Guildford ME/CFS Support Group
(& West Surrey)

Newsletter

June 2015

Future dates

The following ME meetings are open to all members and carers.

6th July 2015 (Monday) 11.15am The Seahorse
The Street, Shalford, Guildford, GU4 8BU
www.theseahorseguildford.co.uk

6th August 2015 (Thursday) 7.30pm The Weyside
Millbrook, Guildford, Surrey, GU1 3XJ
www.theweyside.co.uk
Over the last few years the Weyside was called the Boatman.

28th August 2015 (Friday) 11.15am The Seahorse
The Street, Shalford, Guildford, GU4 8BU
www.theseahorseguildford.co.uk

15th September 2015 (Tuesday) 7.30pm The Weyside
Millbrook, Guildford, Surrey, GU1 3XJ
www.theweyside.co.uk
Over the last few years the Weyside was called the Boatman.

DVD: Invest in ME conference

The 10th Invest in ME conference took place on the 29th May 2015 in London. A DVD of the conference is now orderable but not due for release until July 2015.

The DVD will likely contain 4 discs and will be in PAL format-containing the full presentations from the 2015 conference plus plenary sessions, and the pre-conference dinner keynote speech by Mike Shepherd.

The DVD can be ordered online at: www.investinme.eu/IIMEC10-DVD-Order.shtml

Or by post: Send a cheque for the requisite amount (see above) to -

Invest in ME, PO BOX 561, Eastleigh, SO50 0GQ, Hampshire, UK

Please supply your name and address (and email address if possible).
Cheques should be made payable to Invest in ME

The biological pathogenesis of CFS/ME

Source: www.bmj.com/content/350/bmj.h2087/rr-0

Given the extent of the biological (and legal*) understanding of ME/CFS, it is surprising that some psychologists still claim that CBT and Graded Exercise are serious treatments for the biological illness which they seem to believe is psychological.

Further, it's confusing that some psychologists still refer to the discredited 2004-2010 PACE trial to support their claim. In response to a recent article, in the British Medical Journal, is the following by Jonathan R Kerr, Professor of Epidemiology, Universidad del Rosario, Quinta de Mutis, Bogota, Colombia.

The next newsletter article (on page 3) explores the credibility of the PACE trial. On page 7 are some results from a recent ME association patient survey (1428 respondents) about the effectiveness of CBT, Graded Exercise and Pacing.

By Newsletter Editor

This editorial (1) comes from authors from two of three CFS/ME centres whose prolific academic production in CFS/ME provides almost the sole support for a supposed psychiatric basis for the disease; these centres are Kings College London, Nijmegen Medical Centre in the Netherlands, and the University of New South Wales, Sydney, Australia. However, the scientific basis on which the treatments, Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET), are offered is critically flawed. The original PACE trial conducted by Kings College London, enrolled patients using the 1991 Oxford criteria (2), which allows inclusion of patients with affective disorders. This is in direct conflict with the internationally accepted 1994 CDC criteria which specifically excludes patients with affective disorders. This means that this study was performed using patients whose exact diagnoses are unknown. However, despite this flaw, global insurance companies do not pay sickness benefit to CFS/ME patients on the basis that effective treatments are available. Yet these interventions are not effective in CFS/ME.

CBT helps only a fraction of patients and GET has been shown to exacerbate the symptoms of patients with CFS/ME, which is logical as one of the cardinal symptoms of CFS/ME is post-exertional malaise, and so GET should not be used for CFS/ME patients. Furthermore, the Institute of Medicine in the USA has recently recommended that the name, CFS/ME, should be changed to Systemic Exercise Intolerance Disease (SEID) (3), which again reinforces the truth that exercise therapy should not be used for CFS/ME.

We know that CFS/ME can be triggered by a variety of infections, vaccines, exposure to organophosphate chemicals, and that the pathogenesis involves prolonged immune activation, which results in a flu-like illness that persists for months to years, and we all know how we feel during a flu-like illness, and there is no dispute that flu-like illnesses are caused by viruses. Several infection models have been presented which illustrate very well this progression in patients followed from the time of acute infection to development of CFS/ME. Parvovirus B19 triggers CFS/ME and this is predisposed to by carriage of HLA-DRB1*01, *04 and *07 alleles, is characterised by raised levels of circulating TNF-α and IFN-γ, and CFS/ME triggered by B19 has been cured with intravenous immunoglobulin (IVIG) which is the specific treatment for B19 infection (4). Coxiella burneti also triggers CFS/ME and this is predisposed to by carriage of HLA-DRB1*11 and certain IFN-γ polymorphisms, is associated with chronic immune activation and Q fever-associated CFS/ME is treated successfully with tetracyclines which are the specific treatment for Q fever (5). Epstein-Barr virus triggers CFS/ME, and patients with EBV-triggered CFS/ME have been successfully treated with valacyclovir (6), which is a specific treatment for EBV infection. In all of these models, the infectious agent persists long-term with chronic genomic persistence and antigen presentation, which appears to be important.

* http://meactionuk.org.uk/ME_Judgments.htm

The diversity of infectious triggers and individual responses likely account for the heterogeneity observed in CFS/ME, and the existence of subtypes, which are recognised to be important for the optimal management of patients.

Maybe the big breakthrough in CFS/ME comes when we are free to apply our significant existing knowledge of CFS/ME towards the best investigation and treatment of INDIVIDUAL patients, whom we know have different pathogenetic processes which account for the existence of disease subtypes. Disease subtypes are a feature of multiple chronic inflammatory autoimmune diseases and are taken into account in their management, and therefore CFS/ME is typical of such a biological disease.

Obvious propaganda? - the PACE trial

In 2011 a UK medical journal called the Lancet published the results of a trial exploring the effectiveness of Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) for people with ME/CFS. The 2004-2010 study of 641 participants did not trial house/bed bound patients and concluded that CBT and GET therapies are 'moderately effective' for ME/CFS.

We have covered the PACE trial in our Spring 2011 newsletter but the trial is still referred to by some psychologists. As such, I've included two articles below:

"How to make a disease disappear" and
"PACE trial complaint to the Lancet"

that look at the credibility of the PACE trial.

By Newsletter Editor

How to make a disease disappear

By Professor Malcolm Hooper (February 2010)
Source: www.meactionuk.org.uk/magical-medicine.htm

A formal complaint has been lodged by Professor Malcolm Hooper with the Rt. Hon The Lord Drayson, Minister of State with responsibility for the Medical Research Council (Science and Innovation) about the "PACE" Clinical Trial of behavioural modification interventions for people with Myalgic Encephalomyelitis (ME) / Chronic Fatigue Syndrome (CFS).

PACE is the acronym for Pacing, Activity, and Cognitive behavioural therapy, a randomised Evaluation, interventions that, according to one of the Principal Investigators, are without theoretical foundation.

The MRC's PACE Trial seemingly inhabits a unique and unenviable position in the history of medicine. It is believed to be the first and only clinical trial that patients and the charities that support them have tried to stop before a single patient could be recruited and is the only clinical trial that the Department for Work and Pensions (DWP) has ever funded.

Since 1993, the giant US permanent health insurance company UNUMProvident has been advising the UK DWP about the most effective ways of curtailing sickness benefit payments. The PACE Trial is run by psychiatrists of the Wessely School, most of whom work for the medical and permanent health insurance industry, including UNUMProvident.

These psychiatrists insist – in defiance of both the World Health Organisation and the significant biomedical evidence about the nature of it -- that “CFS/ME” is a behavioural disorder, into which they have subsumed ME, a classified neurological disorder whose separate existence they deny. Their beliefs have been repudiated in writing by the World Health Organisation.

In 1992, the Wessely School gave directions that in cases of ME/CFS, the first duty of the doctor is to avoid legitimisation of symptoms; in 1994, ME was described by Professor Simon Wessely as merely “a belief”; in 1996 recommendations were made that no investigations should be performed to confirm the diagnosis and in 1999 patients with ME/CFS were referred to as “the undeserving sick”.

The complaint is supported by a 442 page Report which addresses areas of major concern about the PACE Trial.

These include apparent coercion and exploitation of patients, flawed methodology, apparent lack of scientific rigour, apparent failure to adhere to the Declaration of Helsinki, the unusual personal financial interest of the Chief Investigator, the vested financial interests of the Principal Investigators and others involved with the trial and the underlying non-clinical purpose of the trial.

The psychiatrists’ unproven beliefs and assumptions are presented as fact and trial therapists have been trained to provide participants with misinformation; therapists have also been trained to advise participants to ignore symptoms, a situation that may in some cases result in death. There are some extremely disquieting issues surrounding the MRC PACE Trial and documents obtained under the Freedom of Information Act allow the full story to be told for the first time.

People with ME/CFS do not seek any special consideration; they simply wish to be treated equally to those who suffer from other classified neurological disorders. As shown in the Report that accompanies the complaint, the MRC PACE Trial clearly demonstrates that people with ME/CFS are not treated equally to those with other chronic neurological disorders.

The Report can be accessed at http://www.meactionuk.org.uk/magical-medicine.pdf

PACE trial complaint to the Lancet

Submitted by Professor Malcolm Hooper (March 2011)

Source:
www.mecfsforums.com/wiki/PACE_trial_complaint_to_the_Lancet,_submitted_by_Professor_Malcolm_Hooper_%28March_2011%29

Having served as an examiner in UK and other universities at graduate and postgraduate level, acted as referee for a number of scientific journals and served on an editorial Board, and having served on the Committee of the Council for National Academic Awards and also of the World Health Organisation, it is my professional opinion, based on the extensive published biomedical evidence about myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and supported by over 2,000 pages of evidence obtained under the Freedom of Information Act (FOIA), that the PACE Trial itself was unethical and unscientific: the Investigators had already formed their opinion about the intended outcome; entry criteria were used that have no credibility; definitions and outcome measures were changed repeatedly; data appears to have been manipulated, obfuscated, or not presented at all (so it cannot be checked), and the authors’ interpretation of their published data as “moderate” success is unsustainable.

Significant problems with the PACE Trial were identified from the outset and were brought to the attention of the Medical Research Council (a co-funder), who for over eleven months failed to respond. The concerns thus became the subject of at least two separate formal complaints at Ministerial level. A formal complaint about the West Midlands Multicentre Research Ethics Committee (MREC) that approved the PACE Trial Protocol was also served on the National Research Ethics Service (NRES) at the National Patient Safety Agency.

The Lancet has published a report of a study about which legitimate and serious concerns were raised that are centred on apparent coercion and exploitation of patients; on the contempt in which patients are seen to be held; on manipulation; on pretension and misrepresentation; on reliance on flawed studies yielding meaningless results; on the remarkable lack of scientific rigour throughout the trial; on the unusual personal financial interest of the Chief Principal Investigator (whose own money funded the PACE Trial entry criteria); on the vested interests of all the Principal Investigators, of the Director of the PACE Clinical Trial Unit and of the centre statistician; on the intentional inclusion of patients who do not suffer from the disorder supposedly being studied; on the lack of individual equipoise, and the failure to adhere to CONSORT (Consolidated Standards of Reporting Trials), to the Department of Health Research Governance Framework for Health and Social Care, Second Edition, 2005; 2:3:1; to the General Medical Council "Good Practice in Research" and "Consent to Research", and to the Declaration of Helsinki (which is clear: "Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research….Reports of research not in accordance with the principles of this Declaration should not be accepted for publication").

On the basis of evidence seen, the underlying non-clinical purpose of the trial had the primary aim of removing patients from benefits (ie. the use of motivational behaviour therapy to achieve the intended result of the cessation of State/insurance benefits for patients with ME/CFS), as those involved with the trial continue to maintain that for people with ME/CFS, "medical intervention is no longer appropriate" and that the aim of therapy is to "reduce healthcare usage" (http://www.meactionuk.org.uk/Problems_and_Solutions.htm).

In one of the MRC secret files about ME/CFS held at the National Archives in Kew (files that are closed for an unusually lengthy period of 73 years instead of the customary 30 years, some of which have been legally obtained), one of the Principal Investigators (PIs) of the PACE Trial (Professor Michael Sharpe), admitted that CBT and GET were "a purely pragmatic approach and without theoretical foundation" (CIBA Foundation Symposium, 12th-14th May 1992, reference S 1528/1). Particularly notable is that the same document states about ME/CFS patients: "The first duty of the doctor is to…avoid the legitimisation of symptoms and reinforcement of disability". Avoiding the legitimisation of the symptoms of ME/CFS was considered by many to be the purpose of the PACE Trial.

The Manuals used in the PACE Trial show that the authors either ignored medical science or that they do not understand medical science. The Manuals describe behaviours and techniques that should not -- and I believe cannot -- be considered ethical by any independent and reasonable observer, particularly the intense pressure on both therapists and participants to obtain the '"right" results for the PIs and their funders (pressures that are supported by participants' published comments). Much of the written information and instruction to therapists and doctors is contradictory and internally inconsistent and appears highly exploitative, as well as revealing an ignorance of ME/CFS.

One of the substantive complaints to the Minister about the PACE Trial can be accessed at http://www.meactionuk.org.uk/magical-medicine.htm and it addresses in detail the numerous ethical and scientific failures of the study.

As Chief Principal Investigator, Professor Peter White was aware of these complaints and in the interests of transparency and under the requirement for disclosure had a duty to bring them to the attention of The Lancet editorial staff before publication of the PACE Trial results, which he failed to do.

For The Lancet to have published an article reporting a study that completely ignored the existing biomedical evidence-base of over 4,000 published papers about the disorder allegedly studied, including documented physiological contra-indications regarding aerobic exercise, is a matter of concern to the international scientific community, as it is in defiance of basic principles of scientific research.

It also contravenes the Elsevier Editorial System (Ethics in Publishing: Instructions to Authors) which, under "Ethics and Procedures (General)", sets out its "fundamental principles" that "the paper should….be appropriately placed in the context of prior and existing research".
Indeed, the UK Department of Health, a co-funder of the PACE Trial, stipulates that: "All existing sources of evidence…must be considered carefully before undertaking research" (Research Governance Framework for Health and Social Care, Second Edition, 2005; 2:3:1).
Not only did White et al ignore the international biomedical evidence-base pertaining to ME/CFS, whilst in their article they make reference to the FINE Trial (Fatigue Intervention by Nurses Evaluation, a sibling of the PACE Trial), they do not point out that it failed (BMJ 2010:340:c1777), and they also failed to take due cognisance of the mixed evidence-base about the efficacy of CBT/GET which shows that those interventions are not effective in general and specifically that they may be harmful for people with ME/CFS. Feedback from almost 5,000 ME/CFS patients via several charities indicates that deterioration following exercise is reported in almost 50% of cases and indeed, in 2002 the Chief Medical Officer's Working Group Report highlighted the disparity between feedback from patients and the reported findings of the Wessely School (see below), stating: "…the data clearly indicate that the York review results (of controlled trials) do not reflect the full spectrum of patients' experience".

For the full version of this article please refer to the source (see page 4 under heading)

ME Association patient survey: CBT, GET & Pacing

Source: www.prohealth.com/library/showarticle.cfm?libid=20400
By Russell Fleming 6th June 2015

Full 294 page report:
www.meassociation.org.uk/wp-content/uploads/2015-ME-Association-Illness-Management-Report-No-decisions-about-me-without-me-30.05.15.pdf

Articles on pages 2, 3 and 4 of this newsletter are about the PACE trial and Cognitive Behavioural Therapy (CBT) and Graded Exercise (GET).

The ME association has recently released the results of a patient survey about the effectiveness of CBT, GET and Pacing. The survey asked 228 questions in total and was completed by 1428 respondents.

A brief overview of some of the results are included below. For the full article please refer to the source above.

By Newsletter Editor

"This is the largest and most comprehensive 'patient evidence' report covering ALL aspects of CBT, GET and Pacing – i.e. efficacy, safety and acceptability – that has ever been produced."

Dr Charles Shepherd
Medical Advisor, ME Association

On 28th May 2015, The ME Association published Part 1 of a report for public consultation called "No decisions about me, without me." It is a 294 page document focusing on courses delivered mainly in clinical settings and includes an executive summary, a complete and detailed analysis, relevant patient comments, and extensive conclusions and recommendations.

Part 2 will focus on self-management and will be published in the near future.

Large numbers of patients with ME/CFS consistently report that prescribed management approaches are not as acceptable, effective, or safe in practice as is often claimed they ought to be.

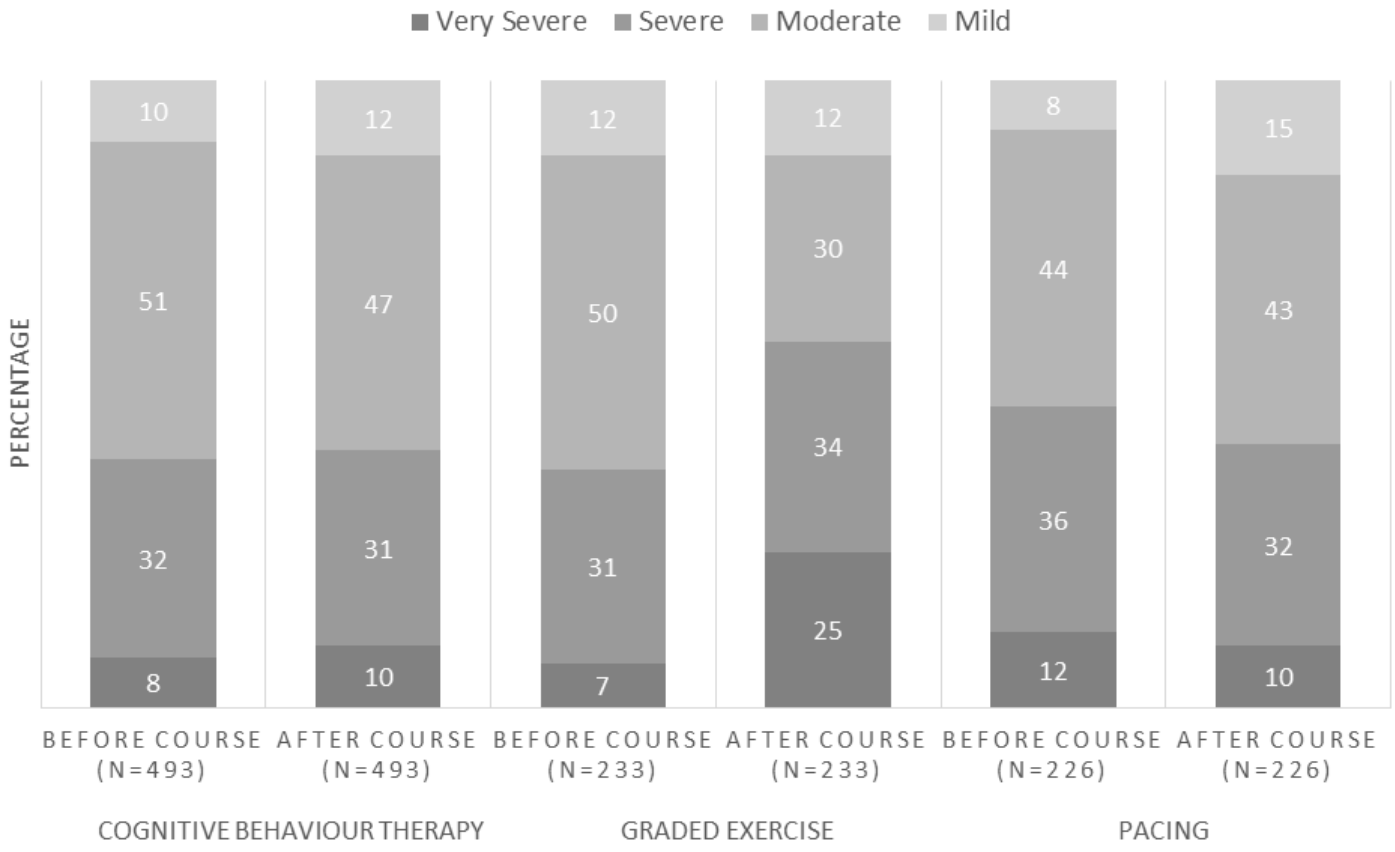
In 2012 the ME Association decided that a new and more detailed patient survey was required to try and better explain the factors contributing to patient reported outcomes, and this report provides quantitative and qualitative evidence of the patient experience.

The report will be used to lobby the UK National Institute for Health and Care Excellence (NICE) and other authorities, including NHS ME/CFS specialist services, to effect improvements which will hopefully lead to better outcomes for patients in the future.

The survey was split into three sections, one each for CBT, GET and Pacing, it asked 228 questions in total and was completed by 1428 respondents. 493 respondents had been on a CBT course, 233 on a GET course and 226 on a Pacing course. Some had been on separate courses for one or more of the interventions; others had been on courses comprising multiple interventions.

Here is an example result:

How did you rate your symptoms before and after your course? (952 responses)



Example conclusions:

Cognitive Behavioural Therapy (CBT)
The ME Association concludes that CBT in its current delivered form should not be recommended as a primary intervention for people with ME/CFS.

CBT courses based on the model that abnormal beliefs and behaviours are responsible for maintaining the illness, have no role to play in the management of ME/CFS and increase the risk of symptoms becoming worse.

The belief of some CBT practitioners that ME/CFS is a psychological illness was the main factor which led to less symptoms improving, less courses being appropriate to needs, more symptoms becoming worse and more courses being seen as inappropriate.

Results also indicate that graded exercise therapy should form no part of any activity management advice employed in the delivery of CBT, as this also had a negative effect on outcomes.

However, the results did indicate that, when used appropriately, the practical coping component of CBT can have a positive effect in helping some patients come to terms with their diagnosis and adapt their lives to best accommodate it.

CBT was also seen to have a positive effect in helping some patients deal with comorbid issues – anxiety, depression, stress – which may occur at any time for someone with a long-term disabling illness.

Graded Exercise Therapy (GET)
The ME Association concludes that GET should be withdrawn with immediate effect as a primary intervention for everyone with ME/CFS.

One of the main factors that led to patients reporting that GET was inappropriate was the very nature of GET itself, especially when it was used on the basis that there is no underlying physical cause for symptoms, and that patients are basically ill because of inactivity and deconditioning.

A significant number of patients had been given advice on exercise and activity management that was judged harmful with symptoms becoming worse or much worse and leading to relapse. And it is worth noting that despite current NICE recommendations, a significant number of severe-to-very severe patients were recommended GET by practitioners and/or had taken part in GET courses.

The ME Association recognises that it is impossible for all treatments for a disease to be free from side-effects, but if GET was a licensed medication, it believes the number of people reporting significant adverse effects would lead to a review of the use of GET by regulatory authorities.

Pacing
The ME Association concludes that Pacing is the most effective, safe, acceptable and preferred form of activity management for people with ME/CFS and recommends that it should be a key component of any illness management programme.

For some, improvement may be a slow process so, whilst they may be somewhat better by the end of a course, the improvement is not enough to take them into a better category of severity for some time, perhaps not until they have self-managed their illness for a few years.

The benefit of Pacing may relate to helping people cope and adapt to their illness rather than contributing to a significant improvement in functional status.

Learning coping strategies can help make courses more appropriate to needs even if they do not lead to immediate or even longer term improvement in symptoms. Importantly, it can prevent symptoms from becoming worse.

The 4i hypothesis: A neuro-immunological explanation for ME/CFS

Source: www.ghrnet.org/index.php/ijnr/article/view/1058

The source article is too long to fully include in our newsletter, but I've included two sections. Section 1 provides a useful overview of ME/CFS that brings together in one place a lot of subjects that are sometimes discussed at our group meetings.

Section 2 provides a brief overview of the 4i hypothesis which puts the immune system as the core issue of the illness. Please refer to the source for a more in-depth understanding of 4i.

By Newsletter Editor

Section 1 - A useful overview of ME/CFS (pages 9 to 13)

Although ME and CFS are often used interchangeably, the case criteria for ME[1] and CFS[2] define two distinct, partially overlapping diagnostic entities[3]. The diagnosis ME requires specific neurological/neurocognitive and immunological symptoms and energy production and/or transport impairment, but the distinctive feature of ME is post-exertional malaise or "neuro-immune exhaustion": 'a pathological inability to produce sufficient energy on demand' resulting into symptom exacerbation, e.g. flu-like symptoms and pain, after minor exertion[1].

The distinctive feature of CFS[2] on the other hand is (unexplained) chronic fatigue, which should be accompanied by at least four out of a eight symptoms, e.g. sore throat, unrefreshing sleep, and headaches.

While post-exertional malaise is not obligatory for CFS[2], "fatigue" is not mandatory for the diagnosis ME[1]. The distinction between patients with post-exertional malaise and without post-exertional malaise seems to be reflected by specific immunological differences[4,5]. Although ME and CFS criteria select partially overlapping, partially disjoint patient groups, the majority of the research into ME/CFS in the last decades has been conducted in patients selected by CFS criteria[2].

However, since many optional symptoms of CFS are mandatory for the diagnosis ME, the CFS criteria also apply to a substantial ME patient subgroup reporting "fatigue" (Figure 1). In conclusion, while ME is a neuro-immunological disease in nature[1], the CFS criteria[2] select a heterogeneous patient population of people with self-reported "chronic fatigue".

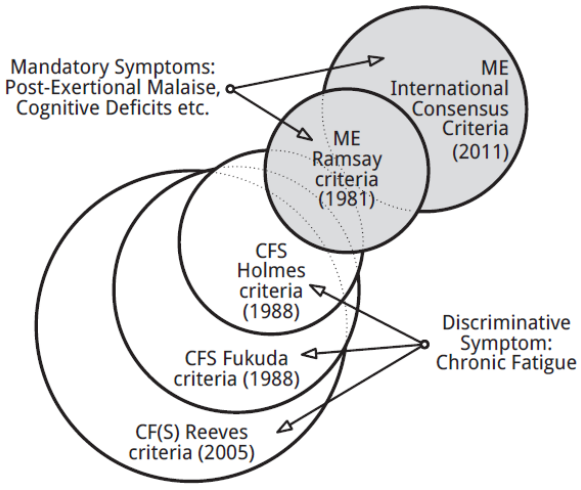


Figure 1 ME and CFS case definitions.

Symptoms

Notwithstanding the debate about the distinction between ME and CFS[6-8] and definitional criteria of ME and CFS[9], including obligatory symptoms, many patients with ME/CFS experience a plethora of symptoms[3], which differ inter-individually and seem to fluctuate in number and severity within an individual over time as a consequence of daily activity[10].

Symptoms experienced by substantial patient subgroups are: post-exertional malaise, "fatigue"/lack of energy, muscle weakness, (muscle/joint) pain, cognitive impairment ("brain fog"), a flu-like feeling, sleep dysfunction ("unrefreshing sleep"), hypersensitivity to food, light, sound and odours ("central sensitisation"), stress intolerance, orthostatic intolerance and depression[9] (Table 1). Various characteristic symptoms can be assessed objectively using well-accepted methods[3], e.g. neurocognitive tests, while other symptoms due to their nature, e.g. (muscle) pain, cannot be assessed objectively.

Table 1: Characteristic symptoms present in many patients with ME/CFS.

Symptom	References
"Fatigue": a lack of energy resources needed for basic daily functioning, "brain fog", post-exertional "fatigue", a "wired feeling" when exhausted, and a flu-like feeling *1	[9,11]
Infectious type symptoms	[5,12]
Muscle weakness/fatigability *1	[13,14]
Widespread muscle and/or joint pain	[15,16]
Orthostatic intolerance	[17,18]
Depression	[19,20]
Headaches	[21,22]
Hyperalgesia and hypersensitivity to light, sound etc.	[21,23]
Neurocognitive impairment	[19,24]
Sleep disturbances	[19,25]
Stress intolerance	[26,27]
Abdominal pain and discomfort	[28,29]
Post-exertional malaise	[30,31]

*1 A clear distinction should be made between the perception of "fatigue", a feeling, and "(muscle) fatigability": a (prolonged) decline of muscle power after repeated muscle contractions, which can be assessed objectively using dynamometers.

Partly due to the heterogeneity[32] of the CFS[2] patient population and the variety of methods employed and samples investigated, research into ME/CFS has yielded contradictory results. However, various typical aberrations (Table 2) have been observed repetitively in the ME/CFS patient population or subgroups thereof[1,33], Several abnormalities are confirmed by differential gene expression[34-37].

Onset

Contrary to gradual onset ME/CFS, sudden-onset ME/CFS is often preceded by a (viral) infection/"flu-like" illness[94,95]. The onset is reflected by distinctive immunological aberrations [96,97] and other abnormalities[98,99]. Several pathogens have been reported to initiate ME/CFS, e.g. Epstein-Barr virus[100], parvovirus B19[101], and enteroviruses[48]. For example, 10-15% of individuals do not recover from infectious mononucleosis and fulfil the criteria for CFS[2] after six months[100,102]. The severity of the acute infection seems to predict the clinical outcome, rather than demographic, psychological, or microbiological factors [102,103].

Table 2: Abnormalities in ME/CFS patients or major patient subgroups

Abnormality	References
Immunological aberrations : • inflammation, • (Th2-dominated) immune activation, • immunosuppression and • immune dysfunction;	[38-41]
which seem consistent with an infectious state;	[42-45]
Infections (reactivating and/or persistent);	[45-48]
Intestinal dysbiosis, inflammation and hyperpermeability,	[49-52]
possibly associated with systemic inflammation;	[53-55]
Enhanced oxidative and nitrosative stress;	[56-59]
Mitochondrial dysfunction and damage to mitochondria;	[60-63]
Hypovolemia and/or low cardiac output and	[11,64-66]
reduced blood and oxygen supply to muscles and brain,	[67-70]
notably in an upright position and during exercise;	[71-74]
Reduced (maximum) oxygen uptake and anaerobic threshold;	[75-78]
Neurological abnormalities (including neuro-inflammation);	[79-82]
HPA axis dysfunction, including hypocortisolism and blunted HPA axis responses to response to adrenocorticotropic hormone (ACTH);	[83-86]
Channelopathy (ion channel dysfunction);	[87-90]
(Long-lasting) abnormal responses to exertion.	[76,91-93]

Infections

Although contradicted by some studies, applying various methods various studies have found (multiple) infections or related antigens in patient subgroups (Table 3).

Table 3: Pathogens/pathogen-related antigens observed in ME/CFS patient subgroups

Pathogen and pathogen-associated antigens	References
Viruses	
Epstein-Barr Virus (EBV, HHV4)	[104-106]
Cytomegalovirus (CMV, HHV5)	[47,107,108]
Human Herpesvirus 6 (HHV6A and B)	[109,110]
Human Herpesvirus 7 (HHV7)	[106,111,112]
Enteroviruses	[113-115]
Parvovirus B19	[116-118]
Bornavirus	[119-121]
Bacteria	
Coxiella burnetii	[122-124]
Chlamydia pneumonia	[46,47,108]
Borrelia burgdorferi	[47,125,126]
Enterobacteria	[50,53]
Other	
Mycoplasma	[127-129]

Intestinal dysbiosis and hyperpermeability

Some studies have observed intestinal dysbiosis[49,51], intestinal inflammation and immune activation[52,130] and intestinal hyperpermeability, conceivably resulting into translocation of enterobacteria to the blood stream, thereby inducing systemic inflammation[50]. Inflammation and immune activation observed in ME/CFS have been associated with these gastro-intestinal abnormalities[53,54]. Bacteriotherapy (transcolonoscopic infusion of non-pathogenic enteric bacteria) showed long-term positive effects (15-20 year) in a substantial subgroup of ME/CFS patients with gastrointestinal complaints in a retrospective follow-up study[131].

Immunological abnormalities
Consistent findings in ME/CFS relate to immunological aberrations:
(a) inflammation[41,132,133]; (b) (Th2-predominant) immune activation[48,134-136]; (c) immunosuppression, especially low NK cell activity (NKCA)[43,137,138], blunted responses to mitogens[38,139,140], and IgG deficiencies, most often Igg1 and IgG3[141,142]; and d) immune dysfunction, e.g. predominance of the humoral (Th2) immune response accompanied by suppression of the cellular (Th1) immune system, possibly due to altered glucocorticoid regulation of the immune response[143,144], and dysregulation of the RNase-L pathway, likely due to cleavage of the native 83-kDa RNase L[145,146].

Increased oxidative and nitrosative stress
Elevated oxidative and nitrosative stress[36,88], increased levels of superoxide (O2-), nitric oxide (NO) and peroxynitrite (ONOO-), oxidative and nitrosative damage to DNA, proteins, lipids etc.[147-149], and antioxidant depletion / increased antioxidant activity, e.g. vitamin A[150], B[151], C[56], D[152], E[56], glutathione[153], super oxide dismutase[62] and zinc[154], have been observed repetitively.

Mitochondrial dysfunction and damage
Some studies have found structural mitochondrial damage, e.g. branching and fusion of mitochondrial cristae /mitochondrial degeneration[63], substantially higher rates of deletion of common 4977 bp of mitochondrial DNA[155] and unusual patterns of mitochondrial DNA deletions in skeletal muscle[59], while other studies implicate mitochondrial dysfunction[60,61,156]. Future research should provide clarity whether hypometabolism[157] and low oxygen uptake[75,78] and extraction[158] in ME/CFS is due to mitochondrial dysfunction and/or mitochondrial damage, circulatory deficits (see next paragraph) or other causes.

Low blood volume, cardiac output and/or blood and oxygen supply
Several studies have established markedly reduced blood volume[64,65,75] and impaired cardiac function, indicated by decreased cardiac index/output and stroke volume[65,66,74], when compared to healthy sedentary controls. Post-exertional malaise, flu-like symptoms and cognitive deficits seem to differentiate those with severe CFS from those with less severe CFS and to predict lower cardiac output[74]. In addition, some studies indicate low cardiac mass[66,159]. So, low cardiac output in ME/CFS could be due to reduced cardiac mass (a ‘small heart‘)[160] and/or hypovolemia[65]. Low cardiac output and/or blood/oxygen supply to muscles[69] and brain[67] and/or mitochondrial abnormalities could explain the low exercise capacity/oxygen uptake[75,161] and elevated (ventricular) lactate levels[68].

Orthostatic abnormalities
Orthostatic intolerance, (delayed) orthostatic hypotension and/or tachycardia (POTS), in patient subgroups has been implicated by various studies[73,162,163]. Orthostatic stress seems to induce cognitive deficits[24,164] and reduced angle-related mental task-activated cerebral blood flow velocity[164]. According to some authors[165], POTS marks a distinct group of patents with distinct phenotypical features. Some studies have also observed abnormalities in (parasympathetic and sympathetic) heart rate variability at rest and on standing[166].

Neurological abnormalities
Over time various researchers have observed various neurological aberrations in ME/CFS patient subgroups[79,81], e.g. diminished grey[82,167] and white matter[82,168], reduced blood flow and hypoperfusion[169,170], glucose hypometabolism in specific regions of the cerebrum and the brain stem[171], an increased number of defects on SPECT cans, predominantly in the frontal and temporal lobes[172], intracranial abnormalities on MRI and SPECT scans[173], neuroinflammation in various brain areas[174], cerebrospinal fluid anomalies suggesting inflammation and immune activation[175,176], and elevated ventricular lactate levels[68].

HPA axis dysfunction
HPA axis hypofunction in ME/CFS[83,177] can potentially manifest itself in (a) low basal levels and diurnal production levels (total production, variation during the day) of stress hormones, especially cortisol (hypocortisolism)[178,179]; (b) hyporesponsiveness of the HPA axis: blunted responses of the pituitary and the adrenal glands to provocation, e.g. reduced cortisol response to ACTH[85,180]; (c) diminished HPA axis responses to stress and exercise[181,182] and (d) enhanced sensitivity of the HPA axis to negative feedback to cortisol[183,184] and increased sensitivity of the cellular immune system to the immunosuppressive effects of cortisol[143,144].

Abnormal responses to exercise
Several studies have established (long-lasting) deviant responses to physical exertion in ME/CFS, when compared to sedentary controls, e.g. substantially lower values for oxygen uptake and workload at peak exercise and at the ventilatory or anaerobic threshold at a second exercise test 24 hours later[77,91,185]; a long-term increase of gene expression of metabolite-detecting receptors after sustained moderate exercise[31]; decreased prefrontal oxygenation during exercise and recovery[71]; (prolonged) severe oxidative stress[93] and (long-lasting) suppression of protective heat shock proteins[92] in response to exercise, especially when a history of high level physical activity and infection is present[150], cognitive deficits induced by exercise[186]; and substantially higher increments of NO metabolites in relation to workload during exercise[187]. Post-exertional malaise in ME/CFS seems to be related to exercise-induced inflammation and immune activation[188,189].

Section 2 – A brief overview of 4i

Based upon observations, it is estimated that 30-60% of people fulfilling the criteria for CFS[2] meet the more strict criteria for ME. Fatigue is not obligatory for the diagnosis ME, and since the majority of the research in the last decades have used the CFS criteria for patient selection, it is unknown how many patients fulfilling the ME criteria don't meet the case definition for CFS. Despite the confusion created by the use of the CFS criteria, various studies have observed typical abnormalities in the ME/CFS patient group or significant ME/CFS patient subgroups.

More consistent findings relate to four types of immunological abnormalities in ME/CFS: inflammation (I1), (Th2-predominated) immune activation and counteractive immunoregulatory responses (I2), immunosuppression (I3), and immune dysfunction (I4). These immunological abnormalities and their direct and indirect sequels can account for various abnormalities observed in ME/ CFS and several typical symptoms, including post-exertional "malaise" and "weakness". ME/CFS often has a sudden, "flulike" onset. Whether the original infection persists and perpetuates the illness or is only a "hit-and-run" infection remains subject to debate.

However, using different methods and samples, various infections have been observed in substantial ME/CFS patient subgroups. Immunosuppression (I3) and immune dysfunction (I4), either due to pathogens modulating and evading the immune system (as an effect) or enabling chronic/reactivating infections (as a cause) or both, seem to play a key role in the etiology. (Chronic) inflammation (I1) and immune activation (I2), both observed repetitively in ME/CFS, can induce and sustain a vicious circle of reactive oxygen and nitrogen species and peroxynitrite. Elevated oxidative/nitrosative stress has various detrimental effects: inflammation (I1), immunosuppression (I3), immune dysfunction (I4), the generation of auto-epitopes (due to oxidative and nitrosative damage to proteins, mitochondria etc.), mitochondrial dysfunction, cardiovascular deficits, et cetera-. Gastro-intestinal dysbiosis and inflammation and intestinal hyper-permeability, found by some studies, could result into translocation of enterobacteria into the blood stream, thereby inducing a third potential immunological stimulus in ME/CFS (i.e. LPS).

HPA axis dysfunction, especially hypocortisolism and HPA axis hypo-responsiveness, can explain some immunological abnormalities, but seem to arise at a later stage of the disease. On the other hand, inflammation, immune activation and oxidative and nitrosative stress can induce hypocortisolism and a blunted adrenal response to ACTH through various pathways gradually.

The endocrine and immunological anomalies in ME/ CFS reflect a paradox: reduced adrenal output (cortisol) combined with suppression of the (cellular) immune system, (possibly) due to enhanced glucocorticoid sensitivity of the Th1 arm of the immune system. Finally, inflammation/immune activation, cardiovascular impairment and low oxygenation/oxygen uptake could account for various neurocognitive and neuropsychological abnormalities found in ME/CFS.

Other authors have proposed alternative explanatory models for ME/CFS. The ONOO-model, with a key role for the self-perpetuating vicious circle of elevated oxidative and nitrosative stress, resulting into peroxynitrite (ONOO-), proposed by Pall et al[305] is incorporated within the 4I explanatory model. The 4I explanatory model is also in line with the NO-induced central sensitisation-model of Meeus et al[306]. The 4I model has commonalities with the neuroimmunological (NI) model for ME/CFS, put forward by Morris and Maes[307]. However, there also some relevant differences. In essence, the NI model is a linear model in which a non-persistent infection induces a vicious circle of oxidative and nitrosative stress and inflammation, neo-epitopes (induced by oxidative and nitrosative damage to proteins) and autoimmunity. The 4I hypothesis embodies key roles for reactivating and chronic infections, immune dysfunction and Th2-dominated immune activation (next to inflammation), HPA axis dysfunction, e.g. hypocortisolism and blunted adrenal responses, enhanced sensitivity of the HPA axis and the (cellular) immune system to the suppressive effects of cortisol, and circulatory deficits[3]. In contrast with the hypothesis that maladaptive stress responses, either due to a stress crash[26] or “allostatic overload”[308], are causing the immunological abnormalities seen in ME/CFS, the 4I hypothesis is based upon the premise that the immunological aberrations and oxidative/nitrosative stress can induce and sustain the endocrine abnormalities and defective stress responses through various pathways.

The 4I hypotheses is consistent with the “alternate homeostatic state”-hypothesis of Craddock et al[309], although, the 4I incorporates an opposing cause-and-effect-relationship between the immunological and endocrine abnormalities in ME/CFS.

Diagram
An diagram to provide an overview of the 4i hypothesis is in Appendix One.

Appendix One – Diagram of the 4i hypothesis