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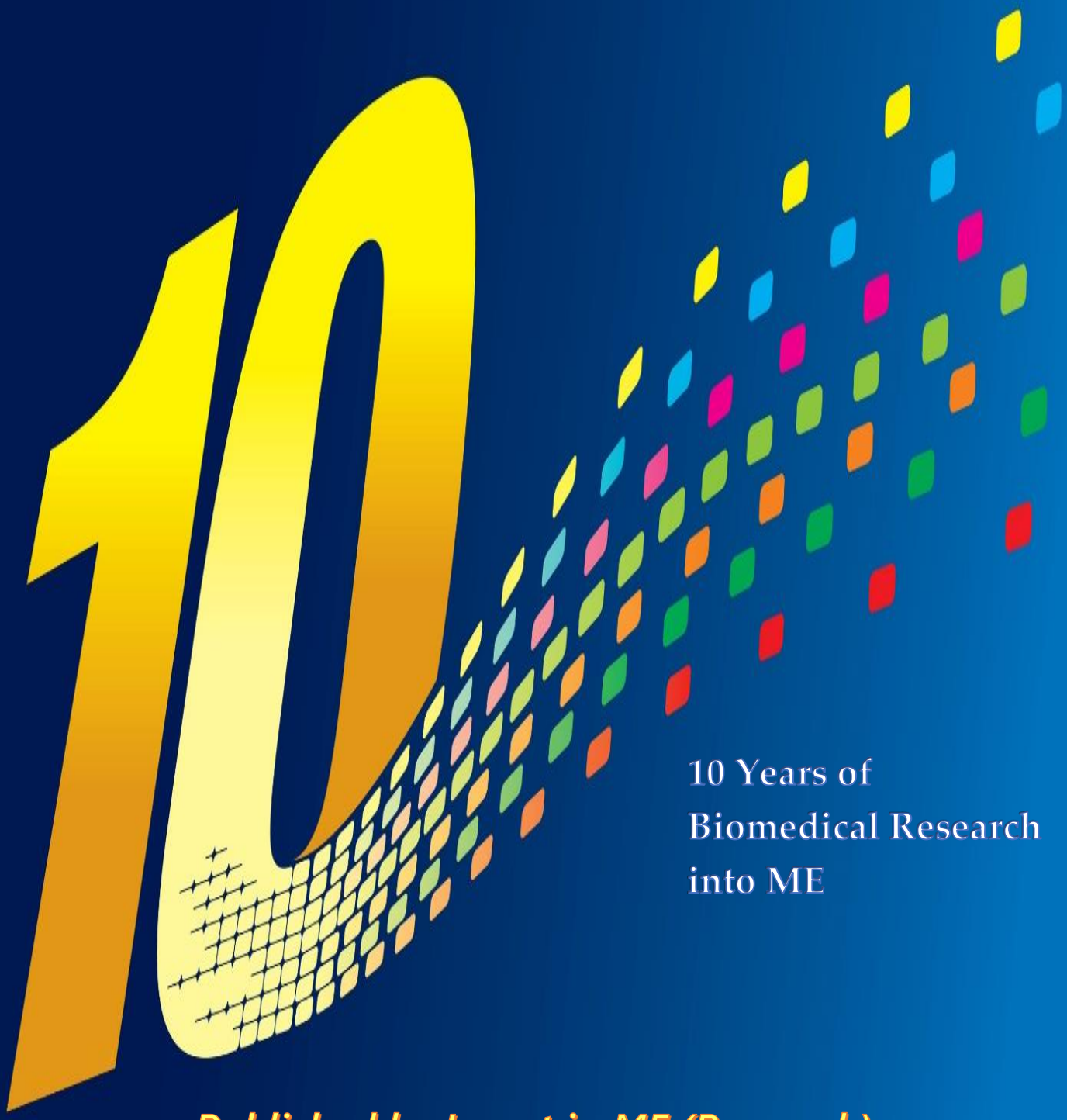

10 Years of
Biomedical Research
into ME

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FOCUSED ON PROGRESS

for people with Myalgic Encephalomyelitis

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Journal of IiME

INVEST in ME COMMENT

IIMEC10 - 10 YEARS

As Invest in ME enters its tenth year as a UK charity then our tenth annual international conference – IIMEC10 – heralds perhaps the realisation of many patients and their families long held wish – that ME has finally entering a stage where sensible and credible research is being planned.

That this is mainly due to the work and will of patients illustrates how much there is still to do – but the hard work of Invest in ME's supporters is beginning to shape a better future.

Invest in ME was established in 2005 and became a UK charity in 2006. The charity trustees are composed of ME patients and parents of children with myalgic encephalomyelitis - ME.

When the charity was formed the aim was to make a difference – to change the way ME was perceived by the society at large and researched by academic institutions, by campaigning for patients' rights and providing a platform for better education about ME and the sparse research which was occurring. This has gradually evolved to include the objective to facilitate and initiate high quality biomedical research in top research institutions.

Raising the profile of ME by improving the education of healthcare professionals about the disease, by raising awareness of the disease amongst the public and media and by facilitating and enabling an international strategy of biomedical research into the disease, has been a full time job for the charity trustees – despite it being performed when time permits, in evenings and weekends and holidays, and when the illness itself allows.

Our conferences started in 2006, the same year that conference chairman, Dr Ian Gibson, produced the so called Gibson Report where a group of parliamentarians chaired by Dr Gibson

looked at evidence about ME from a wide range of sources. Our conference facilitated the hearing of Drs Byron Hyde and Bruce Carruthers. The Gibson report is still a very valuable historical document and if some of the recommendations from the report had been acted upon then people with ME and their families might well be in a different (and better) position today.

This year the US Institute of Medicine produced a report for US diagnostic purposes. Three of the speakers at this year's conference were involved with the report. Professor Betsy Keller was one of the group members and Professor Maureen Hanson and Dr Dan Peterson were among the reviewers.

The IOM working group looked at the published research as well as the so called grey literature in a systematic way and what they found was the shocking fact that little replicable or validated research existed compared to the number of people affected by this disease.

The numerous definitions being used have complicated all research and the lack of some common and agreed protocols and standards has affected diagnosis and therefore treatment.

Samples need to be shared so that different research groups can make sure they are finding the same thing and areas of expertise are being utilised effectively.

Such sharing is taking place with IiME funded researchers at UCL and IFR/UEA and some of the research will be presented at the conference.

Amongst the speakers at the Invest in ME Biomedical Research into ME Colloquium 5 (BRMEC5 – taking placed on the two days prior to the IIMEC10 conference) is Dr Luis Nacul and the rest of the UK biobank team who have also worked on standardising protocols to make sure the samples they collect are as representative of the patient population as possible in the absence of objective biomarkers.

From Haukeland University hospital in Bergen Dr Oystein Fluge and Professor Olav Mella return to present at the Invest in ME conference once again to talk about their current research.

In 2012 Dr Don Staines, co-Chair of the Invest in ME/Alison Hunter Memorial Foundation BRMEC2 Clinical Autoimmunity Working Group, and now professor and co-director at the N.C.N.E.D., stated -

'*The recent discovery from researchers in Norway that an anti- CD20 B cell- depleting drug had a marked benefit in the treatment of ME/CFS has sent a clear message to scientists and medical practitioners around the world that this disease may have an autoimmune origin.*

The findings of Drs Fluge and Mella and their co-workers are consistent with theories previously published that ME/CFS may be an autoimmune disease.

Despite compelling evidence that this disease is linked epidemiologically to infection and the disorder possibly being a post-infection disturbance of the immune system, little funding has gone into studies of autoimmunity. This is clearly a multi-system illness which has been badly managed in terms of the research agenda.'

While the clinicians who made the discovery, Dr Oystein Fluge and Dr Olav Mella, and co-workers, remain guarded in drawing unwarranted conclusions from the study published in PLoS late in 2011, a large multicentre study is now underway. We are delighted to welcome them back to the IIME conference.

We now can see more progress being made. The Chronic Fatigue Initiative funded by the Hutchins Family Foundation has produced research that has been noticed by the media. Drs Mady Hornig and Dan Peterson are among the authors of papers from this initiative. One study published in *Science Advances,* looked at plasma immune signatures and the other one published in *Molecular Psychiatry*, looked at cytokines in spinal fluid of ME/CFS patients. These research results may help in finding biomarkers to aid diagnostics.

This year we are also welcoming back Dr John Chia who is the only ME clinician/researcher concentrating on enteroviruses and ME. The late Dr John Richardson did a considerable amount of work into enteroviruses and ME in the UK and his work and legacy has been carried on by Dr Spurr and Professor Malcolm Hooper – who both participate in BRMEC5.

We are delighted to welcome some new presenters to the conference proceedings.

Professor Ian Charles has taken on leadership of the Institute of Food Research (IFR) in Norwich and we are honoured that he is opening the tenth Invest in ME conference. His track record is impressive and we hope his vision and innovation will help with ME research in the future as the research base for ME at UEA/IFR in Norwich Research Park has enormous potential in finding the cause(s) of ME.

The charity first proposed its centre of excellence in 2010 and with the help of the **Let's Do It For ME** team of volunteers funds were raised for the foundation research project which began at University of East Anglia and the Institute of Food Research in October 2013. This three year studentship is analysing gut microbiota in ME patients. Daniel Vipond is the PhD student taking on this project under the leadership of Professors Simon Carding and Tom Wileman. The patients are selected from Dr Amolak Bansal's CFS clinic at Epsom and St Helier hospital.

Invest in ME want proper education about ME to begin at medical school and one of the best ways is for medical students to intercalate in their course and play a part in the research projects. So fourth year medical students from the University of East Anglia (UEA), Bharat Harbham and Navena Navaneetharaja are also involved in the IFR/UEA gut microbiota research. The charity has for a long while stated the importance of international collaboration and we are pleased that Professor Maureen Hanson enabled Navena to spend over three months at Cornell University in Itacha USA to learn about their gut microbiota research. Meanwhile Bharat is currently working intensely with Professor Angela Vincent in her laboratory at Oxford University.

This is the essence of the IiME approach to research. Finding the cause, working in collaboration, using opportunities for international collaboration, bringing new expertise into studying ME and facilitating the education of healthcare staff.

At the 2012 conference we stated that we were working on an attempt to set up a rituximab clinical trial. Following our Biomedical Research into ME Colloquium 3 in London in 2013 we made rapid progress with our partners UCL.

Dr Bansal along with Dr Saul Berkowitz UCLH is also involved in this, the second IiME funded project which is looking at B cell biology in ME patients as the foundation for a clinical trial of rituximab. This work is being performed by Fane Mensah under the expert leadership of Dr Jo Cambridge. Professor Jonathan Edwards is also involved as an advisor.

"The charity has for a long while stated the importance of international collaboration..."

All of the students involved with IiME funded research projects will be in a panel discussion at the conference – satisfying a long held objective to highlight the next generation of researchers at our conference.

Also being presented in the IiME London research meetings this year is fascinating research from new speakers to the IIME conference/colloquium. Markers to aid in diagnostics may be found from the visual research performed by Dr Claire Hutchinson and her team. Dr Neil Harrison's work on immune brain communication is very relevant

for understanding ME and Professor Jonas Bergquist has been studying the CSF of a Swedish ME/CFS patient cohort.

This year's conference sees the progression of the spectrum of research into ME which is now being realised and we expect this to continue. As per the title of our 2013 conference ME is now "mainstreamed" into scientific research – and we hope it stays there. We believe we are on the verge of significant breakthroughs once research such as the IiME-funded projects are underway.

Preceding the IIMEC10 conference is our annual 2-day research colloquium (BRMEC5) with over 60 biomedical researchers from thirteen countries participating. In an atmosphere of collaboration we hope to make more progress which will lead to change for the benefit of people with ME and their families. BRMEC5 has taken a lot of effort to set up but we believe it is the way forward. Our aim over the last nine years has been to ensure that ME is researched properly in an international collaborative way.

As we enter our tenth year as a charity we feel our strategy for research is succeeding.

Our objective is not to exist as a charity for the sake of it – but to make real progress to understand and eventually overcome ME.

With a little more support and some help our proposal for a centre of excellence can be realised.
With colleagues and friends across the world, and dedicated and able researchers working with us to make progress, these agents for change are making a difference in how ME is researched, perceived and treated.

We have felt a change is underway, despite resistance to progress from some quarters.

Even the recent IOM report has finally conceded what patients have been fighting to make known for a generation – to governments, research councils, health services, the media and the public –

"It is clear from the evidence compiled by the committee that ME/CFS is a serious, chronic, complex, multisystem disease that frequently and dramatically limits the activities of affected patients."

For Invest in ME education and research are the key to progress, and hence change. The IiME conferences have formed a crucial part of this education and our research colloquia form a crucial and productive part of the research.

We may not have the most funding or resources – but we feel we are currently funding and facilitating some of the best research possible and have ideas and plans that can change things forever.

Welcome to IIMEC10.

Our Sponsors

Invest in ME would like to thank those organisations who have sponsored part of the IIMEC10 conference.

We would like to thank Vitae Natural Nutrition who have become a sponsor of the

IIMEC10 pre-conference dinner. Vitae Natural Nutrition is a laboratory that develops natural products based on Science and nutraceutical technology, designed to activate, improve and regulate the biological processes of the body maintaining and extending its functions. Following the vision of a healthier world to live in, Vitae have made important progress in the food supplement field and have generated results. The goal of the team is to invest in progress, seeking more natural solutions through innovation. The cornerstone of the research team is to find more efficient natural solutions through the use of innovation. Vitae have a number of reputable research partners and team members including: Qualified scientists Multifaceted Professionals Strong partnerships with Health Centers, Hospitals, and endorsements from Universities.

We would also like to thank three of our European ME Alliance colleagues for their great support in sponsoring the conference.

The Irish ME Trust, who have supported all our conferences, deserve a special mention.

Our European ME Alliance partners in Sweden and Norway have proven to be also contributed to the conference costs.

The **Swedish RME** group and **Norges ME Forening** have both generously donated to the conference costs. We are very proud to have received such wonderful support from our European ME Alliance colleagues.

Our Research

IMET and RME Sweden also recently donated to the Invest in ME Biomedical Research Fund (BRF) to help us in progressing our base of high-quality biomedical research in Europe.

Our two major areas of research currently revolve around the gut microbiota studies and the rituximab/B-cell research - a solid foundation of biomedical research which is being augmented with new collaborations.

The donations help us with the work being performed by the IFR/UEA in collaboration with Angela Vincent at Oxford University as she has expertise and interest in the role of autoimmunity in neurological diseases, including multiple sclerosis and auto-antibody mediated ion channel and receptor disorders.

This is very topical in light of the clues from the Norwegian rituximab trials as well as recent research that has come from the Chronic Fatigue Initiative funded by the Hutchins Family Foundation.

These studies published by Hornig et al include a serum and a cerebrospinal fluid study. The abstract of the cerebrospinal fluid (CSF) study states –

"Our results indicate a markedly disturbed immune signature in the cerebrospinal fluid of cases that is consistent with immune activation in the central nervous system, and a shift toward an allergic or T helper type-2 pattern associated with autoimmunity."©

These new donations have consolidated the research efforts at the Norwich Research Park where we now have a unique opportunity to establish, for good, our Centre of Excellence for ME using high-quality biomedical research and state-of-the-art research and treatment facilities.

IiME CONFERENCES – 10 Years

Professor Malcolm Hooper

Professor Malcolm Hooper
Emeritus Professor of Medicinal Medicine at Sunderland University.
Malcolm Hooper, via his advocacy and championing of human rights for ME patients, was instrumental in the formation of UK charity Invest in ME

The 10th Annual IiME Conference is a remarkable achievement of the human spirit and deserves the strongest applause and recognition for 10 years of very hard work and the way in which the energy and commitment of the ME community has been harnessed in the interests of patents, carers, scientists and clinicians.

Patients and carers have found reliable information about the illness and been given hope in their demanding and often ignored situations.

A string of eminent and ground breaking international scientists and doctors have addressed the IiME Conferences and reported on their work and accepted the challenge of communicating it without dumbing it down.

This has made the Conferences invaluable in disseminating reliable and up to date information that specialists as well as parents and careers have found encouraging and re-vitalising.

All who attended gained much with some experts making a commitment to engage with the illness and face the challenge of ME, a serious, multi-system biomedical illness that can not to be dismissed or superficially engaged with by the ideological stance of both Government, Insurance Agencies, DWP and NICE - an unholy alliance that is using the now utterly discredited PACE trial to support their stance. The recent draft P2P report has exposed the inadequacies of the somatoform / psychiatric / psychological approach that has sought to resist all the biomedical evidence presented at conference after conference.

The P2P draft report states:

1. the Oxford Criteria (designed and used by psychiatrists) should be retired since they result in a confused and confusing mixture of patients from which only confused and confusing data can be measured which cannot be reliably analysed.
Reliable and objective measurement is noticeable by its absence in many of these studies.
2. Any studies using the Oxford Criteria should not be used to direct treatment (CBT and GET).
The vast number of papers produced by the

"Wessely Scool" particularly the PACE Study are null and void and CBT/GET with ir without antidepressants are comprehensively rejected leaving only the biomedical science to help understanding and guide treatment. Everything must now change - Government, NICE, DWP and the Insurance industry - if evidence-based medicine is accepted. If it is not the P2P judgement stands against them as charlatans, tricksters who no longer recognise truth , scientific or otherwise when it meets them.
This is the greatest triumph of IiME whose support and commitment to truth have been vindicated.
Invest in ME have enjoyed the support of many ME sufferers and carers. They merit the greatest thanks and credit for their vision and enormous amount of work which has been carried out over the last nine years.

Congratulations to all who work so hard often behind the scenes to make the IiME conferences the success they are. The development of the Research Programmes and Colloquiums marked a new and impressive extension of the Conferences and is now bearing much good fruit and further enhancing the vision that was inaugurated with the original Conference.

It is a pleasure and a joy to be associated with their vision and work the ME community owes them a great debt - long may they and the IiME conferences flourish.

Malcolm Hooper

ME PATIENT

"Kaylah is going to do a sponsored horse ride. for IiME because she has struggled with ME since the age of 5!"

– Claire

from IiME's JustGiving pages
https://www.justgiving.com/investinm-e/

M.E. and ME

I ran, I swam, it's who I am
I laughed, had fun, enjoyed the sun.
I was doing such when this begun.

Felt a chill on a good warm day
Aches and pains that won't go away
Like the flu, I heard it said
But arms and legs are made of lead.

Can't remember what I was about to say
Simple words have gone astray
Can't make a choice between two simple things
Someone else is pulling my strings.

I try to read, but it only drains
Focussing harder, just scrambles my brains
The dark clouds descend, lead to despair
The weight of three men sinks into my chair

No outward sign to give a clue
No bandage, mark, no black and blue
Strange, it seems I always look well
Look from this side, then you could tell
Remove the mask for a day to see
The evil face of this beast called M.E.

Like a thief in the night it takes away
Your hope, your strength, your friends
Your likes, your loves your chance to play
And never makes amends

All we want is to be believed
And trusted when we say
Hey GP, can't you see
We didn't ask to be this way

This is real, a real big deal
As big as the 'popular' ills
It needs to be taught, given some thought
Not just a bundle of pills

We don't have a choice, we need a real voice
Give us some hope TODAY
So don't be doubting, we're gonna keep shouting

We're just not going away.

By Bill Clayton

Invest in ME – 10 Years On

Ros Vallings

The first ME/CFS conference I attended was in Dublin in 1994. I had been involved in a small research project with patients with ME/CFS, and that conference sparked my interest further. Research into the illness was just beginning to tick over and I remember a presentation by Mary Ann Fletcher on the role of the immune system – citing NK cells and cytokines – a new language for me, as a GP seeing a few patients with the illness – already acknowledged as some sort of "expert" in NZ as I had actually heard of the illness (dubbed Royal Fee disease when I was a student in London).

From then on I was caught, and since then have attended many International ME/CFS conferences including many of the previous nine organised by Invest in ME, headed by Kathleen McCall.

I have gradually learnt the "language" which seems to grow by the year, and I am sure what I have learnt can have only increased my understanding of this complex illness, and hopefully benefitted my patients. At that first Invest in ME conference we heard of the work of Jonathan Kerr identifying genomic changes – an exciting development.

Dr Ros Vallings

Dr. Rosamund Vallings has over three decades experience in the field of CFS / ME and is one of New Zealand's leading authority on the disease. She was recognized by the Queen in the 2008 New Year's Honours when awarded the New Zealand Order of Merit (MNZM). Dr. Vallings has served voluntarily for over 27 years as President of the ANZMES and latterly as Medical Advisor and Committee Member

Invest in ME is a remarkable organization. From small beginnings and hard fund-raising, it has grown to be internationally acknowledged as a unique leader, both in conference organization and spreading information worldwide about ME/CFS.

The conferences have become particularly special with the inclusion of closed symposia for over 80 invited attendees ahead of the conference itself. This year will be the 5th such addition and will spread over 2 days.

These symposia/colloquia are unique in that, as well as specially invited top ME/CFS researchers and clinicians, invitees have included researchers from other disciplines with potential

for interest in the field. This gives the researchers an opportunity to discuss ideas and network among themselves. As a result the planned idea of collaborative research encompassing many fields of medicine has emerged.

The symposia have been then followed by the more traditional one day conferences with a range of invited speakers – the leaders in their fields of research.

Attendees have included patients, clinicians, research scientists and supporters. There is always a buzz of anticipation and no-one is ever disappointed. Work presented is always backed by reliable research.

Having attended a number of these meetings now, I feel I have learnt a lot watching the growth of research, acknowledgement of the illness and clinical management. From the small beginnings when we knew this illness was real and in some way tied in with the immune system, I have watched the research evolve to encompass every system of the human body. Science has grown alongside, so that many investigative interventions are now possible, including in depth evaluation of the immune system, microbiological and biochemical studies, advanced brain scanning techniques etc.

The search for a biomarker and potential treatment options provide much hope for the future. Inevitably there have been hiccups over the years, with new ideas such as XMRV disappointingly thwarted, but that happens in every branch of medicine. Drugs are now being trialled, and particular inspiration has come from the work of our Norwegian colleagues. Many countries around the world are now involved in research into ME/CFS and clinicians worldwide are better informed.

These IiME conferences and symposia have also provided a wonderful opportunity for clinicians and researchers (some of whom are often quite isolated in their own setting) to get to know each other well, and have ongoing communication and peer support.

So what of the future?

I think that our growing understanding of the immune system and its complexity is holding many answers.

We know now that the workings of the immune system are interspersed throughout the whole body and involve brain, gastrointestinal tract and many other organs. This helps us understand why this illness is so widespread.

Muscle pathology and issues associated with auto-immunity hold promise. This is a multi-system illness, with many potential causes, including likely genetic vulnerability.

Finding a biomarker will give credibility to the illness, but what patients need is more specific treatment. At present we can offer management strategies and medication based on individual needs.

Drug trials are underway looking at auto-immunity, anti-viral agents etc. Paediatric issues are being addressed by a committee set up to provide guidelines for children with ME/CFS. Those with very severe illness have very special needs too.

Invest in ME provides an ongoing forum for development of greater understanding of this complex illness. So much has been clarified from what seemed so complicated to me in the early days.

Medicine is never static and we will all go on learning, particularly due to the supreme efforts of organisations such as Invest in ME.

Thank you, Kathleen and all at IiME for your work in producing these conferences, so that gradually the answers for our many patients will be forthcoming.

ROSAMUND VALLINGS, MNZM

How to Get All Trials Reported: Audit, Better Data, and Individual Accountability

Editorial comment: Although Invest in ME share little in common with this author's views on ME we do feel this article about the publication of research data is useful and would be interesting if applied to the publicly funded PACE Trial, where data has been refused to be released to the public despite Freedom of Information requests.

In this week's *PLOS Medicine*, the World Health Organization (WHO) publishes a landmark position statement, requiring all trials to make their methods and results available [1]. This represents important progress on a long-standing and global structural problem that has a clear, negative impact on patient care. The best currently available evidence shows that the methods and results of clinical trials are routinely withheld from doctors, researchers, and patients [2–5], undermining our best efforts at informed decision making. From this point forward, whenever the methods and results of a trial are withheld, doctors, patients, researchers, campaigners, and health care providers will be able to point at an unambiguous statement from WHO.

Delivering definitive change, however, will require more than positive statements and good intentions. The first quantitative data demonstrating publication bias in clinical trials—and clear call for trial registries—was published in 1986 [6]. Anyone withholding the methods and results of a clinical trial is already in breach of multiple codes and regulations, including the Declaration of Helsinki, various promises from industry and professional bodies, and, in many cases, the United States Food and Drug Administration (FDA) Amendment Act of 2007. Indeed, a recently published cohort study of trials in clinicaltrials.gov found that more

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Competing interests: BG is a co-founder of AllTrials.net, which campaigns internationally for all trials to be registered with their full methods and results available. BG receives academic funding from the Wellcome Trust, and the Laura and John Arnold Foundation, to work on various problems, including publication bias. BG receives income from popular science books and public speaking on problems in science, including publication bias.

Provenance: Commissioned; not externally peer reviewed

than half had failed to post results; and even though the FDA is entitled to issue fines of $10,000 a day for transgressions, no such fines have ever been levied [3].

In the face of such slow progress, this commentary sets out some practical suggestions for auditing, performance tables, accountability, codes of conduct, and better data that should help to drive up standards and prevent trial reports being withheld from those who need them most.

What Should Trials Transparency Look Like, and How Do We Achieve It?

The WHO statement calls for summary results to be both posted on a registry and submitted to a journal within 12 months. However, it is worth noting that academic journal publication may ultimately prove to be a red herring, as an indicator of transparency. Academic publishing decisions can be arbitrary, and introduce lengthy delays in access to knowledge. Furthermore, there is a growing body of evidence demonstrating that journals often fall short of the basic expected standards for reporting of clinical trials. It is commonplace to find that primary outcomes have been switched, for example [7]; findings are routinely "spun" [8]; and compliance with reporting standards such as CONSORT is highly variable. When compared with the long and formal structured Clinical Study Reports created for all industry-sponsored trials, academic papers have been shown to be incomplete and inconsistent [9].

However, since all clinical trials are fundamentally similar—when compared, for example, with the myriad study designs in molecular biology—it has been possible to develop reporting standards and operationalise these. Reporting results onto a structured database, such as the results tab of clinicaltrials.gov [10], has many preferable features: there is minimal delay, there is compulsory reporting of features that are required; and there is no possibility to switch pre-specified outcomes or other forms of reporting misconduct. Put simply, there is a box to report the pre-specified primary outcome, and it has to be filled. Recent research has shown that academic journal reports are inconsistent with those on clinicaltrials.gov [2] and contain less complete information on methods, results, and adverse events [11]. Furthermore, International Committee of Medical Journal Editors (ICMJE) member journals have explicitly stated that they will not reject trial reports on the grounds that the results have already appeared on clinicaltrials.gov, and that they do not regard registry results reporting as prior publication [12]. Lastly, clinicaltrials.gov is clear that they will accept results on any trial, from any era, on any treatment, from any territory. This negates a key defence commonly cited by trialists and sponsors when facing calls for greater transparency: that journals reject "negative" results. All trials can now be reported, immediately, using clinicaltrials.gov as a first or last resort, if the trialist is willing. The question remains: how can we ensure this is done?

The Need for Audit

One key element is likely to lie in medicine's most basic research tool. Audits are routinely conducted on local service issues, such as infection rates, or waiting times, but rarely on broader structural issues such as publication bias, even though the impact of the latter on patient care is likely to be greater and global. Indeed, it is peculiar that for many years trial registration was considered an end in itself, when in reality registration is only of value as the raw material for publication audit.

The basic structure for a routine ongoing audit of results reporting is simple: using a register, identify trials that completed more than 12 months ago; establish, through whatever means, whether results from the trial have been reported; and post the date of results appearing to the register. From this, it is trivial to derive performance metrics for individual companies,

funders, drugs, disease areas, institutions, and investigators.

This is highly specific and accountable information that can be used for practical good. Firstly, the very act of creating such data would allow us to name and shame poor performers, and also to reward best practice. Furthermore, those falling behind can identify and learn from those who are successfully meeting their obligations to patients.

The results of the audit can also be used to inform medical decision making. While it is unwise for doctors to use their prescription pads to pursue political goals, transparency metrics for an individual drug company are valuable context for interpreting data on the benefits of their products. For example, suppose there are two treatments of apparently equal benefit in meta-analysis, but one is made by a company with a proven track record of complete transparency, with 95% of all information available, while the other is made by a company with clear record of withholding information. The clinically cautious approach is to prescribe the treatment for which the results are more reliable, from the company that is more transparent.

"Withholding the results of clinical trials is unethical and harms patients. Those guilty of such misconduct could be banned from conducting further trials on patients"

Audit data can also be used by ethics committees and institutional review boards (IRBs). Withholding the results of clinical trials is unethical and harms patients. Those guilty of such misconduct could be banned from conducting further trials on patients until their previous trials have been made available. Indeed, even in the absence of such audit data, it would be trivial for all IRBs to ask one simple question of all those applying to conduct a trial: "Have you been involved in any clinical trial, which completed more than 12 months ago, for which the results remain inaccessible?"

Professional bodies and professional regulators, similarly, can now incorporate the WHO guidance into their codes of conduct and create mechanisms to ensure it is acted upon, for example by opening formal investigations when contacted over concerns around results being withheld by individual researchers or clinicians, and triggering disciplinary action whenever audit shows that the codes have been broken. It is rare, in professional regulation, to have data on transgressions created so rapidly and so unambiguously; it would be wrong to neglect this opportunity to improve standards. Patient groups, lastly, could write open letters to all companies and researchers withholding methods and results of trials on treatments taken by their members, represent their constituencies by holding individuals to reasonable account, and again help improve compliance.

The Practicalities of Audit

Such audit can be conducted locally, centrally, or ideally, both. Since the recent rejuvenation in policy discussion in the United Kingdom on withheld trials, there have been small local audits conducted by various bodies, including sections of the Health Research Authority (as yet unpublished); the National Institute of Health Research (as yet unpublished); the Medical Research Council (to produce an estimate of publication bias for a 2012 UK parliamentary inquiry into trials transparency [13], but as yet unpublished); and an ongoing audit, on which I am a collaborator, covering trials in the University of Oxford. For the latter, alongside our findings, we also plan to publish our practical experiences of conducting the audit, with a boilerplate protocol that can be used by others in order to help make local audits simpler and produce comparable data. Such audits could and should be conducted and published routinely by all government research funders,

industry sponsors, and institutions, to help ensure that all trials are reported.

Central audit is also desirable, and can be readily worked into existing trial registry workflows. At present, a completed trial without an associated results report on a registry may represent a transgression, but it may also represent an administrative failure. Publishing performance data and acting upon it will incentivise trialists to update their records. Worse still, it is currently impossible to establish on clinicaltrials.gov whether a completed trial has successfully requested an extension for reporting (whatever one might think of such exemptions), because this information is not posted; if data fields on such exceptions are routinely and transparently posted in public onto the database, compliance and transparency rankings can be automatically generated at no cost.

"We cannot make truly informed decisions when vitally important information on the methods and results of clinical trials is routinely withheld"

When discussing efficiencies, it is important to be clear, however, that the cost of even manual audit is trivial in comparison to the cost of conducting a randomised trial. Producing accessible knowledge for clinical decision making is the key purpose of a trial. Once a trial has been conducted—at great cost—and left unreported, then the small and final marginal cost of making its results available represents better value for money than almost any other step in the research process.

What to Do about Past Trials

The emphasis by WHO on having access to all trials, from the past as well as the future, is particularly important and welcome. It is clinically highly relevant because the overwhelming majority of prescriptions today are for treatments that came onto the market—and were therefore researched—over the preceding decades rather than the past five years. The question, however, is how to prioritise access to such information, since there is no sense in resources being deployed on sharing evidence that is no longer relevant to current practice. There are many options. One is to proactively release information, prioritising by some metric of clinical need, such as the number of patients affected; or usage, such as the number of prescriptions issued for that class of treatments; or even a complex model built around power calculations and the likelihood of the withheld data changing the conclusions of the best current systematic review.

A simpler option, however, is for thorough retrospective registration of clinical trials to act as a "menu" from which doctors, researchers, and patients can request further disclosure of full methods and results, with appropriate transparency around the request and adjudication process. This is an attractive option since registration is low cost, but it does present one previously undocumented challenge. Through the AllTrials.net campaign, we are currently conducting an audit of companies' policies on trials transparency, to create a Trials Transparency Index. In doing so, we have met a large number of individual companies to ask about gaps in their policies. One recurring theme, on the issue of retrospective registration, is that registries often require detailed administrative information (such as an IRB approval number) that is not readily traceable 20 years after a trial was completed. It may therefore be pragmatic to take a more permissive approach to completeness of certain data fields, with missing items replaced by an explanatory note where absolutely necessary, in preference to a trial not being retrospectively registered at all.

Conclusion

The position statement from WHO is powerful and welcome, but previous calls for registration were not enough to fix publication bias, and

positive statements require practical implementation. The solution is likely to lie in simple audit, providing better data for individual accountability. This can be delivered at low cost through a routine audit cycle to identify completed but unreported trials on all registries, with public performance tables that will incentivise trialists to ensure their registry entries reflect their compliance. Local audit will facilitate data-checking and ensure local accountability. As with all audit cycles throughout clinical practice this data must be acted on, with those who are guilty of research misconduct in withheld trials exposed to public scrutiny and local performance management; investigations automatically triggered by their professional regulators; and denied access to further trial participants. Lastly, doctors and patients can act on withheld data exposed by audit and consider avoiding treatments—or indeed whole companies—where there is clear evidence that the data on those interventions is comparatively unreliable.

These are simple processes that should have been integrated into the information ecosystem of evidence-based medicine from the outset. We cannot make truly informed decisions when vitally important information on the methods and results of clinical trials is routinely withheld, and yet we have tolerated this simple, fixable, pervasive flaw in evidence-based medicine for many decades. The doctors and patients of the future may well look back on this phenomenon with amazement, much as we look back on mediaeval bloodletting.

Author Contributions

Wrote the paper: BG. Agrees with manuscript results and conclusions: BG. BG has read, and agrees that he meets, ICMJE criteria for authorship.

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ME: The Last and The Next Ten Years

What a difference a decade makes in medicine -- or does it?

The two camps in the ME/CFS "battle" remain as far apart as ever, to the continuing detriment of patients and also to the State's limited resources: it is currently claimed that the cost of "CFS" to the UK economy is up to £3.5 billion per annum.

One camp consists of biomedical scientists and clinicians whose research shows that ME is an organic multi-system neuro-immune disorder with protean symptomatology; some consider it likely to be an autoimmune disease with the target organ being the vascular endothelium.

The other camp consists of a small but influential group of UK psychiatrists and insurance doctors (known colloquially as the "Wessely School") who remain convinced that what they refer to as "CFS/ME" is a psychogenic condition where reported symptoms result not from organic disease but from patients' maladaptive beliefs and behaviour, and that the condition can be fully reversed by graded exercise and cognitive behavioural therapy.

Currently we are at a tipping point, because the "behavioural" camp is slowly but surely being unseated. In the last ten years the quintessence of the ME battleground in the UK has been the focus on pseudoscience, but there is at last a transition underway from pseudoscience to scientific medicine.

Here are some facts, all easily verifiable:
Since 2005, ME has been included in the UK National Service Framework for long-term neurological conditions.

On 30th January 2006 the then Health Minister, Lord Warner, said on the record: *"There is only one World Health Organisation International Classification of Diseases code for chronic fatigue syndrome/myalgic encephalomyelitis, which is G93.3"* (HL3612).

About the Author

***Margaret Williams** has been a prolific writer on the subject of ME over the last two decades or more.*

Her thorough and meticulous commentaries on the inaccuracies, bias and often farcical claims of the psychosocial lobby have aided the ME community in destroying the myths and spin which has been allowed to foster by establishment organisations. A great debt is owed to Margaret Williams for her dedication and professional input to science for the benefit of all people with ME and their families

On 2nd June 2008 the Parliamentary Under-Secretary of State, Department of Health (Lord Darzi of Denham) stated: *"My Lords, the Government accept the World Health Organisation's classification of CFS/ME as a neurological condition….My Lords, I have acknowledged that CFS/ME is a neurological condition"* (HLPQ: Health: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis).

On 21st November 2011 Lord Freud, Minister for Welfare Reform, confirmed in a letter to the Countess of Mar that the Department for Work and Pensions does not consider ME/CFS to be a mental disorder. The letter was unequivocal: "*The Department of Health has indicated that they have 'always relied on the definition set out by the World Health Organisation in its International Classification of diseases (ICD) under ICD code G93.3, subheading other disorders of the brain'. The DWP is in agreement with this view.*

Therefore, for the avoidance of doubt, I can be clear that the Department does not classify CFS/ME as a mental health disorder".
Despite Ministers' clear pronouncements, given that key members of the "behavioural" camp have acquired formidable powers and have

secured established positions as advisors on "CFS/ME" to UK Departments of State, including the Department of Health and the Department for Work and Pensions, and also to bodies such as the Medical Research Council (MRC) and NICE (the National Institute for Health and Care Excellence), it is their behavioural modification interventions (ie. "brain-washing") that prevail throughout the NHS, with the risk of serious iatrogenic harm to patients with ME/CFS.

Many informed observers believe that within the next ten years this situation will be seen for what it is – a truly appalling medical scandal of astounding proportions, but it is a scandal that (via the auspices of the Science Media Centre and the UK media) many UK luminaries, have condoned without question, (http://www.sciencemediacentre.org/film/); (http://www.meactionuk.org.uk/The-SMC-and-its-campaign-against-MECFS.htm).

The "evidence" of the "behavioural" camp

The PACE trial (**P**acing, **A**ctivity, and **C**ognitive behavioural therapy, a randomised **E**valuation) is by far the most contentious clinical research study conducted in the field in the last ten years. Conceived and executed by psychiatrists Professors Peter White and Michael Sharpe, assisted by a behaviour therapist, Professor Trudie Chalder, it was funded by the MRC, the Scottish Chief Scientist's Office, the Department of Health and the Department for Work and Pensions. The PACE Trial is the only clinical trial that the DWP has ever funded and it did so because it was assured that cognitive "restructuring" would successfully remove people with ME/CFS from claiming State benefits. Recruiting began in 2004 and finished in November 2008.

> *"Numerous FOIA requests for the raw data (which does not belong to the Investigators but to UK tax-payers) to be released have been refused on entirely spurious grounds"*

Problems with the PACE trial were legion, a particular one being that CBT and GET participants (but not those in other arms of the trial) were instructed to ignore their symptoms. Such advice has previously been described as "*dangerous*" in a Witness Statement for the High Court (http://www.meactionuk.org.uk/Statements-of-Concern-for-High-Court.htm).

After the trial had started the Principal Investigators abandoned the protocol-defined thresholds for fatigue and physical function required for a "*positive outcome*" and "*recovery*" and replaced them with far less demanding criteria. These changes were such that it became possible to leave the trial with greater fatigue and worsened physical function and still meet the newly-defined thresholds of *"the normal range"* (this is not the same as normal health, but the media was encouraged to report it as synonymous with "recovery"). The re-calculation and construction of *"the normal range"* allowed the claim that participants had "recovered":

"*This study confirms that recovery from CFS is possible and that CBT and GET are the therapies most likely to lead to recovery"* (PD White et al: Psychological Medicine: 2013: doi:10.1017/S0033291713000020).

The Investigators initially claimed that the PACE trial was to study "CFS/ME" but after publication in The Lancet of selective results in February 2011, the Chief Principal Investigator (Professor Peter White) wrote to the editor in March 2011 saying that the PACE trial "*does not purport to be studying CFS/ME but CFS simply defined as a principal complaint of fatigue"*. This was a cause for concern, because funding and ethical approval had been sought and obtained on the basis that the Investigators would be studying "CFS/ME", not "fatigue".

The PACE trial cost UK taxpayers over £5 million and, despite desperate and increasingly ludicrous attempts to proclaim its success, it is widely acknowledged to have failed (http://www.bmj.com/content/350/bmj.h227/rapi

d-responses) and, far from reducing claims for benefits, participants' claims for benefits due to illness or disability actually increased from baseline to follow-up (McCrone et al PLoS ONE 7(8): e40808. doi:10.1371/journal.pone.0040808).

Numerous FOIA requests for the raw data (which does not belong to the Investigators but to UK tax-payers) to be released have been refused on entirely spurious grounds, lending yet more support to the widespread opinion that release would conclusively demonstrate the failure of CBT and GET as vehicles for recovery from ME/CFS, indicating that their proponents have spent their professional lives in a null field.

Given that there is an acknowledged nationwide lack of basic services for ME patients and that most have no access to NHS consultants and never get to see a neurologist, immunologist, endocrinologist or vascular specialist and even have profound difficulty in seeing a GP, the claim that the cost to the UK economy of "CFS" alone is £3.5 billion per annum is questionable (J Psychosom Res. 2012;72:242–7). Patients with ME/CFS experience real difficulty in seeing a GP: not only do many GPs refuse to accept that it is a legitimate disorder, but after the BMJ ran a campaign to list "*non-existent*" diseases that are best left untreated, in which ME features along with big ears and freckles (BMJ 2002:324:883-885) patients with ME were removed from GPs' lists, being tersely informed that: "*This practice does not treat non-existent diseases*".

The two major US institutions that -- despite the glowing reports of the PACE trial's claimed success -- have revised their position on ME/CFS are the NIH and the CDC.

(1) The US National Institutes of Health, one of the world's foremost medical research centres, convened a Pathways to Prevention working group which in December 2014 published its draft Statement entitled "Advancing the Research on Myalgic Encephalomyelitis / Chronic Fatigue Syndrome". It is an important document, as it signifies a major change in attitude towards ME/CFS and casts further doubt on the claimed success of the PACE Trial. The NIH Statement is unambiguous that the Oxford criteria (formulated by the Wessely School themselves and used in the PACE trial) are flawed and lack reliability, thereby confounding the ability to interpret results drawn from studies which used them to select cohorts and noting that use of the Oxford criteria may impair progress and cause harm. This being so, it can be surmised that all previous psychiatric "research" on ME/CFS that used the Oxford criteria (not just the PACE trial) used groups of people who were not properly characterised and thus those results also lack scientific credibility.

The following quotations from the NIH are particularly significant:

"ME/CFS exists.

"The Oxford criteria (published in the Journal of the Royal Society of Medicine in February 1991) are flawed and include people with other conditions, confounding the ability to interpret the science.

"Often, patients with ME/CFS are labelled as lazy, deconditioned, and disability-seeking; this hampers scientific progress. Both society and the medical profession often treat patients with ME/CFS with disdain, suspicion, and disrespect. Patients are frequently treated with psychiatric and other inappropriate drugs that may cause harm.

"There is reproducible evidence of neurocognitive dysfunction with abnormalities in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies. Strong evidence indicates immunologic and inflammatory pathologies, neurotransmitter signalling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities in ME/CFS.

"This is not a psychological disease in aetiology.

"Existing treatment studies (CBT and GET)…(have) not translated to improvements in quality of life. Thus, they are not a primary treatment strategy.

"The focus on exercise programmes has further stigmatised and discouraged research participation.

"Many patients with ME/CFS are misdiagnosed and treated erroneously with potentially toxic therapies that may cause harm.

"Current research has neglected many of the biological factors underlying ME/CFS onset and progression.

"ME/CFS is a chronic, complex condition…with no cure…..Nothing has improved the lives of the patients.

"fMRI and imaging technologies should be further studied as diagnostic tools and as methods to better understand the neurologic dysfunction of ME/CFS.

The Conclusions of the draft report reiterate key findings:

"Specifically, continuing to use the Oxford definition may impair progress and cause harm…Thus, for needed progress to occur we recommend that the Oxford definition be retired".

https://prevention.nih.gov/docs/programs/mecfs/ODP-MECFS-DraftReport.pdf

Since such strong doubts have been raised about the Oxford criteria, the question again arises about the validity and safety of the NICE Clinical Guideline on ME/CFS (CG53) which relies so heavily on Oxford criteria-based research and which promotes directive (not supportive) CBT and GET as the primary intervention for those with ME/CFS. In the light of current knowledge, whether or not clinicians should rely on the NICE Guideline has become ever more imperative, especially in the light of the recent UK Supreme Court ruling that over-turned the long-held Bolam principle (a test used to assess medical negligence; it held that a doctor was not negligent if his actions would be supported by a responsible body of medical opinion; indeed, the accused doctor needed only to find an expert who would testify to having done the same thing). This has now changed: there are new rules of consent and doctors are legally accountable for informing patients of any material risks in any recommended medical interventions (BMJ 2015:350:h1481). This means that psychiatrists who recommend graded exercise therapy for people with ME/CFS must warn them of the potential risks of deterioration with exercise, or be in breach of the law. To many people, it also means that having to inform patients with ME/CFS of the risks of GET (because of the increased cardiovascular risk, which would have to be explained to patients) invalidates the belief that patients are suffering from a behavioural as opposed to a physical disorder.

"psychiatrists who recommend graded exercise therapy for people with ME/CFS must warn them of the potential risks of deterioration with exercise, or be in breach of the law"

The latest NIH draft Statement confirms the long-held belief that the NICE Guideline on ME/CFS should be withdrawn because, as many have claimed from the time it was published in August 2007, it was never fit for purpose, and further doubt must now arise as to how safe it is. Indeed, this has now been acknowledged: in June 2014 Professor Mark Baker, Director of the Centre for Clinical Practice at NICE, said at the Forward-ME Meeting at the House of Lords that the NICE Guideline was no longer meeting the needs of people with ME/CFS and should be replaced.

(2) After publication on 10th February 2015 of the Institute of Medicine's Committee's report (Beyond ME/CFS: Redefining an Illness), the US Centres for Disease Control decided to archive its CFS Toolkit that recommended CBT and GET as interventions for ME/CFS. The conclusion of the IOM Report states: *"It is clear from the evidence compiled by the committee that ME/CFS is a serious, chronic, complex, and multisystem disease that frequently and dramatically limits the activities of affected patients"* (http://www.cdc.gov/cfs/toolkit/archived.html).

The "behavioural" school continues to ignore the evidence (not hypotheses) documented for ME/CFS. The evidence is now so strong that

ME/CFS is a serious multi-system neuro-immune disorder that it becomes intellectually embarrassing for anyone to continue to consider it to be a behavioural disorder.

Recent research from the US posits that true ME (as distinct from ubiquitous chronic "fatigue") is an autoimmune disorder: "*Our results indicate a markedly disturbed immune signature in the cerebrospinal fluid of cases that is consistent with immune activation in the central nervous system, and a shift towards an allergic or T-helper type-2 pattern associated with autoimmunity….Profiles of ME/CFS subjects also differed from those of MS subjects, with ME/CFS cases showing a markedly greater degree of central nervous system immune activation as compared with those with MS"* (M. Hornig et al; Molecular Psychiatry 31st March 2015: doi:10.1038/mp.2015.29).

Dr Oystein Fluge and Professor Olav Mella from Haukeland, Norway, have conducted several studies of the cancer drug rituximab (a monoclonal antibody that targets and destroys the body's B cells, which recover once treatment ceases) on ME/CFS patients. Their theory is that ME/CFS is a variant of an autoimmune disease that affects the body's ability to control blood flow. World-class experts like Fluge and Mella would not use anti-cancer drugs like methotrexate, cyclophosphamide and rituximab, all of which carry a black box warning, if they believed ME/CFS to be a behavioural disorder; the difference between Fluge and Mella and the "behavioural" psychiatrists is that the former actually listen to their patients whilst the latter prefer to impose their own beliefs and control their patients' behaviour.

The above are merely illustrations of some of the many important biomedical research findings published on ME/CFS in the last ten years.

After almost 30 years of UK health care providers' dismissal and mistreatment patients with ME/CFS are aware that finally, a paradigm shift is occurring and the psychiatrists' stranglehold over their disease is being loosened.

That this is so is thanks to charities like Invest in ME who, quietly but resolutely, have done so much to bring about that paradigm change.

During the next ten years, it is likely that the link between the immune defects found in ME/CFS and an infectious or environmental trigger will be discovered and, without doubt, ME/CFS will be added to the long list of organic disorders (including epilepsy, myasthenia gravis, MS, diabetes, migraine, pernicious anaemia, ulcerative colitis, gastric ulcer and Parkinsons) which psychiatrists forcefully asserted were psychogenic until medical science proved otherwise.

ME PATIENT

"A fellow member of the Let's Do It For ME fundraising team for IIME has written this on my behalf as I am too ill to do it myself. I have very severe ME. I got ME at the age of 8. I am now 23. Like some other serious illnesses, ME can fluctuate in severity. You can see from the photos in the picture gallery that whenever well enough, I was out being involved and enjoying life to the best of my ability. My health took a bad turn for the worse in 2012. I went into hospital and then to a nursing home, fed by naso-jejunum tube. The staff helped me and my family to celebrate my 21st birthday there by raising awareness and funds for Invest in ME to help them set up a UK centre of excellence for research and hopefully treatment. People like me with ME desperately need this.

I am being cared for at home now and can listen to audio books for about 15 minutes in the morning and cuddle my guinea pig in the evening. That is all the daily activity I can do with my current level of illness severity. I am asking you to sponsor me to listen to audio books. Thank you for helping me to help IIME."
Rosa

from IiME's JustGiving pages
https://www.justgiving.com/investinm-e/

ME/CFS – Through The Eyes of a Young Researcher

Fane Mensah
University College London

Before I start I would like to introduce myself. I am a 24-year-old researcher (student). I am originally from the Netherlands where I completed a Masters degree in Infection and Immunity.

I came to work with Dr. Cambridge because we share the same interest in B cells, their development, functioning and relation within diseases. She told me that she was going to work on a project on ME/CFS, a disease I had heard of, but did not know the details from.

The only thing I was told was that it is a disease with unknown aetiology with possible involvement of white blood cells called B cells. To learn more about the disease I started reading papers on what was known before I started the research.

Quite quickly I came to the conclusion that it really was a difficult disease to talk about with people, not to mention actually being involved in research. So I just told myself, to get involved in the study and that will hopefully clarify the phenomena of the disease (I hope).
So we formed our small ME/CFS Research Team with the collaboration of Dr. Saul Berkovitz (Consultant Neurologist, UCLH), Dr. Amolak Bansal (Consultant Immunologist, St Helier Hospital), Dr. Arti Sharma (Research coordinator), Dr. Cambridge and myself. We made a plan of how to collect the samples needed, organized ourselves and solved the many logistic issues for the project in a few very busy months.

The process was relatively straightforward; ME/CFS patients who had been seen and assessed by the two Consultants were invited for an appointment with Dr. Sharma and myself. I saw these appointments as a great opportunity to educate myself and see with my own eyes what ME/CFS really involves.

After a few appointments and some formal discussions with patients (and family members) ME/CFS started to make sense to me. Not the scientific immunological or neurological part (which was my main task), but the part of how this disease affects people who used to be healthy (young or old, at the beginning of a career or just in the middle) and now became patients of a disease without a clear diagnostic pattern and no biomedical therapeutic strategy.

Before I went into the lab to perform the research with the group, I already knew that I now wanted to explore this rare, but so *affecting disease. Not just to perform B cell analysis in these patients, but also because of my interest in this condition and my wish to really try and understand the disease.

Patients (ME/CFS) rely on researchers and doctors to provide them with answers to their questions (something they expect from us), but something that has been often ignored by GPs and even in some cases specialists.

This is not an easy situation, because we cannot always give answers to things we are not certain of. But what we can do is educate ourselves by performing research, instead of ignoring the disease or giving false answers.

Luckily, there are groups who try to solve the phenomena behind ME/CFS and funders like Invest in ME who play a really important role in this.

I mention the words "education" and "research", simply because it is an important area which has to be paid attention to! A lot of papers have been published in the last few years, something, which keeps fundraisers, patients and researchers positive.

Although, it is still difficult to fully assess the implication or the interpretation of the findings related to ME/CFS (based on virology, immunology, psychology etc.).

Due to the heterogeneity in the environment amongst other things, (which make comparisons between different groups of patients a problem) research is often difficult to reproduce.

Another issue is the comparison of 'healthy controls' with ME/CFS Patients. Just like ME/CFS patients, healthy controls are also heterogeneous (as we all know everyone is different).

The big difference between ME/CFS and other diseases is that in other diseases we have a clear symptom-based 'biomarker', for example, swollen joints, skin rashes etc. and also diagnostic markers in the blood (antibodies, a clear infection, inflammation etc.), which we can compare with a healthy, if heterogeneous, control group.

This could also be a reason why results are not easily reproduced. Therefore, it could be possible to focus on the group of ME/CFS patients as a whole and see if we can compare different sub-groups within ME/CFS similarly to how we want to compare healthy controls with ME/CFS patients. I am not saying that we should ignore the results with healthy individuals; we should still use this as measurement for clear differences. Significance may thus not lie in the whole population (patients or even HC) but in a sub-group.

Important findings so far describe abnormalities in the immune system and as a result this might affect the nervous system (fatigue and other symptoms), underlying the immune system as an important factor. Instead of thinking of the effect of the immune system on the nervous system, we could also think of an effect or functioning of the nervous system to restore the dysregulated immune homeostasis.

It is really important to focus in different areas and systems, because that is where ME/CFS resides "in different areas".

The collaborative board initiated by Invest in ME, combines different groups from over the world in all these different areas. Extending and strengthening relationships and collaborations will bring us closer to answering those questions we and especially the patients want the answer to.

ME PATIENT

"I've had M.E. for six years now, and it's an ongoing daily struggle. Not just because it sucks being ill 24 hours a day and having no quality of life but because there is no treatment, minimal support and little medical understanding of this illness. Invest in M.E. are a charity trying to change this."
- Leanne

from IiME's JustGiving pages
https://www.justgiving.com/investinm-e/

Better from America?

An Analysis of P2P and IOM Reports on ME

Recently two American institutions have commented on ME – treatment, research and other issues. These reports not only affect US citizens – they can also affect and influence other countries in the way they diagnose and treat peopled with ME or CFS across the world.

The significance of these reports is due to the large amount of time and resource invested in analysing diagnostic criteria, past and current research into ME, funding for ME research and other areas associated with the way this disease has been treated and perceived over the last generation.

As such it was very interesting to compare the views of these bodies and those which Invest in ME have been advocating during the last nine years.

The NIH Pathways to Prevention (P2P) Workshop Report: Advancing the Research on Myalgic Encephalomyelitis / Chronic Fatigue Syndrome was formed to create a research agenda for ME.

Invest in ME submitted a full response to the National Institute for Health after reading the full report. Invest in ME urged the NIH to make a bold move and substantially increase funding for biomedical research into ME. A summary of Invest in ME's comments on the P2P report -

Summary

- It proved useful for an outside group of experts to get an overview of ME/CFS research. But it is clearly not possible to do this successfully by just using a scoring method that works for a well-established disease that everyone agrees upon without any knowledge of the underlying history.
- It does not help that research into ME/CFS has had two opposite viewpoints and the P2P document consequently tried to facilitate both. T**his is a major mistake and is contrary to any common sense or logic.** It repeats the calamitous mistakes of the MRC in the UK
- If the statement is made that ME/CFS is a physical disease then recommendations should follow logically from that statement.
- If there are co-morbidities they should be dealt with in the same way as one would do with co-morbidities in MS, cancer or Parkinson's disease or any other disease.
- We commented that it was, at times, difficult to comprehend what the real objective of this workshop was and we hoped that this was not yet another paper exercise to keep

the patient community seemingly happy whilst the authorities do nothing concrete to remedy the current situation (a tactic used extensively by the establishment for the last ten years).

- It would be well for the NIH **NOT** to follow the UK example where an insincere effort to change is portrayed as real progress but just results in wasted years.
- The mediocrity in terms of provision of correct and up to date definitions and guidelines, scientific research and development of treatments and perception of ME was a direct result, and failure, of the policies of the past.
- We found the first part of this report described what needs to be done – but there were some incomprehensible references to using treatments which have contributed to the abysmal situation in which ME/CFS patients find themselves.
- We believe research into ME needs a strategic approach - but it is meaningless, and destined to fail completely, if it attempts to establish the way forward on foundations which include so much of what has been wrong in the past.
- For a way forward with proper research into ME then we need not just funding, but correctly defined cohorts, standardisation on diagnostic criteria and a collaborative of researchers who will not blur science with politics.
- The NIH have a unique possibility to be bold, to fix this problem once and for all.

Invest in ME suggested the following actions for the NIH to take –

- ✓ The NIH finally and totally abandon all links to the psychosocial model with regard to ME research funding
- ✓ Instead of relying on alternative funding streams elsewhere the NIH should take responsibility themselves for ME/CFS
- ✓ The NIH should invest $50 million per year for the next five years in biomedical research into ME/CFS, and provide correct and current education into the disease which will, in turn, raise appropriate awareness.
- ✓ This would mean an investment of $250 million over 5 years. This amount will still be less than the documented annual cost of ME/CFS of $1 billion as noted in line 6.
- ✓ This will –
  - create scores of biomedical research projects, lots of potential international collaboration, new ideas and new skills to enter the ME/CFS research area
  - facilitate the harnessing of the full potential of academic and research institutes
  - attract new, young researchers into the field of ME/CFS – this the charity has proven already with our B-Cell/rituximab project with UCL where a young researcher is drawn into this exciting area of research
  - galvanise science and eventually form pockets of expertise which will create the centres of excellence for the future.

- ✓ We suggested trying this for a 5 year period
  - With a yearly review of progress can inform every one of the status.
  - After 5 years of such funding a new conference/workshop/committee can be convened and progress can be examined.
- ✓ This will provide the best chance possible for resolving this illness to the benefit of patients.
- ✓ Our guess is that so much progress will have been made in research, in perception and possibly in treatments during that period that the money will be recouped with the

added benefit of giving some people their lives back.

- ✓ The stigma attached to ME as mentioned in the report – which is actually, in our opinion, just ignorant prejudice created by corrupt organisations and individuals - would be swept away.

$50 million per year is really not much.
After 5 years it will probably have built so much momentum that it could carry on by itself through savings in welfare, through new discoveries and, yes, through private donations/funding.
Invest in ME suggested a beginning by inviting NIH to be represented at our fifth Biomedical Research into ME Colloquium in London on 27-28th May 2015 and look the major research initiatives underway or planned.

We invited the NIH to be represented there in London – in order to join our international collaboration effort to resolve this illness in a way that brings hope to patients, brings responsible and proper science to the research area and brings a raising of awareness that will obliterate the monstrous distortions about ME/CFS which have poisoned all chance of making progress in the last generation.

We received no response.

IOM "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness"

Invest in ME looked at the full report from the USA Institute of Medicine (IOM).
There was no public consultation as happened in the P2P or UK NICE guidelines.

The IOM concluded with what has been obvious to patients for a generation – but which has for too long been ignored by governments, research councils, health services and the media

> *"It is clear from the evidence compiled by the committee that ME/CFS is a serious, chronic, complex, multisystem disease that frequently and dramatically limits the activities of affected patients."*

We summarise below our observations after reading through the full report that we feel are worth noting -

- IOM is a respected and influential institute This means that the good points from this report can be quoted elsewhere to aid convincing other healthcare authorities that ME needs to be treated seriously as a systemic disease.
- IOM performed an extensive literature review. This means that the good points from this report can be quoted elsewhere to aid convincing other
- The proposed new diagnostic criteria are clinical criteria for the US healthcare system and there was only one European (and no UK reviewers) involved - so it remains to be seen whether the UK and other European health care authorities will adopt this report
- The IOM criteria allow co-morbidities which seems sensible for clinical purposes as anyone can have more than one disease.
- Care should be taken to avoid misdiagnoses and this is why specialists are needed to oversee diagnosis
- Post-Exertional Malaise (PEM) is obligatory, not optional, for diagnosis and this is the one

> *"The NIH should invest $50 million per year for the next five years in biomedical research into ME/CFS, and provide correct and current education into the disease which will, in turn, raise appropriate awareness"*
> *-IiME Recommendation to P2P*

defining symptom that patients say was missing from CDC Fukuda

- Both the IOM report and the P2P draft report call for more research and highlight the serious lack of research into this area of medicine compared to the numbers of patients involved
- "Literature on mortality associated with ME/CFS is sparse."
- Also subgrouping was a task to be analysed by the IOM committee but due to the sparcity of research that was not possible.
- The implicit result of the above commentary is a direct condemnation of the research and funding policies of the UK Medical Research Council and US National Institute for Health
- This report is essentially far better than the UK CFS/ME NICE guidelines which were heavily biased toward CBT and GET and did not encourage, for example, further investigation into the promising IVIG paediatric research (Rowe, 1997) which the IOM does
- The IOM committee declared unequivocally that ME/CFS is a physical illness, **a disease**
- The IOM definition and the name goes against treatments such as CBT and GET and contradicts the P2P report in that respect.
- The report states that ME/CFS is a diagnosis to be made and provides good suggestions for asking questions and eliciting medical history as well as assessing supportive symptoms such as sleep disturbance and pain.
- There needs to be extensive medical education to make more doctors confident in making the diagnosis but we need centres of excellence (such as proposed by IiME) and experienced consultants to oversee the education.
- Diagnosing patients according to them fitting in the diagnostic criteria rather than by exclusion of other illnesses is good.
- One of the committee's most important conclusions is that a thorough history, physical examination, and targeted work-up are necessary and often sufficient for diagnosis of ME/CFS (a point often emphasized by clinicians speaking at IiME conferences).
- It is also all the more important to invest in fundamental research that can come up with objective and easily implemented tools for aiding diagnostic accuracy.
- *"First and foremost, listening to patients and taking a careful history are key diagnostic tools."*
- Patients who have not yet been symptomatic for 6 months should be followed over time to see whether they meet criteria for ME/CFS at a later time.
- The report mentions objective tests such as CPET or tilt test being useful for gaining social security but not necessarily for diagnosis due to risk for worsening the patient's condition
- The report calls for research into biomarkers and acknowledged there being sufficient evidence for immune dysfunction despite there not being reliable markers for clinical use yet
- The report recognises that most patients never regain their pre-illness levels of health or functioning
- The report recognises inappropriate removal of children from their families in some extreme cases – though perhaps more common in the backward UK environment
- The report rejects childhood trauma and somatisation as being part of paediatric cases
- The IOM recognise the adverse impact on education from this disease for children.

The isolation for children affected by this disease in school years is a major factor which society needs to address and for which schools need to be criticised due to their lack of knowledge of the disease and their apathy in keeping children linked in some way to their school class.

- The report recognises the negative impact on employment and education
- The report stated that the term CFS is not appropriate. This aligns with the P2P report The committee determined that the name "chronic fatigue syndrome" has done a disservice to many patients.
- The report rejected the long established name myalgic encephalomyelitis (ME) stating there not being enough evidence to justify the correctness of the name and that the name "myalgic encephalomyelitis" does not accurately describe the major features of the disease.

  This is something Invest in ME disagrees with.

  Even if one believed the above IOM statement to be correct, it seems to ignore the fact that there are other diseases with incorrect names such as malaria and hay fever and they have not been changed. The UK MRC states that there is now evidence of neuroinflammation in some severe cases of ME. This is no different from, for example, poliomyelitis where the mild cases may appear unremarkable and go even unnoticed.
- In place of ME the committee proposes SEID "systemic exertion intolerance disease" as a name that more fully captures the full scope of this disorder.

  We feel this is not a progressive decision and provides a name not so dissimilar from the ineffectual and inappropriate CFS
- Both the P2P report and the IOM report fail to move away from the association of ME with fatigue as the main symptom. That ought to have been addressed. They should have recommended dropping CFS and used ME until more is known as ME is well established in the name and even US researchers and clinicians have started to use ME instead of CFS in recent years.
- SEID is a clumsy acronym albeit better than CFS.

  The use of a potentially misunderstood fatigue-associated word means that this will be bound to retain the implication of ME/CFS being a fatigue illness
- Systemic and Disease are easy to accept but Exertion Intolerance will not be well understood by the general public and will be confused with exercise (physical) intolerance only.
- It was not totally clear if the recommendation for a name change was to replace CFS or ME or both.
- The criteria are more specific than the CDC Fukuda but wider than CCC or ICC. This may lead to an influx of patients for the few US specialists. Is that the intent? Or is there a plan to train more specialists?
- Is there sufficient infrastructure in place to deal with the large percentage of undiagnosed patients that this report refers to?
- We wondered who would take responsibility for the follow up work or will this expensive report end up like the UK CMO, 2003 report whose recommendations were not acted upon?
- If CFS and ME have traditionally had different criteria as stated in the report and the IOM report used ME/CFS as in the CCC then it was somewhat unclear whether this report meant to combine the two definitions into one
- Most ME, CFS or ME/CFS research has been performed using the CDC criteria and more

recently the CCC or the combination of CDC and CCC and hardly any research has been performed using the ICC or the Ramsay Criteria. The ICC is based on research that has used CCC or CDC criteria. This just goes on to show that researchers use various criteria and then it is used as evidence for any of the acronyms of CFS, ME/CFS or ME depending on the users and it would be sensible to use criteria that are inclusive for diagnosis but allows for specific phenotypes to be selected for research.

- The IOM panel included ICC signatories Drs Lucinda Bateman and Nancy Klimas. The ICC 2011 states that the panel recommended the use of myalgic encephalomyelitis for patients who meet the ICC criteria because a distinctive disease entity should have one name. So does this mean that the ICC should be used for ME and the IOM report for SEID?
- Less than one-third of medical schools include ME/CFS-specific information in the curriculum
- For years ME and CFS patients have been let down by the disbelieving medical profession and hopefully this report benefits patients rather than cause yet more problems
- The few doctors/researchers that have believed in patients have been let down by their colleagues and research funding bodies and we hope that the HHS and NIH now take ME and SEID seriously and allocate funding based on them being physical diseases
- The report acknowledges high societal costs and recommends that the guidelines are revisited in no more than five years to allow new research findings to be taken into account
- *"Ideally, experienced individuals without significant conflicts of interest should conduct a systematic literature review to address the key questions."*
  "Members of this group should clearly disclose their potential conflicts of interest, and the conveners of the group should try to limit the number of members with significant conflicts, who should in no case represent a majority of the group's membership."
- *"There is no adequate evidence to enable comment on the manifestations of ME/CFS across the life course."*
- This is an acknowledgement which NICE and the MRC have never made in the UK where vested interests continue to affect what is funded or reported.

In Conclusion - Going Forward

- Despite *"Patients, advocates, researchers, and clinicians expressed strong opposition to the study, arguing that the IOM lacks the expertise to develop clinical case definitions"* the IOM insisted on continuing this exercise. They therefore set up a unique opportunity to make things better.
- Will this report promote the prompt diagnosis of patients with this complex, multisystem, and often devastating disorder; enhance public understanding; and provide a firm foundation for future improvements in diagnosis and treatment?
- After so long a period where governments, medical research councils, health departments and some of those supporting organisations completely abrogated their responsibilities to patients with this disease then it might be too optimistic to expect one report to overturn all that has been allowed to be wrong with the research into, perception and treatment of ME.
- But a start has to be made.

- In the absence of anything else one must take what one can and build upon it. And there are many good points in the report.
- If the intent to improve the situation for people with ME and their families is honest then elements from this and the P2P report can change the way healthcare professionals treat the disease.
- The good points from this report ought to force and demand a radical rethink of Health Institutes' and Research Councils' policies – something long overdue.
- To exact a greater morality amongst research funders might be one benefit from this.

Name

- Unfortunately, however many good points there may be in this report the name will be something which many will interpret and then relate to their perception of the disease.
- We believe the suggested name is ill thought-out and needs to be rethought.
- Whilst it is obviously logical and correct to remove the term CFS and Chronic Fatigue we feel it is not a sensible strategy to change the name to the suggested SEID at this point.
- Even if the intent was honourable the name will still influence how this disease is treated.
- Just as with food the contents in the tin may be completely ignored due to poor labelling.
- By deciding to tinker with the name of this disease one is also obliged to examine the history and politics behind it and understand why such a name change could offend, discriminate, confound, disappoint or just enrage some patients.
- Playing with the name and using exertion – however the correctness in medicine may be different from lay perception – will still invoke an initial response of this is being a fatigue illness rather than a systemic disease.
- So we suggest retaining Myalgic Encephalomyelitis (ME) until enough current data is found to support or otherwise. ME (itis) is already in the WHO, it does not stop research, it removes the rather useless CFS denigration and still allows a correct view to be presented.

Criteria

- Whilst it may be good that a set of simplified criteria are produced there is the concern that the criteria listed by the IOM report may be too broad. The criteria also need to be validated first to see if they really capture the right kind of patients. At the Invest in ME conferences there have been calls for the need for simple diagnostic criteria.
- However, the committee also added a table with many more symptoms which could be used to support the diagnosis.
- It will require education of doctors to make them able to identify the disease and avoid incorporating misdiagnoses into the assessment. The multiple comments within the IOM report relating to lack of belief from healthcare staff are evidence that this education is important.

Distribution

- An obvious point – but one which needs reaffirming for any diagnostic criteria used -
- *"The criteria proposed here will not improve the diagnosis and care of patients unless health care providers use them"*
- Apart from the name the distribution of the other sensible points from the IOM report needs to be managed, monitored and followed-up in order that uptake of ME being a real systemic disease in ensured.
- In the UK the CMO report of 2002 [10] produced seven recommendations. It would be a disaster if the IOM report ended up like the CMO report in the UK where none of the

recommendations were implemented and the psychiatric lobby who refused to sign the report went on take charge of the fatigue clinics and obtained all of the public research funding.

- At that time the participating psychiatrists should have been left out. But what has transpired is that they have still been allowed to control the debate in the UK.
- We would urge the US authorities to avoid a repeat of that.
- The report makes a major point - *"Key to this effort will be the continued positioning of ME/CFS as a legitimate disease that occurs in both children and adults and should be properly diagnosed and treated."*
- What can be very helpful is if the information emphasises ME/CFS as a serious physical illness and that in itself leads to health care providers taking a correct attitude toward these patients despite there being no cure or effective treatment being available yet. Just informing patients to avoid overexertion in the early stages of the disease can make a huge difference in the outcome of the disease.
- It is good that the committee recommends continuing surveillance of the evidence and revisiting the criteria in no more than five years. But if
- *"The committee recognizes that new and accumulating evidence will likely enable refinement of the diagnostic criteria proposed in this report and possibly define subtypes of the disease or even distinct entities"*

""Clearly a dramatic and immediate increase in funding for biomedical research needs to be made.,IiME suggested $250 million dollars over the next five years"

- IiME Recommendation to IOM"

- then this would also mean that the name SEID would have to be revisited and almost certainly changed.
- The toolkit for screening and diagnosis is an important part of the process. If this is not done properly then it is no good of having all of these recommendations.
- Again, there is a need for centres of excellence such as IiME have proposed [11] and experienced clinicians that can oversee this work.

Research

- The report has underlined a core message from the earlier P2P report – namely how mediocre has been the research to date on such a serious disease;

The IOM report is a major indictment of negligent MRC/NIH/CDC policies, highlighting the way that research and treatment and information about ME have been totally misrepresented over the last generation by false funding policies, flawed research and vested interests.

What a waste of life has been allowed to occur by governments from their failure to monitor progress or listen to continuing and mounting patient concerns; how corrupt and immoral has been the attitude of those leading the organisations which use public funding of ME research, given mainly to researchers who consider ME/CFS a psychosomatic illness?

Our overriding feeling is that the IOM report highlights the complete lack of any strategy to research this disease properly by those entrusted with the responsibility to do just that.

The aim now should be to find a speciality that owns ME/CFS or make ME/CFS a speciality in its own right – and this will not be psychiatry.

The onus is on the IOM and NIH to honour those good points from these reports – and to translate these into action.

Clearly a dramatic and immediate increase in funding for biomedical research needs to be made. IiME suggested $250 million dollars over the next five years.

This will be a long haul. Those in NIH and CDC – as well as those in UK MRC - and the respective government health ministers who have been responsible for ME research and funding and guidelines over the last generation have been incompetent, or worse. So lessons have to be learned from these past failures to ensure the same fatal mistakes are not made again.

We ended our P2P report evaluation thus -
Words are fine and Progress is a fine word – but change is its motivator – and it is action that delivers change.
To make progress we need not mere words and a slow, undeliberate action plan.
To make progress with this illness we need to make a bold changes.

The task now is to implement the good points of this new acceptance of ME as being the real disease that patients already know it is. And we stated to the NIH the following -

This is urgent, lives are dependent on it – Treat it as being urgent!

Invest in ME is a small charity with a BIG cause. If such a small charity and its supporters can organise ten international conferences with delegates from 20 countries, if it can organise 5 biomedical research colloquiums attracting participants from top research organisations in a dozen countries, if it can initiate possibly the two most important research projects for ME in the UK then the NIH should be able to do far, far better – and in a far shorter period of time.

The reports vindicated all that Invest in ME has been trying to achieve these last nine years. And, after reading and commenting on these recent reports, we are frustrated that we do not have the means to correct much of what has been wrong over the last generation. With more support and the means to change things we can make more rapid progress and overcome these establishment obstacles.

Recently the charity has initiated and funded important new research projects in the UK for ME [III]. After some success we only wish it were possible for the MRC in the UK to provide some of their squandered funding instead to IiME. To paraphrase Winston Churchill – Give Us The Money And We Will Finish The Job.

In the meantime we will progress the research foundation we have begun as quickly as possible because, as our advisor Dr Ian Gibson stated –

"Things do not have to be the way they are – we can change things."

Links

I Invest in ME Response to NIH Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Draft Executive Summary
http://www.investinme.org/IIME-Newslet-1501-01.htm

II Invest in ME Response to Institute of Medicine "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness"

http://www.investinme.org/IIME-Newslet-1503-02.htm

III Invest in ME research
http://www.investinme.org/research

International Art Contest
for
Young Artists with ME/CFS

We wish to showcase the artwork of a young patient with ME/CFS, and demonstrate that although seriously ill, these young patients are still capable of great accomplishments

Young artists currently diagnosed with, or recovered from, ME/CFS, and are aged 17 and younger, are invited to submit artwork to be placed on the cover of a new Primer for doctors looking after young people with ME/CFS.

The new Primer will assist pediatricians and primary care physicians in the diagnosis and management of ME/CFS in children and young adults.

Further information and an application form can be obtained from Dr. Kenneth J. Friedman at Kenneth.j.friedman@gmail.com

Contest closing date is June 30, 2016.

ME/CFS–An Invisible Illness No More

THE TRUE BATTLE WITH CHRONIC FATIGUE SYNDROME

by Dena Graham

For an illness that boasts such a myriad of symptoms, you might think that the Chronic Fatigue Syndrome battle starts and finishes there. Each day is a challenge – some more than others. And just when there seems to be a glimmer of light, a temporary 'remission' of symptoms (or at least a waning of them), it rears its ugly head again.

The first year, for many, is taken up with visiting GPs and specialists, trying to find answers. Surely it's not normal to be so ill, so often. And then, when the diagnosis of CFS (sometimes also known as Myalgic Encephalomyelitis (ME)) comes back, there's the inevitable temptation to take to the internet, trying to understand this complaint and find a 'cure'. All this when, some days, you can barely lift your head off the pillow. That should be battle enough.

Except, for many CFS sufferers, the true battle begins when it comes to other people's perceptions of it. To be so ill, yet dismissed by so many, is a harsh blow. Worse when it comes from people who you think ought to know you better.

The battle begins

I can't say exactly how long I've suffered from CFS – it certainly pre-dates any diagnosis and has gone on for at least three years; starting with recurrent throat and ear infections that became more frequent; and the after-effects of which lasted longer. I used to say to my mother that it felt as though there was something 'evil' inside me. I didn't mean this in any paranormal manner – but I wasn't using it as a metaphor either. I simply felt as if there was a something insidious creeping through my body, wreaking havoc. It wasn't normal to feel like your life force was ebbing; and then reach a point where you actually wished you were dead, just so the pain and exhaustion went away.

I finally received a diagnosis about two years ago, after seeing a number of specialists. For anyone who believes that CFS sufferers are malingerers, actively seeking such an unspecified diagnosis, I can assure you that this isn't the case. Not for me, nor for the majority of CFS sufferers. Of course, that's not to say that a handful of people aren't (in the same way that some people may fake whiplash for their own personal means). However, for most people with CFS, that diagnosis is not a positive one. It's an answer without a solution.

I wanted, desperately, to be told there was a problem with my thyroid; a sinus issue; there was even a point, God help me, when I wished to be diagnosed with a minor, treatable form of cancer – because at least then there would be the hope of a cure. When I received the CFS diagnosis, I was told to go away and accept it. The consultant, who specialised in this area, had seen enough patients to realise that this is not the diagnosis people want, nor accept lightly. It leaves them foundering without any medical direction and they inevitably continue to look for answers. Once that diagnosis comes in, you're on your own essentially. Not because the consultants don't believe it exists – but because they don't have anything to offer in the way of treatment.

And so begins a long road of medical denial and frantic research. You try one route after another in the hope of vanquishing this unfathomable complaint. For me, that began with cutting out meat; cutting out dairy; cutting out sodas and only drinking water or herbal tea; whipping up green smoothies; Beta Glucans; Amitriptyline; Chi Machines; Allicin; salt pipes. Believe me, the list was endless – and continues to this day.

Meanwhile, since the array of symptoms is so splendid and wide ranging, I battered my private medical insurance looking for another answer. Because, and I'll say it again, I didn't want to be ill with CFS. It was impacting hugely on my life. I had to take seven months off work, dropping my wage (forcing my husband and I to move out of our home). I had to call on all my reserves to try and 'hide' as much of my illness as possible from my 3 year old daughter – struggling with the guilt of knowing I couldn't do the things I wanted to do with her. I was missing out on her life. I was missing out on my life. Days went by in a blur of pain and frustration.

During this time, a third consultant ran more blood analysis and discovered that I was testing off the chart for the Epstein Barr virus. That was a high point. Why? Because it proved that something had caused this. Glandular Fever, Lyme Disease, Epstein Barr . . . these are just a few conditions that can trigger CFS. And this diagnosis validated me, even if it didn't help the symptoms.

So why was it that important to be validated? Because, by then, I was aware that many people just didn't 'get' this condition – and many others didn't believe it existed. People who I thought were good friends didn't bother keeping in touch to see how I was. I knew that if it had been any other complaint, which didn't carry the CFS stigma, I would have had their sympathy.

CFS – Clearly Fake Symptoms

Even now, having returned to work (again, most CFS sufferers want to work. They don't want their lives to be put on hold. They are not using it as an excuse to opt out or take the easy route) I still face the flack – more so, because people assume that if you're working you're 'cured'. So I often hide how I'm feeling – not wanting to bore people.

On days when I tell people that I feel bad, I've had comments along the lines of 'Oh, I feel like that too'. Or 'I think I might have CFS'. No, you don't. CFS isn't feeling exhausted because you've had a late night or it's four days into the week and you're ready for the weekend. It's not feeling like you're getting older and could do without a commute now. It's unrelenting bone-crunching fatigue, combined with headaches, aching limbs, a low-grade sore throat most of the time, the inability to plan ahead (even for nice things) because you don't know how you're going to feel this time tomorrow.

It's keeping everything crossed that you'll be able to attend a friend's wedding. It's giving up socialising. It's no holidays for three years (even though your addled body could do with a week on a beach) because you couldn't even take the journey to the airport, far less the plane ride itself. It's going to bed early, waking up and still feeling as though you haven't slept. It's climbing out of bed bent double because you can't straighten up. It's either missing taking your child to the park, or going but feeling like death – watching her through tear-filled eyes as you realise that this is time you'll never get back but simply can't enjoy. It's rushing bedtime stories because, some days, you can barely keep your head up. It's not watching your favourite programs when you're off work sick – because this isn't a cosy-up and 'enjoy' kind of ill – it's an obliterating type of illness. It's feeling that every day's a battle and there's no knowing if or when that battle's going to end.

But the worst part of it all is the endless lack of understanding. People who are supposed to be friends don't even bother to see how you are when you're ill. Why? Because they believe that you're malingering? That you're faking your symptoms? Using CFS as an excuse to work from home? Because they think that, surely, you must be exaggerating and nobody could be ill for that long? I don't have the answers – all I know is what the reactions are. The only bright spot is that my employers have taken this on

board; without their support, enabling me to continue working, I would have lost yet another part of my life.

Try telling the man whose leg is hanging off it's not 'real' pain

Recently, my husband overheard a conversation at his work. A colleague, who has MS, was speaking to someone and they were clarifying – ME or MS? The reply was, 'No, the real one, MS'. This hit my husband hard. He is the one who lives with me. It hasn't just impacted on my life, but his too. Meanwhile, his colleague gets injections for her MS and is able to enjoy a pretty normal life. He's heard stories of her going out drinking; socialising with friends; enjoying a tipple with lunch, and he knows I can't do any of that. She was able to go to her work's Christmas party. I wasn't able to go to mine. Yet, when her work duties are restricted, nobody bats an eyelid – despite the fact that she's still managing to maintain a social life. He's sat with me as I've cried tears of pain and frustration – he can see how 'real' it all is. I'm not living a normal life. I'm getting by, clinging to each day by my fingertips. So to hear someone dismiss ME/CFS as a condition that's 'not real' is insulting in the extreme.

If we take symptoms alone as a mark of illness severity and put them on a sliding scale, then it's entirely possible for someone with CFS to be living a far more restricted, pain-filled life than someone with MS (I'm using this as an example simply because the issue was raised about that being 'real' and the other not being real). And let's not forget, people with CFS don't have any medical interventions to help either. Some forms of cancer can have less impact on the body. I don't say this to undermine cancer, in any of its manifestations (it's the worst thing someone can be told they have) – I simply highlight it to demonstrate that, symptomatically, there are people who are treated for cancer and go on to live full, healthy, pain-free lives. As Llewellyn King – executive producer and host of the White House Chronicle – commented, 'The world of CFS is dark indeed — an abysmal place of unmediated pain, disability, hopelessness, financial ruin and sometimes suicide. One doctor told me that if she were to have to choose for herself between CFS and cancer, she would choose cancer. "At least for cancer, there are treatments; if they fail, you die. With CFS you are the living dead." '

Indeed, there are people with CFS who are wheelchair-bound, then bed-bound and, in severe cases, do lose their lives – either through the illness or due to the aforementioned suicide. By the same token, there are a host of recognised diseases and complaints that present with few symptoms and which are eminently treatable. A broken leg might be excruciating but it's fixable. The one thing that can definitively be said about CFS is that it's all about the symptoms. In fact, it's probably one of the few conditions that is so symptom-heavy and solution-light.

Consequently, if I had to hazard a guess why people are so dismissive of CFS, it's possibly because it's been a victim of its name. 'Fatigue' doesn't get anywhere close to summing up the array of symptoms that present. We associate fatigue with tiredness, lethargy, apathy; things that aren't entirely positive. It's easy to simply dismiss someone as lacking get-up-and-go. It leaves out the recurrent viruses, aching limbs, visual flickers and many other lesser-known symptoms. Unfortunately, the name is vague because nobody fully understands it yet. Even the more medical-sounding Myalgic Encephalomyelitis has been shortened to ME – which carries its own negative connotations and harks back to 'yuppie flu'. I suspect though, when it's eventually pinned down and given a specific medical label, it will then be recognised as one of those handful of conditions nobody wants to have the misfortune of contracting.

That said, this shouldn't be a competition of diseases. Whenever anyone is ill, with anything, that person deserves to be treated with

empathy, consideration and respect. Not to be told that their condition isn't 'real'.

So let's talk about those real symptoms

I, and thousands of others, can tell you that CFS symptoms aren't made up or imagined. In fact, I was ticking the CFS symptom boxes before I even knew what they were. I assure you that my muscle pain is very real – and I say this as someone who went through labour without any form of pain intervention. The headaches are real, as is the frequent dizziness that comes with a crash. The recurrent throat flare-ups (and ongoing low-level sore throat that never seems to disappear entirely), they're real too. The burning feeling in the face; the tingling in the extremities; the leaden limbs; the crawling skin; the insomnia; the anxiety; the brain fog; the visual flickering; the neck pain; the regular bone-crunching exhaustion (think jet lag combined with running a marathon and a bout of flu). All these things (and more) are real. And you know what – CFS is such a giving condition that, sometimes, you experience a plethora of symptoms all at once.

I can guarantee you that most CFS sufferers are facing at least two or three symptoms even on a good day. In fact, 'good' days are when you only have a few symptoms at a low level. Our good days would be your bad days. And let's not even talk about what happens to your body if you get a common cold – it can wipe you out for weeks. In three years there have been a handful of days when I've felt normal. Entirely normal. Free from pain, awake, energised. I have felt like I'm walking on air – happy, positive and vital. Yes, your body cries, I remember now, this is how it feels to be well. And then it all comes to a screeching halt.

If it's all in the head, a lot of people are sharing one brain

Recently, I found a GP who is prescribing Low Dose Naltrexone to help alleviate the symptoms of CFS. I did well on this for a while – it was the first thing to ever make me feel relatively normal. However, about three months in, I had a huge crash. I called him and told him that, oddly, since I'd increased the dose it didn't seem to be helping as much. He commented that he'd been hearing this a lot from patients. He said this is yet another reason why he knows that CFS is a genuine complaint – the very fact that the increased dosage is having the same effect on numerous people. Nobody who calls him knows this. Ergo, it proves that something is happening.

In the 1980s, CFS was referred to as 'Yuppie flu' – although it's been around far longer than that. There was an unexplained outbreak among nurses at the Royal Free Hospital in 1955. So either a large group of nurses suddenly came down with a fit of the vapours at the same time, or something's at work here that we still don't understand. Indeed, there was also an outbreak of these symptoms at the Los Angeles County General Hospital in 1934. And as far back as 1750, Sir Richard Manningham reported a syndrome referred to as 'febricula' (little fever). There have also been suggestions in the Lancet and the British Medical Journal that, upon returning from the Crimean War, Florence Nightingale spent years housebound, too fatigued to take visitors. Now she's not the type of woman who strikes me as having been a malingerer. In fact, many consultants will tell you that ME often affects those people who are the most driven – workaholics; people who've studied for degrees; those who have a can-do attitude.

Certainly, the medical profession now recognises CFS as a real condition – even if they don't know what causes it or how to treat it. The most recent evidence indicates that there's a difference in the brain scans of those suffering from CFS http://www.webmd.com/chronic-fatigue-syndrome/news/20141030/brain-scans-yield-clues-to-chronic-fatigue-syndrome.

Furthermore, it's acknowledged that the disability rates of chronic fatigue syndrome patients are on a level with those who have lupus; MS; rheumatoid arthritis and a range of other serious conditions. In some cases, patients are housebound for years, while others have died of the complaint.

And let's debunk another myth. CFS patients are not hypochondriacs. In fact, I now ignore a lot of symptoms, assuming they're part of the CFS bundle. I've had an ongoing ear pain for 12 days that would have sent most other people to the GP. Instead, I've lived with it – as I live with all the other symptoms.

So, if I had to put one message out there to those who are fortunate enough not to have to do daily battle with their bodies – it's to please, please not give CFS/ME/Fibromyalgia sufferers something else to battle. Namely a negative, unsympathetic, dismissive, disbelieving attitude.

Nobody wants to feel this way. If there is somebody at your work who seems to be getting 'preferential' treatment in terms of hours or home working; just consider the fact that they're still trying to work, despite the hurdles they face. And if a friend is housebound or you haven't seen them in a while, consider the fact that they may need your support. They aren't choosing to opt out of life.

Because until CFS gains the same sympathetic recognition as other illnesses, you are sidelining a huge group of people – and this is a condition that can strike anyone at any time. Including the naysayers.

ME PATIENT

We are raising money for Invest in ME a great charity that funds research into ME, a disabling illness that affects my wife Susan, many dear friends and hundreds of thousands of people in this country. I have managed to regain my health from this illness but many sufferers remain chronically unwell and I am taking this opportunity to raise funds for something very close to my heart." Steven

from IiME's JustGiving pages
https://www.justgiving.com/investinm-e/

Anna's story

May 2015

It is with sadness that I realized that I would be unable to attend the Invest in ME conference this year, but in trading e-mails with IiME, they kindly asked if I could submit a short piece on ME.
Well, I stuttered around the house wondering what I could possibly write about until I had to get ready for Anna's graduation. And there it was right in front of me: Anna's story, one of the best stories possible, one that brings tears to my eyes even now. And every word of it is true.

I first met Anna when she was thin and frail, being carried into my office by her father because she could not walk. It would have been about twelve years ago, she was just thirteen.

Anna had been through a difficult time by then, with a lifetime's worth of pain and insults. There are many aspects of her story that bring anger because of the callousness of the medical profession, and joy because there are some patients that medical malpractice cannot injure.

It is very likely that Anna's illness began with Histoplasmosis. This part is a little sketchy because I did not know her at that time, but in retrospect, Histoplasmosis is very likely. She was treated by the infectious disease group at the University of Rochester, a group that was of world renown in Pediatric Infectious Diseases. In reviewing the records the evidence was somewhat flimsy for Histo. Antibodies were +/- and Anna had never been to an area where this illness was prevalent.

But whatever it was, it was severe. Exhaustion and tiredness were present from day one, along with weakness, intestinal dysmotility, generalized pain and killer headaches. She had been ill for about a year before she had come to my office, but in retrospect post-exertional malaise had always been present. Exertional

Dr David Bell

Dr. David Bell graduated from Harvard College and gained an MD degree at Boston University. Post doctoral training in paediatrics was completed with subspecialty training in Paediatric Behavior and Developmental Disorders. In 1978 he began work at the University of Rochester and then 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. David 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).

David S. Bell MD
1 Dunbridge Heights
Fairport, NY 14450

intolerance, as in Systemic Exertional Intolerance Disease (SEID) as some are calling it now. After a two hour visit I made the diagnosis of ME/CFS as she was classic in all respects except that she was more severe than most. Because of the nausea, she was unable to eat and had lost weight, almost 50 pounds. She could not walk and had to be carried to the bathroom by her parents. She had killer headaches.

I was happy to take her on as a patient. The first steps in her treatment were very straightforward: I had to undo the damage done by previous medical personnel. This part of the story is well known to most young persons with ME/CFS.
She was said to be anorexic, and that if she did not begin to eat, she could starve to death. All her GI tests were normal except the motility studies. She was admitted to the behavioral units where she had to walk to the bathroom or pee her pants. And it was not certain that anyone would help her change clothes. The constant message given to her was that there was nothing medically wrong with her, and that her symptoms were a desperate cry for attention due to mental illness.

Unravelling this damage was not difficult. She had been an A student and an athlete, two factors that argued against school phobia. She was socially outgoing and had good friends, the majority of whom were dropping away, another strike against behavior disorder. Her parents were wonderful people, with good communication and absence of scapegoating, an abnormal dynamic that can exacerbate behavior disorders within families.
At first, Anna did not trust me at all, which was a healthy response to the medical abuse she had been subjected to. But after a while the doubts began to fall away. She came to understand her condition which is essential to managing it long term. We talked about brain blood flow, orthostatic intolerance, autonomic nervous system dysmotility, and about the need to have a thick skin.

I have always insisted on complete honesty with young persons with ME/CFS. If they are neurotic, they need to see that neurosis from another point of view. Confrontation with support is the classic technique.

I once told a 14 year old boy that he had ME/CFS, but he did not need to limp to show others that he was ill. Although I confronted him, I said nothing to imply that the rest of his symptoms were bogus – but the limp was.
He did well and never limped again.

A thick skin is necessary. The world is full of evil and everyone comes in contact with it every day. I suggest to everyone to listen carefully to all criticism. If there is any truth to it, try to make changes. If there is no truth to it, discard it, but only after thinking about it carefully.
If someone calls you a hypochondriac, as happened to Anna, consider the possibility. Thinking about it will do no harm. Pile up evidence for and against. Putting together that evidence was the next step for Anna.

I wrote notes saying that Anna was ill, but the teachers did not believe me. I went to her school and argued for home tutoring. The school refused, saying that she had school phobia. I went back to the school and said that Anna had an illness recognized by the CDC, and if they wished to practice medicine without a license, I would take them to court. They agreed to two one hour tutoring visits per week.

I have never been a great fan of the Centers for Disease Control (CDC). But they put together a terrific paper which demonstrated that the likelihood of CFS after an infection was related to the seriousness of the infection at the beginning[1].

Anna said something that caught my attention, "If the CDC says it is a real illness, why does everyone think that I am making up my symptoms?"
This was one of the many questions that Anna stumped me with.

One of the things I used to say to my patients and their parents was that the severity of the beginning of the illness was an indicator of the long term prognosis. Because Anna could not walk for over a year was bad news; it implied that she would not do very well in the long term.

Of course there were school issues.
I wrote notes saying that Anna was ill, but the teachers did not believe me.
I went to her school and argued for home tutoring. The school refused, saying that she had school phobia. I went back to the school and said that Anna had an illness recognized by the CDC, and if they wished to practice medicine without a license, I would take them to court.
They agreed to two one hour tutoring visits per week.

Obviously, this amount of tutoring is negligible. But it taught Anna several things.
First it taught her that I was committed to her and would not put up with discrimination.
Secondly it taught her about the exertion intolerance.
The post-exertion malaise is not just after physical exertion, it occurred after mental exertion as well.
And it taught her about orthostatic intolerance.
If she had her tutoring session sitting up at the kitchen table, she could not do well. But she did better if she was lying down. This observation of Anna's stimulated our office to do a small study, never published. If you ask healthy persons in what position they read, they almost invariably say that they read sitting up in an armchair, except at bedtime. Ask someone with ME/CFS and they say they always read lying down.
Blood flow to the brain, orthostatic intolerance.
And when she came to understand that, she no longer paid attention to people calling her a hypochondriac.

We did a "poor-man's tilt table test" where Anna would stand quietly next to the bed while we monitored her blood pressure and pulse. A healthy adolescent can stand for ninety minutes, although that would cause leg discomfort.

Anna had three abnormalities on this test. Her pulse rate went up to 140 beats per minute after ten minutes of quiet standing, meaning that she had Postural Orthostatic Tachycardia Syndrome (POTS). Her pulse pressure – the difference between the upper and lower number of her blood pressure went down to 10 mmHg, called orthostatic narrowing of the pulse pressure.
And at ten minutes she passed out, almost.
Her blood pressure went to zero.

Paula in our office is very good at predicting when this is about to happen and helped her to lie down. In her case she had three very good reasons to have orthostatic intolerance and reduction of blood flow to the brain.

One specialist wanted to operate on her brain saying that she had Histoplasma meningitis, but the others said not to operate. Doctors.

The years passed. Anna was able to get up and walk around the house a bit, and on good days she was able to get to school.

She did her homework, and despite saying that she was having trouble thinking and reading, she got good grades.

Some days she would use her wheelchair which the insurance company did not want to provide for her.
Some medicines helped a little.

Headaches were the worse symptom now by far. She went to a specialized headache clinic in Philadelphia.
One specialist wanted to operate on her brain saying that she had Histoplasma meningitis, but the others said not to operate. Doctors.

By 2008 Anna decided to go to college. She had learned a neat trick. If she took six hours of classes Monday, Wednesday and Friday, she would spend Tuesday, Thursday, Saturday and Sunday in bed. And it worked.

She did not have much of a social life, and it took six years to get through, but she was getting by. She was succeeding. We had long talks about life. I said that teenage dating and sex were way over-rated.

And yesterday she graduated.
She had two majors and graduated summa cum laude in both.

We cried together at her graduation party. She has done better than very well, she has done fantastic.

She is still not well, but she is getting by.

I was wrong with my poor prediction due to the severity of her illness, but I'm OK with that. Why did she do so well? I have no idea.

But she is smart; she does not feel sorry for herself; she is stubborn; she learned long ago that most of what people say, they know little about; she is forging her own road through life, and I am happy for her.

The only sadness I feel is for the medical providers who have never experienced this type of joy treating their patients.

1. Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon S, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ. 2006; 333.

Matchstick Campaign for ME Awareness

Using Art to Raise Awareness of ME

Art has the power to inspire, to evoke reflection, to see things differently, to force change.

An image can capture a thousand words and express views and feelings and convey a sentiment often far better than several pages of words.

Wolfgang Stiller is an award-winning German artist who currently lives and works in Berlin. Wolfgang has kindly given permission for his matchstick images to be used for raising awareness of ME.

Wolfgang's original and inspired art now allows us to launch the Matchstick Campaign for ME Awareness.

Janet Smart and the Let's Do It For ME team have added a slogan for each image and, in turn,

IiME has developed a brochure featuring these images and describing what the charity and our supporters are doing.

Wolfgang has used a common, everyday item which is often ignored, used and discarded by most people, and turned it into a message which makes one pause and think.

These striking images are used to highlight the situation in which people with ME have found themselves.

The parallels with the way ME patients have been treated over the years are obvious.

To continue to raise awareness throughout the year these wonderful and searching images will hopefully cause people to reflect on the waste of life which has been, and is occurring with regard to this disease.

Yet they will also offer hope that things will change, will improve and serve to highlight that from the ashes of ignorance and apathy will come a better time and patients will regain their health.

Each of the images carries a message - and this message has been related to the work that Invest in ME (Research) and supporters are carrying out.

Copies of brochure and posters available from Invest in ME – info@investinme.org

PRESENTERS at the 10th INVEST in ME INTERNATIONAL ME CONFERENCE

Bios and Abstracts from the presenters at IIMEC10

Dr Ian Gibson

Conference Chair

Dr Ian Gibson, former Labour MP for Norwich North, worked at University of East Anglia for 32 years, became Dean of the school of biological sciences in 1991 and was head of a cancer research team and set up the Francesca Gunn Leukaemia Laboratory at UEA. In 2011 Dr Gibson received an honorary doctorate of civil law from UEA.

Professor Ian Charles

Keynote Speech: Solving ME/CFS: What a Research Park Has to Offer in Resolving a Chronic Disease Such as ME

Professor Ian Charles joins the Institute of Food Research in May 2015 to lead the programme to develop the UK's new Centre for Food & Health to be based at the Norwich Research Park. Professor Charles is returning to the UK from Australia where he was Director of the ithree institute, University of Technology, Sydney. Professor Charles has over 30 years' experience in academic and commercial research. His academic career has included being a founding member of The Wolfson Institute for Biomedical Research at University College London, one the UK's first institutes of translational medicine.

He has also worked in the pharmaceutical industry at Glaxo Wellcome, and has been founder and CSO of biotech companies in the area of infectious disease, including Arrow Therapeutics, sold to AstraZeneca, and Auspherix a venture capital backed company founded in 2013.

His current research interests include infectious diseases as well as the microbiome and its impact on health and wellbeing.

The new Centre for Food & Health will provide a step change for food and *health research, and the translation of science by industry, to benefit society and the UK economy. The Centre will be located at the Norwich Research Park, one of Europe's largest single-site concentrations of research in Food, Health and Environmental sciences.

The multidisciplinary Centre aims to bring together the Institute of Food Research and aspects of the University of East Anglia's Faculty of Science and the Norwich Medical School with the regional gastrointestinal endoscopy facility at the Norfolk and Norwich University Hospital.

With a unique integration of diet, health, nutrition and medicine under one roof, linking closely to world class plant and crop research at the John Innes Centre and bioinformatics at The Genome Analysis Centre (both also located on the Norwich Research Park), it will have the potential to deliver clinically validated strategies to improve human health and wellbeing.

Abstract:
Sufferers of M.E., carers, family and friends, all want to know what causes M.E. in order to determine how the condition can be prevented, treated and cured. We need to better understand the biological, physiological and psychological mechanisms that determine how nutrition, food choice and individual dietary patterns contribute to lifelong health and disease. We also need to know how differences in dietary needs and responses between individuals and population groups at different stages of human life.
Expanding knowledge in these areas we believe will be important to understanding a range of issues including ME.
The science of food, nutrition and health is immensely complicated. Future science has to take an interdisciplinary approach to effectively understand how all these interconnected factors act together.
With over 3000 scientists at the Norwich Research Park, consisting of 4 world leading research institutes, a university and a teaching hospital, it is one of Europe's largest single-site concentrations of research in Food and Health and Environmental sciences.
Having academic excellence across a range of diverse, but related fields, in one location is a very powerful way to deliver a step-change in potential outcomes across a number of health issues.
Importantly, the new centre for food and health, due to open at the end of 2017 at the Norwich Research Park, takes co-location to a new level as it uniquely integrates academic excellence with clinical expertise; by bringing together the Institute of Food Research with aspects of the University of East Anglia's medical school and science faculty with the Norfolk and Norwich University Hospitals' gastrointestinal endoscopy facility, working alongside industry.
The new Institute will provide a novel holistic, systematic and integrated approach to deliver faster innovation as well as helping to inform government policy on a range of gut and diet related issues including M.E.

The development of this new centre, together with the other expertise and facilities located at the Norwich Research Park, puts it in a very good position to lead a UK and European Centre of Excellence for biomedical research for M.E. to provide possible prevention and solutions.

Professor Jonas Bergquist

Proteomics in ME/CFS

Professor Begquist has a background as MD, Associate Professor of Clinical Neuroscience , Sahlgrenska University Hospital and the University of Gothenburg.

Since 1999 , he has been a researcher in Uppsala, Sweden, and in 2005 was appointed professor of analytical chemistry and neurochemistry at the Department of Chemistry - BMC , Uppsala University.

From 2011 he worked also as an adjunct professor of pathology at the University of Utah, Salt Lake City, Utah, USA.

Abstract: Not available at time of printing – but will be made available on Invest in ME web site.

Professor Mady Hornig

Markers of Immunity and Metabolism in ME

Mady Hornig, MA, MD is a physician-scientist in the Center for Infection and Immunity (CII) at the Columbia University Mailman School of Public Health New York, USA where she serves as Director of Translational Research and is an associate professor of epidemiology.

Her research focuses on the role of microbial, immune, and toxic stimuli in the development of neuropsychiatric conditions, including autism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection), mood disorders and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

She is widely known both for establishing animal models that identify how genes and maturational factors interact with environmental agents to lead to brain disorders and for her work clarifying the role of viruses, intestinal microflora and xenobiotics in autism and other neuropsychiatric illnesses that may be mediated by immune mechanisms.

Under her direction, proteomic analyses of umbilical cord samples are identifying potential birth biomarkers for autism in a prospective study in Norway, the Autism Birth Cohort (ABC).

She established that there was no association between intestinal measles virus transcripts and autism, and, with Brent Williams and W. Ian Lipkin at CII, has found altered expression of genes relating to carbohydrate metabolism and inflammatory pathways and differences in the bacteria harboured in the intestines of children with autism.

She also leads projects examining the influence of immune molecules on brain development and function and their role in the genesis of schizophrenia, major depression, and cardiovascular disease comorbidity in adults, and directs the Chronic Fatigue initiative Pathogen Discovery and Pathogenesis Project at CII.

In 2004, Dr. Hornig presented to the Institute of Medicine Immunization Safety Review Committee and testified twice before congressional subcommittees regarding the role of infections and toxins in autism pathogenesis.

Her work in ME/CFS is establishing immune profiles and helping to identify pathogens that may be linked to disease.

Her work on the MIND (Microbiology and Immunology of Neuropsychiatric Disorders) Project, one of the largest studies of immune factors in mood disorders and schizophrenia, examines the role of viruses and immune responses in the pathogenesis of these disorders.

Abstract:

Markers of immunity and metabolism in ME/CFS

Mady Hornig, MA, MD

A diverse range of microbial and immune stimuli has been hypothesized to trigger the onset of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). To date, however, no single factor is clearly implicated, leaving the majority of cases of disease unexplained.

The absence of diagnostic biomarkers seriously curtails the capacity to identify individuals affected by the disorder and to distinguish

them from those who have other fatiguing illnesses.

Under the auspices of the Hutchins Family Foundation-supported Chronic Fatigue Initiative, we recently found evidence of differences in plasma immune signatures in patients with ME/CFS who have recent onset of illness as compared with patients who have been ill for longer periods, and as compared with matched controls.

We are currently investigating whether these stage-specific immune profiles are also correlated with altered metabolites in blood as well as with the bacteria of the gut and oropharyngeal microbiome that help to shape these metabolomic patterns. This work is beginning to elucidate candidate biomarkers for ME/CFS that may both facilitate early diagnosis and promote our capacity to tailor interventions to the specific stage of illness.

Dr Luis Nacul

Epidemiological Evidence on ME/CFS: Current status and implications for research and service delivery

Dr Luis Nacul is Clinical Senior Lecturer at London School of Hygiene and Tropical Medicine

Abstract:

The reported prevalence of ME/CFS varies 100-fold, with the best estimates between 0.2% and 0.7%. The most likely explanations for these variations relate to methodological differences in studies, including in data collection procedures and case definitions used, in addition to differences in population studied. Methodological limitations also restrict the interpretation of findings on risk factors, mechanism of disease and treatment. The distribution and disabling nature of the disease and lack of specific treatment owes to a high burden and economic impact to individuals and society. The presentation will discuss epidemiological evidence on ME/CFS and their limitations, and how they can be used to guide research and services planning.

Dr Amolak Bansal

Diagnosis and Differential Diagnosis of ME/CFS

Dr Amolak Bansal is Consultant, Clinical Immunology and Immunopathology, Epsom and St. Helier University Hospitals NHS Trust, Surrey, UK

Dr. Bansal trained in immunology and allergy from 1989 to 1993 at St. Mary's Hospital in Manchester and at Hope Hospital in Salford. From here he spent five years (1993-1997) as Senior Lecturer and Consultant in Clinical Immunology in the Department of Medicine at the Princess Alexandra Hospital in Brisbane, Australia. From 1997 to the present date Dr. Bansal has worked as a Consultant in Clinical Immunology and Immunopathology at Epsom and St Helier University Hospital. Dr Bansal's key interests lie in allergy, autoimmunity, CFS/ME and immunodeficiency.

Abstract:

Diagnosing CFS/ME

Fatigue is a feature of many common illnesses but is the main and overwhelming problem in

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME).

The latter is poorly understood and accompanied by several additional symptoms that suggest a subtle immunoendocrine dysfunction accompanied by viral reactivation and complicated in some cases by alterations in mood and sleep.

The differential diagnosis of CFS/ME is large and includes primary sleep problems, endocrine dysfunction, alterations of mood, systemic autoimmunity, certain chronic infections and specific neurological disorders.

However, CFS/ME may be confidently diagnosed on the basis of specific clinical criteria combined with normality of specific routine blood tests including those that assess inflammation, autoimmunity, endocrine dysfunction and gluten sensitivity.

An early confident diagnosis is important as it can reduce patient anxiety, encourage early intervention and prevent expensive unnecessary investigations.

Dr Geraldine (Jo) Cambridge

B cells, Rituximab and ME/CFS

Dr Jo Cambridge is Principal Research Fellow Inflammation, Div of Medicine Faculty of Medical Sciences, UCL

Her group focuses its interests on B cell depletion (an idea which they introduced (with the Professor Jo Edwards) approximately 10 years ago for the treatment of rheumatoid arthritis), exploring more precisely how the technique works and trying to explain the marked variation in response between different patients

Abstract:

The newly initiated research into ME/CFS at UCL stemmed from our awareness of the studies of Drs Fluge and Mella showing clinical efficacy of the B cell depleting drug, Rituximab, in a double blind placebo controlled trial in Norway.
Rituximab therapy for non-malignant diseases was introduced by Professor Jo Edwards, initially for Rheumatoid arthritis patients at UCL, in 1998. Secondly, Professor Edwards has emphasised the enormous unmet clinical need for patients diagnosed with this condition and encouraged me to become involved in order to explore possible mechanisms underlying ME/CFS which may be modified or even stopped by removing B cells from these patients.

At UCL, I have been conducting clinically-based research involving patients with a number of different diseases treated with rituximab and other B-cell targeting drugs. Our aim is to maximize the efficiency of their use and to predict imminent relapse in order to allow more rapid intervention before worsening of symptoms.
As a newcomer to ME/CFS, the first thing that struck me from published literature and the age and sex distribution of ME/CFS was the hypothesis of an infectious trigger for the condition but with an 'unbalanced' response of the immune system which may subsequently not resolve. This does not mean that the infectious agent needs to persist. There are a number of ways that B cells could contribute to this.
With the appointment of Fane Mensah, our PhD student in 2014, we have been exploring B cell biology in patients with ME/CFS. His

tenacity has already produced some tantalizing results.
I will outline some of the ways we are approaching the very subtle ways that B cells may be functioning differently in patients and also between patients which will hopefully complement the other research in ME/CFS which we are hearing about at the BRMEC5 Colloquium and IIMEC10 conference.

Dr Neil Harrison

Immune-Brain Communication and Relationship to Inflammation

Dr Neil Harrison **is** Honorary Consultant Neuropsychiatrist, Brighton & Sussex Medical School, UK

Dr Harrison's' work in the laboratory focuses on understanding how infection or inflammation in the body interacts with the brain.
For most these symptoms are usually short lived and relatively mild. However, when the immune system is activated for long periods, such as in people suffering from rheumatoid arthritis, they can become extremely debilitating or even life-threatening.

Understanding how the immune system interacts with the brain is a crucial first step that will form the foundations for future development of novel therapies targeting these common and disabling symptoms.
Most of his studies utilise a combination of functional brain imaging (e.g. fMRI, FDG-PET, EEG, polysomnography), experimental models of inflammation, custom cognitive tasks and diverse measures of peripheral immune status.

Abstract:

Immune-Brain Communication and Relationship to Inflammation

Until recently the brain was considered an Œimmune-privileged[1] site, isolated from changes in immune activity.

However, recent evidence has challenged this and demonstrated clear bi-directional communication between the brain and immune system. Interestingly, activation of one of these pathways has been shown to predict the amount of fatigue experienced after experimental inflammation. In this talk I will review the mechanisms through which inflammation in the body can be communicated to the brain and discuss our current understanding of how this relates to changes in mood, motivation and fatigue.

Professor Sonya Marshall-Gradisnik

Immunological Biomarkers in ME

Professor Marshall-Gradisnik is one of Australia's foremost researchers in the area of neuroimmunology and was instrumental in establishing the Public Health and Neuroimmunology Unit PHANU) at Bond University.

(Much of her work relates specifically to autoimmunity in Chronic Fatigue Syndrome sufferers and she is regularly asked to speak to community groups on behalf of Queensland Health and NSW Health.

Her research in the area of exercise immunology has also contributed to the body of knowledge relating to the effect of doping in sport and she serves as Sports Medicine Australia's national spokesperson in this area.

The vital research conducted by Professor Marshall has attracted more than $1 million in grant funding and she has produced 21 peer-reviewed papers, five book chapters and one provisional patent. In 2008 Dr Marshall was joint leader of the Bond University team responsible for developing the BioSMART program. The team was awarded a prestigious Australian Teaching and Learning Council Award (formerly known as the Carrick Award) for Outstanding Contribution to Student Learning and for the quality of student learning over a sustained period of time.

Abstract: Not available at time of printing – but will be made available on Invest in ME web site.

Dr John Chia

ME and chronic enterovirus infection: An Update on pathogenesis

Dr Chia is an infectious disease specialist practicing in Torrance, California, USA and has published research recently (Chronic fatigue syndrome associated with chronic enterovirus infection of the stomach) on the role of enteroviruses in the aetiolgy of ME/CFS – an area which has been implicated as one of the triggers by a number of studies.
There are more than 70 different types of enteroviruses that can affect the central nervous system, heart and muscles, all of which is consistent with the symptoms of ME/CFS.

By analysing samples of stomach tissue from 165 patients with CFS, Dr. Chia's team discovered that 82% of these individuals had high levels of enteroviruses in their digestive systems.

Dr Chia's research may result in the development of antiviral drugs to treat the debilitating symptoms of ME/CFS.
Dr Chia is President of the Enterovirus Foundation and Assistant Professor at the UCLA School of Medicine.

Abstract: Not available at time of printing – but will be made available on Invest in ME web site.

Dr Claire Hutchinson

Biomarkers: Visual Processing and ME/CFS

Dr Claire Hutchinson is a lecturer in the College of Medicine, Biological Sciences and Psychology at the University of Leicester. As a vision scientist the majority of her work is concerned with how visual sensory information is encoded by the human visual system.

Her research includes healthy visual perception, age-related visual decline, and visual markers of 'non-visual' illnesses.

It is this latter strand of research that led her to study vision-related problems in ME/CFS.

Abstract:

People with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) report a number of vision-related symptoms associated with their condition. These include difficulties with depth perception and focussing on objects, hypersensitivity to light, eyestrain, painful, itchy or dry eyes, problems with visual attention and vision-related headaches.

Despite these vision-related complaints, there has been very little research systematically examining their characteristics and causes.

We have shown that the severity of vision problems in ME/CFS is correlated with their impact on patients' everyday lives and have provided experimental evidence to support the results of questionnaire studies.

Here, I will discuss this work examining visual markers of ME/CFS. I will present a snapshot of our experimental evidence and discuss how particular visual deficits can be mapped onto different stages of the visual processing pathway.

Finally, I will discuss the utility of our work for people with ME/CFS and those treating them with particular reference to how our findings:
(1) may be useful in clinical diagnosis
and
(2) provide insight into the origin (e.g. the eye, the cortical visual pathways, cognitive control of visual processing) of vision-related problems in ME/CFS.

Professor Betsy Keller

Activity guidelines to avoid symptom flares

Department of Exercise & Sport Sciences, Ithaca College Ithaca, NY, USA

Professor Keller is Professor Ithaca College, Dept. of Exercise and Sport Sciences, Ithaca, NY.
Since 2003 Professor Keller has tested persons ill with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) for purposes of research and/or to provide an objective assessment of functional capacity and ability to perform and recover from physical work. Often, these individuals seek an objective indication of illness status to apply for disability benefits.

A two-day exercise test protocol has shown to be instrumental in delineating abnormal responses to and recovery from exercise in ME/CFS patients.

Her report of test results and interpretation has been successful in many cases to support an argument for disability coverage.
There are only a few researchers in the USA who have performed and interpreted the two-day exercise test protocol on ME/CFS patients, and therefore have observed first-hand the anomalous multisystem responses of these patients 24 hours post-exercise.

Professor Keller continues to expand the small body of peer-reviewed evidence of the abnormal recovery response to physical activity in ME/CFS so that most, if not all clinicians, researchers, health insurers and patient family members also understand the deleterious impact of this illness.
To that end, she has collaborated on an NIH R21 grant with PI, Maureen Hanson, from Cornell University to study the effects of exercise in ME/CFS on parameters of

physiological and immune function.
Together they continue to analyze this data and other data collected to better understand how to help those with ME/CFS.

Abstract:
Post exertion malaise (PEM) is an exacerbation of the symptom profile of an ME patient following physical, cognitive or emotional stress. Physical stress that exceeds the physiologic threshold of aerobic metabolism necessitates energy production from anaerobic metabolism to meet energy demands of work.

Energy production via anaerobic metabolism is fast acting and important to meet immediate and short-term energy demands, but produces metabolites that contribute to physiologic fatigue.

A dependency on anaerobic energy production for longer duration activities (> 2 min) will exceed a physiologic threshold of aerobic energy production (aka anaerobic threshold) and contribute to fatigue.
In healthy individuals, the physiologic consequence of exceeding anaerobic threshold is a reduction in work to an intensity at which aerobic metabolism can supply the preponderance of energy.
The reduction in work also enables recovery of anaerobic energy-producing processes. In contrast, exercise studies of ME patients reveal an impaired ability of aerobic metabolism to facilitate recovery following anaerobic work.

In this case, the ME patient will rely predominantly on anaerobic metabolism to power even low-level activities that would not normally provoke fatigue. The altered metabolism will also exacerbate the profile of ME symptoms that are specific to the patient, possibly causing new symptoms to emerge.

With judicious management of physical activity intensity, duration, and recovery, it is easier to avoid post-exertion symptom exacerbation (PEM) than it is to recover from it.

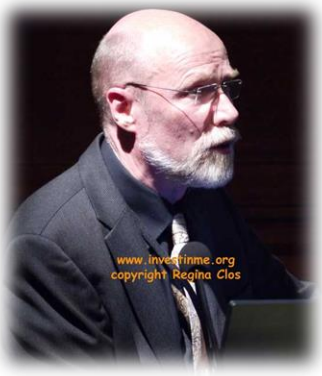
Strategies and guidelines for physical activity management will be discussed with goals of avoiding symptom flares and improving movement efficiency, and with hope for enhancing overall well-being.

Professor Olav Mella / Dr Øystein Fluge

Multi-centre Rituximab Clinical Trial for ME/CFS

Dr Øystein Fluge received medical degree in 1988 at the University of Bergen, and is a specialist in oncology since 2004. He has worked as a Research Fellow with support from the Norwegian Cancer Society and is now chief physician at the Cancer Department, Haukeland University Hospital. Doctoral work emanates from the Surgical Institute and Department of Molecular Biology, University of Bergen.

Professor Mella has performed clinical trials to test the benefit of B-cell depletion therapy using rituximab in ME/CFS patients. Dr. Olav Mella of Haukeland University Hospital in Bergen, Norway began his investigation of rituximab's effects on CFS after treating several Hodgkin's Lymphoma patients who had long standing cases of CFS prior to developing cancer. In 2011 Professor Mella and Dr Fluge published a paper "Benefit from B-Lymphocyte Depletion Using the Anti-CD20



Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study"

Abstract:

Rituximab: a multicenter, double blind, placebo-controlled study of rituximab induction and maintenance treatment in ME/CFS

Øystein Fluge and Olav Mella, Haukeland University Hospital, for the Norwegian cooperative study group (Haukeland University Hospital, Oslo University Hospital Notodden Hospital, St. Olav University Hospital, University Hospital of Northern Norway).

ME is a debilitating disease, often long-lasting, with a high sickness burden and a low quality of life, in addition to costing the patients, their families and society vast amounts of money. There is no established or generally accepted drug treatment. Based on observation of a patient with ME with marked symptom improvement when she was treated for lymphoma with cytotoxic drugs, we did a case study, followed by a small, double blind, placebo-controlled study with the anti-CD20, monoclonal antibody rituximab, that acts by depleting B-lymphocytes. These positive studies were followed by a phase II study of rituximab in 29 patients, exploring rituximab induction followed by maintenance rituximab up to 15 months, with 36 months observation time. That study confirmed that B-cell depletion with rituximab resulted in clinical responses in 2 of 3 patients and that about half of the patients still experienced sustained responses at the end of the observation.

Based on these studies, there is from September 2014 an on ongoing, Norwegian multicenter study of rituximab induction and maintenance. The study is double blind, placebo (saline and albumin) controlled, and has by May 2015 recruited more than 120 of the projected 152 patients. The patients fulfill the Canadian criteria, with sickness duration from 2-15 years. The study is block randomized by treatment center, with a predetermined number of included patients in each center. Induction is with rituximab 500mg/m2 day 1 and 15, maintenance with 500mg flat dose at 3, 6, 9 and 12 months. Observation time is 24 months. The primary end points are temporal development of self-reported fatigue score, and number of patients reaching predetermined, clinical criteria for response. Secondary endpoints are quality of life measured by SF36, levels of physical activity registered by electronic armbands for 7 consecutive days before and after intervention, total level of self-reported function at 6, 12, 18 and 24 months, and number of patients still in response at 24 months. Toxicity will be analyzed.

Based on the assumption that declined ability for blood flow regulation is an important element in symptom maintenance in ME, sub-studies to investigate endothelial dysfunction in large arteries (flow-mediated vasodilation) before and after intervention will be performed in Bergen and Notodden, microcirculatory changes in addition in Bergen. Ergo-spirometry day 1 and 2 before and after intervention will be done in Bergen, Oslo and Notodden in patients sufficiently well to perform ramp bicycle exertion. In Bergen, patients with gastrointestinal symptoms are offered a gastroenterology sub-study before and after intervention.

The study will be unblinded for analysis when the last recruited patient has been observed for 24 months, hopefully in early autumn 2017.

Throughout the study, systematic blood tests are drawn for a central biobank with the aim of elucidating molecular mechanisms behind the symptom maintenance in ME. This part of the

study is supported by the Kavli Foundation. The clinical study is supported the Norwegian Research Council, the Norwegian Department of Health, the Regional Health Authorities, MEandYou crowd-funding, and the Norwegian ME Association.

Finally, we will briefly report on a recently initiated phase II study exploring pulse infusions of another immune-modulating drug, cyclophosphamide, in three groups of totally 40 patients: the largest group consists of patients not previously in our intervention studies, another is non-responders to rituximab, and finally patients with response to rituximab and subsequently recurring.

ME PATIENT

"The reason I'm so proud of one of the charities I support, Invest in ME, is because it is run entirely by a few volunteers who themselves either suffer with the illness or are parents of children with ME.
There are no salaries; every penny that's raised goes where it should go and alongside the Lets Do It For ME team who are also voluntary, what they have achieved is nothing short of phenomenal."

- Stacy Hart, Watford Observer

C10 Conference DVD

The IIMEC10 ConferenceDVD contains 4 discs and is in PAL format- and contains the full presentations from the 2015 conference plus plenary sessions, and the pre-conference dinner keynote speech by Mike Shepherd.

Order it here
http://www.investinme.eu/IIMEC10.shtml#dvd

Check the IIMEC10 Conference Trailer

10th Invest in ME International ME Conference 2015

29th May 2015, London

Conference Agenda

Start	Presenter	Presentation
07.45	*Registration*	
08.55	Welcome to IIMEC10	Dr Ian Gibson
09:05	Professor Ian Charles	Solving ME: What a Research Park Has to Offer in Resolving a Chronic Disease Such as ME
09:30	Professor Mady Hornig	Markers of Immunity and Metabolism in ME
10:00	Professor Jonas Bergquist	Proteomics in ME
10.25	*Coffee/Tea Break*	
10:50	Dr Luis Nacul	Epidemiological Evidence on ME/CFS: Current Status and Implications for Research and Service Delivery
11.15	Dr Amolak Bansal	Diagnosis and Differential Diagnosis of ME
11:45	Professor Sonya Marshall-Gradisnik	Immunological Markers in ME
12.15	UEA / IFR / UCL Researcher/Students	The Next Generation – Panel discussion with Professor Simon Carding
12.35	*Lunch*	
13.40	Dr Jo Cambridge	B-cell biology and ME
14:05	Dr Neil Harrison	Immune-Brain Communication and Relationship to Inflammation
14:30	Dr John Chia	ME and Chronic Enterovirus Infection
14:55	Dr Claire Hutchinson	Biomarkers: Visual Processing and ME
15.15	*Coffee/Tea Break*	
15:50	Professor Betsy Keller	Activity guidelines to avoid symptom flares
16.15	Dr Oystein Fluge/ Professor Olav Mella	Multi-centre Clinical Trial of Rituximab
17.10	Plenary Session	Will ME Be Treatable/Cured?
17.30	*Adjourn*	*(Note that the agenda, format and times are subject to change)*

Running 28 European Marathons - in the name of Friendship

Mike Harley is raising awareness of ME and raising funds for Invest in ME's biomedical research fund by running a marathon in every EU country (currently 28 in total). His first challenge was the Prague marathon that took place on Sunday 3rd May. Then on to Helsinki in the summer.

Mike is doing this because one of his oldest friends, Ian, has been suffering from ME for over 7 years and has been unable to work or lead a normal life.

This is a great example of friendship.

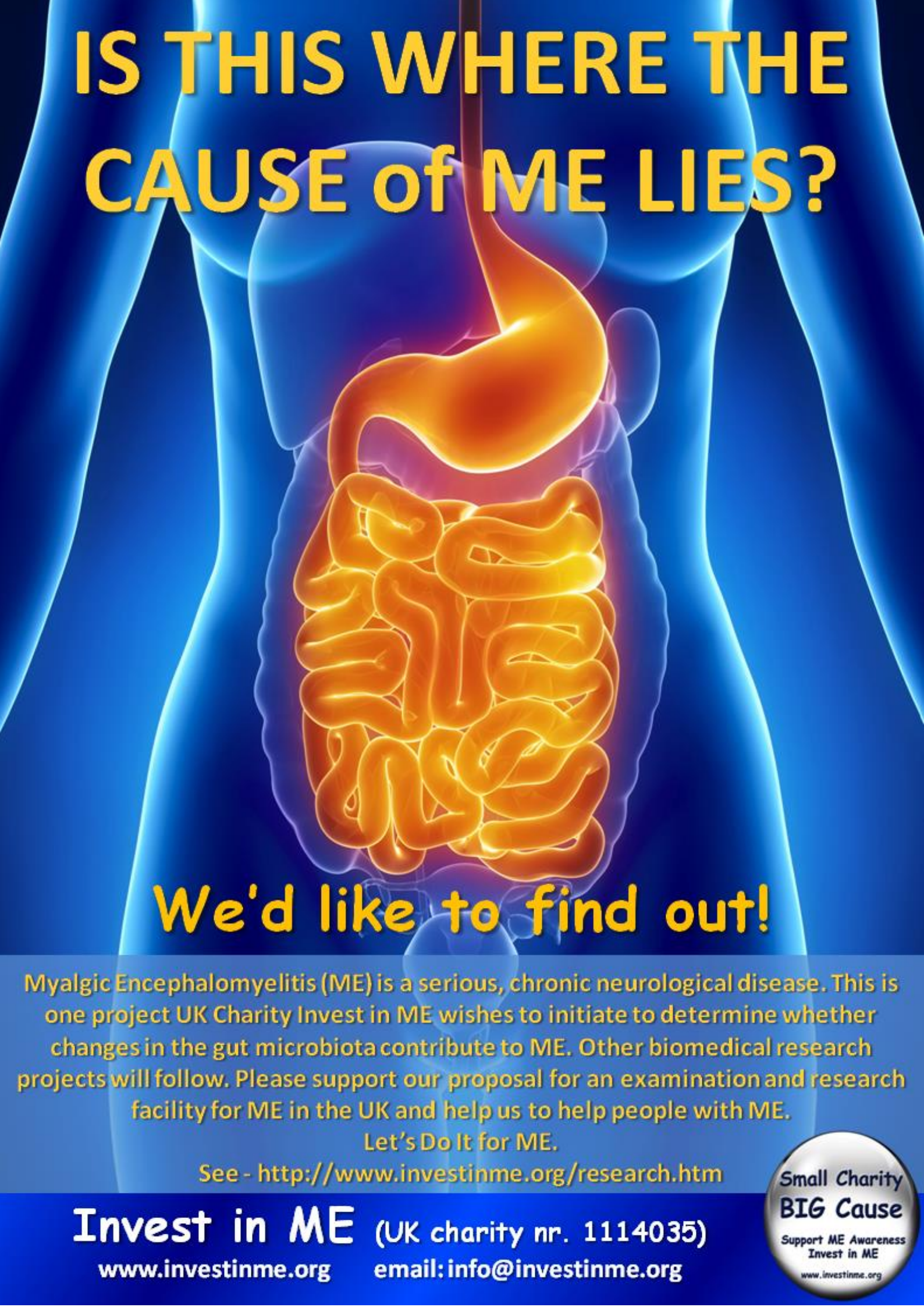
And this is not the only occasion Mike has supported his friend in this way.

Last year Mike, with a group of friends, took part in a very different challenge for the charity (92 football grounds in 92 hrs - http://www.92in92.blogspot.co.uk/) managing to reach over 10 million people (through TV, Press and the football community) and raising nearly £5K for the IiME Rituximab trial fund - http://www.ukrituximabtrial.org/IIMEUKRT%20Donate.htm. Throughout this project Mike met and talked to ME sufferers and their families and this has had a very profound effect on his decision to attempt this new challenge.

Mike will be taking the flag below with him around Europe.

Mike's JustGiving page is https://www.justgiving.com/mikeseumarathons/

IS THIS WHERE THE CAUSE of ME LIES?



We'd like to find out!

Myalgic Encephalomyelitis (ME) is a serious, chronic neurological disease. This is one project UK Charity Invest in ME wishes to initiate to determine whether changes in the gut microbiota contribute to ME. Other biomedical research projects will follow. Please support our proposal for an examination and research facility for ME in the UK and help us to help people with ME.

Let's Do It for ME.

See - http://www.investinme.org/research.htm

Invest in ME (UK charity nr. 1114035)

www.investinme.org email: info@investinme.org

Small Charity BIG Cause

Support ME Awareness Invest in ME

www.investinme.org