chemistry values were normal with the exception of AST 62 U/l (normal range: 0–29) and ALT 54 U/l (normal range: 0–30). After two weeks of treatment with doxycycline, pulmonary infiltrates resolved and hematological and other laboratory results were all within the normal ranges. IFA for *Coxiella burnetii* revealed positive IgM 1:64 and IgG 1:320 in a first and IgM 1:320 IgG 1:640 one month later in a second serum sample. Four months later the patient started complaining of fatigue, disrupted sleep, headaches, and muscle and joint pain. Therapy with corticosteroids was introduced and continued for one month without success. In January 2005 the patient was admitted to the Department for Infectious Diseases, and his routine hematological and biochemical tests were within physiological limits. ELISA for Epstein-Barr virus, cytomegalovirus, HIV, and *Toxoplasma gondii* were

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Chronic Fatigue Syndrome after Q fever (continued)

Table 1. Clinical data of the three patients with QFS.

				CFS criteria before treatment			CFS criteria 1 yr. after treatment		
Patient	Gender	Age (yr.)	Pneumonia – QSF latency (months)	Fatigue >6 months	Minor criteria (No.)	Score	Fatigue >6 months	Minor criteria (No.)	Score
1	male	34	8	yes	5	14	no	2	4
2	female	32	5	yes	4	10	no	1	1
3	male	30	10	yes	4	11	yes	4	8

Table 2. Results of serological and HLA-DR testing in the patients with QFS.

Patient	Acute stage				Chronic stage		HLA- DR
	ELISA		CRB		ELISA		
	IgM	IgG	I sample	II sample	IgA	IgG	
1	n.p.	n.p.	1: 64	1: 1280	0.8 (Neg)	1.0 (Neg)	13
2	1: 320	1: 1280	n.p.	n.p.	1.4	1.6	3
3	1: 320	1: 640	n.p.	n.p.	1.5	2.4	13 (6)

n.p. – not performed.

negative. Transthoracic and transesophageal heart ultrasound showed no signs of endocarditis. Ultrasound of abdomen was also normal. Rheumatoid factor, antinuclear antibodies, and antimitochondrial antibodies were negative. Biphasic ELISA test for Coxiella burnetii showed positive IgA antibodies in phase I (Table 2). After completing three months of antibiotic treatment with doxycycline, the patient still had fatigue, disrupted sleep, headaches, and muscle and joint pain. He still fulfills the criteria for CSF, cannot go back to work, and awaits realization of his retirement (Table 1).

DISCUSSION

Three patients with diagnoses of chronic fatigue syndrome after Q fever are described. Positive IgA antibodies for phase I of the *Coxiella burnetii* growth cycle suggest the possibility of chronic infection and the presence of *Coxiella burnetii* in macrophages [7]. Two of the patients described in this study had positive IgA antibodies for phase I of the *Coxiella burnetii* growth cycle and serology which was consistent with chronic *Coxiella burnetii* infection, while patient No. 1 had negative serology for chronic *Coxiella burnetii* infection (Table 2).

As there are no clinical signs or laboratory tests that could be taken as definite proof of CFS, the disease is diagnosed based on the patients' symptoms and by excluding other diseases with similar symptoms [8]. In the last ten years, Q fever has been included in a group of diseases that are associated with the development of CFS after the acute phase of illness [7].

A recent article by Hickie et al. suggests that post-infective fatigue syndrome can occur after clinical infection by several different viral and non-viral microorganisms. The authors suggest that the CFS phenotype was stereotyped and occurred with similar incidence after Epstein-Barr virus, Q fever, and Ross River virus infection. The occurrence of CFS was predicted in the highest degree by the severity of the acute infection [12]. All our patients had moderately severe acute illness. Helbig and associates suggest a genetic predisposition for CFS[13]. Analyzing patients who had Q fever in England, Ayres and associates established that long persistence of fatigue, increased sweating, blurred vision, and shortening of breath are manifested more commonly in the group of patients that suffered from Q fever than in the control group [14]. Similar results were obtained by

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Chronic Fatigue Syndrome after Q fever (continued)

Marmion's et al. [15] while comparing slaughterhouse workers who had Q fever with a serologically negative control group. Fatigue, headache, disrupted sleep, and muscle and joint pain were significantly more frequent in the group of workers with previous Q fever. Ayres [14] associated shortness of breath in patients after Q fever with possible myocardial lesions after *Coxiella burnetii* infection, that were first referred to by Maisch in 1986 [16]. Lovey et al. [17] established a higher incidence of cardiovascular diseases in patients who had Q fever in comparison with a control group. Later studies by Ayres et al. did not show any significant difference in cardiological measurements that would suggest cardiomyopathy or other heart diseases when comparing a group with CFS after acute Q fever and a group without symptoms of CFS [18].

Thomas et al. did not find any significant differences in the frequencies of fatigue, depression, and lack of concentration between individuals with positive antibodies for *Coxiella burnetii* and serologically negative individuals. The imperfection of this study was that it included all Q-feverseropositive individuals without differentiation between patients who had asymptomatic and those who had symptomatic acute Q fever, as well as the fact that the study was done on a relatively healthy population with little neuropsychiatric morbidity [19]. Although Marmion et al. suggested that the diagnosis of QFS does not require serological criteria for chronic Q fever, low serological titers against *C. burnetti* were associated with chronic fatigue syndrome by Penttila et al. [15,11]. It is therefore not clear if patients with symptoms of CFS and positive serology of chronic Q fever, but lacking other clinical manifestations of chronic Q-fever such as endocarditis or osteitis, as described in the cases 2 and 3 of this paper, should be included in this syndrome. We therefore believe that patients with CFS criteria, positive phase I serology, and without other clinical manifestations of chronic Q fever should be diagnosed as QFS.

Finally, is there any usefulness of antibiotic therapy of post-Q-fever CFS? The results of antibiotic therapy in patients presented in this paper were conflicting: in two cases the symptoms diminished, while the third patient continued to complain of CFS symptoms. These results are based on their clinical findings, before and after the therapy, as well as a questionnaire investigation. Up to now, there are two studies investigating the outcome of QFS therapy. Arashima et al. conducted treatment with minocycline for a period of three months in twenty patients with QFS. The result was satisfactory, and in all patients fatigue resolved, while seven patients with positive PCR test for *Coxiella burnetii* turned negative [20]. The limitation of this study is the absence of a placebo control group. One year later, Iwakami et al. Studied the effects of three months of antibiotic therapy in patients with post-Q-fever CFS. Although they became negative for *C. burnetii* DNA, in contrast to Arashima's study no improvement of their symptoms was observed [21]. Another anecdotal attempt was the treatment of three-year-old girl with post-Q-fever CFS with interferon-g after unsuccessful antibiotic therapy [22].

The idea for such therapy was based on the knowledge that interferon-g induces the killing of monocytes infected with *Coxiella burnetii*. The result of treatment was satisfying and encouraging for further investigations. Although Vissar et al. [23] accentuated the diversity of the immune response of peripheral mononuclear cells in patients with CFS after stimulation with dexamethasone, our patient treated with corticosteroids did not experience amelioration of his symptoms.

CONCLUSIONS

Our case series of patients from southern Croatia, where Q fever is endemic, is in concordance with more detailed data presented in the past from other areas of the world. Therefore we can conclude that a substantial number of patients develops CFS after acute Q fever in spite of appropriate antibiotic therapy during acute infection. The results of prolonged antibiotic therapy in such the patients are inconsistent. Efforts to establish diagnostic criteria as well as therapeutic recommendations for post-Q-fever CFS require further investigation.

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Chronic Fatigue Syndrome after Q fever (continued)

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ME Comment

Palliative care is not good enough, and does not stop the progress of the illness. Increasing numbers of PWME in our population, and the high incidence in families as well as in certain areas of the country, point to a disease that is communicable. In disregarding these signs, those responsible for the health of our whole population are guilty of what in history will be seen as criminal negligence

- Deborah

ME Story

The future…..

There is no cure and therefore no treatment offered by the NHS. As a result I have joined thousands who have tried every avenue desperately trying to get better, spending over £1000 of my own money and having ongoing expenses for supplements which have been trialled and recommended. All I can see is an ongoing battle with the symptoms - the main one being fatigue - and spending more and more money in the hope of getting better. I know I am not as affected as some but I still find it hard.

Although my GP has been very helpful (he diagnosed the illness very quickly, has referred me to a specialist and asked for Cognitive Behaviour Therapy for me) he cannot give me a timescale or a prognosis.

There is a desperate need to find the cause of this illness and give sufferers a chance of getting their life back. In the meantime, there needs to be a standard 'help package' as the only information I have is what I have found from the internet or from other sufferers.

There seems no end to this at the moment so I join all those who are demonstrating today as one of a large number of highly successful, intelligent and able people who have been struck down and had their lives turned upside down, often overnight. We are willing to work and want to get better, rather than rely on benefits but that is all we are offered.

- Judith

The Reality and Nature of ME/CFS

By

Professor Malcolm Hooper Eileen Marshall Margaret Williams

At the launch by the US Centres for Disease Control in November 2006 of its "Toolkit" to promote better awareness of the reality of ME/CFS, Anthony Komaroff, Professor of Medicine at Harvard, said there are over 4,000 papers on the biomedical nature of ME/CFS. This extensive medical literature spans over 60 years. No-one who is aware of this wealth of information can credibly doubt the reality, the validity and the devastation of this organic multi-system disease.

Although the precise cause(s) is yet to be determined, the symptoms of ME/CFS are not "medically unexplained" and it remains beyond reason that the existence of so many documented abnormalities in people with ME/CFS should simply be disregarded and denied, including the following:

Abnormalities of the central nervous system

include abnormalities of brain cognition, brain perfusion, brain metabolism and brain chemistry; there is evidence of low blood flow in multiple areas of the brain; neuro-imaging has revealed lesions in the brain of approximately 80% of those tested and according to the researchers, these lesions are probably caused by inflammation: there is a correlation between the areas involved and the symptoms experienced; abnormalities on SPECT scans provide objective evidence of central nervous system dysfunction; there is evidence of a chronic inflammatory process of the CNS, with oedema or demyelination in 78% of patients tested; there is evidence of a significant and irreversible reduction in grey matter volume (especially in Brodmann's area 9) which is related to physical impairment and may indicate major trauma to the brain (which could also explain the low recovery rate); there is evidence of seizures; a positive Romberg is frequently seen in authentic ME/CFS patients

Abnormalities of the autonomic and peripheral nervous systems:

There is evidence of dysautonomia in ME/CFS patients – see, for example, "Standing up for ME" by Spence and Stewart: Biologist 2004:51(2):65-70; according to Goldstein, ME/CFS represents the final common pathway for a multi-factorial disorder causing autonomic dysfunction

Cardiovascular dysfunction:

There is evidence of haemodynamic instability and aberrations of cardiovascular reactivity (an expression of autonomic function); there is evidence of diastolic cardiomyopathy; there is evidence of endothelial dysfunction; there is evidence of peripheral vascular dysfunction with low oxygenation levels and poor perfusion and pulsatilities; there is evidence of abnormal heart rate variability and evidence of abnormal orthostasis; there is evidence of abnormally inverted T-waves and of a shortened QT interval, with electrophysiological aberrancy; there is evidence of abnormal oscillating T-waves and of abnormal cardiac wall motion (at rest and on stress); there are indications of dilatation of the left ventricle and of segmental wall motion abnormalities; there is evidence that the left ventricle ejection fraction – at rest and with exercise – is as low as 30%; there is evidence of reduced stroke volume

Respiratory system dysfunction:

There is evidence of significant reduction in many lung function parameters including a significant decrease in vital capacity; there is evidence of bronchial hyper-responsiveness

A disrupted immune system:

There is evidence of an unusual and inappropriate immune response: there is evidence of very low levels of NK cell cytotoxicty; there is evidence of low levels of autoantibodies (especially antinuclear and smooth muscle); there is evidence of abnormalities of immunoglobulins, especially SIgA and IgG_3, (the latter having a known linkage with gastrointestinal tract disorders); there is evidence of circulating immune complexes; there is evidence of a Th1 to Th2 cytokine shift; there is evidence of abnormally diminished levels of intracellular perforin; there is evidence of abnormal levels of interferons and interleukins; there is evidence of increased white blood cell apoptosis, and there is evidence of the indisputable existence of allergies and hypersensitivities and positive mast cells, among many other anomalies, with an adverse reaction to pharmacological substances being virtually pathognomonic

Virological abnormalities:
There is evidence of persistent enterovirus RNA in ME/CFS patients; there is evidence of abnormalities in the 2-5 synthetase / RNase L antiviral pathway, with novel evidence of a 37 kDa binding protein not reported in healthy subjects or in other diseases; there is evidence of reverse transcriptase, an enzyme produced by retrovirus

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The Reality and Nature of ME/CFS

(continued)

retrovirus activity, with retroviruses being the most powerful producers of interferon; there is evidence of the presence of HHV-6, HHV-8, EBV, CMV, Mycoplasma species, Chlamydia species and Coxsackie virus in the spinal fluid of some ME/CFS patients, the authors commenting that it was surprising to find such a high yield of infectious agents on cell free specimens of spinal fluid that had not been centrifuged

Evidence of muscle pathology:

This includes laboratory evidence of delayed muscle recovery from fatiguing exercise and evidence of damage to muscle tissue; there is evidence of impaired aerobic muscle metabolism; there is evidence of impaired oxygen delivery to muscles, with recovery rates for oxygen saturation being 60% lower than in normal controls; there is evidence of prolonged EMG jitter in 80% of ME/CFS patients tested; there is evidence of greater utilisation of energy stores; there is evidence that total body potassium (TBK) is significantly lower in ME/CFS patients (and abnormal potassium handling by muscle in the context of low overall body potassium may contribute to muscle fatigue in ME/CFS); there is evidence that creatine (a sensitive marker of muscle inflammation) is excreted in significant amounts in the urine of ME/CFS patients, as well as choline and glycine; there is evidence of type II fibre predominance, of scattered muscle fibre necrosis and of mitochondrial abnormalities

Neuroendocrine abnormalities:

There is evidence of HPA axis dysfunction, with all the concomitant implications; there is evidence of abnormality of adrenal function, with the size of the glands being reduced by 50% in some cases; there is evidence of low pancreatic exocrine function; there is evidence of an abnormal response to buspirone challenge, with a significant increase in prolactin release that is not found in healthy controls or in depressives; there is evidence of abnormal arginine – vasopressin release during standard water-loading test; there is evidence of a profound loss of growth hormone; even when the patient is euthyroid on basic screening, there may be thyroid antibodies and evidence of failure to convert T4 (thyroxine) to T3 (tri-iodothyronine), which in turn is dependant upon the liver enzymes glutathione peroxidase and iodothyronine deiodinase, which are dependant upon adequate selenium in the form of selenocysteine (which may be inactivated by environmental toxins)

Defects in gene expression profiling:

There is evidence of reproducible alterations in gene regulation, with an expression profile grouped according to immune, neuronal, mitochondrial and other functions, the neuronal component being associated with CNS hypomyelination

Abnormalities in HLA antigen expression:

Teraski from UCLA found evidence that 46% of ME/CFS patients tested were HLA-DR4 positive, suggesting an antigen presentation

Disturbances in oxidative stress levels:

There is mounting evidence that oxidative stress and lipid peroxidation contribute to the disease process in ME/CFS: circulating in the bloodstream are free radicals which if not neutralised can cause damage to the cells of the body, a process called oxidative stress: in ME/CFS there is evidence of increased oxidative stress and of a novel finding of increased isoprostanes not seen in any other disorder; these raised levels of isoprostanes precisely correlate with patients' symptoms (isoprostanes being abnormal prostaglandin metabolites that are highly noxious by-products of the abnormal cell membrane metabolism); there is evidence that incremental exercise challenge (as in graded exercise regimes) induces a prolonged and accentuated oxidative stress; there is evidence of low GSH-PX (glutathione peroxidase, an enzyme that is part of the antioxidant pathway: if defective, it causes leakage of magnesium and potassium from cells)

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ME Story

He was here 2 and a half hours and told me to get rid of my "energise DVD (from the charity ME Research UK)", that ME was all due to deconditioning and negative behaviour patterns. He said the only one keeping me in that bed is me. The confusion is due to me not using my brain, hearing problems due to not using my ears, light sensitivity due to not going out in the light and so on and so forth. Why should I expect a blue badge when that would only discourage me from walking, he said.

I felt humiliated and ridiculed by someone who was clearly a psychiatrist of some description. He said he gave seminars to students on "people like me".
He seemed to enjoy the whole thing.

-Julie (UK person with ME)

The Reality and Nature of ME/CFS

(continued)

Gastro-intestinal dysfunction:

There is evidence of objective changes, with delays in gastric emptying and abnormalities of gut motility; there is evidence of swallowing difficulties and nocturnal diarrhoea; there is evidence going back to 1977 of hepatomegaly, with fatty infiltrates: on administration of the copper response test, there is evidence of post-viral liver impairment -- an increase of at least 200 in the copper level is the expected response, but in some severely affected ME/CFS patients the response is zero; there is evidence of infiltration of splenic sinuses by atypical lymphoid cells, with reduction in white pulp, suggesting a chronic inflammatory process; there is evidence that abdominal pain is due to unilateral segmental neuropathy (Gastrointestinal Manifestations of Chronic Fatigue Syndrome: H Hyman, Thomas Wasser: JCFS 1998:4(1):43-52); Maes et al in Belgium have found significant evidence that people with ME/CFS have increased serum levels of IgA and IgM against the LPS of gram-negative enterobacteria, indicating the presence of an increased gut permeability resulting in the autoimmmunity seen in many ME/CFS patients; this indicates that the symptoms of irritable bowel seen in ME/CFS reflect a disorder of gut permeability rather than psychological stress as most psychiatrists believe (gastro-intestinal problems are a serious concern in ME/CFS, and 70% of the body's immune cells are located in the GI tract)

Reproductive system:

There is clinical evidence that some female patients have an autoimmune oophoritis; there is evidence of endometriosis; there is evidence of polycystic ovary syndrome; in men with ME/CFS, prostatitis is not uncommon

Visual dysfunction:

There is evidence of latency in accommodation, of reduced range of accommodation and of decreased range of duction (ME patients being down to 60% of the full range of eye mobility); there is evidence of nystagmus; there is evidence of reduced tracking; there is evidence of problems with peripheral vision; there is evidence that the ocular system is very much affected by, and in turn affects, this systemic condition.
The above list is by no means comprehensive but merely gives an overview of documented abnormalities seen in ME/CFS that can be accessed in the literature, as well as in the abstracts and reports of international Clinical and Research Conferences [**http://tinyurl.com/3xocuc**].

This was an extract from the document "CORPORATE COLLUSION?" which may be found at the ME ACTION UK site at ***http://tinyurl.com/2wxsb8***.

ME Parent's Story

We feel this improvement has emerged because of our developing confidence in being able to reject medical approaches to Suzy's severe ME, and to the departures we chose to make from these conventional treatments.

For example:

1. No longer trying to wake Suzy twice a day.

This was a very difficult decision, which we knew would be a controversial one.

But the fact that after a few months she managed her hour awake without us having to sit silently beside her, and that the hour ceased to be broken, reassured us that we'd done the right thing.

2. Forgetting about the concept of 'graded exercise'

We were certain that the graded exercise program Suzy followed in the early stages of her ME was a big mistake.

We had no hesitation in no longer sticking to any kind of graded exercise routine (which might be beneficial for those patients with less severe ME). Instead we took the approach of letting Suzy do what she felt she could do----- which for nearly two years was nothing at all.

This is a second option we are convinced we made the right choice over.

3. Stopping the involvement of psychologists

A third decision we know to have been the right decision, was to stop the involvement of psychologists in an illness we are convinced is not psychological.

4. Choosing to see less (which eventually became nothing) of doctors.

We eventually accepted that to us, the only safe path was to manage Suzy ourselves by following our own instincts.

We had become more and more sure that Suzy needed as much of a stress free environment as possible; an environment we tried to ensure she got.

- Parents of Suzy (UK person with ME)

Children and Young people with ME– A Personal Overview of the Last 20 Years

By
Dr. Nigel Speight

Introduction

Having just retired after 25 years as a Consultant Paediatrician with a special interest in ME, I have been asked to give this personal take on the last 20 years regarding young people with ME and the way the medical profession has treated them.

Overall the profession has not (in my opinion) exactly covered itself in glory in many instances. It is possible I received an over-pessimistic picture in that the cases coming to me from other areas tended to be self-selected hard-luck stories. Nevertheless there were some definite cases which in my view amounted to "Child Abuse by professionals", and of course these were mainly due to ignorance about or disbelief in the reality of ME on the part of otherwise well-meaning professionals.

Fortunately there is currently a brighter picture and better understanding and acceptance of ME in the profession. However, I was still called in on two cases of Care Proceedings in young people with ME in the South of England in the last 6 months of my career.

My personal story regarding ME

I was never taught anything about ME during my student training or subsequent training in paediatrics, and became a consultant in a state of almost total ignorance on the subject, like most of my peers. I had a slight advantage in that two of my nephews developed the condition, and as they had both been keen sportsmen and were desperately unhappy at being unable to continue sport I had an instinctive reaction of belief in ME as a genuine organic/physical illness, and a natural scepticism for the widespread view that it was "all in the mind".

About 23 years ago I saw my first case, a 13 year old young lady who announced her diagnosis to me. Her symptoms "rang true" to such an extent that this experience cemented my belief system along the lines of an organic causation. The late Alan Franklin had an almost identical introduction to the condition at about the same time

Subsequently I took an increased interest in the condition and cases just seemed to gravitate to me, both locally, regionally and from all over the UK. By the time of my retirement I had seen personally c 200 cases in North Durham, 150 in the Northern Region and another 150 from further afield, including Northern Ireland, the Isle of Man and Scotland. Many of the cases who came from further afield did so because of failure to obtain an official diagnosis of ME which had led the family to feel threatened in a number of different ways, the worst being threats of Care Proceedings, fines for non-school attendance, and threatened withdrawal of benefits (or failure to be granted benefits in the first place).

The controversy as to the nature of ME

Seeing young people develop ME out of the blue in the absence of any psychological trigger made me question the widely held belief that ME is a "psychosomatic" disease.

Dr. Nigel Speight

Dr. Nigel Speight was, before his retirement, consultant paediatrician at The University Hospital of North Durham, County Durham, Dr Speight is one of the most renowned authorities on ME and children in the UK.

I felt as if I was the little boy who remarked that the Emperor's new clothes were non-existent. Accordingly I sent a questionnaire to all consultant Paediatricians in the Northern Region, sometime in the mid 1980s. I was heartened by the response, in that a clear majority (19 versus 7, with about 10 don't knows) shared my belief that ME was primarily a physical illness which can affect people who are at least initially psychologically normal. Most of these doctors were general paediatricians. When I repeated the exercise with Child Psychiatrists, they almost universally refused to tick any of the boxes on offer but instead deplored the question and gave me lectures on the mind-body continuum!

Basically, this was a reflection on how Psychiatry has been allowed to dominate the field of ME for the 30years since 1970, when McEvedy and Beard first alleged that Royal Free Disease had all probably been a manifestation of mass hysteria in nurses. (They did not actually see any of the cases but just constructed their hypothesis form a review of the notes) The discipline of Adult Medicine seemed only too happy to abdicate the field to psychiatry, possibly because with increasing specialisation there wasn't an "ology" that would own ME. (eg Neurology,

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Children and Young people with ME – A Personal Overview of the Last 20 Years
(continued)

Immunology, Rheumatology, Microbiology etc, although in each of these specialties there were individuals who took an interest)

I continued to attempt to fly the organic flag. For instance I demanded the right of reply at the annual paediatric conference in Cambridge after a prominent Child Psychiatrist had been invited the year before. Addressing an audience of c 80 paediatricians I won a majority vote on a show of hands at the end of my lecture. Agreeing to see cases from outside my own area was a further very effective way of highlighting the continuing controversy.

My general approach to young people with ME

The first person to influence me was Dr Betty Dowsett who was invited by one of our local GPs who believed in MEto give a lecture in our hospital. She gave such a clear exposition of the clinical features that she made the condition both "real" and respectable for me, and I felt empowered to make the diagnosis myself in future. Subsequently I heard both Dr Alan Franklin and Dr David Bell talk on the same occasion in Newcastle and this increased my confidence in understanding the condition. I remember that Dr Franklin said we are training younger doctors to be too dependent on performing tests on patients and losing the clinical skill of history taking as a result.
I rapidly realised that ME sufferers want above all for their condition to be accepted by their doctor and their symptoms validated. They are enormously grateful for this and very forgiving of our failure to cure them. They then wish their doctor to remain engaged with them and their condition, and not to be discouraged by the failure of the patient to recover. Too often doctors reject patients with ME on the grounds that there is "nothing they can do for them". Even this is preferable to the "one way ticket to the psychiatrist approach" which is again understandably perceived as a form of rejection by the patient.
This need for validation was brought home to me by my seeing a young teenage girl in a wheelchair sobbing her eyes out at a meeting for young people. I asked her mother what was the matter and who had upset her, only for her to reply "Its all right, those are tears of joy – she has just heard a lecture by Dr David Bell after which she said "thank goodness there is one doctor in the universe who understands what I have been suffering from these last three years" "!

Another telling anecdote is that of a highly intelligent 6yr old girl with ME whose paediatrician allegedly told her "There can't be anything wrong with you because all your tests are normal" (How many times have the ME community heard something to this effect?) The girl replied with perfect logic and even better grammar "Maybe I've got a condition for which you have not yet invented the right test"!

The challenge of the Very Severe Case

My first very severe case took me by surprise and I made big mistakes in her management. I had already diagnosed her while she was still in the moderate range of severity only for her to deteriorate suddenly following a further viral infection. In retrospect I realise that I was more concerned for my own position than her welfare, in case I had missed some other more treatable diagnosis. (This is an almost universal fear in doctors confronted with ME) I accordingly referred her to tertiary specialists for second and third opinions, and she was subjected to numerous upsetting tests and examinations over a three day period in hospital. This so traumatised her that she had difficulty forgiving both me and her parents over the next three years, and this may well have delayed her recovery. Subsequently every fresh professional whom I introduced to her care managed to upset her further, giving me grounds for being very sceptical of the orthodox teaching of the virtues of a multidisciplinary approach!

Too often doctors reject patients with ME on the grounds that there is "nothing they can do for them".

Even this is preferable to the "one way ticket to the psychiatrist approach"

Things were further set back when the GP insisted on calling a meeting where the Health Visitor wondered out loud if perhaps the father was sexually abusing his daughter; minutes were sent to the family in a spirit of openness! (Not surprisingly the family changed their GP practice after this episode) Fortunately she eventually made a good recovery despite having been bed-ridden and tube-fed for 3 years. My next case was almost exactly similar but I handled her according to my new convictions. I strictly limited her from too much contact with other professionals, simply sharing her care with her GP, our home nursing service and our dietician (to supervise her tube-feeding) This second case did much better emotionally, and made a total recovery within 2 years.
I did not involve Child Psychiatry, Physiotherapy, Occupational Therapy or any other disciplines and she did not appear to suffer from their absence, making a total recovery in 2 years after 9 months of tube-feeding. In my experience of cases in the rest of the country, this scenario of the paediatrician being panicked by meeting a very severe case is really quite common and has contributed to some of the cases referred to Social Services.

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Children and Young people with ME – A Personal Overview of the Last 20 Years
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Child Protection Cases

Every one of these was a nightmare for the young person and the family and in my view added insult to injury for young people deserving sympathy and support but getting the opposite. I was involved in over 20 of these cases, all of which reached the stage of a Child Protection Case Conference. There was usually a combination of one or several of the following factors operating to lead to a Child Protection approach:

- Single mother
- A disbelieving and usually absent father
- Other frustrating medical problems eg allergies
- A record of the family having put pressure on doctors/SSD etc in the past eg for second opinions, SSD support etc
- A lack of an official diagnosis of ME
- Another family member suffering from ME, often "unofficially"
- Severity of the ME, deterioration or failure to respond to some form of medical regime
- A reluctance on the part of the family to be referred to Child Psychiatry, especially if it involved admission to a unit and restriction of parental access
- A tendency for the case to be driven by doctors who had never actually been clinically responsible for the young person, who had not therefore taken a history and were thereby prone to disbelief (usually Community Paediatricians, often concerned about poor school attendance)
- **A failure of doctors and/or Social Workers to actually talk to the young person**
- A belief on the part of doctors in the efficacy of their "treatments", leading to the mother or young person being blamed for the failure to respond.
- A frequent tendency to invoke the spectre of Munchausen Syndrome by Proxy (MSBP, aka Factitious and Induced Illness) whereby the mother is alleged to be inventing/exaggerating her child's symptoms for some perverse motive of her own.
- A distressing sense of self-righteousness on the part of the professionals involved and a reluctance to open their minds to the possibility they were perpetrating a grave injustice. The term "group folly" sprang to mind as each professional sheltered in the security of the group decision, scared to break ranks.

In this last respect Chris Clark (Former CEO of AfME) said to me after hearing some of these stories "It actually smacks of sadism". The good news is that in every case bar one I was able to reverse the Child Protection juggernaut by my report for court. In addition to making an official diagnosis of ME, I spoke to the young person on his/her own, was often able to assert that the young person was "Gillick competent" and did not consent to be taken into care.

I would love to say that we have seen the last of this sort of case but fear we have not.

In this last respect Chris Clark (Former CEO of AfME) said to me after hearing some of these stories "It actually smacks of sadism".
The good news is that in every case bar one I was able to reverse the Child Protection juggernaut by my report for court. In addition to making an official diagnosis of ME,

> *In my experience of cases in the rest of the country, this scenario of the paediatrician being panicked by meeting a very severe case is really quite common and has contributed to some of the cases referred to Social Services.*

I spoke to the young person on his/her own, was often able to assert that the young person was "Gillick competent" and did not consent to be taken into care.
I would love to say that we have seen the last of this sort of case but fear we have not.

Grounds for Hope

I personally think that the Report of the CMO's Working Party of 2002 was the best thing to happen to the ME Community in terms of asserting the genuine (i.e. organic) nature of the condition. I believe its potential has been under-utilised by the ME lobby in their support.

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Mother of Children with ME

We're so aware of how the years are passing since our son and daughter were diagnosed with ME and how cruel it is for all the children with ME that they have missed out on their childhood as well as suffering enormous pain.

We live for the day that someone like Jonathan Kerr will say that there is something that can be done to help, if not cure, all those who suffer from these terrible illnesses.

Children and Young people with ME – A Personal Overview of the Last 20 Years
(continued)

It was significant that the Psychiatrists on the Working Party refused to sign up to it on the grounds that it placed too much emphasis on ME being an organic condition!
The Gibson report is also likely to prove very helpful in its call for more biomedical research.
The College of Paediatrics Guidelines were useful in making ME more of an official condition and helping paediatricians to accept its reality, and their responsibilities.
Like many I have my doubts on the NICE Guidelines and feel they are inferior to the CMO's report. Similarly I sense some scepticism over the new Treatment centres on the part of many ME sufferers. Time will tell.

The Role of Chronic Infections

Ironically, in the last 12 months before I retired I became very interested in the Lyme Disease/Tic born chronic infection story and am sorry to be unable to pursue it to a conclusion. I attended a fascinating conference in Leicester organised by Lyme Disease Action and heard a brilliant lecture by a doctor from New England called Dr J Burrascano. Over the last year I have come to regard two of my severe cases as likely cases of Lyme
disease and was treating them with prolonged courses of antibiotics with some possible improvement. I would recommend the LDA website for anyone interested:
http://www.lymediseaseaction.org.uk/.
The exciting thing about this area is the possibility of treatment, and of course the model of chronic infection pointing to an organic causation.

One last question.

Someone who cycled from Land's End to John of Groats for AfME was accommodated by ME families the length of Britain on his ride. At the presentation ceremony he asked the following interesting question "Does ME only attack nice people and their families, or can it attack anyone and then turn them into nice people?"
Fascinating question which I have often asked myself! Any suggestions/comments?

ME Story

The following week the psychiatrist asked to see me at the hospital, in a manner that I interpreted that would not benefit Sophia if I refused. I had no option but to comply. I was told that if Sophia refused to go to the M.E. clinic, or if she did not recover within the following 6 months, that she would be sectioned under the Mental Health Act, then added that if I tried to stop this, then the psychiatrist would go to the courts to have me removed as the nearest relative. Furthermore, if I did not open the door when they would come to take Sophia away, that the police would be called to "smash the door down". When I asked how much better Sophia would get by these proposed actions, the reply was given that it was "none of your business, that it was for the courts to decide". The psychiatrist wanted to arrange for me to see a psychologist so that I could understand the good that the psychiatrist was doing to Sophia.

I refused.

(from The Story of Sophia and M.E. – http://www.investinme.org/Article-050%20Sophia%20Mirza%2001.htm)

(It is now almost 2 years since Sophia Mirza died from ME)

ME Story

Before I had ME, I happily worked as a full-time lecturer for seven years, did classical ballet, contemporary dance and flamenco classes after work, travelled and lived an entirely full life.

I have no history of mental illness, no current symptoms of depression and have never taken any medication for these conditions.

Considering the appalling misunderstanding of this illness and terrible social pressures, I am amazed by, and proud of, the bravery of ME sufferers across the country.

For my part, I find misunderstanding of this illness as difficult to cope with as the illness itself. Maybe it's time for psychiatrists to address their unhelpful beliefs about this illness and their repressed reasons for continuing to block biomedical research.

- Sarah

ME Story

The following is a true story told by the parent of a child with severe ME. It should be emphasized that this is a recent and ongoing experience of one family – happening in the UK in this year. The name of the child has been changed for this story.

ROSE

Our daughter Rose got the flu when she was nine, in 1998, and never really recovered from it. She saw different doctors and had scans and blood tests. One consultant said it was idiopathic pain syndrome which our GP said means "I don't know".
At this time Rose was unable to climb the stairs – she went up and down stairs on her bottom. They also mentioned school phobia - had Rose been bullied or was she too clever for school?

Rose tried to carry on at school for a while. The physio she was seeing advised her to walk to and from school. She would arrive home with her face white and fall asleep even at dinner.

Over the next few years Rose got worse. In January 2001 Rose fell to the floor and was not able to walk again. My husband took her to the doctors as she was unable to eat or walk.
The doctor said that the best place for her was in school.
Then we were sent to see a psychiatrist who felt Rose should be seeing a consultant paediatrician because she had started to drink excessive amounts.
He was kind but didn't know much about ME. A registrar told us that Rose had ME/CFS and they would speak to the consultant.

We went to many meetings at the hospital. The local team kept giving Rose physio and hydro. Rose got worse. She was given lots of different therapies - even art therapy.
We were told that if we went against the professionals we would have a Child Protection Order (CPO) served on us.
By 2003 Rose was bed bound and on a NG Tube. She saw a new consultant who was nice and did listen to our concerns when we met him.

Over the next 3 years whilst going back and forth to the hospital, for two lots of five week stays Rose was made worse – what with the travelling, noise and people in and out of Rose's room, with nurses that had never seen severe ME before and who could not understand that Rose could only remember what was happening on the current day. Her memory became so bad. She was repeatedly asked questions she could not answer. This upset Rose a lot.

She was paralysed over her body, fed by NG Tube and was sensitive to light, noise and touch and in a lot of pain.

By April 2006 Rose had a PEG fitted after a four and half month stay in hospital, following emergency admission, during which I stayed with her all of the time. As with Rose's memory problems, she would not know me and from the experience of previous stays, the hospital staff would not give her medicine on time.

We were told that if we went against the professionals we would have a Child Protection Order (CPO) served on us.

She was in terrible pain all of the time and not receiving her medication made her worse.
I was called an over-protective mother at times.

By the time we left they wanted Rose to go to rehab, though my husband and I didn't want this for Rose. We felt we were not being listened to.

After one meeting we agreed to visit three places in order to show we were willing to have a look, but we reduced this to one place as Rose's consultant was retiring. We visited this hospital but we felt it was not suitable for Rose.

In the summer of 2006 Rose started having blackouts and no feeling in her arms and this progressed slowly up her arms and legs. At the moment she has no feeling above her knees and elbows.
The consultant then referred us to another consultant who felt we could go and meet. But this never happened. After this things went along quickly. What was happening in the background seemed to be out of our control.

(continued on page 43)

ME Story – ROSE (continued)

The new consultant came to visit Rose and after this there was another meeting which was organised with Rose's team. The consultant said that some of the symptoms Rose had were not due to ME (i.e. memory loss and paralysis) and that her ME could be a cloak for PRS (Pervasive Refusal Syndrome).

We went home to find out what PRS was and all the people in the meeting did the same.

We felt very angry about this diagnosis of PRS. Yet people couldn't understand why we felt this way and didn't understand why it mattered.
It matters to us after reading about it.
After all, the psychiatrists Rose has seen over the years had never mentioned this to us.

So Rose had to do a 6 week diagnostic test for PRS with two 6-second sessions of physio, adding on 10% each week and starting with 10 minutes high activities. This included education, art therapy and visitors.

Even if Rose was unconscious from blacking out then someone had to read to her and the curtains had to remain open - 10% each week.

Then there were low activities which would be performed all day. This consisted of someone reading to Rose, listening to the radio, chatting with someone or listening to the TV in the background. If she was watching TV then it had to be turned off after a certain time and then listening to music on Cd player.

After the six weeks we were told that Rose did not have PRS as she never got worse during the six weeks.
We felt those 6 weeks were a nightmare. We prayed every day for Rose not to get worse during this time.
The timetable continued after the 6 weeks and when I asked what would happen if Rose got stuck on 25 minutes the reply was that she must be scared of going to school.

The consultant said that the some of the symptoms Rose had were not due to ME (i.e. memory loss and paralysis) and that her ME could be a cloak for PRS (Pervasive Refusal Syndrome).

Rose has not been to school since she was 11 years old (seven years ago)!

We got to 20mins on the timetable and the pain and light sensitivity got worse.
She kept getting infections.

We eventually stopped the timetable. If we had kept going Rose would have been made far worse.

We are now doing our own plan for Rose - most of it taken care for by Rose.
Now we are left trying to find an adult consultant for Rose - one who understands severe ME.

I wanted to tell Rose's story as the phrase PRS still makes feel sick.

One member of Rose's team mentioned a couple weeks ago that they had forgotten who this was all about!!

More ME stories, including all of these contained in this Journal, are available at –

http://www.investinme.org/mestorygallery1.htm

Stories from parents of people with ME may be found at -

http://www.investinme.org/mestorygallery2.htm

ME in Parliament

Countess of Mar: "If a group of people refuses graded exercise and cognitive behaviour therapy, on the basis either that they are afraid or that they know it will not help them, will they be penalised?"

Lord McKenzie of Luton (Parliamentary Under-Secretary, Department for Work and Pensions; Labour Peer): "there is no requirement for individuals to carry out any specific type of activity or treatment. That cannot be sanctioned".

- Hansard *Hansard (Lords) on 28th February 2007, column GC198*

IiME Comment – NICE Guidelines on ME

In August the National Institute for Health and Clinical Excellence (NICE) published their official document for clinical guidelines. The document was developed for use in the NHS in England and Wales regarding chronic fatigue syndrome / Myalgic Encephalomyelitis (CFS/ME).

After almost universal criticism of the draft guidelines from ME patient groups in the UK the guidelines were intended to be revised. IiME was not original stakeholder (IiME only became a charity in May 2006) but became a stakeholder on October 2006 and have submitted our response to the draft guidelines. We have analysed the official guidelines and the summary below is from our response (which can be seen from this address **http://tinyurl.com/25wtjq).**

Background:

Invest in ME (IiME) is a UK charity of people with Myalgic Encephalomyelitis (ME/CFS) or parents of children with ME/CFS. The work we perform is unpaid and voluntary and the charity has no paying subscribers. We therefore are independent and do not have any ties to, or receive any finance from, the NHS or from government departments which could influence our opinions when analysing these guidelines.

Invest in ME have examined the Full version of the NICE guidelines for CFS/ME (covering ME/CFS patients). IiME's review is available at **http://tinyurl.com/25wtjq**

In the Preface Professor Richard Baker states that

> "*The publication of this guideline presents an opportunity to improve care for people with CFS/ME.* "

That was a very true statement.
It is a sad failing of NICE, however, that these guidelines fail to grasp this opportunity and instead deliver a weak and ineffectual document that seemingly attempts to retain much of the ignorance and prejudice existing within healthcare provision for ME/CFS.
IiME believe these guidelines provide little to further the treatment of ME/CFS and this is an opportunity missed.

The NICE guidelines lack any vision in moving forward the treatment of people with ME/CFS.

NICE have chosen only to use the evidence which satisfied a predetermined view –

- that CBT and GET are preferred methods of treatment for ME/CFS
- that there is doubt about the true nature of ME/CFS
- that CFS incorporates ME/CFS within its catchment

The remit for NICE was documented at - (http://guidance.nice.org.uk/download.aspx?o=111640) and this was already limiting in deciding the end product–

"To prepare for the NHS in England and Wales, guidance on the assessment, diagnosis, management of adjustment and coping, symptom management, and the use of rehabilitation strategies geared towards optimising functioning and achieving greater independence for adults and children of CFS/ME."

Baker states that -

> "In developing the guideline, we kept in mind the overall goal of improving care for people with CFS/ME, that is, improving diagnosis, enabling patients to receive therapy appropriate for, and acceptable to them, and providing information and support, with the patient's preferences and views firmly driving decision-making. "

Yet how can diagnosis be improved if NICE refuse to adopt consistent, standard guidelines and deem diagnostic tests to be out of scope?

NICE have ignored the overwhelming evidence showing the organic nature of the illness and use a deplorable spin on the facts which does not serve ME/CFS patients, their families or healthcare staff who are genuinely interested in helping.

The end-result seems to be an exercise in producing a pre-determined view of ME/CFS from an official organisation, supposedly independent, yet who seemingly have little conscience for the effects their document will have on patients and their families.

The views of most ME/CFS support groups show that ME/CFS must be seen as a distinct and separate illness from CFS.
The guidelines are quite biased and narrow-looking which mix far too many illnesses and attempt to subjugate ME/CFS into a bag of common illnesses all falling under the term CFS.

This, we feel, is part of the problem faced by healthcare staff and others – by broadening the view of what ME/CFS is it will inevitably dilute the requirements for diagnosing and treating ME/CFS patients.

NICE have done a major disservice to people with ME/CFS who are needlessly suffering from the perceptions of a systemically-biased health service which maintains outdated views with little good scientific evidence.

The NICE guidelines fail to deliver in the areas of epidemiology, diagnosis, terminology, treatments and potentially cause infringement of human rights.

(continued on page 45)

IiME Comment – NICE Guidelines on ME *(continued)*

By pre-determining a view that CBT and GET are the most useful therapies NICE has shown itself as disingenuous – an organisation that is not interested in really helping people with ME/CFS.

Compare the NICE guidelines for ME/CFS with the NICE guidelines for other neurological illnesses such as MS and Parkinson's etc.

- For **MS [CG8 Multiple Sclerosis NICE]** there is no recommendation for GET for patients.
- For **Parkinson's [CG35 Multiple Sclerosis NICE]** there is no recommendation for CBT or GET!

Also,

- For **Dementia [CG42 Dementia NICE] –** no recommendation for GET for patients.
- For **Epilepsy [CG20 Epilepsy NICE] –** no recommendation for GET for patients.

This questions the impartiality of NICE and shows a disturbing bias behind the recommendations made in the NICE guidelines.

In reviewing the stated objectives with the guidelines IiME conclude that none have been satisfied.

Objective: Increasing the recognition of CFS/ME

The guidelines provide nothing new for patients and carers. The few places where the document has requested that healthcare professionals take the illness seriously and that the recognition of this is paramount are good.
However, essential research showing the multi-system nature of ME/CFS is not discussed – enteroviruses, orthostatic intolerance, oxidative stress etc. – none of these are allowed to be discussed in detail. Yet without a basic understanding or awareness of the pathology of the illness how are healthcare staff supposed to recognise the true nature of ME/CFS?
Result: FAILURE

Objective: Increasing the recognition of ME/CFS can only be achieved by increasing the knowledge of the illness itself.
The recommendations that propose non-functional and biased psychiatric therapies as a management technique will lead to more harm and probably contribute to fostering even more antagonism between healthcare staff (especially those who are untrained in ME/CFS) and the patient/carer. NICE have deliberately ignored essential biomedical research which would undoubtedly increase knowledge of healthcare staff on the multi-system pathology of this illness.
Result: FAILURE

Objective: Influencing practice in the 'real world'
By stating that CBT and GET are the most useful therapies NICE has shown itself unwilling to move the issue of ME/CFS into an area which offers any real hope of progress. These guidelines will not influence practice but will lead to already established myths being perpetuated.
The absence of emphasis on the lack of funding for biomedical research into ME/CFS will not help to alter the government's position on this subject and therefore gives little to change the current unsatisfactory position where patients are given possible harmful GET.
The guidelines will not inform healthcare staff of the missing link in research into ME/CFS – funding for biomedical research.
The guidelines show little awareness of biomedical research being carried out or performed in the past.

They fail to mention the links between ME/CFS and vaccines, epidemics or organo-phosphate poisoning.

They should include references to new research so that healthcare staff can be aware of the overwhelming evidence of the neurological origins of this illness.

The guidelines state that a patient/carer can refuse any therapy without it impacting the relationship with the healthcare practitioner(s). We hope this is so but we are afraid that it will not.

In the face of insurance companies forcing ME/CFS patients to undergo potentially harmful GET or useless CBT or DWP procedures to prove they are ill due to the lack of acceptance of the authenticity of the illness then we doubt if these guidelines are forceful enough to influence the '*real world*' and avoid this from happening. In such instances recourse to litigation may be the only possibility for ME/CFS patients.

It might have been useful for these guidelines to detail what avenues are open for legal aid for ME/CFS patients who wish to challenge insurance companies and others who insist on ME/CFS patients undergoing GET or CBT against their will.

The guidelines do little to influence '*real world*' issues when they avoid recommending prescription supplements or complementary therapies which are known to help.

The guidelines do little to influence 'real world' issues such as the frequent need for parents to battle with schools for the rights of their children with ME/CFS.
Result: FAILURE

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Comments on NICE

I am an M.E sufferer who has made a remarkable recovery and it certainly was not brought about by CBT and graded exercise - quite the opposite.

If I have made errors along the way, I would say it was being treated with anti-depressants and trying to exercise in the early stages – Judy

IiME Comment – NICE Guidelines on ME *(continued)*

Objective: Improving access to appropriate services, and supporting consistent service provision

The guidelines provide nothing new for sufferers and carers. Little is given in support of ME/CFS patients in their dealings with DWP staff and no reference is made regarding how ME/CFS patients are meant to deal with the harassment and bias of insurance companies who propose psychiatric treatment for ME/CFS.
If the service provision is providing treatments which are unfit for ME/CFS then consistency is meaningless.
Result: FAILURE

Objective: Emphasising the need for multidisciplinary working

These guidelines patently fail to achieve this due to the concentration on psychological therapies at the expense of real research from published biomedical research papers.
Although there are a few statements stating that multi-disciplinary working is required the bias toward psychological therapies in these guidelines means that there is little credit given to non-psychiatric disciplines in treating and managing ME/CFS.
Result: FAILURE

Objective: Improving care for patients, particularly for those with severe CFS/ME

The guidelines offer little for severely affected. There is no provision for specialist treatment – simply rehashed dogma relating to therapies which are entirely inappropriate for severely (and moderately) affected pwme. There is little here for carers.
Result: FAILURE

Objective: Providing guidance on 'best practice' for children with CFS/ME

The guidelines add little new of relevance which doctors would not already know today. The best practice is not psychiatric therapies where the onus is on the patient to attend CBT meetings. It does little to move the debate on for children or their families. No mention of ME being responsible for more school absence than any other illness.
Result: FAILURE

Objective: Balancing guidance with the flexibility and tailored management, based on the needs of the patients

By emphasising GET and CBT as primary treatments it is not possible to state that these guidelines help in basing management on the needs of patients. Its predilection for asserting that activity and exercise help ME/CFS patients already undermines any confidence that the ME/CFS community may have about the impartiality of these guidelines.
It fails to recommend prescription supplements which can be tailored to manage symptoms of the illness, based on

(continued on page 47)

Comments on NICE

On 22nd August (2007), the day on which the appalling NICE Guidelines have been published, I just want to congratulate all at Invest in ME for the excellent DVD of the recent Conference.

If only the representatives of NICE had bothered to attend and take note, if only the nay sayers who extol the psychosocial paradigm could have the integrity to listen to a much more persuasive argument, then we as sufferers of many years or many decades standing, might be experiencing a much happier and healthier state of affairs now.

Let's hope that the call to arms opined by many of the speakers who gave their time and wealth of knowledge at the Conference can now be realised in terms of pressure from those who truly understand this illness to ensure a volte-face by those who pretend they do yet are blinkered by their own egos' and self satisfied aggrandisement.

- Rosie

Comments on NICE

Good things in the NICE guidelines...

"Healthcare professionals should be aware that - like all people receiving care in the NHS - people with CFS/ME have the right to refuse or withdraw from any component of their care plan without this affecting other aspects of their care, or future choices about care. ".

- Joss

IiME Comment – NICE Guidelines on ME *(continued)*

the needs of the patient. There is nothing flexible with the continued advocacy of useless or dangerous psychiatric therapies.
Result: FAILURE

Objective: Facilitating communication between practitioners and patients, and their families or carers.

The emphasis on psychological therapies posing as treatments using heavily skewed data will inevitably influence GPs and paediatricians – especially if they have little time available for ME/CFS patients. The subject matter is skewed to allow a multitude of fatigue-related patients to be included in this study. If it purports to be for ME/CFS then the studies need to use patients with ME/CFS – not CFS or other fatigue conditions.
Result: FAILURE

By pre-determining the result based on its requirements to view this illness as a broad chronic fatigue illness NICE has failed to grasp the reality, failed to analyse and use proper research, failed to respond to patients' demands and requirements and produced a document that will continue to allow this illness to be blended into a nebulous fatigue syndrome which only benefits psychiatrists interested in funding of their projects and other organisations who depend for their existence on paying members.

NICE call for "Avoidance of dogmatic belief in a particular view." Yet this is itself hypocritical and biased as all of the evidence and recommendations made by NICE are using psychiatric paradigms for treatment.
The MRC has failed to fund biomedical research yet has paid millions of pounds for trials of psychiatric therapies. Could one foresee any progress being made, for example, in understanding MS if all research was performed on coping strategies for MS sufferers?

NICE have demonstrated no vision, no ideas and, seemingly, no wish to progress the treatment and perception of ME/CFS.
The official NICE guidelines for ME/CFS are a mediocre effort by an organisation which again fails the people for whom it purports to provide instructions and information. One can only ask was it sensible to have these guidelines made at all at this stage without better analysis and research?

If much of the evidence was of poor quality then perhaps these guidelines are premature. IiME believe, however, that there is much research which NICE, if genuinely interested in progressing the treatment and perception of ME, could have used to improve knowledge and treatment of this illness.

These guidelines have taken over two years to prepare and it will be another two years before they are revised.

Invest in ME suggest they should be revised immediately.♦

Facts About ME

"We need more research to understand the various subgroups of CFS and to discover treatments that address the true biologic underpinnings of this illness. We need to educate health care professionals about this illness and keep at it until every doctor (and) nurse can quote the diagnostic criteria".

"We know that (ME)CFS has identifiable biologic underpinnings because we now have research documenting a number of underlying pathophysiologic processes involving the brain, the immune system, the neuroendocrine system and the autonomic nervous system".

- From "The State of (ME)CFS Research" by Professor Nancy Klimas, University of Miami Medical School

From "Fast Facts: Top Ten Discoveries about the Biology of (ME)CFS"
by Dr Christopher Snell-University of the Pacific

1. (ME)CFS is not a form of depression and many patients with (ME)CFS have no diagnosable psychiatric disorder.
2. There is a state of chronic, low-grade immune activation in (ME)CFS.
3. There is substantial evidence of poorly functioning NK cells.
4. Abnormalities in the white matter of the brain have been found.
5. Abnormalities in brain metabolism have been discovered.
6. (ME)CFS patients have abnormalities in multiple neuroendocrine systems in the brain.
7. Cognitive impairment is common in (ME)CFS patients.
8. Abnormalities of the autonomic nervous system have been found, including a failure of the body to maintain blood pressure, abnormal responses of the heart rate and unusual pooling of the blood in the veins of the legs. Some studies also find low levels of blood volume.
9. (ME)CFS patients have disordered expression of genes that are important in energy metabolism.
10. There is evidence of active infection with various herpes viruses & enteroviruses in (ME)CFS patients. Other infections can also trigger (ME)CFS, including the bacterium that causes Lyme disease.

The PACE TRIAL

By

Professor Malcolm Hooper Eileen Marshall Margaret Williams

The FINE trials were discussed in the last issue of the Journal of IiME. Using flawed diagnostic criteria, which exclude neurologically ill patients, these trials were criticised in an article by one participant.

Another set of trials, also funded by the Medical Research Council (MRC), are the PACE trials.

Both are described by the MRC as '..complementary trials into various treatments options for CFS/ME which aim to improve quality of life for those who are ill.'

As with the FINE trials the PACE trials are equally controversial – taking a substantial amount of funding from an illness which has seen little spent on biomedical research.

Professor Colin Blakemore, former head of the MRC, stated in the last issue of the Journal of IiME that the PACE trial is a 'large clinical trial of new approaches to treating CFS/ME ". The PACE trial, he said, cost (£2,076,363)."and "The PACE trial will be comparing three treatments given to patients in a clinical setting, one of which is Adaptive Pacing Therapy (APT). This treatment is popular with many patients but has not been scientifically evaluated before. With the help of Action for ME, APT has been adapted to enable the researchers to test it rigorously within the trial. ". Later in the article Professor Blakemore states "The PACE trial;" uses "Cognitive Behavioural Therapy, graded exercise, adaptive pacing and usual medical care for chronic fatigue syndrome".

In the following extracts, taken from the document **CORPORATE COLLUSION?** the background to the PACE trial is examined in more detail.

The MRC PACE trial into "CFS/ME"

On 15th May 2003 the MRC announced the funding of two trials to evaluate the effectiveness of "rehabilitative treatments" for "CFS/ME".

The first trial, known as the PACE trial (Pacing, Activity and Cognitive behavioural therapy: a randomised Evaluation) was to take place in six clinics over a period of four years. Action for ME declared that it was proud to announce its support for the four-year study which *"will evaluate pacing against other exercise and behavioural-led approaches in the care of people with ME".*

The PACE trial was to be led by Dr (now Professor) Peter White of Barts, Dr (now Professor) Michael Sharpe of Edinburgh, and Dr (now Professor) Trudie Chalder of Kings College, London. It was to be co-funded by the MRC, the Scottish Chief Scientist's office, the English Department of Health and the Department for Work and Pensions.

The second trial was the FINE trial (Fatigue Intervention by Nurse Evaluation), a form of what the MRC terms "rehabilitation therapy" to be delivered by specialist community nurses in patients' own homes -- though what "fatigue intervention" has to do with severely affected ME patients who require tube feeding was not specified. It was to be led by Alison Wearden PhD at the University of Manchester and was to be wholly funded by the MRC.

The MRC media release proclaimed that with the PACE trial, "*people can be helped towards recovery";* in the media release, Peter White said: *"I'm particularly pleased that the study has been designed in collaboration with the leading patients' charity Action for ME".*

The Authors: Margaret Williams, Eileen Marshall and Professor Malcolm Hooper are well respected authorities on ME as well as being ME patient advocates and form an established team whose aim is to expose and prevent the injustice perpetrated on patients with ME/CFS in the UK by those whose job is to help, not abuse, such patients.

Professor Hooper is Emeritus Professor of Medicinal Chemistry University of Sunderland. Both Eileen Marshall and Margaret Williams formerly held senior clinical posts in the NHS.

One month later, the ME/CFS community became aware that on 12th-13th June 2003, Peter White delivered a lecture entitled "Central Nervous System and Autonomic Nervous System Responses to Exercise in Patients with CFS" in Bethesda, Maryland, USA, at which Dr White explained that the cognitive behavioural model of CFS posits that the symptoms and disability of CFS are perpetuated predominantly by dysfunctional illness beliefs and avoidant coping. White said that beliefs associated with a poor outcome in CFS include the belief that exercise is damaging, that the cause of CFS is a virus, and that CFS is a physical illness.

(continued on page 49)

The PACE TRIALS *(continued)*

The MRC website described the FINE trial as follows: "Pragmatic rehabilitation is delivered by specially trained nurses who give patients a detailed explanation of symptom patterns. This is followed by a treatment programme focusing on graded exercise. CFS/ME does not refer to a specific diagnosis".

In response to an enquiry from a Member of Parliament, on 24th October 2003 Professor Colin Blakemore (who had just succeeded Professor Sir George Radda as CEO of the MRC) wrote: "(Your constituent) has raised three main points. The first is that research should be done into the causes of CFS/ME before looking into treatments. It is appropriate to explore potential interventions in the absence of knowledge of causation. For example, the cause(s) of diabetes is not known, but knowledge of the underlying pathophsyiology has meant that effective treatments have been developed. (Re:) the second point (referring to MRC funding priorities), the key factor in deciding whether a proposal is funded or not is the quality of the science and its potential contribution to human health. Neither the PACE nor the FINE trials will provide a cure for CFS/ME but that is not their purpose. The trials are intended to assess a number of possible treatments (sic) to see if they are beneficial to those suffering from CFS/ME".

The UK ME/CFS community noted with bemusement that it is customary for the trial protocol to have been rigorously scrutinised, modified if necessary, and approved by the relevant Ethics Committee before funding was granted. This appeared to be a case of the psychiatric lobby rushing things through willy-nilly.

As Christine Hunter of the Alison Hunter Memorial Foundation in Australia pointed out, knowing the cause and knowing the pathophysiology are two different things: pathophysiological research was a priority for diabetes, so why not for ME/CFS? (Christine Hunter's daughter Alison tragically died from severe ME aged 19; the cause of death on the death certificate stated: "Severe progressive ME". The pathologist confirmed that Alison had severe oedema of the heart, liver and brain. Alison also suffered seizures, paralysis and gastrointestinal paresis).
On 16th January 2004, Dr Charles Shepherd from the ME Association posted an item on Co-Cure ACT:RES in which he said: *"In response to recognition for more research, the MRC went on to conclude that research into the underlying cause should not command any high priority. Instead, the MRC recommended yet more money should be spent on researching lifestyles and psychological aspects of management, the results of which may not add any significant information to what patients and their doctors already know. The situation regarding a lack of any encouragement to researchers to pursue the underlying physical cause of ME/CFS remains indefensible".*
There was considerable confusion about both the start date for the trials and the entry criteria, with The Times correspondent Peta Bee claiming on 2nd February 2004 that the MRC trial was: *"now in its second year"* ("Fit to fight fatigue", The Times, 2nd February 2004). The BMJ concurred: *"Exercise is the best way to fight chronic fatigue syndrome. In the MRC study, now in its second". year, patients are advised to follow a carefully graded plan. Dr Trudie Chalder, from King's College, London, says: 'The psychological benefits of following a fitness routine for people with CFS are great'*

Since in January 2004 the MRC's website stated that the start date was 2nd January 2004 and that the Oxford (Wessely School) criteria were being used, it was confusing to be informed just one month later by the BMJ that the trial was in its second year.

It was even more confusing to be informed by the Health Minister (Lord Warner) on 26th February 2004 that the entry criteria for the trials: *"have not yet been finalised"* (Hansard: 26th February 2004: HL1273).

Matters became yet more perplexing when the Health Minister confirmed on 10th March 2004 that: *"the current estimated start of recruitment of patients into both trials is the summer or autumn of 2004. Unconfirmed criteria for both trials are that participants will meet the Oxford diagnostic criteria for CFS".*

In March 2004 an advertisement for "PACE Trial Manager, Research Grade 3, Centre for Psychiatry, Institute of Community Health" to be based at St Bartholomew's Hospital, London (closing date 6th April 2004), announced: *"This is a prestigious MRC funded study of promising new treatments (sic) for a condition of considerable public health importance. Other members of the team include Professor Simon Wessely. The lead statistician is Dr Tony Johnson. The Clinical Trials Unit of the Institute of Psychiatry will be leading on database management and analysis".* Then came the following: *"Mind body medicine and liaison psychiatry are relevant research areas for our centre. Recent successes include studies using the General Practice Research Database (GPRD).* ***The GPRD studies have shown that diagnostic labels for CFS used in UK primary care have radically changed in the last 14 years and that these labels both reflect and affect prognosis".***

What exactly was this radical change in diagnostic labels, who was responsible for it, and on what evidence did it rely? The ME community has little doubt about the answers to those questions.

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The PACE TRIALS *(continued)*

The PACE Trial Identifier (the Funding Application to the MRC)

In about April 2004 the UK ME/CFS community managed to obtain a copy of the PACE Trial Identifier, which unless one is involved in the process, is usually impossible. The Identifier contained misleading statements (*"Predictors of a negative outcome with treatment include membership of a self-help group, being in receipt of a disability pension [and] focusing on physical symptoms")*; vital information was totally omitted; it referred to "treatment" when it would have been more accurate to describe the proposed interventions as "management strategies"; there was to be no subgrouping, and it relied on the biased Systematic Review from the CRD at York.

It stated that the results of the trial: *"will allow health planners, clinicians and patients to choose treatment on the basis of both efficacy and cost (and will) define the essential aspects of effective treatment".*

It acknowledged that: *"There is a discrepancy between patients' organisation reports of the safety of CBT and GET and the published evidence of minimal risk from RCTs".*
It undertook to monitor for any adverse effects: "*We will undertake a detailed assessment, at home if necessary, for any subject who drops out of treatment for this reason, following which they will be offered appropriate help".*
"Appropriate help" was not defined.
It described CBT: "*CBT will be based on the illness model of fear avoidance. There are three essential elements: (a) assessment of illness beliefs and coping strategies, (b) structuring of daily activity, with a graduated return* to normal activity, (c) challenging unhelpful beliefs about symptoms and activity".

It described GET: "*GET will be based on the illness model of both de-conditioning and exercise avoidance. Therapy involves an individually designed aerobic exercise programme with set target heart rate and times"* (3.4).

The inclusion criteria were to be "the operationalised Oxford criteria for CFS. **We chose these broad criteria in order to enhance recruitment**. Subjects who also meet the criteria for 'fibromyalgia' will be included" (3.6). The Oxford (1991) criteria were formulated by the Wessely School and have been criticised for being too broad -- they specifically include those with psychiatric fatigue and they potentially capture people suffering from "fatigue" that occurs in 33 different disorders -- and for specifically excluding those with neurological disorders such as ME. The Oxford criteria have no predictive validity and have never been adopted for use outside the Wessely School. They were superseded by the US Centres for Disease Control (CDC) Fukuda criteria in 1994.
The assumptions of outcome were given: "*At one year we assume that 60% will improve with CBT (and) 50% with GET".*
Information about the day-to-day management of the trial said: "The trial will be run by the trial co-ordinator, with the PI (Principal Investigator). He/she will liaise regularly with staff at the Clinical Trials Unit (CTU) who will be responsible for randomisation and database design and management (overseen by the centre statistician Dr Tony Johnson), directed by Professor Simon Wesssely".
The UK ME/CFS community noted with some surprise the involvement of Dr Tony Johnson, Deputy Director of the MRC's Statistical Unit at Cambridge, because his published views on CBT were already known. In 1998, Johnson published a major review entitled "Clinical trials in psychiatry: background and statistical perspective" (Statistical Methods in Medical Research: 1998:7:209-234) in which he came to some unequivocal conclusions.
Johnson noted that psychiatric studies have been beset by poor design, inadequate data and incorrect analysis, and he noted the existence of studies produced by psychiatrists that claim *"inordinate enthusiasm"* for certain therapies.

The Oxford (1991) criteria were formulated by the Wessely School and have been criticised for being too broad -- they specifically include those with psychiatric fatigue and they potentially capture people suffering from "fatigue" that occurs in 33 different disorders -- and for specifically excluding those with neurological disorders such as ME.

He stated that a major requirement in any clinical trial is to determine the nature of the disease which will be investigated; he noted: "sophisticated technological examination is important in psychiatry to eliminate organic causes of psychiatric symptomatology", a view that Wessely School psychiatrists seem not to share.
Wessely maintains that there is an attractive cost implication of CBT ("The only treatment strategies of proven efficacy are cognitive behavioural ones. We have developed a more intensive therapy; this form of therapy is acceptable to patients, safe, and more effective than either standard medical care or relaxation therapy. It has also been shown to be cost effective". "Chronic fatigue syndrome. A practical guide to assessment and management" Sharpe M, Chalder T, Wessely S et al. Gen Hosp Psychiatry 1997:19:3:185-199) but Johnson disagreed, stating that a course of psychotherapy typically lasts for 12 weeks or longer and "a major limitation is its cost".

The involvement of Dr Tony Johnson in the PACE trial

Dr Johnson's involvement in the PACE trials merits

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The PACE TRIALS *(continued)*

closer scrutiny. He is the son-in-law of Dr Elizabeth Dowsett, who was formerly Medical Advisor to and President of the ME Association and who is currently Medical Advisor to the 25% ME Group for the Severely Affected. Correspondence exists between an ME/CFS sufferer and Dr Johnson himself, but which also involves Dr Anthony C Peatfield, Head of MRC Corporate Governance and Policy. The correspondence arose from the MRC's Biostatistical Unit's progress report for the years 2001 to 2006 that was placed on the website of the MRC Biostatistics Unit (BSU), taken from the BSU's Quinquennial Review of 2006.
One part of the Quinquennial Review states: "*Our influence on policy-makers has largely been indirect, through scientists' work on advisory committees, in leading editorials, in personal correspondence with Ministers, Chairs or Chief Executives (such as of Healthcare Commission or NICE), Chief Medical Officers and Chief Scientific Advisers, or through public dissemination when the media picks up on statistical or public health issues that our publications have highlighted.*

"The Unit's scientists must remain wary of patient-pressure groups. Tony Johnson's work on chronic fatigue syndrome (CFS), a most controversial area of medical research, has had to counter vitriolic articles and websites maintained by the more extreme charities and supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations".

This contention that "CFS" research is beset with vitriol and "extreme" charities was re-iterated by Johnson himself in his own Report within the Quinquennial Review; under "Chronic Fatigue Syndrome (CFS), with P White, T Chalder (London), M Sharpe (Edinburgh)", Johnson's Report stated:

"*CFS is currently the most controversial area of medical research and characterised by vitriolic articles and websites maintained by the more extreme charities supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations. In response to a DH (Department of Health) Directive, MRC called for grant proposals for investigations into CFS as a result of which two RCTs (PACE and FINE) were funded and have started despite active campaigns to halt them. I am part of the PACE study, a multi-centre study comparing cognitive behaviour therapy, graded exercise training, and pacing in addition to standardised specialist medical care (SSMC), with SSMC alone in 600 patients. I have been fully engaged in providing advice about design of PACE and I am a member of both Trial Management Group and Trial Steering Committee. I am not a PI (Principal Investigator) because of familial involvement with one of the charities, a perspective that has enabled me to play a vital role in ensuring that all involved in the PACE trial maintain absolute neutrality to all trial treatments in presentation, documentation and assessment*".

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ME STORY

It seems psychiatrists and insurance companies hold a very firm grip of the Department of Health's approach to ME proving, perhaps, that ME treatment in Britain is dictated more by financial considerations rather than by medical or ethical ones. It is a shame that Britain must lag behind the rest of the international community, leaving young, talented people on incapacity benefit, when they could successfully be treated with anti-virals and immune modulators as in other countries. While psychiatrists protect their academic careers rather than their patients, there will be more victims of ME like Sophia Mirza.

Just how many psychiatrists want to do a squealy u-turn mid-career, hold up their hands, say 'we were wrong' and thereby relinquish research funding for psychiatry?

None.

They'd rather stay in denial and hold onto their academic careers by their fingernails at the cost of their patient's health. Just how many insurance companies want to pay out to ME patients when they can suggest the illness can be treated with mind over matter approaches that seem to cost the NHS very little? This is, of course, false economy: if ME patients were medically treated it would in fact save the government in costly CBT programmes, incapacity benefit and DLA. If ME patients were treated properly as in other countries like Canada, the insurance companies wouldn't shirk paying up because there wouldn't be the same volume of applications for medical retirement. This piece of commonsense evades the psychiatrists with a stake in receiving research funding. Well, I suppose it would.

- Sarah(UK person with ME)

The PACE TRIALS *(continued)*

Johnson's Report on "CFS" research rang alarm bells within the ME/CFS community, since it openly stated that he, personally, had a "vital" role to play in ensuring what ought to have been taken for granted in any MRC trial, namely the "absolute neutrality" of the PACE trial.

Upon seeing this on the MRC BSU website, an ME/CFS sufferer wrote first to the MRC Biostatistics Unit and then to Dr Johnson himself, requesting the names and details of all the charities, patient groups, journalists, Members of Parliament and "others" who have little time for research investigations, together with references for all the vitriolic articles and websites mentioned on the MRC BSU website.
There was no acknowledgment from either the MRC BSU or from Dr Johnson; however just after the letters had been sent to the MRC, it was observed that much of Dr Johnson's Report had been removed from the MRC BSU website, indicating that this was a matter of some importance to the MRC.
In statistical terms, the deletions from Dr Johnson's Report amounted to a substantial 42% of the entire Report.
Almost a full month later, a letter dated 10th October 2006 was received from Dr Anthony Peatfield, which said: "You
refer to some text that was recently published on the website of the MRC Biostatistics Unit. The comments to which you refer were drawn from a progress report produced by an individual member of staff. The comments have now been removed from the website. I would like to take this opportunity to apologise, on behalf of the MRC, for any offence these comments may have caused either to yourself or any other individual. While the comments were ill-judged, it was not the intention of the individual who wrote them, nor the Unit in publishing them, to cause offence".

Curiously, Dr Peatfield further advised that should anyone else contact the MRC about this same matter: "we shall reply to any further requests such as your own as indicated in the third paragraph, above", meaning that he would simply offer an 'apology' regardless of what information or clarification was being requested.
Peatfield's reply implied that those damaging comments were not made by anyone of significance at the MRC, when in fact they had been written by the Deputy Director of the MRC Biostatistics Unit who was intrinsically involved with the actual design of the PACE trial.

Out of ten Reports that constituted the Quinquennial Review, the only individual report from which sections were removed, including the Abstract, is that of Dr Johnson.
he Abstract could not, however, be removed from the Review Index, where all ten Abstracts by different individuals are located, with links to their full documents. In the case of Dr Johnson's "re-edited" document (see below), the link to the Abstract no longer works, but the link works for all the other Abstracts. Was this a ploy by the MRC to conceal Johnson's Abstract, with its references to his close association with the Institute of Psychiatry (see below)?

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ME Patient Carer's Story

Birgitte is put into the nursing home in August 2004. The head nurse receives a treatment manual for seriously sick ME patients (written by the Norwegian ME organization) and promises to follow this. At this point in time Birgitte was able to sit in a wheel chair, could use the toilet and could move her arms and legs.

However, she is put under conditions of extreme stress in the nursing home. Due to a total lack of knowledge and competence of this illness the nurses and the nursing home doctor still think she has a psychiatric illness. The treatment manual from the Norwegian ME organisation is, therefore, not being used and the patient is getting more and more ill.

The leaders of the nursing home say it is the patient's own fault and that she is manipulating the situation. The patient says she cannot tolerate noise and light (something very common for ME sufferers). She has to fight, explain, manage, and several nurses are unfriendly and rough. – Leiv (carer from Norway)

ME Story

I have applied for DLA (probably one of the hardest things I have ever done) and have been rejected, despite being mostly housebound. Do these people think that I want to be like this? That to give up my future is an easier option? Or do they think that behind their backs I am secretly earning money and living it up? Why do they not think that it would be a good idea to ask for a report from a GP when assessing my claim?

How do they think a visiting doctor can assess my capabilities by sitting in my lounge with me for an hour? So many questions and so few answers.

- Alice

The PACE TRIALS *(continued)*

Amongst large amounts of text removed from Dr Johnson's Report were details of exactly how influential Dr Johnson has been within the MRC and with the Institute of Psychiatry, particularly in terms of securing MRC funding, along with other details of his close connections to key individuals involved in the PACE trial. The following extracts are taken from the Abstract, which was removed in its entirety from the body of Dr Johnson's Report:

"Abstract
"I have initiated, developed, and collaborated in both clinical trials and epidemiological studies in four challenging medical specialties working with a large number of collaborators geographically dispersed throughout UK, Europe, and beyond. These have resulted in major advances in the understanding of the efficacy of cognitive therapy.
"Over many years my programme has contributed to the successful completion of the three largest clinical trials, all of major international importance. My programme will be exploited in the future in further collaborations with the pharmaceutical industry.
"I have enabled a successful collaboration linking the research programmes of this Unit with the MRC Clinical Trials Unit (MRC CTU) in London, that has resulted in the establishment of a new Clinical Trials Unit dedicated to mental health and neurological sciences at the Institute of Psychiatry in London. The linkage has enabled my expertise in clinical trials to be extended to chronic fatigue syndrome and the setting-up of a major MRC study to evaluate the efficacy of four different interventions.
"I have advised many clinical trialists on the setting-up of organisational structures including Steering and Data Monitoring Committees, and Management Groups".

Some of Dr Johnson's credentials, however, remained on the MRC BSU website: "I present my eighth and final Unit review report since joining MRC Neuropsychiatric Research Unit in 1968; a period exceeding 37 years during which I have been very privileged to engage fully in the research programmes of MRC, be a co-editor for 18 years of the first major journal in medical statistics (Statistics in Medicine), found an international society (Society of Pharmaceutical Medicine), draft the Constitution for another (International Society for Clinical Biostatistics), and contribute to UK Government, European, and International working parties and committees.
"In view of my retirement in September 2008 I describe only my research programme over the past five years without reference to the future". The following text was removed: "but note that none of my projects will terminate in the near future, for they will be continued and expanded by others, many of whom I have trained for that purpose. My role within MRC changed radically in 2001, resulting in my switching from independent band 2 to core scientist. My expertise in clinical trials was needed to expand the activities of the Department Without Portfolio into areas such as mental health (and) chronic fatigue, currently the focus of government health policy". From the above, it can be seen that Dr Johnson is an influential figure in the MRC BSU and, as Deputy Director, his in-house review was a substantial document.

Johnson's Report was an important official communication from one professional to others. Coming from such a senior figure within the MRC, and considering his level of involvement with the PACE trials, Johnson's adverse comments about CFS would have carried considerable authority and influence.
Disturbingly, it seems that in his material which was removed from the MRC website, Johnson revealed that he had used data (which he described as a *"perspective"* that he had been able to obtain through *"familial involvement with one of the charities"*) to assist in the design of the PACE trial. If this is so, what is he implying? The PACE trial is about challenging ME/CFS sufferers' beliefs: is Johnson somehow using the *"perspective"* he has obtained through *"familial involvement with one of the charities"* to design a trial whose aim is to promote a management regime that has already caused so much harm to members of that charity?
Most disturbingly of all, as mentioned above, Johnson stated that he was playing a *"vital"* role in maintaining *"absolute neutrality"* by *"all involved in the PACE trial"*. This clearly indicates that Johnson believed that without his own *"vital"* role, "*absolute neutrality*" would <u>not</u> be achieved.
The word "vital" means "essential", so was Johnson effectively conceding that he knew the PACE trial was fundamentally biased but that he – as an individual -- was dealing with the people involved in the trial who are known to be intent on dismissing "ME" and on promoting their own beliefs about the use of CBT/GET for those with "CFS"? Why is it only his own *"vital"* role that will ensure the "*neutrality"* of the PACE trial?
Having taken seven months to reply to a letter that had been sent to him personally, on 7th November 2006 Johnson attempted to exonerate himself, stating that the views he had expressed were not intended to represent the views of the MRC and that they had been *"the initial version of my progress report"*, and writing: "*I regret the words that I used"*.
Having earlier informed colleagues in his Report that: "*CFS is currently the most controversial area of medical research and characterised by vitriolic articles and websites maintained by the more extreme charities supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations"*, Dr Johnson stated in his letter: *"I did not have specific individuals or groups in mind and consequently, I cannot provide you with the names and details of the charities, patient groups, journalists, Members of Parliament, and others, who I believed had little time for research. I do not have, and I have never*

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The PACE TRIALS *(continued)*

thought about, attempting to compile such a list. Similarly, I do not possess, and have never possessed, a list of vitriolic articles and websites, so I cannot provide these".
Also in his letter of 7th November 2006, Dr Johnson simultaneously did "*not know when CFS/ME became controversial or why" but nevertheless proffered his speculation that "controversy sometimes arises when the evidence base is slender as many views and ideas can be put forward without any means of resolving them. The publication of a large number of research papers in the medical literature, some of poor quality or based on small samples only leads to further confusion*".

This is an interesting piece of conjecture, given that the post of Statistician Clinical Trials Unit (CTU) Division of Psychological Medicine Ref No: 06/A09 is described as the "Johnson_Wessely_Job" (07/07/2006) at the The Institute of Psychiatry where: "The team works under the direction of Professor Simon Wessely, the Unit Director. The team is supported by the regular input of a Unit Management Group from within the Institute of Psychiatry. The statisticians within the Unit also have regular supervision meetings with Dr Tony Johnson from the MRC Clinical Trials Unit. The post holder will be directly responsible to the CTU Manager (Caroline Murphy), supervised by the CTU Statistician (Rebecca Walwyn) and will be under the overall direction of the Head of Department, Professor Simon Wessely".

Against the evidence that mixing study populations is inadvisable, the PACE trial is mixing at least three different groups of patients.

As no satisfactory response had been received to a perfectly valid request for further clarification (i.e. the names of individuals involved with the PACE trial who, Johnson believed, would, without his own *"vital"* intervention, be unable to maintain the requisite "*neutrality*" which he was able to ensure through his "*familial involvement*" with one of the charities), the ME/CFS sufferer wrote again with the same request. Over five months after that request, Dr Johnson sent a further letter dated 2nd April 2007 in which he wrote: "*The issues that you raise here are complicated. First it is important to realise that there is a substantial range of opinion among clinicians about the relative merits of some treatments".*

Johnson's reply was a five-page masterpiece of confabulation but still did not answer the question asked. Instead, amongst other diversions, he wrote at length about SSMC (standardised specialist medical care) for those with ME/CFS as part of the PACE trial, causing another ME/CFS sufferer to ask: "What is the accepted definition of standardised specialist medical care (SSMC) for those with ME/CFS? In order to achieve an accurate assessment of the PACE trial outcomes, there must be a definition of standardised

'in designing the trial we had to guess the outcomes and our guesses (were) mostly based on published studies"..

specialist medical care, so what is this definition and where is it accessible? (It is a matter of record that there isn't one). Tony Johnson accepts that an early design for the current PACE trial did not include an SSMC group but he seems to have expediently overlooked the reality that there is **no** SSMC for those with ME/CFS, as Catherine Rye made plain in 1996 about the Sharpe et al paper of the Oxford trial of CBT/GET: '*I am a sufferer and participated in the Oxford trial. There are facts about the trial that throw into doubt how successful it is. It is stated that patients in the control group received standard medical care. I was in that group but I received nothing' "*
(Independent, 30th March 1996, page 16).

The same ME/CFS sufferer also asked:
"What is Tony Johnson's statistical rationale for deliberately mixing patient cohorts in the PACE trial? Against the evidence that mixing study populations is inadvisable, the PACE trial is mixing at least three different groups of patients.

"Fibromyalgia patients are included in the Principal Investigator's own selection of those with "CFS/ME" for the MRC PACE trial, as well as those with other states of chronic fatigue, including psychiatric states, yet all three categories are taxonomically different and are classified differently by the WHO.
Fibromyalgia is classified at ICD-10 M79.0; ME/CFS is classified at ICD-10 G93.3 and other fatigue states are classified at ICD-10 F48.0.

"In a reply dated 15th April 2005 to Neil Brown, Simon Burden of the MRC wrote: 'When researchers put together a proposal they are required to define the population they are studying'. Why does this basic requirement not apply to the PACE trial and how will the outright abandonment of this MRC principle affect Johnson's statistical analysis of the PACE trial?
"How does this accord with what Simon Burden asserted was the MRC's requirement for 'the high scientific standard required for funding'?

"Johnson acknowledges in his reply (on page 4) that: 'It is important to realise that there is a substantial range of opinion among clinicians about the relative merits of some treatments'. Indeed, this is so. What, then, is his statistical explanation for the MRC's undue reliance on the ill-founded beliefs of Wessely School psychiatrists, given the large body of undisputed published evidence that their beliefs about the nature of ME/CFS are simply wrong? Johnson states in his reply: 'in designing the trial we had to guess the outcomes and our guesses (were) mostly based on published studies". For what statistical

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The PACE TRIALS *(continued)*

reasons did the MRC rely on Wessely School studies, when there is abundant published criticism of those very studies and their flawed methodology in the literature?

"This published criticism is readily accessible to all and sundry. The work of the Wessely School on "CFS/ME" has been stringently criticised in the international literature for flawed methodology; particularly for use of a heterogeneous patient population (studies using mixed populations are not useful unless researchers disaggregate their findings); for selective manipulation of others' work, claiming it supports their own findings when such is not the case; for their focus on the single symptom of "fatigue" whilst ignoring other significant signs and symptoms associated with the cardiovascular, respiratory, neurological and immunological systems; for generating conclusions before generating the data to support such conclusions; for advising Government bodies that the reported biomedical abnormalities 'should not deflect the clinician away from the biopsychosocial approach and should not focus attention towards a search for an 'organic' cause', and for their recommendation that no advanced tests should be carried out on "CFS/ME" patients when it is those very tests that reveal the unequivocally organic nature of the disorder.

We believe that the money being allocated to the PACE trial is a scandalous way of prioritising the very limited research funding that the MRC have decided to make available for ME/CFS, especially when no money whatsoever has so far been awarded for research into the underlying physical cause of the illness. We therefore believe that work on this trial should be brought to an immediate close and that the money should be held in reserve for research that is likely to be of real benefit to people with ME/CFS.

- ME Association

"Throughout his reply, Johnson uses the terms: 'In designing a clinical trial (of CBT/GET) we have to estimate the number of patients'; 'Estimation essentially requires a guess at what the results will be'; 'In guessing what the results may be…'; 'The assumptions we make…'; 'Broadly, we assumed that around 60% of patients in the CBT group would have a 'positive outcome' at one year follow-up….'; 'We speculated that….', ***so there is now written confirmation from the MRC Biostatistics Unit that the whole PACE trial is based on guessing, speculation and assumption. Would Tony Johnson explain how this accords with the MRC's supposed requirement for high standards?".***

It was suggested that Johnson be asked to explain how statistics had suddenly become a matter of guesswork, speculation and assumption.

In his Report, Johnson had referred disparagingly to *"websites maintained by the more extreme charities"* but did not mention that it was two of the UK's major charities (The ME Association and the 25% ME Group for the Severely Affected) that were calling for the PACE trial to be halted.

The ME Association has been adamant that the PACE and FINE trials should be halted and on 22nd May 2004 posted the following on its website (which was printed in its magazine "ME Essential" in July 2004):
"The MEA calls for an immediate stop to the PACE and FINE trials

"A number of criticisms concerning the overall value of the PACE trial and the way in which it is going to be carried out have been made by the ME/CFS community. The ME Association believes that many of these criticisms are valid. We believe that the money being allocated to the PACE trial is a scandalous way of prioritising the very limited research funding that the MRC have decided to make available for ME/CFS, especially when no money whatsoever has so far been awarded for research into the underlying physical cause of the illness. We therefore believe that work on this trial should be brought to an immediate close and that the money should be held in reserve for research that is likely to be of real benefit to people with ME/CFS. We share the concerns being expressed relating to informed consent, particularly in relation to patients who are selected to take part in graded exercise therapy. The Chief Medical Officer's Report (section 4.4.2.1) noted that 50% of ME/CFS patients reported that graded exercise therapy had made their condition worse, and we therefore believe that anyone volunteering to undertake graded exercise therapy must be made aware of these findings".
It is notable in this respect that Lord (David) Sainsbury of Turville, who at the time was responsible for the MRC, stated in the House of Lords: "*Because the trial participants will have provided informed consent, they will receive no compensation if they become more ill, whether or not as a result of the particular treatment"* (Hansard [Lords]: 18th November 2004: 4830).

The ME Association notice additionally called for all further work on the FINE trial to be halted, saying the MEA *"is not convinced by the evidence so far put forward in support of this approach".*

From this whole episode concerning Dr Johnson's Report, the ME/CFS community was left in no doubt about the bitter contempt for sufferers, some charities, and those MPs who support them that exists at the MRC, or that the seam of Wessely School dismissal and denigration does indeed run deep.

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The PACE TRIALS *(continued)*

Representations to the MRC setting out concerns about the PACE trials

It is known that enormous public and professional concern was expressed to the MRC about the PACE and FINE trials. Some of the written representations were sent by Recorded Delivery. Few were acknowledged and all seem to have been disregarded.

There can be no credible doubt that the Oxford criteria exclude those with ME as distinct from the Wessely School definition of "CFS" and this was confirmed in 1991 by psychiatrist Anthony David (colleague and co-author with Wessely) who described the Oxford criteria shortly after they were published:

"British investigators have put forward an alternative, less strict, operational definition which is essentially chronic fatigue in the absence of neurological signs (but) with psychiatric symptoms as common associated features"

Those legitimately expressed concerns include the following:

Concern about the huge waste of money at UK tax-payers' expense

Originally the MRC PACE and FINE trials of CBT/GET were said to be costing £2.6 million, but according to Michael Sharpe, one of the Principal Investigators, the current figure is £4 million. From the figures awarded by the MRC for "fatigue" research on the National Research Register, the amount that has gone to biomedical research into ME/CFS is virtually non-existent. In March 2005, the MRC confirmed that since 2002, it had funded two further studies into "CFS/ME" (one for Professor Creed [see below] on psychiatric aspects and one on "Chronic fatigue (*sic*) and ethnicity"), and that it had received 12 applications for funding related to CFS/ME that were not granted. Of the applications that the MRC rejected, seven were under the heading "Pathophysiology of CFS" and included studies regarding genetics / biomarkers, immunology and neuroimaging; three were regarding epidemiology, as well as studies in primary care and clinical and laboratory characterisation of ME/CFS. As mentioned above, the ME Association pointed out that the results of these psychiatric trials may not add any significant information to what patients and their doctors already know, so on what ethical grounds does the MRC justify spending such a vast amount of money to the exclusion of studies with real potential to benefit ME/CFS sufferers?

As William Bayliss stated on an internet group on 2nd Nov 2004: "*The MRC's PACE trial has been very cleverly designed to exclude most true ME sufferers and include sufferers of mental illness. As such, the trial is a deceitful national scandal and a gross abuse of taxpayers' money*"

Concern about the design of the study

This is an area of extreme unrest, because the design of the study may well be relevant to the aims of the study, and these are known to be the nationwide promotion of CBT and GET as the management regimes of choice. It is apparent to many people that by using the all-encompassing Oxford criteria, the trial objectives have been set so as to achieve this pre-determined agenda and to meet the requirements of political and commercial paymasters.

The Oxford criteria expressly include people with psychiatric disorders in which "fatigue" is a prominent symptom (thereby, as noted above, potentially catching at least 33 other disorders that fit the Oxford criteria), but expressly exclude people with neurological disorders; indeed, the Oxford criteria claim to use people with neuromuscular disorders as controls, so by any logical reasoning, ME/CFS (an internationally classified neurological disorder) would be excluded.

There can be no credible doubt that the Oxford criteria exclude those with ME as distinct from the Wessely School definition of "CFS" and this was confirmed in 1991 by psychiatrist Anthony David (colleague and co-author with Wessely) who described the Oxford criteria shortly after they were published: **"***British investigators have put forward an alternative, less strict, operational definition which is essentially chronic fatigue in the absence of neurological signs (but) with psychiatric symptoms as common associated features***"** (Postviral syndrome and psychiatry. AS David. British Medical Bulletin 1991:47:4:966-988). Given such clarification, how can it be ethical for the MRC to claim that the PACE trials will include those with Ramsay-defined ME?

The MRC, however, insists that people with "CFS/ME" will be included in the trials.

It is known that enormous public and professional concern was expressed to the MRC about the PACE and FINE trials. Some of the written representations were sent by Recorded Delivery. Few were acknowledged and all seem to have been disregarded.

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The PACE TRIALS *(continued)*

On 16th June 2005, Dr Sarah Perkins, Programme Manager for the MRC Mental Health Board, wrote: ***"The main entry criteria for the PACE trial are the Oxford criteria. Their use will ensure that the results of the trials will be applicable to the widest range of people who receive a diagnosis of CFS/ME.*** *The exclusion criterion of 'proven organic brain disease' will be used to exclude neurological conditions of established anatomical pathology. It will not be used to exclude patients with a diagnosis of ME".*

Concern that the MRC classifies "CFS/ME" as a mental disorder

Given that the psychiatric lobby demands 100% proof of an organic pathoaetiology for ME/CFS before they will "allow" it to be accepted as a "real" organic disease as distinct from a mental disorder, why does the MRC not require a similar standard of proof from these psychiatrists that ME/CFS is a mental disorder, as they assert?

It cannot be emphasised enough that what Wessely School psychiatrists choose to call "CFS/ME" is not Ramsay-defined ME and should not therefore be included as though it were the same disorder. To do so is both a failure of a duty of care towards patients and a corruption of the scientific process.
Without doubt, the false beliefs about ME/CFS demonstrated by the MRC are known to be carefully-constructed "policy-based evidence", as can be seen from the 32 page Report from a Working Group of the Medical Research Council's own Neurosciences and Mental Health Board (NMHB) Strategy and Portfolio Overview Group (SPOG) of January 2005. The aim of that Report was to consider the balance of the current MRC research portfolio, and it confirms what the UK ME/CFS community has long recognised – the MRC has considered "CFS/ME" as a mental disorder and will continue to do so: at paragraph 6.2 the Report is unequivocal: "*Mental health research in this instance covers CFS/ME".*

Other points of note in the SPOG Report include:

- the MRC research agenda should be optimally aligned with the injection of Government funding
- mental health represents a vast potential market for pharmaceutical companies
- under "Mapping the UK research portfolio in mental health", the Report states: "*The analysis will capture all peer-reviewed grants that are live at a given date, which will be classified in terms of a list of mental health conditions based upon ICD-10 classifications*" (could this explain the determination of Wessely School psychiatrists formally to re-classify ME/CFS as a "mental" disorder?).

In a BBC Radio Five Live broadcast transmitted on 22nd February 2005, the Chief Executive of the MRC, Professor Colin Blakemore, exhibited a serious lack of knowledge about ME/CFS, claiming that it does not matter whether "CFS/ME" is an organic or psychological condition. Does he really see no need to search vigorously for the cause(s) of ME/CFS? If not, why does such an approach relate only to ME/CFS and not to all illnesses whose cause is as yet unknown, including cancer, multiple sclerosis and lupus?

That the MRC specifically and deliberately classifies "CFS/ME" under "mental health" research is at diametric variance with the Health Minister's written confirmation given one year prior to the publication of this MRC SPOG Report, which demonstrates the determined defiance of medical science by the psychiatric lobby.

Concern about mixing study cohorts

The WHO is resolute that taxonomic principles must be observed, but the at the behest of the psychiatric lobby, the MRC is sanctioning the breaching of these taxonomic principles in the "CFS/ME" trials by deliberately mixing study cohorts from the outset. Is this not contrary to the high standards that the MRC claims it requires for all the studies it agrees to fund?

Given that the psychiatric lobby demands 100% proof of an organic pathoaetiology for ME/CFS before they will "allow" it to be accepted as a "real" organic disease as distinct from a mental disorder, why does the MRC not require a similar standard of proof from these psychiatrists that ME/CFS is a mental disorder, as they assert?

The PACE and FINE trials are flawed from the outset by this deliberate mixing of study cohorts and by excluding those with true ME yet claiming that the results will refer to those with ME.

This is important because **"the management of the two conditions is different. Patients with ME/CFS should be advised not to increase their activities gradually until they feel 80% of normal, whereas patients with fibromyalgia may benefit from a regime of increasing activity"** (D. Ho-Yen; BMJ 1994:309:1515).

By lumping together as many states of "chronic fatigue" as possible into what they insist is one "somatoform" syndrome, the psychiatric lobby ignores the known and established differences between fibromyalgia (FM) and ME/CFS, and many in both the FM and ME/CFS communities believe they have a right to know why patients suffering from two different disorders are to be amalgamated in the MRC trials that claim to be studying "CFS".

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The PACE TRIALS *(continued)*

In his letter of 15th April 2005 to Neil Brown, Simon Burden of the MRC (referred to above) stated that researchers applying to the MRC for funding are *"required to define how they will find participants in the study"*. In the case of "CFS/ME" -- which is to include fibromyalgia -- the methods include financial inducements (which in other areas may be described as "bribery"). If clinicians have to be tempted by financial rewards to refer patients to these MRC trials, then something is very wrong, but such financial inducements are indeed being offered to GPs to identify and refer patients to the new "CFS" Centres and into the PACE and FINE trials. This was confirmed in July 2004 by Minister of State Dr Stephen Ladyman MP at the All Party Parliamentary Group on Fibromyalgia (now disbanded).
Further, in the case of the MRC FINE trials, whilst in the Patient Information Sheet patients are assured that "*Your GP is not being paid for his or her participation in this trial*", there is a different message for the GP because in the GP invitation letter it states: "*Practices will be recompensed by the Department of Health for time spent in identifying and recruiting patients (£26.27 per referral*)". Does such a discrepancy accord with the MRC's own definition of "high standards"? (On the subject of high standards, what can be the explanation for the MRC-funded FINE trial literature using the term "*myalgic encephalitis*", which is not the same as "myalgic encephalomyelitis"? Is accuracy no longer considered a component of "high standards"?)

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It is a matter of record that Whiting et al expressly excluded FM studies from the Systematic Review of the literature that was commissioned by the Policy Research Programme of the Department of Health and carried out by the Centre for Reviews and Dissemination at the University of York. The systematic review is unequivocal: **"Studies including patients with fibromyalgia were not selected for the review"** (JAMA 2001:286:1360-1368). Why, therefore, on whose authority and on what evidence, was it decided to include patients with FM in the MRC trials of CBT in a "CFS/ME" population?

Of foremost significance is the fact that fibromyalgia is classified as a distinct entity in ICD-10 at section M79.0 under Soft Tissue Disorders and it is not permitted for the same condition to be classified to more than one rubric, since ICD categories are mutually exclusive.

The literature itself is quite clear about this distinction, stating that up to 70% of those with ME/CFS have *concurrent* FM, and those who have both FM *and* ME/CFS have worse physical functioning than those who have ME/CFS alone.
Some illustrations from the literature make these distinctions clear:

1991: in spite of some overlap, FM and ME/CFS do not represent the same syndrome. (Primary fibromyalgia and the chronic fatigue syndrome. AJ Wysenbeek et al *Rheumatology Int 1991:10:227-229*)
1996: "*fibromyalgia appears to represent an additional burden of suffering amongst those with (ME)CFS*" (Fibromyalgia and Chronic Fatigue Syndrome – similarities and differences. Dedra Buchwald and Deborah Garrity. *Rheum Dis Clin N Am 1996:22:2:219-243*)

1997: levels of somatomedin C are lower in FM patients but higher in ME/CFS patients (Somatomedin C (insulin-like growth factor) levels in patients with CFS. AL Bennett, AL Komaroff et al. *J psychiat Res 1997:31:1:91-96*)

1998: "*recent studies suggest that (co-existent FM and (ME)CFS) may bode much more poorly for clinical outcome than CFS alone. In contrast to (significantly) elevated CBG (cortisol binding globulin) levels in patients with CFS, no differences were observed in FM patients. Differences in secretion of AVP may explain the divergence of HPA axis function in FM and (ME)CFS*" (Evidence for and Pathophysiologic Implications of HPA Axis Dysregulation in FM and CFS. Mark A Demitrack and Leslie J Crofford. *Ann New York Acad Sci 1998:840:684-697*)

1998: there is no evidence for elevated Substance P in patients with ME/CFS, whereas levels are elevated in patients with FM (CFS differs from FM. No evidence for altered Substance P in cerebrospinal fluid of patients with CFS. Evengaard B et al *Pain 1998:78:2:153-155*)

2001: patients with FM are **NOT** acetylcholine sensitive (Investigation of cutaneous microvascular activity and flare response in patients with fibromyalgia. AW Al-Allaf, F Khan, J Moreland, JJF Belch. *Rheumatology 2001:40:1097-1101*)
2004: patients with ME/CFS **ARE** acetylcholine sensitive (Acetlycholine mediated vasodilatation in the microcirculation of patients with chronic fatigue syndrome. VA Spence, F Khan, G Kennedy, NC Abbot, JJF Belch *Prostaglandins, Leukotrienes and Essential Fatty Acids 2004:70:403-407*)

2003: endothelin-1 is **RAISED** in fibromyalgia (Increased plasma endothelin-1 in fibromyalgia syndrome. Pache M, Ochs J et al *Rheumatology 2003:42:493-494*)

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The PACE TRIALS *(continued)*

2004: endothelin-1 is **NORMAL** in ME/CFS (Plasma endothelin-1 levels in chronic fatigue syndrome. Kennedy G, Spence V, Khan F, Belch JJF *Rheumatology 2004:43:252-253*)

More recent (2007) evidence from Spain presented at the ME Research UK (MERUK) International Research Conference on 25th May 2007 at Edinburgh demonstrated that FM and ME/CFS are two different diseases with two different genetic profiles and that there are very clear distinctions, with a 95.4% specificity. Many polymorphisms in the genes were different (Genetic Profiles in Severe Forms of Fibromyalgia and Chronic Fatigue Syndrome Dr Estibaliz Olano: this presentation is available on DVD obtainable from MERUK, telephone number 01738-451234).

Consultant rheumatologists who have sufficient experience with both syndromes have observed clinically that in FM, the muscle pain is helped by gentle stretching and exercise, whereas in ME/CFS, exercise makes muscle pain worse.

Importantly, on 3rd June 1998, Baroness Hollis from the then Department of Social Security sent a letter to Lindsay Hoyle MP (reference POS(4) 3817/88) which says: "*The Government recognises that fibromyalgia syndrome (FMS) is a condition which can cause a wide variety of disabilities from mild to severe. In some cases it can be a very debilitating and distressing condition. People with FMS who need help with personal care, or with getting around because they have difficulty in walking, can claim Disability Living Allowance to help with meeting related expenditure*". From this letter, it is clear that Government already recognises fibromyalgia as a distinct entity.

Further, in the Chief Medical Officer's UPDATE of August 2003 (a paper communication from the CMO sent to all doctors in England) entitled "Improving Services for Patients" there is an item entitled "*Fibromyalgia – A Medical Entity*". This means that the CMO considers fibromyalgia to be a separate, stand-alone medical entity (and the fact that it is designated a "medical" disorder means that it is not considered to be "psychiatric" disorder).

Is the MRC still content that the PACE trial proposal states: **"Those subjects who also meet the criteria for "fibromyalgia" will be included"**, given that FM is classified by the WHO as a quite separate disorder from ME/CFS, with discrete biomedical and genetic profiles that are entirely distinct from those found in ME/CFS?

How can the deliberate inclusion of patients with fibromyalgia in trials that purport to be studying "CFS" not result in skewed and meaningless conclusions when the patients being entered in the PACE trials are, from the outset, not clearly defined?

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Concern about Ethical Standards in the PACE Trial

Mrs Connie Nelson wrote to the MRC asking four pertinent questions about the PACE trial: (a) who will decide if the patient has been harmed? (b) in the event of such harm, what will be the speciality of the clinicians who will visit the patient at home? (c) what will be considered a "serious adverse event" within the PACE study? and (d) what would be considered "appropriate help" if the PACE study exacerbates a patient's condition?

On 26th July 2005, Dr Sarah Perkins replied: "*The investigators responsible for this trial have established a robust set of procedures regarding the management of any adverse events*". Included in adverse events was listed "*any episode of self-harm*". Dr Perkins explained that: "*As part of the peer-review process, a comprehensive assessment of any safety and ethical issues was made before the award of the trial grant*" and she said the PACE trial was "*proceeding under good clinical practice guidelines, which includes independent supervision. This comprises an independent Data Monitoring and Ethics Committee*".

On 25th August 2005, Mrs Nelson again wrote to the MRC asking for the composition of the Data Monitoring and Ethics Committee. She pointed out that as this was a publicly funded trial, she would like to know who was on that Committee; she also asked for a copy of the "comprehensive assessment" of safety and ethical issues undertaken as part of the peer-review before the award of the trial grant, saying that -- given the evidence that exercise makes ME/CFS patients worse -- this may help clarify why the trial was ever funded.
Mrs Nelson further asked whether an ME relapse would be recognised and accepted as "clinical change", given that many people feared that the assessor(s) may not believe in ME or in the reality of a relapse. Her final question asked if the published papers of the PACE trial would include – as is normal practice for contentious treatments – details of all drop-outs and adverse events in each trial group.
On 21st September 2005, Dr Perkins provided the names of PACE Trial Steering Committee Members and the membership of the Data Monitoring and Ethics Committee. Names of particular concern to the ME/CFS community included Professor Janet Darbyshire (MRC Clinical Trials Unit); Professor Peter White; Professor Michael Sharpe and Professor Tudie Chalder. The Observers

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included two names of particular concern: Professor Mansel Aylward and Mr Chris Clark of the charity Action for ME. The three names on the Data Monitoring and Ethics Committee were Professor P Dieppe, Dr C Feinmann and Professor A Fletcher. Dr Perkins then stated: "*Although we are committed to being as open as possible, we have decided not to release peer review comments".*

Concern about misleading information supplied by the MRC

In December 2005 a Member of Parliament informed a constituent that: "*It is encouraging to see that epidemiological research is being conducted which may yield improved understanding of (ME/CFS)"*, when the reality was that the MRC had granted Professor Francis Creed funding for yet more psychosocial research, Professor Creed being well-known for his Wessely School views about "CFS/ME" (see http://www.meactionuk.org.uk/Proof_Positive.htm). Creed is Professor of Psychological Medicine at the School of Psychiatry and Behavioural Sciences at Manchester; one of his main research areas is somatisation disorders (which the Wessely School insist includes "CFS/ME"). He is Editor of the Journal of Psychosomatic Research and has failed to respond to letters written to him in his editorial capacity asking that the Journal present a more accurate and balanced view of ME/CFS. The Member of Parliament had thus been misled. Many MPs erroneously believe that the Government has done a good job in funding the well-publicised "CFS Centres" and are unaware that those Centres will deliver only psychotherapy regimes that have already been shown to make some ME/CFS patients worse.

It seems that the Trial Investigators will have the option to "select out" patients whom they believe will not respond in the desired way to the programme or who are too unwell to remain in the trials.

Concern about post-funding alterations to the study Identifier and Protocol

Following the outcry by the ME/CFS community about the use of the Oxford criteria as entry into the PACE trial, the MRC announced that a "*secondary analysis"* would be performed using the *"London criteria"*.

Was this approved by the Data Monitoring and Ethics Committee, given the legitimate concern about the so-called "London" criteria that was submitted to the MRC?

The "London" criteria have never been published and are not available as a reference for identification. They were mentioned in the National Task Force Report in 1994 as being one of nine different proposed definitions and descriptions.
The "London" criteria have never been used in research (before criteria can be used in research, they need to be submitted for peer review and published in an accessible form).
The "London" criteria have not even been consistently defined – there are different versions of them and a definitive version has not been identified.
The authors of the "London" criteria remain to be established as there are divergent claims about who the authors might be.

The "London" criteria have never been accepted into common usage, nor have they ever been validated or operationalised.
On what scientific basis can the MRC approve any "*secondary analysis*" using non-existent criteria? The "London" criteria have no justifiable or validated legitimacy that would in any way provide acceptable criteria for use by the MRC.

Moreover, no amount of "*secondary analysis"* using any additional criteria can select patients with ME/CFS who were by definition excluded from the MRC trials in the first place by virtue of neurological disorders being expressly excluded from the Oxford entry criteria (which basically catch patients with chronic "fatigue").

It should be noted that the so-called "London" criteria are not the same as the Dowsett and Ramsay clinical criteria for investigation of ME, which are exceedingly useful (Postgrad Med J 1990:66:526-530).

Other post-funding amendments to the PACE trial are more worrying.

It seems that the Trial Investigators will have the option to "select out" patients whom they believe will not respond in the desired way to the programme or who are too unwell to remain in the trials.

The list of what constitutes an "adverse reaction" has been shortened.

Regarding outcome measures, the only objective measure of improvement seems to have been dropped, in that it seems the trialists no longer propose to use an actometer (an objective measure of activity) as an outcome measure of improvement.
The only symptom actually being measured is subjective "fatigue", which is not an objective scientific measurement and cannot therefore provide a robust clinical evidence base.
"Recovery" has been re-defined. It will now be defined by participants meeting all four of the following: (i) a Chalder Fatigue Questionnaire score of 3 or less; (ii) an SF-36 physical function score of 85 or above, rather than the working age norm of 90 (the SF-36 measures social and

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role functioning); (iii) a Clinical Global Impression (CGI) score of 1 (the self-rated CGI has a score range of 1 – 7 and provides only a subjective interpretation), and (iv) the participant no longer meeting the trial entry criteria. To most people, "recovery" means being able to return to full-time work and being able to be self-supporting. Did the MRC Data Monitoring and Ethical Committee approve such significant changes to the trial protocol after funding had been granted? If so, was this in collusion with one of the MRC trial sponsors (ie. the Department for Work and Pensions)?

As it seems there will now be no objective evidence from the MRC PACE trials of no activity improvement, will this particular sponsor of the trials continue to maintain that there is no physical disability in ME/CFS patients who are claiming benefit?

Of particular concern was the refusal of the MRC to heed the evidence that aerobic exercise (as in graded exercise that is part of the PACE trial) might be dangerous for some patients with ME/CFS and the fact that the Principal Investigators of the PACE trial were not screening for potentially life-threatening cardiac anomalies in trial participants.

Concern about the competing interests of the psychiatric lobby who are running the MRC trials

Concerns have been expressed that it is simply wrong for the psychiatrists who are carrying out these MRC trials to be paid for studying the regimes which they themselves formulated (Gen Hosp Psychiatry 1997:19:3:185-199), particularly in view of the proven evidence of their commercial interest in obtaining their desired outcome from these regimes.

Concern about the MRC's refusal to heed the existing evidence that CBT/GET does not work

As outlined above in the section on NICE, the proponents of the CBT/GET regime themselves are on record as stating that in relation to ME/CFS, it is not *"remotely curative"*, that relapses occur, that the very modest benefits do not last, and that *"many CFS patients, in specialised treatment centres and the wider world, do not benefit from these interventions"*.

Further, as noted above, the CRD Systematic Review of CBT/GET studies (the Wessely School "bible") points out that there is no objective evidence of improvement and that the subjective gains may be illusory (JAMA 2001:286:1360-1368).

As also mentioned above, the MRC's Chief Executive Officer, Professor Colin Blakemore, stated on 24th October 2003: "*Neither the PACE nor the FINE trials will provide a cure for CFS/ME but that is not their purpose. The trials are intended to assess a number of possible treatments to see if they are beneficial to those suffering from CFS/ME"*.

Given that this information is already known, the ME/CFS community pleaded with the MRC to halt the PACE and FINE trials and to use the money in a more constructive way. The MRC ignored these requests.

Concern about the persistent refusal to heed the evidence that graded exercise may be dangerous for people with ME/CFS

Substantial published evidence of the organic basis of Ramsay-defined ME/CFS (ICD-10 G93.3) was submitted to the MRC. There are over 4,000 such papers. It was all dismissed or ignored.

Of particular concern was the refusal of the MRC to heed the evidence that aerobic exercise (as in graded exercise that is part of the PACE trial) might be dangerous for some patients with ME/CFS and the fact that the Principal Investigators of the PACE trial were not screening for potentially life-threatening cardiac anomalies in trial participants.

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 documented in the literature since that time, for example, Wallis (1957); Leon-Sotomayer (1965) and Ramsay (1950s-1980s). 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 he 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/CFS held in Sydney, Professor Mina Behan from Glasgow (now 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].

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The PACE TRIALS *(continued)*

The difficulty with some of the earlier references is that the documented clinical observations may not have been scientifically evaluated and 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.

The Government, Big Pharma and the medical insurance industry all prefer to accept the Wessely School dogma that "CFS/ME" is *"medically unexplained chronic fatigue"* and is therefore a primary behavioural disorder. It is the case that the Government-funded "CFS" Centres will employ only the psychiatric interventions recommended by the Wessely School.

Because this is such a crucial issue, the cardiac anomalies that have been documented in ME/CFS are summarised here.

An update of the paper by Carol Sieverling was 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.
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 ME/CFS patient (sometimes referred to as Chronic Fatigue and Immune Dysfunction Syndrome or CFIDS in the US) is in heart failure.

The New Jersey team looked at many things in CFIDS patients: what they found was the "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 of blood 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 the 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

This important paper says that, without exception, every disabled ME/CFS patient (sometimes referred to as Chronic Fatigue and Immune Dysfunction Syndrome or CFIDS in the US) is in heart failure.

to keep the pulse going. This is critical to understanding what Cheney believes happens in CFIDS patients.
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.

To quote Cheney: **"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 always 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.

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 low a cardiac output. This compensation is what is going on in the CFIDS (ME/CFS) 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. 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.
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/CFS in a patient by noting this prioritisation.

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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 from a drop in Q than the liver, the gut, the muscles and the skin.

Certainly, Cheney's submission seems to tally with the experience of long-term ME/CFS sufferers about the order in which tissue perfusion is sacrificed.

The first to be affected 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 cannot go upstairs. If things get still worse, the patient begins to experience fibromyalgic pain in the muscles. Cheney posits that if the 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 that can be tolerated, 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, they can still think and make great demands on the brain, and energy is energy, whether it is being used physically or cognitively.

ME Story

I haven't seen a doctor in years. It doesn't seem worth it, somehow, as they have no answers and, besides, I can't stay upright long enough to make it to the surgery.

I become light headed very quickly now and have to lie down before I fall down: something else that used to happen on exertion and which now happens all the time.

- Christine

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": manifestation 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.

(continued on page 64)

The PACE TRIALS *(continued)*

Part "b": the event horizon: (once this line is passed, there is no going back): Cheney's view is that when the microcirculation defect within the heart itself begins to impact Q, 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 involves the lungs.

The sixth affected system is the lung and kidney: this leads to congestive heart failure 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 cause of death due to compensated idiopathic cardiomyopathy.

A patient will know if s/he eventually loses the ability to compensate if, when they lie down, they are short of breath.

Cheney's view is that cardiac muscle has lost power because the mitochondria are dysfunctional (ie. there is an energy-production problem in the cells).

As long ago as the 1980s, 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, causing 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 is bad enough when patients do not perfuse their muscles and joints (because of poor microcirculation) but it is 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/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.

(continued on page 65)

ME Comment

Having watched the (IiME) Conference DVD I was amazed at:-

- *The groundbreaking science presented by the researchers/scientists.*
- *The level of knowledge of ME by the doctors/physicians.*
- *The empathy from other speakers who understood ME from all angles. (Health, Financial, Social etc.)*
- *The quiet confidence amongst all the speakers that biomedical science will break the chains of the psycho-social model of ME.*
- *The fact that many of the speakers understood that assessment, management and treatments offered to ME sufferers are, unfairly, weighted in the psychiatrists favour. (A few speakers vocally expressed their opinions and well done to them for doing so. They spoke truthfully.)*

- Caroline

Facts About ME

The incidence of psychiatric co-morbidity in ME/CFS has been greatly over-emphasised:

a study in the Journal of the Royal Society of Medicine (2000:93:310-312) found that of patients in a tertiary referral centre who had received a psychiatric diagnosis, 68% had been misdiagnosed, with no evidence of past or current psychiatric illness.

The PACE TRIALS *(continued)*

Since Professor Cheney has shown that in ME/CFS patients, cardiac output struggles to meet metabolic demand, how can forced aerobic exercise which forms a major part of the MRC PACE and FINE "rehabilitation" trials 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/CFS?

Perhaps they are 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?

Since Professor Cheney has shown that in ME/CFS patients, cardiac output struggles to meet metabolic demand, how can forced aerobic exercise which forms a major part of the MRC PACE and FINE "rehabilitation" trials help such patients remain as functional as possible?

ME Story

Since there is such lack of awareness, no exposure in the media and no public consciousness about ME, I find it very frustrating to have to continually explain myself.

Even if some people understand and believe I have a real physical illness, I feel that people have a nagging belief that there may be a psychiatric component to it.

Due to fear of being misunderstood, I feel that the less I explain my situation the better off I am.

However, since I am either unemployed or a part-time worker, it's embarrassing not to have a "suitable" explanation for being off work.

I hate to think that people might consider me a layabout or an idler.

You have to have ME to even start to understand and appreciate the constant struggle sufferers face if not each day, most days.

-Rebecca (pwme from Malta)

Concern that the Principal Investigators of the MRC PACE and FINE trials repeatedly reject published evidence of biomarkers of ME/CFS

The psychiatric lobby repeatedly asserts that there is no single, definitive biomarker for "CFS/ME", yet they themselves are the very people who are instrumental in preventing the research in the UK that would be likely to demonstrate such a biomarker. Even when potential biomarkers are demonstrated by means of non-MRC funding, for example, the finding by Kennedy et al from Dundee of raised levels of isoprostanes that precisely correlate with ME/CFS patients' symptoms – a laboratory finding that is unique to ME/CFS (Free Radical Biology & Medicine 2005:39:584-589). Other useful biomarkers already exist, including hsCRP (high sensitivity C-reactive protein, a well-established marker of inflammation) and low NK (natural killer) cells, but the psychiatric lobby will not accept such compelling findings as evidence that their own beliefs about the nature of "CFS/ME" are erroneous.

Concern about the uncritical acceptance of the "evidence" for the alleged effectiveness of CBT/GET

The Systematic Review from the Centre for Reviews and Dissemination (CRD) has been exposed in the Hooper & Reid Review (mentioned above) and this evidence has been submitted to the MRC. It is beyond belief that the MRC continues to condone the acceptance of such a flawed "evidence-base" for the basis of the PACE and FINE trials, or that the Data Monitoring and Ethics Committee apparently remains unaware of (or uncaring about) this evidence.

The Countess of Mar was so concerned at the damaging and destructive influence of the Wessely School that she requested a meeting with Professor Blakemore. This took place at the House of Lords on 20th April 2004 and lasted for two hours. Earl (Freddie) Howe was also present.

(continued on page 66)

The PACE TRIALS *(continued)*

Both the Countess of Mar and Earl Howe were seasoned debaters in the House of Lords and both were profoundly disturbed at what occurred at that meeting, the outcome of which was fruitless.

Professor Blakemore was accompanied by Elizabeth Mitchell of the MRC and she did most of the talking. It was apparent that as far as the MRC was concerned, Professor Wessely is greatly revered and what he says about "CFS/ME" will be accepted. It was also apparent that the MRC's mind had been made up and was firmly closed. There was to be no consideration of the biomedical evidence that proved Wessely et al to be wrong.

On 10th May 2004, an article called "Why won't they believe he's ill" by Jerome Burne in The Independent quoted the Countess of Mar: "*A campaigner who has long opposed the purely psychiatric approach is scathing about the MRC trials. '**They are a farcical, cynical exercise and a huge waste of money' the Countess of Mar said".*** The article continued: "

The disregard of the illness was reflected on a practical level – they said that if I recover from exercise in ten minutes then I am working at the right level.

I abided by this rule and later crashed due to delayed and accumulated effects. How this is ethical I do not know.

*'Whatever their findings', says Dr Vance Spence, Senior Research Fellow at the University of Dundee and a leading scientist in the field, 'they won't tell us anything useful about the best way to treat CFS/ME because they are not properly selecting patients with the disease. There is widespread concern about this' ".*In a letter dated 11th May 2005, Professor Blakemore confidently claimed that the PACE trials *"were peer-reviewed and awarded funding on the basis of the excellence of the science".*

'Whatever their findings', says Dr Vance Spence, Senior Research Fellow at the University of Dundee and a leading scientist in the field, 'they [the PACE trial] won't tell us anything useful about the best way to treat CFS/ME because they are not properly selecting patients with the disease. There is widespread concern about this'.

Concern about patients' dissatisfaction with the MRC trials

In January 2005 there were disturbing accounts posted on the internet by participants in the FINE trial, and people made known their wish to withdraw. One person who had been forced to suspend from university gave the reasons {see Invest in ME page - http://www.investinme.org/Article-015A%20FINE%20Trials-Alice.htm}

"Data they collected about me was misleading. Only questionnaires were used; the questions were leading and did not reflect my true feelings. Also, the researchers spent 2-3 hours with me each time, which was so exhausting that I didn't really know what my replies were.

The trial totally disregards ME/CFS as an illness. It is based on a theory that symptoms are due to de-conditioning and maladapted beliefs about exercise. The disregard of the illness was reflected on a practical level – they said that if I recover from exercise in ten minutes then I am working at the right level.

I abided by this rule and later crashed due to delayed and accumulated effects. How this is ethical I do not know. The therapist had very selective hearing and she would adapt whatever I said to fit into what she wanted to hear (I have examples). The therapist was critical of me and was unsupportive. I believe the consent process was unethical. I was not aware what I was letting myself in for (they did not explain the details of the intervention until after I had consented). In addition, the de-conditioning theory was presented as fact (I have since read research that goes against the de-conditioning theory).

It frightens me to think that this research will be used to support clinics offering this in the future".

(continued on page 67)

The PACE TRIALS *(continued)*

In respect of the FINE trial, it is worth noting that the trial information says that for severely affected participants who are isolated, the trial may be carried out by means of the telephone or by computer. The sheer impracticality of these two methods reveals how little understanding the Principal Investigators have of the reality of the daily lives of those with severe ME/CFS. How many home-bound severely affected ME/CFS patients have got – or are able to use – a computer? Who is going to pay for the purchase and installation of a computer for those who do not possess one, and who is going to pay for and arrange lessons in basic computing skills (even supposing participants were well enough to undertake such lessons)? People who are severely affected by ME/CFS are unable to talk on the telephone for more than just a few minutes, so three-hour telephone sessions are unfeasible, but none of these practicalities seems to trouble the MRC Principal Investigators or the Data Monitoring and Ethics Committee.

Overall, there has been immense concern registered about the MRC PACE and FINE trials and about the psychiatrists who are leading them.

The support of AfME for these MRC PACE and FINE trials is disturbing; even more disturbing is the fact that AfME's website states: "*Some evidence suggests that the inactivity and resulting loss of fitness (de-conditioning) that occurs with ME can make the illness last longer and that graded exercise can help to reverse this".* Perhaps AfME is unaware of the results of a Belgian study on over 3,000 patients with "CFS" who were referred to multi-centre clinics. Out of those who undertook the "rehabilitation" programme consisting of CBT and GET, whereas before "rehabilitation", 18.3% were in paid employment, following "rehabilitation", this figure was reduced to 14.9%

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(ie. participants were working less hours after "rehabilitation"). Equally, perhaps AfME is unaware of a Dutch study which found that at the one year follow-up following "rehabilitation", 17% of ME/CFS patients who were previously working were no longer able to do so.

It is AfME's duty to be aware of the medical literature and to use it effectively to support the best interests of its members. Moreover, AfME seems to be extraordinarily inconsistent: in its press release of 22nd August 2007 issued to coincide with the publication of the NICE Guideline on "CFS/ME", AfME stated: *"Many patients have reported little or no benefit from CBT and others have experienced seriously adverse effects from GET"*, yet the following week, in an Editorial in the BMJ (1st September 2007:335:411-412), AfME's CEO, Sir Peter Spencer, agreed with psychiatrist Peter White that these same interventions show *"the clearest research evidence of benefit"*.

AfME might care to consider just why the MRC has a secret file of records and correspondence on ME/PVFS that dates from at least 1988 and is held at the Government Archive at Kew, and why this file is deemed so sensitive and controversial that it has been classified as top secret and cannot be made public until the 1st January 2023. AfME may like to recall that members of the CMO's Working Group were threatened with the Official Secrets Act. In the best interests of its members, AfME might also wish to ascertain exactly why the MRC so resolutely rejects grant applications for biomedical funding into ME/CFS (see http://www.nationalarchives.gov.uk/search/quick_search.aspx?search_text=myalgic).

The full document "CORPORATE COLLUSION?" may be found at the ME ACTION UK site at –

http://www.meactionuk.org.uk/Corporate_Collusion_2.htm

Attitudes of Mental Health Practitioners to the Hippocratic Oath

Psychiatry has been one of the major areas of contention from the ME community regarding why and how it is implicated in the treatment of myalgic encephalomyelitis. A research paper on how the Hippocratic Oath and psychiatry are perceived to co-exist was made by Dr. Marek Marzanski and colleagues from the Coventry PCT. We asked Dr. Marzanski for permission to republish this paper and he happily agreed. Our intention was to publish the paper in full here. However, the Royal College of Psychiatrists refused to give permission for publication in our Journal – but were happy for us to describe briefly the article and redirect to their site for the content (see link below).

Dr. Marzanki's research "Attitudes of mental health practitioners to the Hippocratic Oath: tradition and modernity in psychiatry" was carried out in 2004 to determine whether psychiatrists believe that medicine should be practised according to the principles of the Hippocratic Oath. Via an anonymous postal questionnaire a survey was carried out at a mental health unit in Coventry.
A modern version of the Hippocratic Oath is shown in summarised form on the right.

Those psychiatrists taking part in the survey ranged from junior doctors to consultants with an age from late twenties to over 70. Eighty percent were male.

The results showed over 80% of the psychiatrists believed that medicine should be practised according to the Hippocratic Oath. However, the results showed that support for different statements derived from the Oath to be at a considerable variation.

The questions ranged from treatment of teachers and other colleagues, the welfare of patients and the psychiatrist's attitudes toward the patient.

As Dr. Marzanski points out "Articulated in a contemporary form, Hippocratic values such as avoiding harm, acting in the best interest of the patient, compassion, integrity, honesty and respect for human life maintain their relevance and prove that goodness in medical practice does remain continuous across the ages."

The survey suggested to the author that the majority of psychiatrists agreed that medicine should be practised in accordance with the principles of the Hippocratic Oath – although the small survey might not be representative of UK psychiatrists in general.

It would be an interesting study to assess the answers from Dr. Marzanski's studies when directed toward psychiatrists who are involved in dealing with ME patients on a regular basis.

Dr. Marzanski's research paper can be found at this address –
http://pb.rcpsych.org/cgi/reprint/30/9/327

The Hippocratic Oath

(A Modern Version)

I swear in the presence of the Almighty and before my family, my teachers and my peers that according to my ability and judgment I will keep this Oath and Stipulation.

To reckon all who have taught me this art equally dear to me as my parents and in the same spirit and dedication to impart knowledge of the art of medicine to others. I will continue with diligence to keep abreast of advances in medicine. I will treat without exception all who seek my ministrations, so long as the treatment of others is not compromised thereby, and I will seek the counsel of particularly skilled physicians where indicated for the benefit of my patient.

I will follow that method of treatment which according to my ability and judgment, I consider for the benefit of my patient and abstain from whatever is harmful or mischievous. I will neither prescribe nor administer a lethal dose of medicine to any patient even if asked nor counsel any such thing nor perform the utmost respect for every human life from fertilization to natural death and reject abortion that deliberately takes a unique human life.

With purity, holiness and beneficence I will pass my life and practice my art. Except for the prudent correction of an imminent danger, I will neither treat any patient nor carry out any research on any human being without the valid informed consent of the subject or the appropriate legal protector thereof, understanding that research must have as its purpose the furtherance of the health of that individual. Into whatever patient setting I enter, I will go for the benefit of the sick and will abstain from every voluntary act of mischief or corruption and further from the seduction of any patient.

Whatever in connection with my professional practice or not in connection with it I may see or hear in the lives of my patients which ought not be spoken abroad, I will not divulge, reckoning that all such should be kept secret.

While I continue to keep this Oath unviolated may it be granted to me to enjoy life and the practice of the art and science of medicine with the blessing of the Almighty and respected by my peers and society, but should I trespass and violate this Oath, may the reverse be my lot.

Energising ME Awareness

The IiME International ME/CFS Conference London 23rd May 2008

It is Invest in ME's intention to continue with the London conference as an annual event and to provide a platform for researchers, healthcare staff, support, educational professionals, ME support groups and people with ME and the media, to enable the most relevant science, research, information and news on ME to be heard.

Our 2008 conference is scheduled for **23rd May 2008** in London.

More details will be announced during the coming months so please visit our web site.
We shall also be sending out details via our free newsletter to all our subscribers.

We hope again to work with our UK regional and international contacts to enable this.

More details will be available on our web site in due course.
Contact: meconference@investinme.org.

Energising ME Awareness

The IiME International ME/CFS Conference London 23rd May 2008

Welcome to London

We believe it is important to provide a possibility for people within government, health departments, social services, education and the media to be able to be informed of the the status of research, treatment and information related to Myalgic Encephalomyelitis.

Invest in ME offers the chance for researchers, medical practitioners, healthcare staff, people connected with, or interested in, the care of people with ME to present at the conference.

We again hope to provide platforms for the following -

- Epidemiology
- Diagnosis
- Pathology
- Treatments and Protocols for ME
- Research
- Nutrition
- Care

The conference will again highlight the need for empirical evidence based on valid, modern and scientific diagnostic and treatment protocols. The conference will provide a chance to hear the latest news on ME from the most prominent speakers within the ME community - in ME Awareness Month 2008.

The above pictures of London and the conference were taken by Regina Klos (www.cfs-aktuell.de). More pictures from the conference taken by Regina may be found here- http://www.investinme.org/International%20ME%20Conference%202007%20-%20review%20gallery%202.htm

ME Conference Comments

"...thanks for organising a conference with such impressive speakers & at such reasonable cost. As a humble parent, most conferences are completely out of my price range, so was really delighted to be able to attend. I picked up lots of info & have realised that I need to do loads more h/w to really be on top of all the stuff that's been discovered since my daughter first became ill – 10 yrs ago." – Helen

"Many thanks for the wonderful conference. It was a great atmosphere and very uplifting to know of the wonderful work and people involved in helping us ME Sufferers. … It was a conference of excellence and it honoured us as well as raising us up!" – Jane

"I profited so much, I learned so much, I've met so many people I haven't met before - all this was so impressive." - Regina

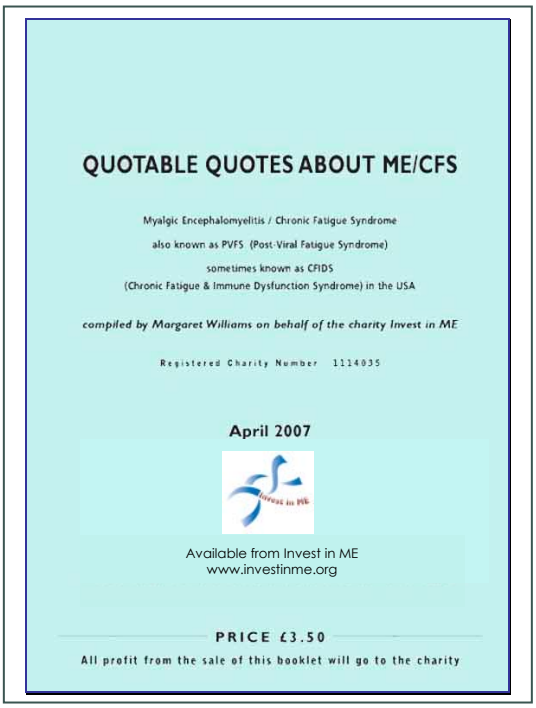
"I thought it was fantastic, massively informative, encouraging, inspiring, necessary. It was very powerful hearing so much material from the doctors, researchers and speakers themselves, very, very impressive. I do agree that the speakers all came across as deeply humane. As a patient there was an enormous amount of useful applicable material and info on research hot from the lab so to speak. " – Nikki

See other comments at http://www.investinme.org/International%20ME%20Conference%202007%20-%20review%20feedback.htm

EDUCATIONAL MATERIAL from IiME

INTERNATIONAL ME/CFS Conference DVDs

Invest in ME have available the full presentations from both of the International ME/CFS Conferences in London of 2007 and 2006
These professionally filmed and authored DVD sets each consist of four discs, in Dolby stereo and in PAL (European) or NTSC (USA/Canada) format. Containing 9 ½ hours (2007 DVD set) and 6 hours (2006 DVD set) – with all presentations plus interviews with ME presenters and news stories from TV programmes.
These DVDs have been sold in over 20 countries and are now available as an educational tools – useful for healthcare staff (GPs, paediatricians, occupational therapists and others connected with the treatment of ME), researchers, scientists, educational specialists, media, ME support groups and people with ME and their carers/parents.
Full details can be found at http://www.investinme.org/InfoCentre%20Education%20Homepage.htm or via emailing IiME at meconference@investinme.org.
Price £15 each (UK), £16 (Europe) and £17 (USA/Canada/Australia/New Zealand) - including p&p.



Quotable Quotes on ME/CFS

This 42 page booklet has been compiled by Margaret Williams and contains a plethora of quotes from ME experts and from others relating to ME, ME/CFS, CFS/ME and CFS. This is an invaluable document for researchers, healthcare staff, politicians, media, ME support groups and people with ME.

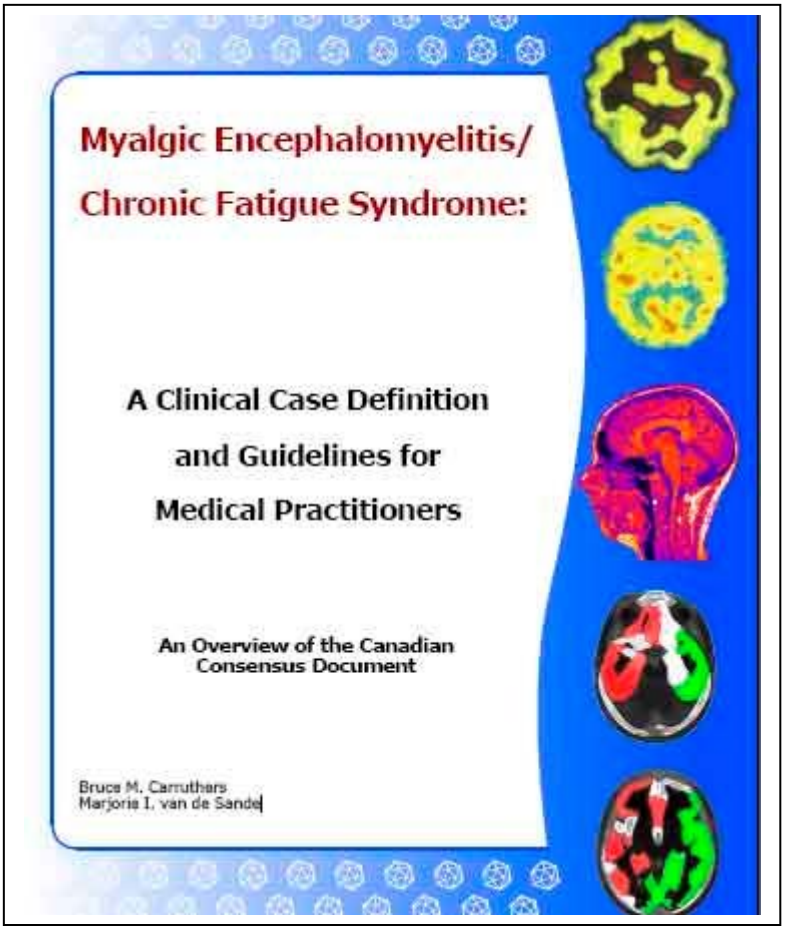
The booklet will aid those composing letters, performing research, verifying analysis and for general reference purposes.

Price £3.50 + £1 postage/packing for UK delivery (for Europe and USA/Canada/Australia/New Zealand please email for costs of p&p).

http://www.investinme.org/IIME%20ME%20Quotes%20Order%20form.htm

EDUCATIONAL MATERIAL from IiME

Canadian Guidelines



Invest in ME are the UK distributors for the Canadian Guidelines.

Described even by NICE as "*the most stringent*" guidelines available these are proper, up-to-date clinical guidelines which can also be used as a base for research criteria.
Findings from the study by Leonard A. Jason PhD (Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome) indicated that the Canadian criteria captured many of the cardiopulmonary and neurological abnormalities, which were not currently assessed by the Fukuda criteria.
The Canadian criteria also selected cases with *'less psychiatric co-morbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurological symptoms*' and individuals selected by these criteria were significantly different from psychiatric controls with CFS.

The Canadian Guidelines provide a means for clearly diagnosing ME and were developed specifically for that purpose.

They are an internationally accepted set of guidelines for which many in the ME community have been campaigning to be adopted as the standard set of guidelines for diagnosing ME.

The Canadian Guidelines are available from IiME and the price is 46p per copy plus postage & packaging.

To order please contact Invest in ME via this email address: info@investinme.org

NEWSLETTER

Order our free newsletter.

We aim to publish monthly via html, plain text or PDF.

Support International ME Awareness Month May 2008
www.investinme.org