

The Journal of IiME

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***From
Invest in ME***



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Also including the IiME International ME/CFS Conference 2008 section

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It is one year since we produced the first Journal of IiME as a means of providing a combination of biomedical research, information, news, views, stories and other articles relating to myalgic encephalomyelitis (ME/CFS) – basically, a broad spectrum of information on ME/CFS. Our aim was to distribute this for free four times a year. Due to the current size and financial limitations of IiME we can only provide a snapshot of the wealth of experience which already exists and continues to increase and we currently are only able to produce two copies a year. But we hope to change that in the future.

However, this will be our third Journal and, coinciding as it does with the 3rd IiME International ME/CFS Conference, we can look at the last two years and begin wondering if a sea change is occurring in the perception of ME based on good science, objective data, effective advocacy and a realisation (finally) from government and healthcare organisations (albeit forced by pressure from patient groups and researchers) that obfuscation and systemic bias are no just or effective way to provide healthcare.

Diagnosis is at the heart of the problems surrounding ME and diagnostic criteria are critical. One of the IiME's aims was to campaign for such a diagnostic test and this may well be achievable before long. Last autumn's Journal of IiME reported on work by Dr Sakudo at Osaka university using Visible and near-infrared (Vis-NIR) spectroscopy on serum samples. Dr Sakudo stated that as ME can only currently be diagnosed by skilled doctors then the diagnosis requires experience and sophisticated techniques - and even with a skilled doctor, it takes a long time to reach a final clinical diagnosis. Vis-NIR spectroscopy would enable an objective and rapid diagnosis and would not require experience and skill. Dr Sakudo returns this month with an article as commentary on the possible application of visible and near-infrared spectral patterns in serum to provide emerging clue to biomarkers for chronic fatigue syndrome.

Dr Tae Park runs his own CFS clinic in Seoul, Korea and he attended the Invest in ME International ME/CFS Conference in London in May 2007 and wanted to return this year to briefly speak at the conference (which we will try to fit in the plenary section or as a poster presentation). Dr Park has supplied another short article on improved renal function based on treatment with IVIG.

Sidsel Kreyberg is a Norwegian doctor who has specialised in pathology and is head of the ME Registry in Norway. Dr Kreyberg has conducted a small survey of those caring for the severely ill ME patients. Her article provides a good insight into the difficulties in caring for this group of ME patients in institutions. The normal rules of rehabilitation do not apply to ME patients and it is important to take the lead from patients. The patient experiences are very important and should be listened to. Eight institutions which had cared for severely affected ME patients were contacted. The objective was to obtain "hands-on" experience of how one could give adequate services in the future for severely ill ME patients, without

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consideration of existing constraints in resources. As Dr Kreyberg states quite explicitly "grass roots" experiences especially can be as important as recommendations and therapy suggestions from professionals who do not know what the care situation involves.

Dr David Bell has been involved in ME/CFS for many years and in his latest Lyndonville newsletter he explains mitochondrial disease and the type of secondary mitochondrial disease ME/CFS patients experience - the inability to sustain activity. He clearly illustrates why ME/CFS has nothing to do with deconditioning.

Dr Les Simpson has also studied ME for many years and his aim has been to enable patients to manage their condition better. Dr Simpson provides a very interesting article based on his research of the shape of red blood cells in ME, an area not mentioned very often. He states that ME is one of many chronic disorders with changed red cells which will impair capillary blood flow and that ME is unique insofar as the factor(s) responsible for changes in red cell shape can switch off and, during remissions, red cell shape populations can return to normal.

We also have another article from Margaret Williams which, although published on our web site in January, is still valid and worthy of reading.

There is already a great fund of knowledge available for the healthcare departments, organisations and staff to appreciate the multi-system nature of ME/CFS and the need to stay current with biomedical research data.

The articles in the JIiME, a small subset of the exciting potential of possibilities to treat and cure this illness, continue to frame the thought – what could be possible if proper funding were available for a national or international biomedical research strategy?

And where better to demonstrate this potential than with the IiME International ME/CFS Conference 2008. We have a section at the end of the Journal covering the conference and including abstracts and agenda for the event. The theme of the conference is Sub Grouping and Treatments for ME/CFS and we believe some of the best biomedical research currently available. It promises to be an event full of objective data and established experience which cannot be disputed.

The unique blend of biomedical research, objective data presented by our distinguished speakers is testament to the increasing knowledge regarding myalgic encephalomyelitis.

Returning to our opening paragraph if a sea change in the perception of ME/CFS is occurring then it will be based on the good science and objective data (represented by our conference speakers), effective advocacy (represented by conference delegates from ten different countries and from ME support organisations across the world) and a new realisation from government and healthcare organisations (represented by the presence at

the conference of the Chief Medical Officer's Office and the Medical Research Council).

Enjoy the Journal. Enjoy the conference.

Postscript:

IiME organise an annual international conference, produce educational DVDs from the conference, produce a Journal and regular newsletter and a web site containing information for all. We are also involved in lobbying for better education and proper funding for ME.

In the spectrum of material we use and are supplied there are variations in terminology regarding myalgic encephalomyelitis. We often refer to this illness as ME and that is where we believe it should remain - the illness has been called Myalgic Encephalomyelitis in the U.K. since 1956.

However, other acronyms are used. The WHO ICD-10 G93.3 category lists ME, CFS and PVFS.

Many of our distinguished contributors and presenters use CFS and in America CFS is commonly used.

The UK government, despite officially accepting the WHO classification of ME as a neurological illness and thus implicitly accepting the term ME/CFS to describe the illness, confuse matters even more by using a combination of CFS and CFS/ME.

NICE were criticised by IiME in mixing CFS and CFS/ME in their draft guidelines for CFS/ME.

Research (and research funding) is often based on using the term CFS and attracting healthcare professionals to events such as the IiME international conferences has to allow for the fact that many still refer to ME as CFS.

This subject is a major issue in itself and there are debates currently ongoing regarding name change. Representing this illness properly requires a correct nomenclature. Sub grouping and treating ME will require correct and consistent terminology.

However, as extremely important as this is, IiME nevertheless do not wish to spend all of our time on winning the battle (on the correct name) but losing the war (on getting proper funding for biomedical research and up to date education for healthcare services on the real pathology behind ME). Whilst continuing to use the term ME or ME/CFS in our material we will be referring to the neurological illness myalgic encephalomyelitis and hope that readers will not be too confused by the additional use of CFS or CFS/ME by contributors and presenters. The inconsistency of terminology exists in all countries and by many organisations.

We will return to this subject in a later issue of JIiME.

Possible application of visible and near-infrared spectral patterns in serum to provide emerging clue to biomarkers for chronic fatigue syndrome

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Abstract

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. Here, we propose that changes of molecules having hydrogen-containing functional groups are reflected in spectral patterns in sera of CFS patients. This is hypothesized from visible and near-infrared spectroscopy, which detects hydrogen-containing functional groups and shows the presence of common factor(s) in CFS patients' sera, implying that the common factors bear hydrogen-containing functional groups. In this regard, the above findings would facilitate the search for biomarkers for CFS.

Key words: Vis-NIR; chronic fatigue syndrome; biomarker; chemometrics.

Chronic fatigue syndrome (CFS) is a debilitating disorder involving persistent fatigue lasting for more than six months with symptoms such as fatigue, pain, breathing problems, depression leading to digestive disturbances, low-grade fever, difficulty in concentrating, and weakness of the immune system and muscles (Fukuda, 1994). The problems of this disease are that the symptoms are not resolved by sufficient rest (Fukuda, 1994). This disease causes individual problems but also economical problems. Although the incidence of CFS is 0.4% in the United States and other countries (Jason, 1999) and 0.26% in Japan (Kuratsune, 2007), economic losses caused by the disease are estimated as high as 9.1 billion dollars per year in the United States (Reynolds, 2004) and 408 billion yen per year in Japan (Kuratsune, 2007). CFS patients sometimes suffer from the symptoms but also social problems so the abnormality can not be clearly recognized. Recent 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 (Jason, 1999; Reyes, 2003), 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 (Vernon, 2006). This may be at least in part due to the heterogeneity of the symptoms of CFS patients (Vernon, 2006). At present, CFS is diagnosed based on the presentation of symptoms and exclusion of other medical entities (Fukuda, 1994). Most molecules reported as abnormalities in CFS blood have no clear consensus (Table 1).

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The paper is submitted for publication in *Journal of IiME* as "Commentary".



Our research group

Some of the Medical spectroscopy group at Department of Virology, Research Institute for Microbial Diseases, Osaka University—virologist (Kazuyoshi Ikuta), spectroscopist (Akikazu Sakudo), physician (Yukiko Hakariya), and clinical laboratory technologist (Takanori Kobayashi).

Possible application of visible and near-infrared spectral patterns in serum to provide emerging clue to biomarkers for chronic fatigue syndrome

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The main problems in CFS studies can be attributed to the objectivity of diagnosis and absence of biomarkers. Therefore, recently, we have developed a novel method using visible and near-infrared (Vis-NIR) spectroscopy and chemometrics, and showed that Vis-NIR spectroscopy provides promising diagnostic tools for CFS (Sakudo, 2006). Furthermore, the results also imply the presence of common factors among CFS patients' sera (Sakudo, 2006).

For essentially all clinically relevant biomolecules except hemoglobin, Vis-NIR radiation of the biomolecules is absorbed due to the combination and overtone of vibrations such as stretching and bending of hydrogen-bearing functional groups such as C-H, N-H, O-H (Murray, 1993). This is because peaks in Vis-NIR spectra are due to hydrogen-containing functional groups. Our recent findings indicate that Vis-NIR analysis combined with chemometrics analysis of serum achieves complete

separation of CFS patients from healthy controls (Sakudo, 2006). This approach deserves further evaluation as a potential novel strategy for instrumental diagnosis of CFS. More importantly, results of chemometrics analysis, such as principal component analysis (PCA) and soft-independent model of class analogy (SIMCA), suggest that unknown factor(s) in serum are commonly present in all CFS patients (Sakudo, 2006). Important peaks of PCA loadings and SIMCA discriminating power indicate at absorption by common CFS biomolecules possibly bearing hydrogen-containing groups of Vis-NIR radiation occurred in that wavelength.

If our hypothesis that CFS common factors have hydrogen-containing functional groups (Fig. 1), detailed band assignment would provide promising CFS biomarkers. The first choice for identification of CFS

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Table. 1 Abnormality in blood of CFS patients

Autoantibody levels	Vernon, 2005
Cytokine levels	Patarca, 2001
Low production of immunoglobulin	Patarca, 2001
Elevation of activity of 2'-5' oligo-adenylate synthetase	Nijs, 2005
RNase L levels	Nijs, 2005
Lymphocyte subset	Patarca, 2001
Low NK activity	Whiteside, 1998
Impaired ACTH and cortisol responses	Cleare, 2003
Melatonin levels	Cleare, 2003
Levels of DHEA and DHEA-S	Cleare, 2003
Opioid system and AVP	Parker, 2001
Changes in growth hormone level	Allain, 1997
Decrease of acylcarnitine	Kuratsune, 1994
Reduced folic acid level	Jacobson, 1993
Levels of various B vitamins and vitamin C	Werbach, 2000
Levels of sodium	Werbach, 2000
L-tryptophan levels	Werbach, 2000
L-carnitine levels	Werbach, 2000
Coenzyme Q10 levels	Werbach, 2000
Levels of essential fatty acids	Werbach, 2000
Levels of magnesium in RBC	Werbach, 2000
Decreased level of zinc in serum	Maes, 2006

NK: natural killer ACTH: adrenocorticotrophic hormone DHEA: dehydroepiandrosteronedione

DHEA-S: dehydroepiandrosteronedione sulphate VP: arginine vasopressin RBC: red blood cell

Possible application of visible and near-infrared spectral patterns in serum to provide emerging clue to biomarkers for chronic fatigue syndrome

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biomarkers is to use Vis-NIR spectra of the molecules listed in Table 1 to compare sera from CFS patients and healthy donors. Although it is possible, this strategy may not be the best choice, because the peak signals of Vis-NIR spectra are broad and weak, so it is difficult to identify differences between two groups. Another barrier preventing identification of CFS biomolecules by Vis-NIR spectroscopy is the limited information about Vis-NIR spectra of biomolecules. Infrared (IR) spectroscopy is also vibrational spectroscopy, similar to Vis-NIR spectroscopy (Stuart, 1997). Moreover, the absorption observed in the IR region is dependent on hydrogen-containing bonds. The mechanism of IR spectroscopy is similar to Vis-NIR spectroscopy but there are differences: the absorption observed in IR is due to fewer overtones than Vis-NIR, resulting in a sharp and high intensity band in IR. Furthermore, there is abundant information on IR spectra. IR spectra databases can be obtained commercially from several companies, such as KnowItAll Informatics System (Bio-Rad Laboratories, Philadelphia, PA, USA), which contains 0.22 million IR spectra, including biomolecules. By combining chemometrics analysis of IR spectra from CFS blood with IR spectra database, we can identify potential candidates for CFS biomarkers. From this knowledge, we propose that IR spectroscopy may provide a better choice for identification of CFS biomarkers related to Vis-NIR spectroscopy.

Acknowledgments

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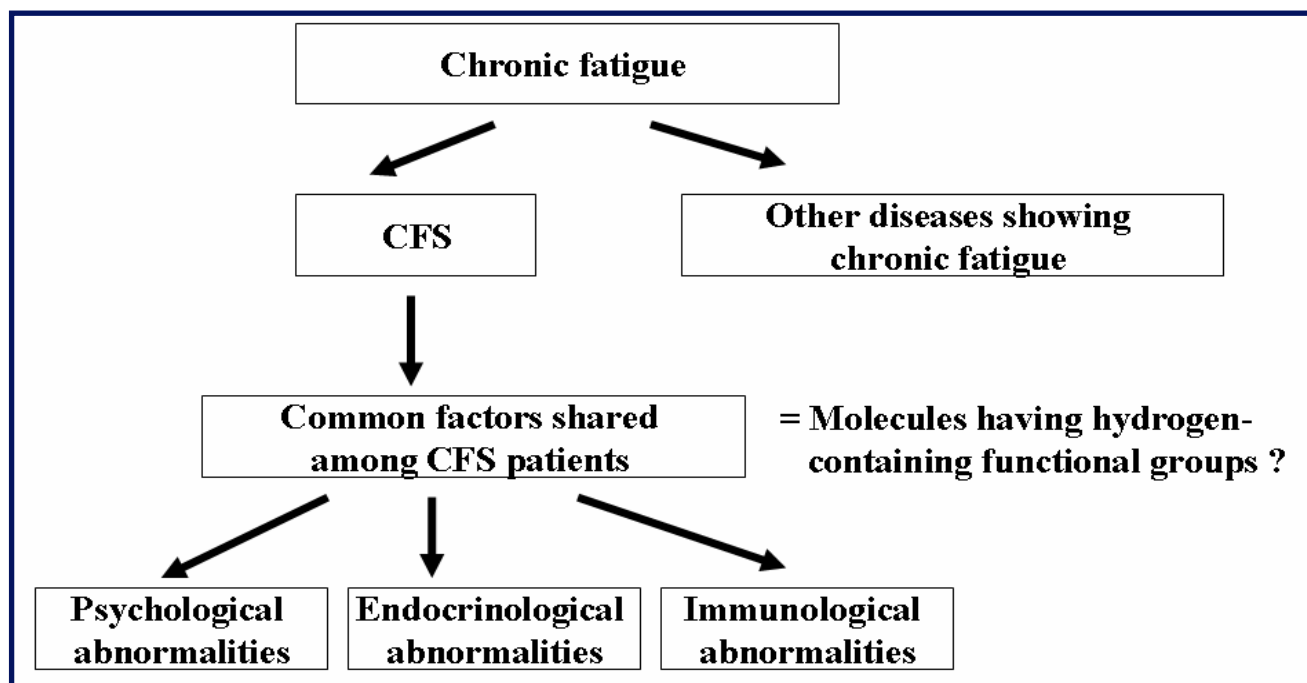
discussions.

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Sakudo et al., Fig. 1. CFS common factors have hydrogen-containing functional groups?



Possible application of visible and near-infrared spectral patterns in serum to provide emerging clue to biomarkers for chronic fatigue syndrome

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ME Story

ME patients are unfortunate with their doctors. While most other patient groups have a trusting relationship with the medical profession, far too often ME patients complain of neglect, abuse, misdiagnosis and stigma. Our patients have a visceral dislike of the psychiatric construct of ME, and for good reason. Besides the disadvantages of misdiagnosis, it forces them into a clinical environment where the validity of their opinions is routinely delegitimized, where their right to give informed consent is often not respected, and where in some cases they may be subjected to involuntary detention. These are fears which lurk in the minds of all ME patients. For Sophia Mirza they became a nightmare reality.

- Horace Reid

([on the story of Sophia Mirza](#))

Person With ME

I have just read about your book ([ME Book Project](#)), what a good idea!

I have had ME for nearly 4 years now and I can say that it has devastated my life, everyday just feels like walking against the wind. Where once I could participate, now I can only observe. I have become a very diluted form of who I once was. Well done for trying to highlight this illness.

- Melanie

Improved Renal Function in CFS/ME Patients with IVIG

By Dr Tae Park

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 will be in attendance and briefly speaking at the IiME conference in May 2008

Objective of study:

To prove the effectiveness of IVIG tx in CFS/ME patients.

Method of study:

The study was made by checking the GFR of 125 CFS/ME patients by s-creatinine clearance with cockcroft-gault formula.

There are several studies about the effectiveness of IVIG tx in CFS/ME patients.

But there have been no reports as to how they improve. It has been known that CFS/ME is really an inflammatory disease of the CNS, mainly from micro-vasculitis.

Also the immunoglobuline is the only drug to improve the CNS inflammation at the present time.

Here we report that there is real measurable evidence to show that there is improved renal blood flow in CFS/ME patients with IVIG tx.

We randomly selected 125 patients who met the 1994 Fukuda criteria .

We found there were significant renal blood flow improvements in 60 patients (50%) with IVIG tx, .

We also found significant improvement of patients' sx, especially fatigue, sleep disorders, muscle pain and, most of all, they showed marked improvement in the cognitive functions. Among the improved cognitive functions displayed patients showed remarkable improvements in comprehension and concentrations. The improvement of renal blood flow are between 35% to 60% of previous GFR.

These findings of improved renal blood flow may be evidence of improved cerebral blood flow. Furthermore, they may explain the improvement of cognitive functions and other symptoms of CFS/ME patients with IVIG tx.

This study will lead to further investigation of CFS/ME tx with IVIG tx.

Facts on ME

There can be no doubt that NICE ignored the international evidence that ME/CFS is a biomedical, not psychiatric, disorder, claiming that studying this evidence fell out with its remit.

Such a claim is mystifying, since knowledge of the existing evidence-base ought surely to be mandatory before producing a national Guideline on the management of any disorder, especially given that adherence to such a Guideline is obligatory throughout the NHS (and hence for affiliated agencies such as the Department for Work and Pensions and Social Services).

- Margaret Williams



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ME Story

I caught glandular fever and just afterwards in my nurse training found I was always getting tonsillitis. In 1996 I came down with a serious set of symptoms which included palpitations, chest pains and very sore joints. I was so ill that I was admitted to hospital with pericarditis.

I was unable to walk for 6 weeks. I took ages to respond to treatment and over the next few months I was given so many blood tests which eventually concluded I had a virus from the enteroviral family related to polio

- Sue

Experiences of Care in Institutions with Severely-Ill People with ME

By

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(Invest in ME have helped in translation of this article from Norwegian to English and have been given permission to republish the article, which first appeared in Norsk Tidsskrift for Sykepleieforskning, 2007; 9: 2, 16-26)

ABSTRACT

Caring for seriously ill ME-patients: A small survey

Norwegian medical professionals generally lack the knowledge and experience needed to diagnose and provide advice on how to manage Myalgic Encephalopathy. The subject is also absent from the education of nurses and other health workers. Experience must, for now, be accepted as key to understanding and managing this largely unexplained disorder.

Seven nursing homes here outline which extra resources would be necessary to adequately treat and care for seriously ill ME-patients, according to their experience. Apart from suggesting specialised units, the answers comprise technical adjustments to provide maximum protection from sound and light, advanced ventilation systems, flexible kitchen facilities and individually adapted dietary regimens; medical advisors; and a carefully selected and limited number of carers to look after the ME-patient around-the-clock. Stability, predictability and consistency are necessary for the patients to cope, and a small team will enable the carers to cooperate, be alert to signs of adverse reactions, and take adequate measures to prevent deterioration. Routines for debriefing staff working with patients in a permanent crisis-like condition was called for; and extra time and resources to support relatives that assist in planning and caretaking, speak on behalf of the patient, and are crucial in providing know-how - all of which necessitates increased staff in general.

Key words

English: Myalgic encephalopathy, chronic fatigue syndrome, nursing, rehabilitation, experience

Introduction

Myalgic Encephalopathy, ME, is discussed more often in the media than in professional healthcare curriculum literature. The condition is often given other names such as "Chronic Fatigue Syndrome", "fatigue syndrome" or "lack of energy", which are more or less vague definitions of various longstanding fatigue states (Lindal, Stefansson & Bergmann, 2002; Jason, Helgeson & Torres-Harding, 2003; Kennedy, Abbot & Spence, 2004).

In addition to subjective symptoms, which come and go, such as self-reported fatigue, nausea and malaise, ME is characterised by reduced stamina brought on by physical or mental activity, otherwise known as *activity intolerance* or increased fatigability (objective exhaustion). These patients are thus *exercise intolerant* (Hyde, Goldstein & Levine, 1992). In addition they are different from other "low energy" patients in that they are at times disablingly intolerant of sensory stimuli, have markedly reduced tolerance for alcohol, medicines and various food stuffs, with disturbances in autonomous, hormonal, neurological and immunological functions, disturbed body clock, and pains which are not relieved by treatment. In a fully developed illness there are symptoms from all organs and bodily systems. Symptomology is constantly changing. Lack of explanation for a cause gives rise to psychiatric interpretations. Recent studies, however, show changes in the peripheral circulation which can explain a lot of the

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Experiences of Care in Institutions with Severely-Ill People with ME (continued)

phenomena of changing symptomology over time. (Streeten & Bell, 1998; Rowe, 2002; Peckerman, Lamanca & Dahl, 2003; Khan, Spence & Kennedy, 2003; Khan, Kennedy & Spence, 2004; Spence & Steward, 2004; Kennedy, Spence & McLaren, 2005).

Clinical presentation of ME is a condition with large disturbances in the ability to restore the physiological balance. This means *prolonged recovery time* with subjective symptoms and objective loss in physical and mental functions after activity and stimulation. It depends on the individual how much can be tolerated, and the capacity varies within the course of the illness. The capacity can also vary considerably within one day. Patients benefit from reducing activities to a level which, from experience, can be tolerated without provoking symptoms, and therefore need to be protected from stimuli that provoke symptoms. Increased recovery time makes it necessary to rest after activities and stimulation so that symptoms ease and physical and mental functioning is slowly improved. Problems with circulation make it furthermore necessary to lie down a lot; completely flat in severe cases.

ME patients need help in stabilising their condition despite the severity of the illness. When activity limitations are exceeded, there is an increase in symptom intensity, increasing deterioration and ever increasing recovery time. The illness has from experience an inherent tendency for slow improvement over months and years as long as it is not provoked. The best prognosis is for young people who are allowed to rest from the start of their illness, for grown up married or for co-habiting couples or for the ones who have marked improvement during the first 12-18 months.

The World Health Organisation classifies ME together with Post Viral fatigue Syndrome (PVFS) as a neurological illness (G93.3, ICD-10), but have not given criteria. The character of the illness is described in the literature, often in the form of symptom lists or set of criteria (Hyde, Goldstein & Levine, 1992; Kreyberg, 1999). The knowledge of the nature of the illness is spread considerably from person to person via formal or informal networks among people with personal experience, also within doctors. The illness is difficult to understand, and what one sees can be difficult to intermediate because connections between cause and effect often are the opposite compared to what one sees in other illnesses. The limitations of the illness are seen clearer *after* activity and stimulation than beforehand, and there are no adequate concepts to describe the subjective symptoms. Those who try, will often be interpreted in the psychosomatic model of understanding, either are ill themselves or speak for the ill.

One of the reasons why ME is still considered a somatic illness is that it can develop as a direct consequence of

another physical illness or trauma. It can also begin acutely after a latency period of several months or years after exposure, possibly in connection with a new unrelated illness episode. It is easiest to diagnose acute, fulminant cases and cases that occur during epidemics. In a fully developed illness the presentation is the same despite the triggering event or the way in which the illness started. ME can therefore be seen as a type of general reaction.

The pattern of increasing loss of physical and mental functioning after activity is especially noticeable with the most severe cases, whose reaction most likely shows up straight away. Upon recovery the reaction can be delayed or overruled. Even if the ill person is careful the reaction can happen after hours or days, or even after a longer period, and one has to take this experience into account.

The reaction can be abrupt, dramatic and long lasting. Activity level can therefore be increased only in small steps within periods of improvement. If there is a reaction the activity level has to be down regulated straight away. The ill person will feel *beforehand* if there generally are energy reserves and will *spontaneously* increase their activity level, expose themselves to stronger stimulus, try new food and more. So the ill person must not be encouraged or stimulated but benefits from adjustment.

Observation over time is necessary if one wishes to avoid exposing these very vulnerable patients for lengthy, painful and potentially harmful investigations which can neither confirm nor rule out the diagnosis with today's routine examinations. At best one achieves ruling out another illness which is only necessary if there is clinical suspicion (Holmes, Kaplan & Ganz, 1988). However, suspicion of another illness comes up often because of the changing symptom flora, where new symptoms show up constantly. It is therefore important that healthcare professionals and others who take care of such patients have certain knowledge of the everyday presentation of the illness. The following sums up a quick survey which was carried out in the autumn of 2006, motivated by the upcoming nursing home reform in Oslo and knowledge of the case of what is officially on offer for ME patients being taken up by parliament (Dåvøy, 2007). Many seriously ill ME patients are cared for at home by their families, often for years, without essential support, respite care or guidance. It is mainly patients themselves and their families who have the knowledge around this area and it is spread via distinct networks.

The illness presents itself more or less the same despite sex, age and over national borders, and is most easily recognised in serious cases, those in need of care. For this reason one could expect experiences in

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Experiences of Care in Institutions with Severely-Ill People with ME (*continued*)

institutionalised care situations to be fairly similar, even with relatively restricted material.

A Small Survey

In all eight institutions which had been known to have taken in a severely affected ME patient, were contacted by telephone. It varied whether it was the ward nurse or someone else in the team around the patient who answered the phone. They were told about the objective, which was to obtain an enunciation from a person with "hands-on"-experience with a severely ill ME patient in an institution, with the idea of how one could give adequate services in the future for this patient group, without taking into account the existing restrictions in resources. It must be said quite explicitly that especially "grass root" experiences can be as important as recommendations and therapy suggestions from professionals who do not know what the care situation involves. It was left to the departments themselves to decide who would formulate the answers. The following questions were asked: *Which resources should you be provided with to be able to offer adequate care for a seriously ill ME patient? State reasons for your answer based on your own experience.*

Seven of the institutions gave written answers by e-mail, post or via both. The eighth considered that ME was not the reason for the patient's care need and their experiences were irrelevant for our study.

One institution asked for the question to be provided in writing but had reformulated the given problem when they gave their answer. This didn't affect the outcome and was only taken as a novelty. In three cases single statements were elaborated upon after renewed contact.

The study's starting point was five women and two men who needed care. In one case the patient lived with the parents but was cared for by permanent staff from a nearby institution. In one occasion the ill person lived in a care home connected to a nursing home. In one occasion it was a rehabilitation centre that admitted patients on a short term basis, with a clear target of improvement during the stay. In this case the place was used as a half way house because of lack of space elsewhere. In one case it was a short term department within a nursing home that ran the rehabilitation. The others were ordinary nursing homes.

Some of the institutions didn't have any previous experience of ME, whilst others had experience of several ME patients with unequal grades of severity. The extent of this experience material is not known.

The relatives were involved in to different extents in the daily care and acted partly as advisers. In a few places the staff also functioned in a supportive role for relatives.

RESULTS

The answers are concentrated especially on economical support for physical efforts, extra staff, individually adjusted eating and extra time. One wished for regular staff with a limited amount of chosen carers and guidance both before and after the stay. A few were also concerned about how one could look after relatives and carers after meetings with patients in a permanent crisis. The special problems that materialised when patients got more energy became more apparent in various degrees and are in the borderline toward rehabilitation.

Screening against sound

The fewest could look after the need for complete sound proofing. Amongst the suggestions were a private room in an area with least noise pollution, a sound proofed room, a sound proofed door and eventually one's own screened ward. In one case there was a built in sound proofed room within a supportive housing accommodation.

Common dining areas were too noisy. Even if a few could physically get to the dining area themselves, the food had to be brought to the room.

Many pointed out that the staff had to perform tasks quietly and be aware of their voice level, use of equipment such as plastic utensils, finish as quickly as possible, not talk unnecessarily, possibly use cards instead of spoken words, make sure that housekeeping tasks were done in such a way that the patient was not burdened.

Many noticed that tolerance for sound and talk improved as the condition improved and then it was mostly the ill person themselves who initiated discussion with the staff and exposed themselves to sound from the radio or sang to themselves.

Screening against light

The patient's need for complete black out could mean problems in caring. Many wished for lights that could be dimmed gradually. In one ward it was suggested, in order to avoid a gap between the window and screening, to install a roller blind inside the double glazing and additionally double curtains.

Comfort for lying down

For patients who spend most of the time in bed it was identified by one institution of the special need for a good bed/mattress.

Temperature and air quality

One place which took in several ME patients pointed out that a normal ventilation system was not good

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Experiences of Care in Institutions with Severely-Ill People with ME (*continued*)

enough. The ill people had to have even temperature and could feel uncomfortable by the heat in the summer. For the consideration of both the patients and carers the need for good air circulation meant installation of an air conditioning system, especially where there was extra sound and light proofing.

Kitchen and food

Customised food was seen to some extent differently depending on the routines of the institution and reflected somewhat the knowledge of, or acknowledgment of food intolerance problems with ME. It was difficult to register if a patient deteriorated due to certain foods.

In one case a special diet was only present if there was a doctor's note. It was, however, known that many institutions avoided usual foods such as milk, sugar and flour. Even this caused extra work.

A few found it natural to work with a dietitian and adjusted the food according to the patient's wishes. Others called for a nutritionist and for a possibility to order special food.

To have enough time for feeding was, as a rule, seen as the biggest problem. It was simpler if the ill person took all food in a liquid form. The need for extra time for feeding was seen throughout as a resource problem which had to be solved by adding extra staff elsewhere.

Purely physically some pointed out the need for a private kitchen for more flexible solutions for the ill person and their families to be able to cook for themselves. The relatives could then also more easily function in a supporting role for the ill person and at the same time offload the staff.

Staff

In addition to special physical efforts, there was a need for extra human resources. There was a wish for a regular, stable staff with the fewest possible people, who could cover the ME patient's need 24 hours a day. "[...] all care such as tidying up, feeding, washing and so on takes at least three times as long as one is used to." This demands such large resources that it requires increased staff in the ward as a whole.

Among other things it was wished for a limited amount people involved with every ME patient because "it is difficult for the patient to relate to too many of the staff". Here one wished for a lot of accommodation to reduce the amount of people in the team.

A few involved also wished for everyone concerned to be able to see warning signs of deterioration and take precaution- " for example sleep, chest pain, blurred vision, runny eyes, headache, pressure on the forehead, sweaty palms, cold extremities, tingling of toes and

fingers, sound of voice". The carers also had to act as the ill person's spokesperson to the outside. ME patients have to mobilize to be able to talk and cannot always talk when it suits others.

Forward planning

Prediction and the possibility of being as well prepared as possible for what is happening and when, is vastly important for the ME patient to be able to manage the daily life. Ordinary home nursing care doesn't therefore work well. To be able to take care of the patient's "physical, psychological and social needs demands a certain amount of understanding of the diagnosis (complexity of problems)", as expressed by one of the carers. For example, to understand the consequences if one arrives a few minutes late. "We set alarms and change times for other tasks so that we can be precisely with an ME patient. If we don't attend we know the consequences for the patient becoming worse and having to, for example, rest a day or two afterwards to recover." Another one explains how deterioration was triggered by the cleaning staff being five minutes late.

The two institutes which followed detailed instructions from relatives, and took patients' wishes to the point, had experienced that this worked and the ill person improved. A leading caregiver was surprised at how little extra work it took to make carers come at agreed times and do all the tasks exactly in a way the patient advised – even though the ill person could additionally call for help outside the agreed times.

Many called for information well in advance before the patient arrived to the ward, while others had had enough information from relatives. Many put weight on the usefulness of important people in the ill person's network. Many on the other hand called for professional guidance, courses and seminars. The setting up of an ambulant specialist team was suggested, possibly regional ME wards.

Cooperation

Coaxing and stimulation can have the opposite effect of that which was intended. The ill person wants to, but can't, and becomes frustrated over coaxing – if it is not always so well meant: "It is important when advising the staff connected to the ME patient that one has to think differently compared to how one thinks with other patients in the ward, for example patients in rehabilitation, long term patients, and others." As a consequence of improvement there is often a need for stimulation and a big need for talking. "Let the patient make contact without him being bombarded with impressions...". One can for example "respond with cards or simple nods". In other words: Let the ill person take the initiative themselves.

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The staff often became tired in one way or another. It could be to do with constant arranging, the special considerations one had to take into account all the time, and to be related to the ill person's problems of accepting the diagnosis, their frustration of not being able to do as much as they wanted, set backs and so on.

It was pointed out that a care plan was important to ensure that everyone gave the same treatment. Carers who would be part of the team had to be carefully chosen:

"The medical follow up [...] is important, but the personality of the carers [...] is equally important and has to be appraised accurately. One has to have both nurses and nursing assistants in the team, but it is not necessary to have only professional staff as long as they [...] understand the illness and are willing to take on the challenge. The illness and its symptoms can seem challenging and the staff have to be well prepared and in a position to handle this in a confident way both in the presence of the patient and others. It demands confident people who can pacify and who can see the fluctuations the illness brings. It can be difficult to tackle the behavioural pattern when the care is very detailed and it is the patient who steers what shall happen and when. The negotiation of this (with the ill person, added by writer) can have negative consequences for the illness development. It is important that the staff themselves are willing to be in with the resource team because this is demanding 'one to one' care. [...]"

The staff also has the need for 'debriefing'. This is not common in a nursing home and one has to set aside a way and time for this.

The role of Relatives

ME is a long term, demanding condition which takes the relatives' time, and where all involved have to live with great uncertainty not only for the future, but for what every single effort can bring on – the daily as well as the extra ordinary ones. The risk for a relapse is always present, and poorly ME patients have very small margins. In this context the relatives were mostly seen as a resource. Often they were in a position to guide both beforehand and during the stay, and they acted in various degrees as relief persons. They were also better than the staff in registering a patient's deterioration and could act as spokespersons for the ill person. Many take on the role as the extended arm of the ill person.

The staff expressed on the other hand also a wish for enough time and resources to be able to look after the relatives better: "As it often involves young people it is important that one has also time for the family [...]. The life situation for the whole family becomes very insecure, both because at the moment there is so little knowledge

of the illness itself, individually how the illness runs its course and what timescale we are dealing with."

COMMENT

The results confirm the expectation of relatively similar answers even though not everyone brought in the same points. The task opened up for suggestions and reflections, and it was varied how thoroughly reasons were given. Some opinions appeared already during the first contact and are included to complement the picture.

Everybody emphasized structure initiatives, especially in connection with screening and dining area, and professional guidance. A few also called for readiness for conflict solving and "debriefing". Several pointed out the need for specially selected staff, great flexibility and extra time because ME patients put demands on staff resources both physically and psychologically. To be able to prioritise ME patients, it was necessary to have extra staff to solve problems elsewhere in the ward. Alternatively one had to set up personal ME wards. Even though relatives were seen as a resource, a few also saw the need to be able to better look after the relatives, also family members who were not directly involved in the care.

Some of the differences in the answers are due to different prerequisites regarding the physical conditions of the institution and existing competence. Some are also due to unequal aims regarding the stay and treatment environment in general. Those who actively rehabilitated differed from the pure care wards, mainly regarding expectations of results.

Obviously frustration regarding the illness was expressed more clearly by both those among the ill and carers who aimed for advances via mobility. Even if the expectation is improvement over time with ME, the improvement is mostly very slow, with major or minor relapses when limits are exceeded or with extra strain which is outside the ill person's control, such as moving, infection or a shock of noise. An approach with preplanned aims is in contrast with the nature of the illness unless the aim is stabilisation, which can be achieved most easily by screening against sense stimulation and limiting activity to a level the ill person can tolerate without bringing on a reaction. At the same time there needs to be an activity plan within the tolerance limit. The thought process is in other words opposite of the usual rehabilitation, where active or passive mobility is guided by tolerance levels being pushed in order to get results.

With stabilisation over time the tolerance ability in different areas increases unevenly. There is being created a palpable energy reserve which can be used

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in *small doses* with pauses in between in such a way that there is time to register a prospective reaction. The improvement starts with a concept of finding out what the ill person can tolerate out of the different challenges, and then these are tested out carefully with gradual introduction of light and sound, new foods, elevated position and so on, and active movement of muscles and joints, preferably without weight bearing to start with. It is considerably harder to work *against* gravity than it is *with* it, a relationship that was described as early as 1934 (Gilliam, 1938). Planning and personalised exercises can be useful so that the ill person doesn't spontaneously increase physical activities too soon and too long while improving. Passive mobilisation and/or massage is validated if it increases well being. ME patients experience well being with an activity within tolerance limits and do not need encouraging. They rather need to be told to take rest breaks *before* they reach their performance limit so that they don't push for a reaction ahead of them, with increased symptoms and lengthened recovery time as a result.

The impression was that rehabilitation institutes aimed to find an optimal balance between pushing the limits carefully and thereafter stabilising with rest, but found it difficult to calculate the length of the necessary stabilisation, or what would trigger a reaction. The result was frustration both among patients and carers when there was a relapse. It is possible that some of the pressure of expectation is created by the false impression that micro training is favourable with ME. Such an approach goes against all experience and is based on a concept of *fatigue* being caused by an underlying lack of motivation, which is postulated in the so called Oxford criteria (or similar psychosomatic interpretations) which form the basis of many of the studies concluding that GET (Graded Exercise Therapy) or CBT (Cognitive Behavioural Therapy) are good for "chronic fatigue syndrome" (Kreyberg, 2004a).

CBT and GET are activating therapies which do not take into account the ME patient's tolerance limits in any other way than that taking part is voluntary. The therapy is offered and therefore caters for the patient's experience of being ill. Such recognition gives hope after years of rejection and disbelief, which many have met within the health care system and/or family. Studies which show positive outcomes for treatment in no circumstances include the most severely affected patients who are not able to attend treatment.

The principles of ME treatment are the same regardless of the severity of the illness, but the ill person's performance abilities are diverse, and efforts for relief follow thereafter. One has to know the

condition can go within hours or days from being self-supporting in several areas to needing fulltime care, and even someone with a high grade of autonomy can be totally exhausted during parts of the day, without an ability to have a conversation, call for help or look after oneself.

A severely affected patient is extremely vulnerable and unstable so that the smallest effort can trigger a reaction. Small details will influence the everyday life a great deal in good and bad, both for the ill person and carers. This can be both demanding and rewarding. It is a big improvement when the ill person can do something themselves, for example lift a glass up to the mouth or type in a telephone number. This saves the ill person from sensory input, which is being loaded by having a helper in the room. But the glass has to be kept at the right height, not be too heavy and so on. The care has to be creative, and carers have to learn from one another.

Rehabilitation and care go thus hand in hand, even for the very severely affected. Whether it deals with care or organising an activity by oneself, one has to be aware of the pattern of the ill person's limits which are not usual in other illnesses – and this at such a detailed level is difficult to imagine. In addition one has to be practically odour free, sound free and invisible.

The carers have to develop increased awareness in order that the patient can be saved from using energy to give instructions. They have to do their work and then leave the room because every attendance drains the mental capacity of the patient. On the other hand it can help if (*continued on page 15*)

Facts on ME

In ME/CFS there are three main abnormalities in gene expression studies: these involve the immune system, mitochondrial function and G-protein signaling.

There are seven genes upregulated in ME/CFS – those associated with apoptosis, pesticides, mitochondrial function, demyelination and viral binding sites

– J Kerr, St. Georges, London

(as listed in the IiME Quotable quotes Booklet)

Experiences of Care in Institutions with Severely-Ill People with ME (*continued*)

someone is around when there are severe and constant symptoms because it gives security and certain diversion.

It can be impossible to hold a tooth brush, fork or pen or hold a telephone conversation, yet still be possible to press an sms message with the hand resting on support. Such apparent inconsistencies in what the ill person can and can't do, show a totally characteristic pattern, but often becomes a source of conflict amongst the staff.

These conflicts have to be acknowledged early and have to be solved by someone who knows the nature of the illness.

Improvement requires more stimulation and contact and the staff becomes easily overworked when the ill person's capacity increases. The capacity to talk by oneself is greater than the capacity to take input from others or enter into discussion, which demands adaptation of concentration from outgoing to incoming. All adjustments are abnormally demanding with ME. Even though this wasn't directly formulated, this insight was expressed in different ways, also considering the difficulties with transport, change of staff and similar.

One area where the answers were somewhat different involved food and food intolerance. Food intolerance increases symptoms, and a severe patient becomes just quieter. It is obvious that one can't experiment with activities even if the rules allowed one to do so, and that the institution should be able to take this into consideration. Here the rules have to be adjusted to the nature of the illness. It is known from experience that people with ME all over the world spontaneously change to a lighter diet with lots of fruit and vegetables. Thinking of the unstable circulation that is a trademark of ME, it is maybe not unexpected as one knows that several litres of blood is redirected to the intestine after a meal, and that the composition of the diet's nutritional content can make a big difference. (Waalder, Erikse & Janbu, 1990; Waalder & Eriksen, 1992; Eriksen, Waalder, 1994; Waalder & Toska, 1999).

Those who didn't have previous experience of ME patients, wished to a greater degree for medical justification to support the care being given. A few also expressed a certain ambivalence toward relatives' strong opinions. Those who knew the patient and/or relatives beforehand, were more open for their expertise even if the illness was not medically understood. Even though performance targets were not asked for here, it was clear that systems which were outlined by patients/relatives were followed because they worked well.

There is no overview of how ME is distributed in the population. Hospital statistics can show the relative emphasis of those with the strongest resources. There can be a large hidden number among drug users,

students and the young unemployed, farmers, artists, pensioners, vagrants and misdiagnosed people in locked wards in psychiatric hospitals (Kreyberg, 2004b).

This small survey shows how important experience is in the work with ME. It would be preferable to do a wider survey of the competence that exists all around the country, and build on this in order to begin to establish adequate and decentralised services for a very vulnerable and forgotten group of patients as soon as possible.

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ME Story

Throughout school, I was always exhausted and finally came down with EBV when I was sixteen. Although all my friends had mild cases of this, I was incapacitated to the point that I was hospitalized at times and had to leave school for months while I recovered. By now, I was beginning to wonder about my health. I was the "sickest" person I knew with the lowest pain tolerance, despite eating well and exercising. The GP hardly acknowledged me, and told me that it was normal and that I should stop being a hypochondriac. To appease me, he ran various tests and after finding nothing serious or conclusive, told me that he had been right and I should just rest.

Now, nearly eight years later, going from a student at the top of my class with an unlimited future to a dependent, rather helpless person with no real hope for healing is something that only others in this situation can understand. Meeting new people, and having them ask, "what do you do?" makes me cringe. The amount of shame and isolation at times is unbearable, but there is also a glimmer of hope that with greater understanding will come better treatments or at least compassion.

- Vickie

Student Doctor

"I am horrified, but not entirely surprised by the behaviour of the GPs and psychiatrists involved in this case (the Sophia Mirza story).

I am currently medical student, and I can promise you that I will never forget this case when I am a doctor.

I think that the attitudes towards CFS are changing (no doubt largely thanks to Sophia and her mother), but there are still many women who are treated as mentally ill, simply because doctors cannot readily explain the causes for their disease.

I send my wishes for full recovery of all the patients using [this site](#) and thank you for sharing your story."

- Daphna

ME News from Around Europe *from Sweden*



Legislative Victory in Sweden for People with ME/CFS

In Sweden, there is still an abysmal lack of specialist care (or any care for that matter) for ME/CFS-patients. However, there is some good news to report. We gained some attention (and many new members) last year when a well-known MP spoke of her illness in an evening newspaper. ME/CFS, like many other illnesses, is still in practice an illness of criteria, in spite of progress in research done in recent years. This has lead physicians and, even more so, representatives of the Social Security system in Sweden to wrongly assume, that the patients are fit and able to work.

Even some of those who are severely afflicted have been refused Social Security benefits, because of lack of objective, measurable signs of their illness.

"You can be cured of ME/CFS if you jog in the woods 10 kms, 3 times a week".

In a regional law court, the local association RME Västernorrland recently reached a successful verdict for one of its members. It states that the grade of disability of a person should be the ground on which compensation from Social Security should be based, regardless of objective medical findings. Although this verdict is not of precedent character, RME Sweden still considers it to be a great victory, bringing us hope for the future.

More news from Sweden:

In 2007, RME, the Association for ME/CFS patients in Sweden, carried out a questionnaire survey amongst their members aiming to assess and elucidate the current situation for ME/CFS patients in Sweden. The survey comprised 142 questions. The aim of the survey is to increase knowledge about ME/CFS and to improve medical care for this group of patients. We are currently presenting the results of our survey to political, social and medical authorities. 210 out of 380 members filled out the questionnaire, i.e. 55 %. 183 of these fulfil the Canadian criteria for ME/CFS. 178 have been given the diagnosis. 136 fell ill after infection.

been most difficult with having this illness. Here are three typical answers:

"Being so exhausted that I just can't stand upright or feel any interest in what is going on around me. The inability to think clearly or concentrate on anything".

"The physical "restrictions" because of exhaustion, the social isolation due to lack of energy".

"The attitude of authorities, medical service providers and people around me in general. Suspicion,

making light of the illness, questioning it and the constant struggle to try to be taken seriously and get adequate help".

33% of the participants in the Survey were told by physicians that the illness does not exist, in spite of the fact that most of our members were diagnosed with the illness by (other) physicians! More than 33% have heard comments such as:

"If you have ME/CFS we don't take any tests".

"That illness is not listed anywhere".

"If one wants to get ones' health back one does".

"The illness is not considered or regarded as a diagnosis".

"You can be cured of ME/CFS if you jog in the woods 10 kms, 3 times a week".

"It is not an illness but an imagined syndrome". Etc.

We are hoping that this survey will help us change the general attitude toward ME/CFS-patients in Sweden.

In Stockholm, the regional health care authority has commissioned a report into the situation for patients with ME/CFS. After several years delay this report is now to be presented at the end of May. Two patients' representatives have been included in the reference group connected to the report, along with a number of health care professionals with varying degrees of understanding of the illness. At this point we don't know the outcome of this report, but we are hoping for the best. After the report comes out, the county parliament will probably address a motion to reinstate a specialist ME/CFS clinic. This is important for all of the country, because where Stockholm leads other regions may follow.

On May 28th 2008, RME Stockholm are arranging an event on the theme of providing medical care for patients with ME/CFS. The main speaker will be Dr. Daniel Peterson, and we will also hear from two Swedish physicians (Prof. Birgitta Evengård and Dr. Olof Zachrisson) as well as leading regional healthcare politicians. This will be a well-timed event which will tie together the healthcare report, the RME patient survey, and the desperate need for medical care, and we plan to make a big fuss in the media! (If anyone wants to help out, feel free to contact us at stockholm@rme.nu)

Another local association, RME Göteborg, is planning two seminars in the autumn of 2008 – one for physicians and other health care personnel and one for ME/CFS-patients in the region. So far we are happy to note that two physicians, who are both well known in Sweden, have accepted our invitation, namely Dr. Paul Kavli, Norway, and Dr. Daniel Peterson, Nevada, USA. We hope that we will be able to carry this out in a successful way and that it will lead to positive results for us, who have this debilitating syndrome.

This article was supplied by RME— the Association for ME/CFS patients in Sweden.

ME News from Around Europe *The Netherlands Calling!*



The developments in the Netherlands in the last years do not raise any hope for improvement in the future. After all those years it has become clear that solid medical facts alone will not be sufficient to win the "war against ME".

In 2005 the Health Council of the Netherlands, which almost completely consisted of proponents of the psychosocial school, published its "biased" Advisory Report for the Dutch Government: ME doesn't exist, CFS has no biological origin, but must be considered a stress/personality disorder, biomedical research is useless, most patients can recover by cognitive behavioral therapy. The report trivialized, ignored or dismissed all available biomedical evidence. It can be found at: <http://www.gr.nl/pdf.php?ID=1169&p=1>. Although all state members are bound by international law (WHO), CFS was "not recognized as a disease" by the Dutch Minister of Health. ME does not even exist...

Thanks to the combined effort of many (Dutch and foreign) patients writing politicians, supplying them with facts about ME/CFS, CBT/GET and "evidence-based medicine", the parliamentarians "decided" that more than half the budget should be spent on medical research. The Funding Allocating Organization decided otherwise! Politicians did nothing to correct the "error" of the executive agency, despite conflicts of interest (e.g. allocating budgets to yourself/colleagues etc).

Patients are represented by some organisations with a "good working relationship" with the Wessely-driven "Fatigue Experts" of Nijmegen University or who are unwilling to make clear

choices, (e.g. ME/not CFS, Canadian Guidelines/not Fukuda or Reeves). The fact that there are almost no medical specialists dedicating their case to patients, means many ME patients do not feel to be represented.

When the occasion arises (for example the publication of the very poor results of the Belgium "expertise centres", implementing the "CBT/GET-paradigm", and the publication of the Gibson Enquiry Report) patients write to politicians to plead for a fundamental change of course.

The response of the new Dutch Health Minister to a petition, backed up by 20 pages of solid scientific facts, (for a summary see diagram Science and Fiction—below), didn't address a single issue put forward: CBT/GET is the only answer...

The dramatic situation of patients in the Netherlands will only change when scientific breakthroughs in the future can no longer be denied and/or when ME patients are represented by ME patient advocacy organizations making clear choices and organizing a creative, action-based, international strategy. That's why the Invest in ME, MERUK and IACFS conferences are raising hope.

Facts speak for themselves and will prove that patients were right all along.

This article was supplied by Frank Twisk and Jan van Roijen

	Science	Fiction
	Biomedical school Physicians	Biopsychosocial school Psychologists/psychiatrists
	Facts	Ideas and models
	Scientific contribution: 90% Media/political attention: 10%	Scientific contribution: 10% Media/political attention: 90%
Illness (scope)	M.E. The <u>characteristic</u> symptoms: • Exercise intolerance and • Neurocognitive problems	Medical Unexplained Syndromes: Chronic Fatigue (Syndrome), whiplash ..
Diagnosis	Clinical criteria e.g. Canadian Guidelines: hard - objective - physician (developed by international experts)	Symptom criteria CDC 1994 criteria (or Oxford criteria): soft - subjective - patient (developed by "fatigue experts")
Research	Scientific criteria Parameters Hard - objective - scientist	
Physical abnormalities	Many (too many to mention) More than 3.500 studies!	None Abnormalities denied: no arguments!
Cause (Explanation)	The big picture (derived from studies): Dysfunctional, hyperactive immune system ⇔ (persistent) infections with great impact on: • the (autonomic) nervous system, • the cardiovascular system, • the respiratory/energy system etc. ⇔ exercise capacity↓, recovery time↑	Dysfunctional beliefs/behaviour (past): Thinking that you are physically ill and avoidance of activity makes you ill.. Reduced stress response (now): infections a consequence, not a cause.
Therapy	• Eradicate infections: antibiotics, antivirals, • Improve the immune system: immune modulators, globulines, ... • Restore the intestine flora: probiotics, ... • Reduce oxidative stress: antioxidants, supplements, ...	Cognitive Behavioral Therapy: Learn to think you are not really ill: "learn" to cope with "illness". Graded Exercise Therapy: Exercise will result into recovery. Medical Therapy: Strictly forbidden: it will affirm illness!

ME News from Around Europe *from Finland*



RESEARCH from Finland (*Tutkimus Suomesta*)

An academic dissertation by Jaana Renko from Tampere University, Finland entitled Bacterial DNA Signatures in Arterial inflammation (2008) found signs of past bacterial infections in arterial plaques. Atherosclerosis develops over time starting often in childhood. Plaques develop in arterial walls resulting in narrowing of blood vessels. The plaques contain chronic inflammation and it has been thought for some time that bacteria are involved in causing the inflammation. The most identified of these bacteria are **Chlamydia pneumoniae** and oral bacteria.

Jaana Renko examined arterial samples from autopsies and surgeries and found high overall diversity of bacterial DNA in the atherosclerotic coronary and abdominal artery samples. Her study supports the theory that past infections increase the risk of developing atherosclerosis. It is not clear whether the bacterial findings are the cause or consequence of the illness. It may be that it is easier for bacterial DNA to stick to the damaged arterial wall. This study showed the role of inflammation and possibly infection in the role of atherosclerosis.

see <http://acta.uta.fi/pdf/978-951-44-7249-7.pdf>

Chlamydia pneumoniae is implicated in the development of ME/CFS in some cases and is one of the sub groups for which further research is required. The most common causes of death among people with ME/CFS are heart failure, cancer and suicide (Jason et al. 2006). According Jason et al. people with ME/CFS died 25 years earlier than rest of the population.

Canadian Guidelines

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

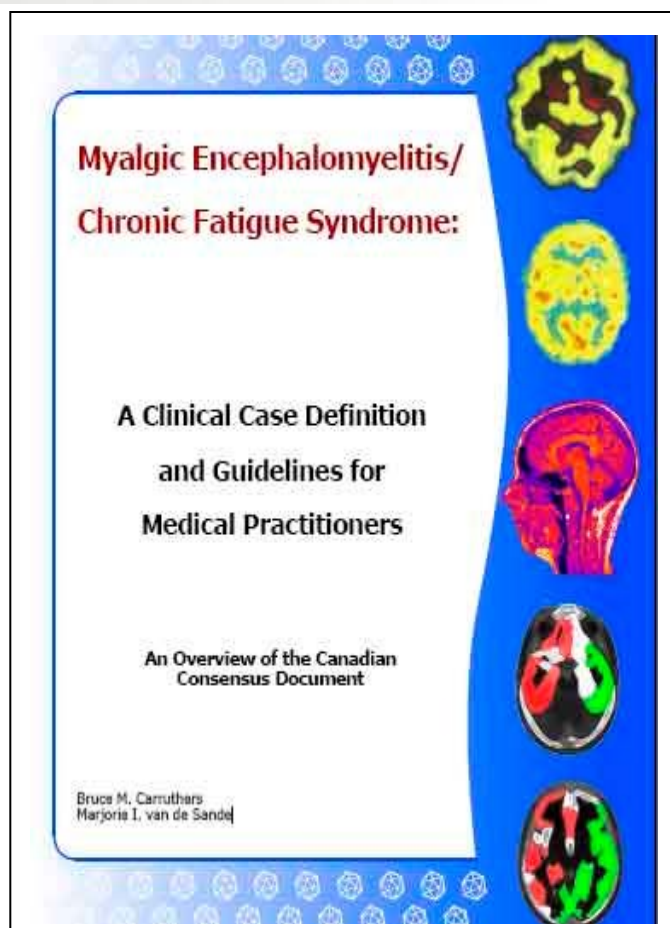
Described even by NICE as "*the most stringent*" guidelines available these are proper, up-to-date clinical guidelines which can also be used as a base for research criteria.

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. The price is 46p per copy plus postage & packaging.

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

ME/CFS as a Mitochondrial Disease

By Dr David Bell

(www.davidsbell.com)

(Invest in ME have been given permission by Dr. Bell to republish this article which first appeared in the Lyndonville News Vol 5 Nr. 2 April 2008)

Introduction

I get so angry when I read the nightmare stories many of you have experienced. All you did wrong was to get sick. Then the medical industrial complex made your life miserable. The medical industrial complex includes the drug companies who are not interested unless they make a big profit, the health insurance companies who will use any excuse to deny patients medications or testing, and the disability industry who survive only because they take your money and deny benefits if you get sick. All of this is done under the guise of "modern evidence-based medicine". But evidence-based medicine only works in illnesses like hypertension where you have enormous funding.

I think I have become an old codger. Cynical, disappointed..... Enough of that. In my office I have a sign for ME/CFS patients "Whining will be allowed for ten minutes only".

Clinical Notes

In the past week I have seen two patients who had an exercise lactate test which showed an elevation of blood lactate after mild exercise. They were told by their physician that they had "mitochondrial disease". They were advised to take some vitamins, maybe some CoQ10, and have a nice day. Like nearly everything else, the term mitochondrial disease left these patients feeling bewildered and somewhat lost. While I agree that ME/CFS is a mitochondrial disease, this term needs clarification because ME/CFS is a mitochondrial disease like no other.

Until recently, when a child was diagnosed as having a mitochondrial disease, it was a disaster, even a death sentence, for it meant that there were major abnormalities in the mitochondrial or nuclear DNA that regulated energy production. Without energy (ATP) it is impossible to survive. These diseases are called MELAS, Kearns-Sayre, Leber hereditary optic neuropathy and so on.

Nearly three hundred mitochondrial illnesses have been identified from genetic mutations. It is a specialized area of pediatrics, where it is possible to measure severe abnormalities in the mitochondria on muscle biopsy testing. This is what most clinicians think of when the words mitochondrial disease are mentioned, but these illnesses do not, in general, apply to ME/CFS. Many

David S. Bell, MD

Dr Bell completed post doctoral training in pediatrics in 1976 with subspecialty training in Pediatric Behavior and Developmental Disorders.

In 1978 he began work at the University of Rochester but soon began a private practice in the town of Lyndonville, New York.

In 1985 nearly 220 persons became ill with an illness subsequently called chronic fatigue syndrome in the communities surrounding Lyndonville, New York. This illness cluster began a study of the illness which continues today.

Dr. Bell is the author or co-author of numerous scientific papers on CFS, and, in 2003 was named Chairman of the Advisory Committee for Chronic Fatigue Syndrome of the Department of Health and Human Services. Publications include A Disease of A Thousand Names, (1988) and The Doctor's Guide to Chronic Fatigue Syndrome, (1990).

Dr. Bell currently practices general medicine in Lyndonville, New York with his wife Nancy, a family nurse practitioner. Roughly half of the patients seen in the practice suffer from chronic fatigue syndrome, fibromyalgia, orthostatic intolerance, and/or myalgic encephalomyelitis.

patients with ME/CFS have had muscle biopsies and most of the mitochondrial tests on these biopsies are relatively normal. We will return to why! this is in a bit.

What are mitochondria?

Think of mitochondria as the power factories of the cell. Nearly every cell in the body has them, usually around 500 or so in every cell. They take in oxygen and glucose and put out carbon dioxide and energy (ATP). There are two hundred different steps in this process and we will quiz you after this article. Actually all you need to know is ATP, the prime energy

(Continued on page 21)

ME/CFS as a Mitochondrial Disease (*continued*)

storage chemical (battery) of the body, and oxidative phosphorylation (ox-phos) the complex electron transport chains that do the major work. Because the mechanism of energy production is essential to nearly every cell, a defect will have symptoms in every organ system. Sound familiar?

Oxidative metabolism, the ability to utilize oxygen to produce energy, is quite efficient, and it is fascinating to look at the theories of how they came to be part of our cells. However, when the energy demand is excessive, the cells revert to a more primitive, and less efficient, form of energy production, anaerobic metabolism (metabolism without oxygen). For an interesting study on the anaerobic threshold in ME/CFS, see the literature review article that follows.

When to suspect mitochondrial disease. In a recent review article (Haas 2007) there is a list of symptoms that suggest looking for mitochondrial disease. Among these symptoms are neurologic symptoms such as ataxia, myoclonus, and encephalopathy, exercise intolerance, sensitivity to general anesthesia, and constipation. A score sheet has been developed to help in when to suspect mitochondrial disease and most ME/CFS patients would fall into the positive range. For lots of information on mitochondria please go to www.mitosoc.org, but remember that they are talking about "conventional" mitochondrial disorders, not ME/CFS.

There is another form of mitochondrial disease, or secondary mitochondrial disease. In secondary mitochondrial disease the primary problem is not with the mitochondria, but some other problem messes up mitochondrial function. There are many illnesses where the primary defect ends up causing problems with the generation of energy in mitochondria. For example, thyroid hormone is needed for successful oxidative phosphorylation. With hypothyroidism (low thyroid) energy production is impaired and fatigue, weakness, temperature regulatory problems, and difficulty concentrating result. This is one of the reasons that when you start to describe fatigue to your primary care physician, he or she begins to write out a script to test for thyroid hormone.

So what is the problem? Why has ME/CFS not been diagnosed, studied and classified as other mitochondrial diseases? There are several reasons:

- a) Mitochondrial disease is thought of by clinicians as a fatal disease of infancy, not one that occurs later in life.
- b) Mitochondrial disease is usually thought of as a fixed, structural disease, and ME/CFS is a relapsing, remitting illness with some persons even becoming entirely well.
- c) Mitochondrial diseases are hard to diagnose, requiring muscle biopsies and detailed ox-phos testing
- d) Ox-phos testing is often normal in ME/CFS, and this

has been the critical piece that has diverted attention from mitochondria.

e) Physicians are used to thinking of organ-specific diseases (liver, kidney, etc) and mitochondria are in all cells.

f) Few physicians have taken ME/CFS seriously until recently, and research in this area has been scant.

Of the above reasons, only reason "d" is important to us here. In 1990 I did a muscle biopsy study on ten ME/CFS patients with Dr. June Aprille. All ten persons had relatively normal ox-phos studies. Although we did not publish this finding, it is consistent with the few published studies that have been done. How can you have mitochondrial disease when the mechanism tests normal? I think that the answer to this paradox is just around the corner.

Hypothesis: If you have a patient with emphysema who is sitting in an armchair, he or she is not out of breath. You can measure the damage in tests, but to make symptoms, you have to "stress" the system – make the patient run up and down stairs. If a person with G-6-PD deficiency is sitting quietly, the blood looks normal. But feed this person fava beans and abnormalities quickly become obvious.

Persons with ME/CFS keep themselves at a balance point. They rest for two hours, then do a half hour of activity, then rest, then do more and so on. The worse the illness, the less overall activity is possible. If a ME/CFS patient does absolutely nothing for a few days, they usually feel pretty good. But go to the shopping mall for eight hours and the crash occurs. Here is the problem: in the patients studied for mitochondrial disease, they have been resting up (staying above the balance point) and a muscle biopsy done at that moment will probably not show much. But have a ME/CFS patient exercise, and then study mitochondrial function. My hunch is that the ox-phos reactions will be seriously impaired, but this has not been systematically and methodically done. For me, this hypothesis is generated by the VanNess, Snell, and Stevens study described in the next section.

There are lots of studies that implicate mitochondrial problems; Dr. Kuratsune and carnitine. Dr. Vernon and genomics; Dr. DeMeileir, Dr. Pall, Dr. Cheney and many others. But this problem cannot be studied in tiny fragments. It is time for a good study to look at the different steps of the body's ability to generate energy. Lets hope we get to see it within our lifetimes.

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(Continued on page 22)

Review of the "Two-day Exercise Test"

Literature Review

Review of the "Two-day Exercise Test"

In the most recent *Journal of Chronic Fatigue Syndrome* (Vol 14, Number 2, 2007) there are two articles which may be the first to offer an objective proof of disability in ME/CFS. More importantly, if shown to be correct, they may give us an avenue to test and measure the biochemical abnormality which causes the symptom pattern. In this short review I would like to review these two papers and present a case of pediatric CFS which demonstrates the same abnormalities.

In the first of these papers, Margaret Ciccolella, a lawyer, teams up with Staci Stevens, Chris Snell, and Mark Van Ness of the University of the Pacific to review the legal issues surrounding exercise testing and disability (1). As everyone familiar with CFS well knows, insurance companies require proof of disability, which a standard exercise test may or may not demonstrate. However, even if disability is present, insurance companies have been quick to say that the patient was not trying hard enough, or that the patient is de-conditioned. The second paper of this series by VanNess, Snell and Stevens explain the two-day exercise test and presents results for six patients with ME/CFS (2).

As clinicians have observed, the symptom of "post-exertional malaise" is one of the most distinguishing features of CFS. This symptom is listed as one of the eight in the criteria of the Centers for Disease Control (3), and is central to the diagnosis in the recent Canadian Case Definition (4) and the proposed pediatric case definition (5). It is beginning to look like the symptom of post-exertional malaise is at the root of disability, and may be central to the pathophysiology of this complex illness spectrum.

A person with ME/CFS may be at home for several days doing little except basic activities of daily living. When this patient decides to go shopping, he or she will drive to the mall and shop for one or two hours. During this time, observers would say that the person looks entirely well, not appearing disabled. However, following this activity the patient will experience an exacerbation of pain and other symptoms of ME/CFS. This exacerbation may last one, two or three days, and, in my opinion, the more severe the illness, the longer and more severe the exacerbation. This phenomenon is known as post-exertional malaise. The symptoms of the illness (malaise) are exacerbated by mental, physical or emotional activities (post-exertional). In an employment environment, the patient may be able to do a job well for one or even several days. However disability lies in the inability to sustain this normal ! level of activity. The two-day exercise test is the first to begin to explain this phenomenon.

The exercise test is no different from what has been used

for years. The patient exercises on a stationary bicycle (bicycle ergometry) and breathes through plastic tubing to measure the concentration of oxygen and carbon dioxide as well as the total amount of air. The six female patients and six sedentary matched control subjects of the study were all able to achieve maximal exertion. The ME/CFS patients had a slightly lower VO₂max (maximal oxygen utilization) than controls (28.4 ml/kg/min vs. 26.2 ml/kg/min) and lower VO₂ at anaerobic threshold (15.01 ml/kg/min vs. 17.55 mg/kg/min) on the first day of exercise testing. These values are not dramatic nor are they statistically significant. It is on the second day that interesting results are seen.

The same test was repeated the following day for all twelve subjects. As is often the case, sedentary controls improved slightly in their ability to utilize oxygen, going from 28.4 to 28.9 ml/kg/min for VO₂max and from 17.55 to 18.00 ml/kg/min for oxygen utilization at anaerobic threshold. The CFS patients however worsened in both categories: VO₂max fell 22% from 26.23 to 20.47 ml/kg/min, and oxygen utilization at anaerobic threshold fell 27%, from 15.01 to 11.01 ml/kg/min. To put this into perspective, these values are in the severe disability range on the AMA guidelines, and the decline in function from day one to day two cannot be explained by inactivity.

Sedentary or de-conditioned persons do not change their oxygen utilization because of an exercise test. Even patients with heart disease, cystic fibrosis or other diseases do not vary more than 7% from one day to the next. However, the patients with ME/CFS in this study had a significant drop; something occurred because of the test on the first day interfered with their ability to utilize oxygen on the next day. And this is exactly what patients with ME/CFS have been describing with the symptom of post-exertional malaise. As the authors state, "The fall in oxygen consumption among the CFS patients on the second test appears to suggest metabolic dysfunction rather than a sedentary lifestyle as the cause of diminished exercise capacity in CFS."

Conclusions: The results of the two-day exercise testing are objective and not dependent upon subjective symptoms. Moreover hypochondriasis, intentional falsification, and/or poor effort can be detected by the physiologic parameters. Therefore the two-day exercise test, if confirmed in a larger trial, could become a clinical trial end point. More importantly, evaluations could be designed which would demonstrate the specific metabolic abnormality generated by the exercise of day one and demonstrated on the second day exercise test. It would be my hope that these findings be explored without delay.

1. Ciccolella M, Stevens S, Snell C, VanNess J: Legal and Scientific Considerations of the Exercise Stress Test. *JCFS* 2008, 14(2):61-75.

(Continued on page 23)

Review of the "Two-day Exercise Test" *(continued)*

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4. Carruthers B, Jain A, DeMeirlier K, Peterson D, Klimas N, Lerner A, Bested A, Flor-Henry P, Joshi P, Powles ACP *et al*: Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition. diagnostic and treatment protocols. *J Chronic Fatigue Syndrome* 2003, 11(1):1-12.
5. Jason L, Bell D, Rowe K, Van Hoof E, Jordan K, Lapp C, A G, Milke T, Torres-Harding S, De Meirleir K. A Pediatric Case definition for myalgic encephalomyelitis and chronic fatigue syndrome. *J CFS* 2006, 13:1-44

Lyndonville News

Volume 5, Number 2; April 2008

Information and Support for the ME/CFS/FM Community

David S. Bell MD, FAAP, Editor

Facts on ME

Before medical science discovered the aetiology of multiple sclerosis and Parkinson's Disease, people afflicted with those disorders were subjected to medical dismissal and to charges of hysteria. Those with ME/CFS are suffering the same fate, because even though so much is now known about the pathology, precise causation remains elusive.

Causation will continue to remain elusive as long as Wessely School psychiatrists advise the UK Government that no tests should be performed on those with ME/CFS, especially immunological and neuro-imaging, investigations which, when carried out elsewhere, have already delivered evidence of the organic nature of the disorder.

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as listed in the liME Quotable quotes Booklet)

Person With ME

Dear liME,

Thoroughly enjoyed reading April's newsletter. Packed full of information and sensible opinions on all aspects of ME research.

I agree with liME that it is wise to be wary of the plan to "fertilise cross-disciplinary research activity in this field."

I believe that any attempt to co-ordinate research amongst researchers who promote that ME is the same as CF, under the guise of CFS, will not bring about any medical understanding of the cause and progression of the illness.

I also believe that it would be ethically wrong to work in tandem with any psychiatrist, or follower, who works to the premise that ME is just another form of CF called CFS and that it should be researched, treated and managed as such.

The MRC neither understands nor cares that ME sufferers will never forgive or forget the unnecessary suffering caused by the opinions of a few psychiatrists. If they did understand they would realise that it is quite a repulsive notion to promote the idea that our tormentors will now become our saviours.

It is simply too late for the bad guys to become the good guys. (Will they admit that they were wrong all along?)

When will the MRC, DoH, CMO and the NHS inform psychiatrists that they should not be involved in ME research at all?

Until this happens ME research will continue to stagnate in the CF pool.

On a lighter and more positive note, "Good luck" on May 23rd when liME hosts the third ME conference.

I look forward to ordering my DVD and learning about biomedical research into ME.

- C

WHO GETS ME AND WHY

The role of impaired capillary blood flow in ME

INTRODUCTION

There is no doubt that one of the major problems facing those who suffer from myalgic encephalomyelitis (ME) is the persisting disagreements about the name of the disorder. To a great extent this was exemplified by a group in Florida who decided to change CFS to ME. For that reason alone it is important to recognise Ramsay's concept of ME so that those with the problem can be identified and separated from other illnesses such as chronic fatigue syndrome (CFS) and post-viral fatigue syndrome (PVFS). Until this happens, ME people will continue to be disadvantaged.

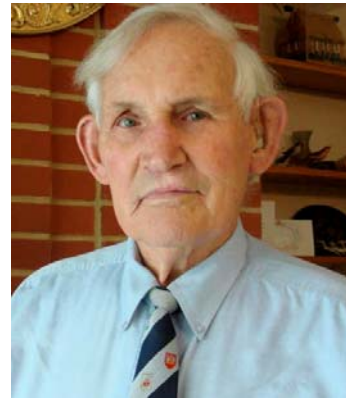
In the preface to the second edition of his book, "Myalgic encephalomyelitis and postviral fatigue states," published in 1988, Dr. Ramsay wrote, "When on the occasion of a recent ITV programme on the subject of myalgic encephalomyelitis, an immunologist stated that 'ME and PVFS are regarded as synonyms' I realised that my objection to the latter term was fully justified and that it was incumbent on me to show that such a statement is blatantly untrue." He stated also, "The clinical identity of the myalgic encephalomyelitis syndrome rests on three distinct features, namely:

1. a unique form of muscle fatigability whereby, after even a minor degree of physical effort, three, four or five days, or longer elapse before full muscle power is restored;
2. variability and fluctuation of both symptoms and physical findings in the course of a day;
3. an alarming tendency to become chronic."

In the text, Ramsay discussed the multiplicity of symptoms in three groups. 1. Muscle phenomena. He noted, when discussing the time for the restoration of normal muscle power, "...it is important to stress the fact that cases of ME of mild or even moderate severity may have normal muscle power in a remission." 2. Circulatory impairment. This was manifested as cold extremities and facial pallor. 3. Cerebral dysfunction was manifested in many ways including memory problems, difficulties with concentration and emotional lability. It seems rather surprising that Ramsay did not link the dysfunction of muscles and brain to the recognised problems of circulatory impairment. He stated however, "The chronic case can take two different forms. In the first there is a recurring cycle of remission and relapse. In three doctors who contracted the infection between 1955 and 1958, the alternation of remission and relapse continues. The second form is more tragic and no remission occurs." It is clear that remissions play a large part in Ramsay's concept of ME.

The introduction, by the Centers for Disease Control in

By Les Simpson



Leslie Owen Simpson currently lives in Dunedin, New Zealand, but has lived in 6 countries and from 1991 travelled and lectured extensively. He graduated from the University of Otago, majoring in botany and zoology and later worked in the field of tissue transplantation. He became a WHO lecturer in medical biology at the Central Medical School, Suva, Fiji, with a brief to establish a medical biology department and train technical staff. After a spell in teaching he was appointed research officer in the Pathology Department, Otago Medical School, studying the pathobiology of the first animal model of lupus erythematosus, the NZ Black Mouse. After a post-doctorate in experimental pathology he worked as a senior research officer. Although retired in 1985 he has continued to work full time in unpaid appointments as honorary research fellow, first in the Pathology Department and then in the Department of General Practice. In 1999 he set up Red Blood Cell Research Limited and continued his research on red blood cells and privately funded much of the research. He has had 125 letters or articles published in medical journals as well as numerous other articles in journals and textbooks.

the USA, in 1988, of the term chronic fatigue syndrome (CFS), almost immediately made life more complicated for ME sufferers, as the criteria for CFS were much more inclusive. Not only were ME patients gathered under the CFS umbrella, but also the results of Americans studying CFS tended to be adopted as being relevant to ME, and to a large extent Ramsay's experience was ignored. In most countries, despite the opposition of small groups, ME people were diagnosed as having CFS, even though there were no accepted

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WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

pathophysiologies for either diagnosis.

To a large extent this is the current situation. For example, a 2001 English publication titled "What is ME? What is CFS?" (1) discussed ME mainly in terms of the findings of American investigators, only a 1981 paper by Ramsay was quoted and no reference was made to either edition of his book. In 2007, The Nightingale Research Foundation published, "The Nightingale myalgic encephalomyelitis definition," (2) even though in their 1992 book, Dr. Hyde had suggested that "encephalopathy" was a more appropriate term. Primary ME was defined as, "...an acute onset biphasic epidemic or endemic (sporadic) infectious disease process where there is always measurable and persistent diffuse vascular injury of the CNS in both the acute and chronic phases. Primary ME is associated with immune and other pathologies." The concept of "...persistent diffuse vascular injury," would rule out any involvement of Ramsay-style remissions. It is clear that the possible role for shape-changed red cells as recorded in my paper in the 1992 book, was rejected.

At a meeting of Canadian and American investigators who were interested in ME, a consensus was reached and released as the Canadian Consensus. In 2007, a review was published under the title, "Definitions and aetiology of myalgic encephalomyelitis: how the Canadian consensus clinical definition of myalgic encephalomyelitis works." (3) It was noted, "To improve clinical observation, the Canadian definition and diagnostic protocol lays out several regions of pathophysiological dysfunction, as necessary components of the syndrome of myalgic encephalomyelitis, but the particular expression of symptoms within each region is contingent between individuals and their particular pattern is left open to be decided by clinical observation of the individual and later diagnostic classification." This 59 word sentence is typical of the writing, but the enclosed message is far from clear.

It was noted also, that, "The possible aetiology of myalgic encephalomyelitis is under scientific observation. This is done by experiment and by controlled observation. Many observers are following various lines of investigation and observation as to the aetiology of myalgic encephalomyelitis, which we are following with interest." This statement seems not to recognise that ME has been studied for 50 years. The crucial factor is whether or not like is being compared with like. Given the degrees of difference in the various definitions, there seems to be a grave danger that apples are being compared to oranges.

In general, two features of the paper stand out. No mention was made of Ramsay's work or of remissions and there was no indication that blood flow was a problem. Therefore it seems that because of the conflicting views of experts and a general lack of agreement concerning the aetiology and pathophysiology of ME, a small section of the community will continue to suffer a reduced quality of life while experiencing a variety of symptoms, which, if

they are lucky may disappear for variable periods of time during remissions.

WHO IS AT RISK OF DEVELOPING ME?

In any group of people who suffer from the same viral infection, most return to full health in less than 14 days, while a small proportion become chronically unwell. This implies that those who continue to be unwell (?ME people) are different from the normal population in some feature.

About the time I became involved with ME in 1983, I was developing an interest in the measurement of blood viscosity and blood filterability. Initially I studied blood samples from the blood donor panel, but through the good offices of Prof. J.C. Murdoch, who had a clinical interest in ME, I obtained blood samples from 21 female and 11 male patients with ME. Control samples were obtained from age and gender matched blood donors. Blood viscosity was measured at four shear rates and blood was filtered through polycarbonate filters with 5 micron pores at four levels of negative pressure. The results were published in 1986 (4) and showed that although there were differences in the results from blood viscometry of ME people and controls, they did not reach statistical significance. In contrast, at the lowest filtration pressure, the values for ME females were significantly different from controls, (an indication of stiffened red cells) but the differences in the male values did not reach significance. An examination of the data revealed that some ME values were near normal and would have influenced the results. The implications of the results were that ME people could be at risk of blood flow problems in the microcirculation because of the effects of poorly deformable red cells. It should be noted that for the assessment of filterability, EDTA-anticoagulated blood was used and filtration took place within half an hour of the sample being drawn. Subsequent developments from the simple technique included the washing of the red cells in saline, but such treatment greatly changed blood filterability. Our report concluded, "... advances in our understanding of the aetiology of the disorder will come from investigations in the acute phase, and blood rheology may be of value in identifying those who are acutely affected." Although non-ME subjects may have poorly filterable blood for 12 to 14 days after an infection, ME blood remains poorly filterable as long as they are symptomatic.

So ME people respond to agents which change the internal environment, by stimulating change in red cell shape and making them less deformable, probably because of a persisting, but unidentified factor in the blood. As will be discussed later, that factor has the capacity to switch off, resulting in a remission. Until the factor has been identified, it seems inappropriate to

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WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

consider cure, as an endpoint and my objective in treatment is simply to improve the quality of life of sufferers.

To a large extent it seems that clinicians take red cells for granted, ignoring the fact that the loss of the nucleus as the cell leaves the bone marrow, renders it incapable of independent existence, and at the mercy of its environment. There are many published reports which record the different ways in which red cells respond to change in their environment, both in vivo and in vitro, with the change in shape associated with reduced deformability. The significance of the reduction in deformability is that the average diameter of capillaries lies between 3.5 and 5 microns, whereas the diameter of a red cell is between 7.5 and 8 microns. Therefore, in order to traverse a capillary bed, red cells must be able to deform and any reduction in red cell deformability will increase the resistance to flow in the microcirculation.

A 1970 editorial (5) titled, "The importance of erythrocyte deformability," concluded that,

"...the remarkable deformability of normal mature erythrocytes appears to depend on at least three factors: (1) maintenance of the biconcave shape which in turn depends on a high ratio of surface area to cell volume; (2) normal internal fluidity of the cell which in turn depends primarily on the properties of normal haemoglobin; and finally (3) intrinsic membrane deformability which is significantly affected by the relationship between intracellular ATP, calcium and magnesium and may be affected by pH and oxygen tension in local regions of the microcirculation."

Therefore it can be expected that any change in the cell environment which alters any of those three factors will lead to a reduction in cell deformability. Although viral infections, which will alter the internal environment, are considered to be key factors in the aetiology of ME, other infections, inoculations, vaccinations, severe emotional upsets, herbicidal sprays and heavy physical activity have been reported as causal factors in ME. All those factors will alter the red cell environment. However, it needs to be emphasised that although everyone exposed to such changes will show shape-changed red cells, only a small proportion will go on to develop the symptoms of ME.

So those who are at risk of developing ME have some physiological difference which leads to a reduced ability to restore red cell shapes to normal. The action of the unknown factor [or factors](#)

involved may persist for 15 to 20 years or longer.

WHO GETS ME?

As the problems of poorly deformable red cells in

traversing a capillary bed will be greatest in small capillaries, it is proposed that a key factor in determining who gets ME is the anatomical feature of smaller than usual capillaries. The random distribution of clusters of small capillaries provides a basis for understanding the idiosyncratic nature of the symptoms of ME. This implies that some cases may exhibit only a few regions which become symptomatic, whereas other cases may have symptoms in many regions of the body. While the presence of smaller than usual capillaries may have little functional effects when red cells exhibit normal deformability, their presence will become obvious after exposure to an agent which alters the internal environment and stimulates change in the shape populations of red cells. Furthermore, during remissions, when red cell shape populations return to normal, normal functional status indicates normal rates of capillary blood flow.

Because a requirement for normal tissue function is a normal rate of capillary blood flow which delivers sufficient oxygen and nutrient substrates to sustain normal function and to remove metabolic wastes, it is clear that when shape-changed, poorly deformable red cells are in the circulation, capillary blood flow will not be normal. The severity of the consequences of impaired capillary blood flow will be determined by the tissue involved. Muscles, the central nervous system and secreting glands are particularly sensitive to oxygen deprivation which may lead to body wide dysfunction. It is not surprising that in ME most symptoms relate to those tissues.

Therefore it is proposed that those people who develop the chronic condition we call ME, share the common anatomical feature of having smaller than usual capillaries, the distribution of which will be marked by the development of symptoms when some agent induces change in red cell shape which makes them poorly deformable. Because many other chronic disorders exhibit changes in the shape populations of red cells, the presence of such cells is not diagnostic for ME. A 1992 paper (6) noted that, "Subjects

with the characteristic (of smaller than usual capillaries) would always be at risk of developing red cell shape-related impairment of capillary blood flow."

Thus, those who will get ME are the small proportion of the population who by chance have smaller than usual capillaries. The severity of the symptoms which develop in the presence of poorly deformable red cells will reflect the extent to which small capillaries are present in the microcirculation. Limited observations have left me with the impression that black and brown-skinned races have a lower incidence of small capillaries.

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WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

BLOOD FILTERABILITY AND RED CELL SHAPE

The findings of reduced blood filterability stimulated the thought that some change in the surface features of red cells might be involved (in the terms of Weed's concept). To explore this possibility, a technique used for the rapid examination of theatre specimens by electron microscopy was adapted to study red cell morphology. The key factor was that the blood samples (3 to 5 drops of venous blood) were fixed immediately by being added to 5ml of 2.5% glutaraldehyde in 0.1M cacodylate buffer at pH 7.4. After fixation for overnight, at least, the cells were dehydrated in ascending concentrations of ethanol to absolute, then passed through three changes of pure, dry acetone. A drop of the acetone-suspended red cells was placed on a glass cover slip fixed to an aluminium stub with double sided adhesive tape. After air-drying, the cells were gold-coated in a sputter coater, then photographed under standard conditions in a scanning electron microscope. The cells in the resulting micrographs were classified into six different shape classes and the proportions expressed as percentages of the total number of cells counted. The first series of blood samples assessed in this way came from healthy blood donors, and from the first sample it was clear that the current teaching that all red cells were biconcave discocytes was not sustainable.

In 1989 I was able to report that the red cells in immediately fixed blood samples from healthy animals and humans could be classified into six different shape classes. (7) Later in the year I reported that blood samples from patients with acute ME showed increased proportions of cup forms (stomatocytes), a form which is known to be poorly deformable. (8) At a meeting in India in 1992, I discussed the red cell shape changes which had been found in six chronic disorders. (9)

Studies of the relevant literature, while preparing those reports, revealed that there had been earlier reports concerning changes in the shape populations of red cells. From 1974-78, there had been several reports concerning red cell shape in patients with muscular dystrophy. However, only one study (10) used immediately fixed blood samples, and the results were different from those studies which had manipulated the blood cells prior to fixation. The authors (10) noted that they were unable to prevent unfixed red cells from changing shape, even in their native plasma in a refrigerator. This is the expected response of red cells to a changing environment. In 1977, it was reported that patients with Huntington's Disease had increased proportions of stomatocytes (cup forms). (11) Because increased proportions of stomatocytes would have an adverse effect on capillary blood flow, it is of interest that a 1985 study reported impairment of cerebral blood flow which

was shown to correlate with cognitive impairment of patients with Huntington's Disease. (12) Even though it was very likely that stomatocytes were responsible for the impaired cerebral blood flow, no reference was made to the 1977 study. In general there was no clinical interest in changed shape populations of red cells, and such reports provoked little continuing interest.

However, Mukherjee et al (13) were stimulated by our 1986 study of poorly filterable blood, to embark on a study of red cell morphology in ME people. They reported the presence of small numbers of grossly abnormal red cells. But the cells examined had been washed and centrifuged prior to fixation, and it is very likely that the abnormal cells were a result of the preparation technique. In the 13,000-odd immediately fixed blood samples relating to a number of chronic conditions in eight countries, which I have assessed, I have never seen a cell with the features of that described by Mukherjee et al.

At the Cambridge Symposium on ME in 1990, I reported that blood samples from another 99 patients with acute ME showed similar values for increased cup forms to those of the previously reported 102 cases (14). It was noted also that there were small numbers of cases which presented with increased proportions of flat cells or cells with altered margins. In hindsight, it now seems likely that those changes were the beginning of a trend to chronic ME, as by 1992 only about 5% of cases were presenting with the cup forms of acute ME, and increased flat cells was the most common feature of chronic ME. It should be noted that the title of the paper I submitted made no mention of chronic fatigue syndrome, and this was added to the title by the editors, without discussion.

Thus, the information relating to reduced blood filterability is reinforced and possibly explained by the changed red cell morphology seen by scanning electron microscopy, so impaired capillary blood flow can be expected. What is important is that change in the cell shape populations is not a benign event. Remember, for example, that Weed (5) had noted that the deformability of red cells depended upon, "...maintenance of the biconcave shape." Possibly of greater physiological importance were the findings of Vandergriff and Olson (15) that red cell shape was a determinant of the rate of uptake and release of oxygen. For example, crenated cells (cells with altered margins) were found to have a 45% reduction in the uptake of oxygen and a 23% reduction in release rate.

TIREDNESS, MUSCLE DYSFUNCTION AND CAPILLARY BLOOD FLOW

It is particularly unfortunate that the term 'fatigue' is used so frequently in the ME literature. Both Funk and

(Continued on page 28)

WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

Wagnall and the Oxford Concise dictionary define fatigue as the consequence of long-continued exertion, but ME people do not have to run up stairs to feel tired. The authors of a 1921 study of industrial fatigue noted that they could not measure or define 'fatigue' and it was recommended that, "The term fatigue should be absolutely banished from precise scientific discussion." (16) Sir John Ellis noted in a paper titled "Malaise and fatigue," (17) that patients seldom used such terms. Instead, "They complain of being tired and not feeling well...they say they are knackered, bushed, beat, washed out, drained or utterly exhausted.... They add that it started gradually some time ago, and then say their tiredness is inexplicable." Although the use of the term 'fatigue' may invite controversy, muscle fatigue is an accepted physiological condition. In accordance with the idea that poorly deformable red cells would impair capillary blood flow sufficiently for muscle function to be interrupted by an inadequate oxygen delivery rate, this concept was tested in ME people and in healthy subjects. A healthy young woman acted as a guinea pig and it was found that the repeated pulling of a trigger until trigger finger fatigue, led to a three-fold increase in cells with altered margins in the 35 seconds taken to induce muscle fatigue. (18) Unexpectedly, in applying for approval for a study involving ME people, the Ethics Committee ruled that ME was an unknown entity, but approval was obtained by substituting "subjects with chronic tiredness," for ME. The study took place at a weekend residential meeting of members of ME support groups where 69 ME volunteers took part. (19) After a 5-drop blood sample had been taken, the trigger of a model revolver was pulled repeatedly until the onset of trigger finger fatigue. A second blood sample was obtained and the

number of trigger pulls and the elapsed time were recorded. Five minutes later the procedure was repeated. Subsequently the procedure was repeated in 72 healthy controls who were police officers, firemen, army personnel, nurses and teachers. In general, the results showed that at baseline, ME people had different red cell shape populations from controls and they had fewer trigger pulls with greater changes in their post-trigger pulling blood samples. It was concluded that, "The association of increased nondiscocytes and impaired muscle function could indicate a cause and effect relationship. This would be in agreement with the physiological concept of fatigue as a consequence of inadequate oxygen delivery."

So it is relevant that in his textbook of human physiology, (20) Griffiths noted that muscle fatigue probably was due to oxygen deficiency and the effects of localised accumulations of metabolites including lactic acid, "...when the metabolites were not removed because of impaired capillary blood flow." Wiles et al (21) considered that energy generation would fail if there was an enzymatic block in

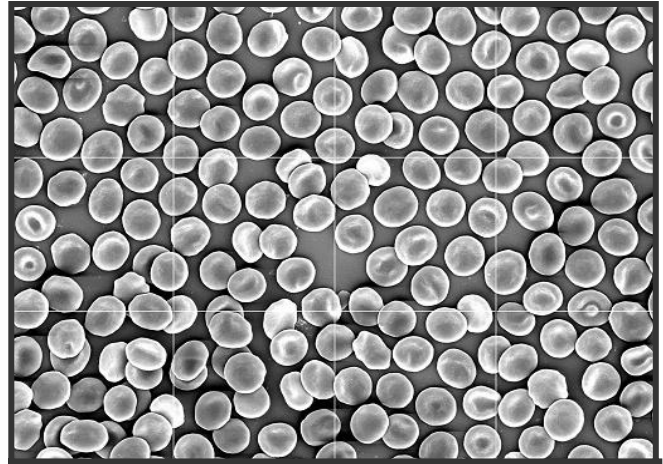


Fig 1: A scanning electron micrograph which shows the red cell population typical of chronic ME, where flat cells are the dominant type. If you look carefully you can find cells with surface features such as bumps, (cells with surface changes) and cells with irregular margins (cells with altered margins). Cells with the shape of biconcave discocytes can be seen at the margins at 2 o'clock, 5 o'clock and 9 o'clock. According to textbooks all red cells have this shape. Note that none of these cell types are 'abnormal' as they are part of the cell shape populations of normal blood.

the glycogenolytic pathway or if there was a failure of oxidative metabolism. They considered the limiting features of energy generation to be blood flow and oxygen delivery.

While much has been written about 'Tired patients,' and 'Tiredness,' a 1960 paper by French (22) is of special interest. French considered that, "Tiredness is a symptom rather than a clinical condition," and that, "Tiredness is a 'whole' symptom. It is felt throughout the patient's body and is not confined to regions, anatomic structures or specific physiological functions, but rather it emanates from the natural whole of the human body and mind." His study involved 1170 patients, of whom 105 complained of tiredness. After discussing the possible contributions of a number of factors, French concluded, "There is no doubt that oxygen lack is the first cause of tissue cell exhaustion, which is manifested early by clinical tiredness."

BRAIN DYSFUNCTION AND CAPILLARY BLOOD FLOW

It is postulated that the effects of shape-changed, poorly deformable red cells will impair capillary blood flow on a wide basis, with the most severe effects relating to region: small capillaries in tissues which are sensitive to oxygen deprivation.

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WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

Because tiredness is a major problem for those who suffer from multiple sclerosis, (MS) at the conclusion of our 1986 study on ME, we investigated the filterability and other aspects of blood samples from members of the local Multiple Sclerosis Society. As with ME, the rate of blood filterability was much less than that of healthy controls and there were changes in red cell morphology. A possibly relevant implication of these changes is that in 1983, Swank et al (23) had shown by xenon washout that in MS subjects, "...there occurred a progressive, generalised decrease in cerebral blood flow and in red cell delivery with age, which was significantly greater than observed in normal subjects. The rate of decrease in cerebral blood flow and red cell delivery correlated directly with the rate of progress of the disease.

Studies using single photon computed tomography (SPET or SPECT) have shown in other conditions with shape-changed red cells, that there can be significant reductions in regional cerebral blood flow. The relevance of this is that on March 30 1994, Dr.D.C.Costa presented his findings from a SPET study of ME patients at the annual general meeting of the British Nuclear Medicine Society. He reported that ME/CFS patients, "... had a generalised reduction in brain perfusion, " and that, "... brainstem blood flow was significantly lower than in patients with depression and that both patient groups had significantly lower brainstem blood flow than in healthy subjects." Even though I had published three reports concerning the effects of nondiscocytic red cells in ME patients prior to 1994, Dr.Costa hypothesised that the reduced demand for oxygen in the brain related to an overactive immune system which resulted in an excessive production of cytokines.

Dr.Costa's comparison of the cerebral blood flow of ME/CFS with depression draws attention to a significant literature concerning SPECT scans and depression. Perhaps the most informative was a study by Bench et al (24) which showed that a region of the brain with impaired blood flow during depression, showed normal blood flow rates when the depressive episode resolved.

Evidently the regions associated with reduced blood flow have diagnostic significance as shown in another study by Dr.Costa. Lucey, Costa et al (25) reported that in some psychiatric disorders, there were significant differences in regional cerebral blood flow, as defined by SPET. While whole brain blood flow correlated with anxiety, there were significant regional cerebral blood flow differences between patients with obsessive compulsive disorder and post-traumatic stress disorder and controls.

REMISSIONS – THE CORNER STONE OF RAMSAY'S CONCEPT OF ME.

Even though Ramsay had described remissions as a feature of ME, and gave examples of the

remission/relapse cycle, remissions are unrecognised by American investigators and are little recognised in other countries. This situation could be a possible consequence of ME being considered as the result of a persistent infection or a persistent immunological abnormality, or the consequence of localised pathology, as such beliefs would be incompatible with the remissions which Ramsay recorded.

My first experience with a remission related to a young woman who delivered a blood sample about 9am one morning. She explained that she had been too unwell to have had a blood sample taken earlier. On checking the details on her blood test request form it was noted that she had checked the box 'well with no symptoms.' pointed out that if she was well when she had the blood drawn then it was likely that the results would be normal. About 4pm on the same day she returned with another blood sample. She had 'crashed' about 3.30pm, for no discernible reason, and gone to the laboratory for another sample. The request form was marked 'severely unwell.' When the samples had been assessed it was found that the morning sample was normal and the afternoon sample was grossly abnormal. What factor or factors switch off to restore red cell shape populations to normal with improved wellbeing, and switch on to become symptomatic with changed red cell shape populations, remain unknown. However, the observation is consistent with Ramsay's comment that during remission muscle function returns to normal.

Those observations led to an attempt to gain some insight into the frequency of remissions and concomitant changes in ME people in New Zealand. A panel of 37 females and 11 males who had been diagnosed by a physician as having ME at least 2 years previously, gave informed consent to take part in a 40 week-long study. At commencement and at four-weekly intervals thereafter, the panel met to record their symptoms and level of wellbeing and to provide a 5-drop sample of venous blood for red cell shape analysis. A total of 519 blood samples (401 female, 118 male) were assessed.

While the majority of blood samples showed the increased flat cells of chronic ME, normal results occurred sporadically. At one extreme there were five women who were unwell and had abnormal blood tests in 11 of 11 blood samples. Because of the four-week space between samples it is not known if remissions had occurred in the interval or if the women were in the group noted by Ramsay, who did not have remissions. At the other extreme was a woman who was well, with normal blood tests in 6 of 11 samples. The most frequent result, for both sexes, was to have two remissions during the 40 weeks of the study. The findings led to the conclusion that remissions were not uncommon events.

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WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

Such findings are in accord with the idea that ME is a dysfunctional state arising from inadequate rates of delivery of oxygen and nutrient substrates, rather than a condition associated with tissue pathology. That viewpoint is consistent also, with the improved wellbeing of patients who respond to agents which improve red cell deformability and thus increase capillary blood flow.

TREATMENT OPTIONS

The major factors in the development of the dysfunctional state manifested as the symptoms of ME are the presence of randomly distributed clusters of small capillaries and the effects of shape-changed, poorly deformable red cells on the rate of capillary blood flow. As it is not possible to influence capillary size, treatment should be aimed at improving red cell deformability, as remissions show that the red cell changes are reversible.

1. Acute ME. As reported at the Cambridge Symposium, a chance event led to an investigation into the possible benefits of injections of vitamin B12 as hydroxocobalamin. A female patient reported that her general practitioner had given her an injection of hydroxocobalamin (Neo-Cytamen) and within 24 hours she felt much better. A blood sample was taken and revealed that her level of cup forms was reduced greatly. However, another patient failed to benefit from a similar injection and there was no change in her cup form value. The improved status of the responder was maintained with injections at about 10 day intervals. Through the co-operation of general practitioners it was found that 15 of 29 cases of ME responded to injections of hydroxocobalamin with symptom relief and reduced cup forms. However, there is no explanation of the mode of action of the B12 or why it was ineffective in 50% of cases.
2. Chronic ME. Some understanding of how the red cell changes in chronic ME might be relieved is based upon two early studies which investigated the effects of prostaglandins on red blood cells. Kury et al (26) used a spin-labelling technique to assess factors in red cells which influenced cell deformability. They reported that prostaglandin E1 (PGE1) increased red cell deformability, while the pro-inflammatory prostaglandin E2 (PGE2) had the opposite effect. By means of a filtration technique based upon standardised paper filters, Rasmussen et al (27) showed that PGE1 improved the filtration rate, while PGE2 had the opposite effect. Those observations were consistent with the findings of Kury et al, but in addition it was reported that catecholamines also reduced the rate of filtration. That finding could help to explain why both emotional and physical stress are causal factors in the relapses of ME people.

Although cis-linoleic acid is the basic precursor for

PGE1, it has to be elongated to gammalinolenic acid (GLA) in a reaction mediated by the enzyme delta-6-desaturase. However it is known that in a number of situations the enzyme becomes dysfunctional, impairing the synthesis of GLA. For that reason it has been found useful to use plant sources of GLA. The most effective source is oil of evening primrose although it is unclear why it is responsible for higher production of PGE1 than other plant oils, even if their GLA content is higher. Manku et al (28) have reported that 2 grams daily of oil of evening primrose had no effect on the blood levels of PGE1, while 4 grams daily of the oil caused a significant increase in the concentration of PGE1 in the blood. So at least 4 grams daily of oil of evening primrose is needed to be effective. It needs to be emphasised that for unexplained reasons, not all individuals respond to that dose of evening primrose oil.

The omega-3 fatty acids also have the ability to improve red cell deformability and may offer an alternative. The smallest omega-3 is the plant-derived algalinolenic acid which requires a functional delta-6-desaturase to elongate it in the synthesis of eicosapentaenoic acid. Because of the potential problems of delta-6-desaturase it is preferable to take omega-3 in the form of fish oil which is rich in eicosapentaenoic and docosahexanoic acids. Having demonstrated previously, by the use of a spin-labelling technique, that the lipid bilayer of the membranes of diabetic red cells were very viscous, (29) Kamada et al (30) reported that sardine oil taken orally, increased the fluidity of the lipid bilayer and increased the cell deformability. Although some ME people have responded to fish oil, I have not been able to identify which patients will respond to what oil. A lack of funding has prevented investigations into the performance of the oils by double-blinded randomised studies. However, on the result sheets concerning red cell shape analyses, in addition to the results, and a copy of the micrograph there is a suggestion that the effects of the changed red cells might be reduced by a daily intake of 4 grams of oil of evening primrose or 6 grams of fish oil. It is noted also, that if no benefit is perceived by 6 weeks, then another treatment should be tried. A patient in Denmark failed to respond to evening primrose oil or fish oil, but responded to pentoxifylline.

About 1988 a medical detailer reported that a general practitioner in a country town (Oamaru) was using pentoxifylline (Trental) to treat his ME patients. But before I could arrange a meeting the doctor was killed in a freak accident at a car rally where he was acting as a marshal. As many studies have shown that pentoxifylline improves red cell deformability and reduces blood viscosity, it has the properties to be helpful for ME people but no reports of its use in ME have been located.

Despite the lack of placebo-controlled studies, I have had many letters and emails from people who have
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WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

responded to one of the oils, with a restoration of a near-normal lifestyle. My responses to such messages emphasise the need to persist with the effective treatment, while at the same time recognising that they are not cured and are still at risk.

THE IMPORTANCE OF LIFESTYLE IN ME

Even though persistent tiredness is a daily problem, it has to be accepted that long-term bed rest will have an adverse effect on muscle function. For that reason the daily programme should include provision for a period of low-intensity physical activity, such as walking 50 yards up the street and back again. Each week the distance walked should be increased, maybe in concert with an increase in speed. An interesting observation relating to a daughter with fibromyalgia was that when she was immersed up to her chin in a warm physiotherapy pool, the buoyancy provided by the water allowed her to do arm and leg exercises that she could not do on dry land.

ME people should not get involved in arguments and they should walk away when they see stressful situations developing. Both arguments and stress may raise the blood levels of altered cells sufficiently to cause a relapse.

Give careful consideration to the nature of your diet. High levels of fat and cholesterol increase the stiffness of red cells. Try and increase your dietary intake of green vegetables and of oily fish. If this is too expensive, have a tin of sardines in oil two or three times a week.

Because low temperatures have an adverse influence on blood viscosity, it is important to dress warmly and if possible spend your time in a warm room.

THE ORIGINS OF THE DATA ON WHICH MY CONCEPTS REST

According to the entries in my daily diary, between January 1991 and December 2000, I spoke to 274 meetings in six countries. Although the great majority were ME groups, in the USA and Canada, I met CFS and CFIDS groups also. From about 1997, fibromyalgia groups were included.

Either during such visits or later, arrangements were made for an experienced venepuncturist to collect 5 drop blood samples which were mixed immediately with fixative. When the samples had been evaluated, reports were prepared and submitted for publication. However, reports submitted to Australian, New Zealand and South African journals were rejected.

After giving an illustrated lecture to an ME audience in Victoria, British Columbia, I was approached by Dr. Abram Hoffer who introduced himself as the editor of the Journal of Orthomolecular Medicine. He invited me to submit a written version of the talk he had just heard. So in early 1997, a paper titled, "Myalgic encephalomyelitis (ME): a haemorheological disorder

manifested as impaired capillary blood flow," was published. (J Orthomol Med 1997; 12: 69-76). Later in that year I was able to publish the red cell shape analysis results of blood samples from 1558 female and 620 male members of ME organisations in four countries. (J Orthomol Med 1997; 12: 221-6) The numbers involved in that report are so large that it would be strange if the data were not relevant.

In other reports I have summarised the information provided by 632 Americans with chronic disorders, and the red cell shape analysis results. In addition there is a report relating to the blood samples from 623 women with fibromyalgia, who resided in four countries. An intriguing aspect of that report is that the blood samples showed similar high values for flat cells to those of people with chronic ME. However, an analysis of the symptom lists showed that the first recorded symptom by the majority of ME people was tiredness, whereas in the fibromyalgia group the first symptom was pain.

CONCLUSIONS

What began as a study of various aspects of the blood in ME people finished up as a study of the red cell shape populations in a wide range of chronic disorders. In those disorders which have been studied by SPECT scans, the reported reductions in regional cerebral blood flow were consistent with the expected effects of shape-changed, poorly deformable red cells.

So ME is only one of many chronic disorders with changed red cells which will impair capillary blood flow. It would seem that ME is unique insofar as the factor or factors responsible for the changes in red cell shape, can switch off. During the resulting remission, red cell shape populations return to normal. Unfortunately, at this time, there is no diagnostic feature which can identify the group identified by Ramsay as having unremitting ME.

Even though many different factors may initiate the blood changes which are typical of ME, it needs to be emphasised that the baseline changes may be increased by secondary factors which alter the internal environment, such as emotional stress or physical over-activity or hormonal changes as in the pre-menstrual week. Such changes will precipitate relapses. In addition, the immune response to inoculations, vaccinations or other infections will worsen the severity of symptoms and the level of body dysfunction.

While the search for the primary problem continues, in order to improve the quality of life of sufferers, urgent attention is needed to define the actions of agents which can improve the deformability of red blood cells in order to provide an effective treatment. However, because of the official reluctance to investigate the pathophysiology of ME, sufferers may need to explore the potential benefits of those agents which will improve red cell deformability, on their own initiative.
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WHO GETS ME AND WHY - The role of impaired capillary blood flow in ME (continued)

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ME Story

I have never known how such an illness can be so debilitating and so destructive yet virtually ignored by so many people. It is awful. I hope one day to be free of the ignorance.

- Paul

Essential investigations for people with ME/CFS?

By Margaret Williams

On 14th January 2008 Fred Springfield drew attention on Co-Cure to a Review Article associated with inflammation in medically ill patients ("Identification and treatment of symptoms associated with inflammation in medically ill patients"; Robert Dantzer et al; Psychoneuroendocrinology 2008;33:18-29). The Review was the result of a meeting on 28th and 29th May 2007 in Bordeaux, France, on inflammation, psychiatry, neurosciences and psychoneuroimmunology, attended by experts from the US, France, the UK and Israel.

As noted by Fred Springfield, whilst not relating specifically to ME/CFS, the Review may nevertheless be of interest to the ME/CFS community, whose members may be aware that there is evidence of low-grade (but still important) inflammation in ME/CFS -- see, for example, "Low grade inflammation and arterial wave reflection in patients with CFS"; VA Spence et al, Clin Sci 2007, Epub ahead of print: doi:10.1042/CS20070274, which contains 54 references and demonstrates that, despite the recent reporting that markers of post-infective fatigue syndromes are not sustained into the chronic phase of the illness and play no role in persisting symptoms, hsCRP levels in (ME)CFS are indeed indicative of chronic, low-grade, sub-clinical inflammation. (Within the last ten years, researchers have developed a high sensitivity immunoassay known as hsCRP, which is a much better assay and a more sensitive marker than CRP, as it can measure levels below 10mg/L. Whilst some clinicians may still regard low levels as unimportant, nevertheless at these levels, measurement of conditions indicative of chronic, low-grade inflammation are now possible).

The Review recommends testing for a standardised set of inflammatory biomarkers, but the NICE Guideline on "CFS/ME" issued in August 2007 specifically proscribes such tests.

The following are quotations that might be relevant for people with ME/CFS:

"The most harmful and costly health problems in the Western World are originating from a few diseases (and) in addition to the specific symptoms that are characteristic of each of these conditions, most patients experience non-specific symptoms that are similar in all these conditions and include depressed mood, altered cognition, fatigue, and sleep disorders".

"The possibility that immune-to-brain communication pathways represent the main biological mechanism for symptom burden experienced by medically ill patients has now gained credibility in the medical community".

Margaret Williams is a well respected authority on ME as well as being an ME patient advocate. Margaret Williams formerly held senior clinical posts in the NHS.

"This meeting brought together clinicians and basic scientists with a common interest in understanding inflammation and associated symptoms in medically ill patients (and it) focused on: (a) predominant symptoms associated with inflammation, (b) markers of inflammation at the periphery, (c) possible markers of brain inflammation associated with low-grade peripheral inflammation in humans, (d) animal models of inflammation-associated symptoms, and (e) domains of intervention for controlling inflammation-associated symptoms".

"Among the myriad of questionnaires that are available to categorise or assess fatigue, sleep disorders, altered cognition and pain, none specifically refers to inflammation-associated neurobehavioural alterations".

"The diagnostic tools that are favoured by psychiatrists are clearly not the best ones. As pointed out by Joel Dimsdale (San Diego, CA), the concept of somatisation that is used for characterising symptoms in the absence of any detectable disease is of little operational value, if not misleading".

"For instance, the enduring fatigue experienced by the vast majority of breast cancer survivors could easily be labelled as somatisation disorder according to the 4th Edition of the Diagnostic and Statistical Manual of Mental Disorders".

"Making fatigue a somatisation disorder overlooks the fact that fatigue has both mental and physical components, thereby denying a possible organic aetiology to explain such fatigue".

"Furthermore, this emphasis on the lack of an organic basis favours missed diagnoses (e.g. fatigue and thyroid abnormalities, or fatigue and inflammation)".

(continued on page 34)

Essential investigations for people with ME/CFS?

(Continued)

"Inflammation is not a stable condition. In a given individual it can fluctuate rapidly according to a number of environmental factors (e.g. stressors) and internal variables (e.g. diurnal variation of cortisol)".

"Basic aspects of diagnosis of behavioural disorders remain controversial and lack solid scientific foundations".

"In order to provide consistency, all studies examining the potential impact of inflammatory pathways should include a standard set of inflammatory biomarkers (which should include) the acute phase proteins, CRP, sialic acid and haemoglobin; the inflammatory mediators, prostaglandins E2 and C3A and the innate immune cytokine IL-6 as measured by the high sensitivity (hs)-enzyme-linked immunosorbent assay (ELISA) in plasma.

These biomarkers, especially hs-CRP and IL-6, have been found to reproducibly identify the presence of an activated immune response in a number of disorders.

Most of these assessments can be run in certified commercial or hospital laboratories".

"There have been significant advances in imaging techniques during the past ten years (and) a variety of imaging techniques have enabled inflammation in the brain to be viewed in real time. However, except in conditions of severe systemic inflammation, signalling of systemic inflammation to the healthy brain does not involve structural damage".

"It is important to highlight the distinction between signalling by molecules typically associated with inflammation and an inflammatory response *per se*. During systemic inflammation there is induction of IL-1 β and other proinflammatory cytokines, but there is no inflammatory response in the brain. It is of interest that microinjection of IL-1 β into the brain at concentrations that would typically give rise to inflammation in peripheral tissues does not lead to typical inflammation within the brain parenchyma. This indicates that the biological significance of IL-1 β in the brain parenchyma is different from that in other tissues".

"Although we have the necessary tools to image inflammation in the brain, it seems we do not have sufficiently sensitive tools to image signalling in the brain consequent to a systemic inflammatory response".

"Proinflammatory cytokines induce the production of

several downstream inflammatory mediators, such as prostaglandins and nitric oxide. Proinflammatory cytokines and other inflammatory mediators are produced by accessory immune cells, such as macrophages and monocytes in the periphery, and microglia within the central nervous system. Targeting cell trafficking into the central nervous system is unlikely to be a very useful approach since symptoms of sickness are dependent on the activation of brain cytokine signalling independently of any blood cell recruitment".

"Peripheral infections can sensitise or exaggerate existing brain inflammatory processes (and) elevated cytokine levels in blood have the potential to reverberate and activate central nervous inflammatory systems".

The Conclusions of the Review note the intense discussion at the meeting that resulted in a series of recommendations for improving understanding of the relationship between inflammation and subjective health complaints.

These recommendations note that because inflammation-associated sickness symptoms are a major impediment to human health, research on the mechanisms and treatment of such symptom burden in physically ill patients should be strongly encouraged; that clinical tools for assessing inflammation-associated symptoms should be standardised; that there should be a minimum set of inflammatory biomarkers; that brain neuroimaging techniques should be used for revealing the brain structures that are influenced by peripheral inflammatory processes and whose ability to process information is impaired by excessive amounts of interoceptive stimuli (caused, it seems, not – as asserted by Wessely School psychiatrists -- by aberrant focusing on normal bodily sensations or by "remembered illness" but by inflammatory processes), and that the high presence of inflammation-associated symptoms in physically ill patients provides a background against which it is possible to test alleviating effects of therapies targeting immune-to-brain communication pathways.

The Review notes that despite major advances in the understanding of the immune-to-brain communication pathways that underlie the pathophysiology of symptoms in inflammatory conditions, little has been done to translate this knowledge to the clinics.

As NICE is now in the process of contacting selected people asking for their input on the advisability of it producing guidance on the use of Ampligen in "CFS/ME", might NICE also be persuaded to seek the input of experienced vascular biologists on the advisability of it recommending specific testing for inflammation in ME/CFS?