

Journal of liMER

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Research into ME

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International ME Colloquium / Conference

LONDON



#BRMEC8

#IIMEC13

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"This organization has been working in the trenches of ME, and it has been a notable and significant contribution to the field. Invest in ME has been able to increase awareness and disseminate knowledge to scientists, clinicians, and patients within the ME community. With limited resources, but unlimited creativity and imagination, these patients and their supporters have showed the world what can be done."

- Dr. Leonard A. Jason

Invest in ME Research

- an independent UK charity finding, funding and facilitating a strategy of high quality biomedical research into Myalgic Encephalomyelitis, as defined by WHO-ICD-10-G93.3
- focuses on biomedical research into ME and the education of healthcare staff, the media, government departments, patient groups and patients
- run by volunteers with no paid staff - no funding from government or government organisations
- overheads are kept to a minimum to enable all funds raised to go to promoting education of, and funding for biomedical research into, ME
- a small charity but we do far more than most with growing number of supporters with big hearts and determination to find the cause of myalgic encephalomyelitis and develop treatments
- funding more biomedical research than many other organisations
- we have links nationwide and also internationally and facilitate international collaboration
- founder member of the European ME Alliance (EMEA)
- organises annual research Colloquium and public Conference attracting delegates from 20 countries
- to bring best education and research to bear on ME and find/facilitate the best strategy of research
- focused on setting up UK/European Centre of Excellence for ME to provide proper examinations and diagnosis for ME patients and coordinated strategy of biomedical research in order to find treatment(s) and cure(s) - <http://www.cofeforme.eu>
- the charity welcomes support for our work – www.investinme.org/donate



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Patients with any illness are recommended to consult their personal physician at all times.

Welcome to IIMEC13

A Foundation of International Collaboration in Biomedical Research

From the Chairman of Invest in ME Research



Invest in ME Research is an independent UK charity facilitating and funding a strategy of biomedical research into Myalgic Encephalomyelitis (ME or ME/CFS) and promoting better education about ME.

The charity was built on the firm belief that biomedical research into ME was crucial in order to make progress in treating this disease. The education of healthcare staff, the media, government departments, patient groups and patients was also to be a priority - but something that would develop from the research being undertaken.

Although forcing research into ME into the mainstream of academic and clinical consideration has taken too long we do sometimes wonder where we would be if we had not started our conferences and, later, our research Colloquiums.

The international conferences were organised from the beginning to provide a platform for research and a means of facilitating education about ME.

The research Colloquiums now attract researchers from around the world to a meeting where they are free to discuss, share and collaborate.

Collaboration and working together have been themes for our Colloquiums - with real international cooperation forming that can only lead to a better future for patients than would otherwise be the case.

This year we again have representatives from both the USA National Institute of Health (NIH) and Centres for Disease Control (CDC) attending our Colloquium and Conference - endorsing our view of international collaboration as a critical means to an end.

We can also see some of the spin-offs that have occurred due to our Colloquium taking place - either research projects, collaboration in planning projects or in other events taking place.

Both the Colloquium and Conference are high quality, forward-looking events that serve to improve knowledge of this disease and generate and improve international collaboration into ME.

As always the charity takes on the task of producing a high-quality DVD of the conference with all of the presentations included. This serves as a historical record and is an educational tool for doctors and clinicians - demonstrating the seriousness of this disease. For 2017, our conference DVD reached even more countries and allowed us to inform a wider audience.

Yet how do we speed up research and move the direction away from the flawed approach to ME research that has been the strategy of establishment organisations that have not responded to the needs of patients?

The strategy that Invest in ME Research has created is to develop a Centre of Excellence for ME based on high-quality biomedical research and international collaboration.

There are now four PhD students performing biomedical research into ME at the Norwich Research Park, where the hub for the UK Centre of Excellence for ME is proposed. The charity continues to fund research at UCL also by supporting the remainder of another PhD studentship there.

The charity is doing more than most to provide a sound foundation for research into ME and spends more, proportionately, of its income on biomedical research and associated activities than any other UK charity.

The Invest in ME Research strategy of bringing in researchers from other fields to help and improve biomedical research into ME is working. Our conferences bring together patients, researchers, clinicians and healthcare staff and allow knowledge and

experiences to be shared – and IIMEC13 and BRMEC8 will see us entering our thirteenth year in doing this.

Our BRMEC8 is again a two-day event with biomedical researchers invited from around the world. This year will be the biggest yet with almost 100 top biomedical researchers participating from over a dozen countries.

The IIMEC13 Conference allows researchers, clinicians and patient/ groups/patients and carers to mix with each other, discuss together and network with unique opportunities – all enabling a greater understanding of this disease.

IIMEC13

In order to bring the best education and research to London each year we welcome all support for these events as there are significant costs involved in achieving this. We are therefore extremely grateful to our friends and supporters who have helped us via online donations. We also wish to thank our sponsors for IIMEC13.

The Irish ME Trust



A word of thanks to the Irish ME Trust who, yet again, will be sponsoring one of the speakers to the conference. IMET have been a constant friend and supporter of IIMER, and of ME patients. They have been a leading member in the European ME Alliance.

The Irish ME Trust has sponsored a speaker at all of our conferences and we would like to thank them for their continued support.

Norges ME Forening

Norway's ME Association (Norges ME Forening) is sponsoring the IIMEC13 conference.



Norges ME Forening has been a long-standing supporter of IIMER we are very grateful for this kind donation. Thank you NMEF.

Solve ME/CFS Initiative

Solve ME/CFS Initiative (SMCI) has sponsored an liMER conference for the first time but has already granted awards to two of the research groups which currently have research underway that is being funded by liMER. Thank you SMCI.



Welcome to those attending **Thinking the Future 2018, BRMEC8 Colloquium, IIMEC13 international ME Conference and European ME Alliance AGM.**

Welcome to London,

Kathleen McCall

In This Issue

This issue of the journal contains views on the current state of research and advocacy in ME, looking at past mistakes and false views that still pervade the landscape today and have affected the perception and treatment of ME, and especially the research. Has research moved on?

We have an opinion piece from Professor Ola Didrik Saugstad on the situation in Norway. If anyone were in doubt of the danger from lack of progress then the story of our friend, Anne Örtegren, is sobering. It is easy for patients to continue to believe in those who have failed them but we feel there are better choices. News from the Quadram Institute Bioscience ahead of their move to a state-of-the-art research, researchers such as Leonard Jason who still provides input to ME research. We have the UK Biobank presenting at our Colloquium – an article of the work of this national/international resource is in the Journal – answering the question what can the UK Biobank do for ME. liMER continue to use our efforts to develop the UK/European Centre of Excellence for ME in Norwich Research Park.

The Only Form of Graded Exercise Therapy Acceptable for People with ME

Thanks to Paul Kayes

Exercise can be really beneficial for people with ME, but it needs to be the right kind of exercise.

This is a list of activities for us to work through as part of a Graded Exercise programme.

Don't take it on all at once, aim to undertake one exercise daily - IT WILL make you feel better, promise.

.....

Exercises:

- Beat around the bush.
- Jump to conclusions.
- Climb up the walls.
- Wade through the morning paper.
- Drag my heels.
- Push my luck.
- Make mountains out of mole hills.
- Hit the nail on the head.
- Bend over backwards.
- Jump on the band wagon.
- Run around in circles.
- Toot my own horn.
- Pull out all the stops.
- Add fuel to the fire.
- Open a can of worms.
- Put my foot in my mouth.
- Start the ball rolling.
- Go over the edge.
- Pick up the pieces.
- What a Workout!
- Rest At Last.
- Face Book Time.



Progress in ME – or standing still?

liMER has been trying to make progress in research and treatment of ME for twelve years and we do see a change in the last few years with all of the charity's views on how to make progress having proven to be accurate.

Yet we should be further than where we are today.

liMER have not just tackled NICE. We have tried to engage with the CMOs of all countries in the UK. We have also taken up the matter with the Medical Research Council – inviting them to our conferences and Colloquiums and raising issues regarding the lack of funding for research. The responses have been poor.

Although, to be fair, it is maybe not the MRC with whom we take issue as it does some excellent work in many other fields. It is, instead, those whom the MRC have charged with responsibility for ME.

They have failed miserably - or succeeded completely - depending on whether the objective was to make progress in research or to be gatekeepers for stalling any progress.

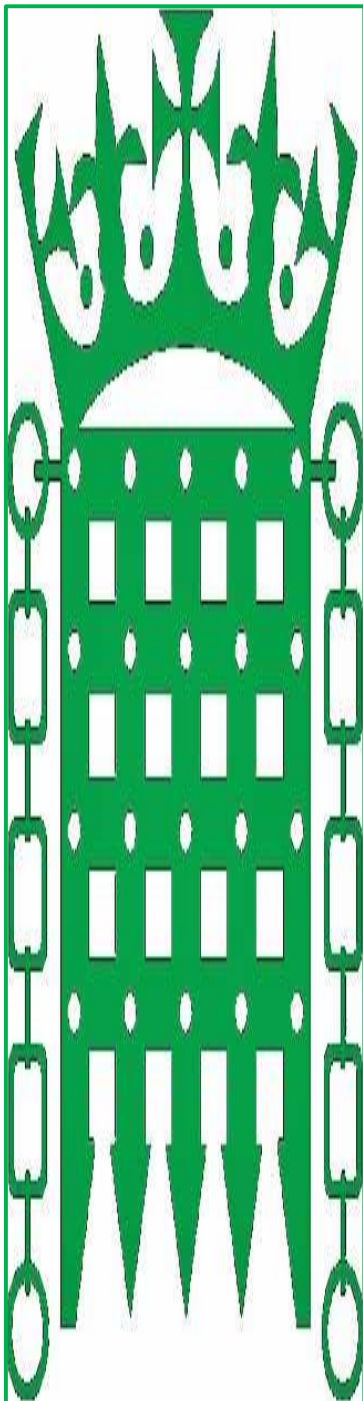
If anyone doubts the lack of progress made let us look back to a time long before the disastrous PACE Trial, way before the worthless "expert panels", before the Gibson Inquiry, even before the CMO report of 2002.

In 1988 in Parliament MP Jimmy Hood tabled a motion – **"to require an annual report to Parliament on progress made in investigating the causes, effects and treatment of myalgic encephalomyelitis"**

30 years ago!

It is worthwhile reading again.

https://api.parliament.uk/historic-hansard/commons/1988/feb/23/myalgic-encephalomyelitis#S6CV0128P0_19880223_HOC_296



Myalgic Encephalomyelitis

HC Deb 23 February 1988 vol 128 cc167-81674.36 pm

§Mr. Jimmy Hood (Clydesdale)

I beg to move, That leave be given to bring in a Bill to require an annual report to Parliament on progress made in investigating the causes, effects and treatment of myalgic encephalomyelitis. First, I should like to pay tribute to the many sufferers who have written to me in the past few days telling me of their personal suffering from the illness myalgic encephalomyelitis—an illness that is also known as post-virile fatigue syndrome.

The ME illness was first observed in Britain 33 years ago in 1955, but it was observed in other countries as early as 1939. Research into the disease is being carried out in Britain at St. Mary's hospital in Paddington, Glasgow university and establishments elsewhere. Research is also being carried out abroad, notably in Australia and the United States of America.

Research shows that ME appears to be caused by virile infection, combined with a disfunction of the immune system. There is no doubt that ME is an organic disease. The nature of the disease is such that it primarily strikes the central nervous system, the brain and body muscles. Its most common symptom is a profound weakness of the body, which results in even the most active of people being confined to their bed for long periods, sometimes years.

Another symptom that is more distressing than that is the illness's effect on the brain. Some normally bright, alert people find themselves unable to function. Their concentration goes; they have difficulty speaking; and even conversation leaves them completely exhausted. Sufferers lose their jobs and their lives come to a halt. Children affected lose out on their

education, sometimes for years. For many children the disease totally devastates their lives.

The greatest suffering of all is the anguish caused by misdiagnosis. On top of the physical and mental stress caused by the disease, sufferers' agonies are compounded by being told that they are well, that there is nothing wrong with them, that they are malingering, or that they are neurotic. It is widely acknowledged that many incidences of suicide result from the refusal of doctors to accept that sufferers are ill from myalgic encephalomyelitis.

The Bill is a simple measure which merely requires the Secretary of State to make an annual report to Parliament describing the progress that has been made in investigating the causes, effects, incidence and treatment of ME. Such 168a report would be of enormous value in drawing the attention of the medical profession, sufferers themselves and others to whom sufferers may turn for help to what is known about the illness. I cannot emphasise enough how vital it is to give proper recognition to the condition, as the failure to recognise the reality of the illness causes sufferers such great and wholly unnecessary distress.

The following are authentic examples of suffering caused by ME. A mother wrote to me saying:

My son aged 18 died from this miserable illness last March. He was away at university and had been ill on and off for two years. It all started with an attack of glandular fever. Now we look back over this time and so many things fit into a pattern. He was an active, bright young man with a zest for living and life. This illness got in his way. She concluded by telling me that her son committed suicide.

Then there was Jill from Sussex, who said:

I have been to hell and back with this devastating illness. I am still not recognised or getting proper benefits. I have received hundreds of letters about similar experiences from all over Britain, as well as Northern Ireland and the Isle of Man.

Many well-known persons are afflicted with the disease.

Sufferers include the Dean of Westminster; David Provan, a Scottish international footballer who had to retire from a promising career; a famous ballet dancer who is now confined to a wheelchair; and Clare Francis, a well-known adventurer and authoress. I inform the House that one of its Members, my hon. Friend the Member for Pontypridd (Mr. John), who is a sponsor of the Bill, is a sufferer.

I submit that the case for justice for ME sufferers is proved beyond all doubt. I have tried today to resist the temptation to speak in strong terms about the failure of the medical profession to recognise myalgic encephalomyelitis and the failure of the Department of Health and Social Security to recognise the plight of ME sufferers. The sufferers are denied proper recognition, misdiagnosed, vilified, ridiculed and driven to great depths of despair. They look to this House for justice. For them all I commend the Bill to the House.

Question put and agreed to.

Bill ordered to be brought in by Mr. Jimmy Hood, Mr. Alfred Morris, Mr. Jack Ashley, Mr. Brynmor John, Mr. Don Dixon, Mr. Alan Meale, Dr. Lewis Moonie, Mr. Sam Galbraith, Ms. Harriet Harman, Mr. Jimmy Wray, Mr. Tom Clarke and Mr. Jerry Hayes.

Look again at the first two paragraphs of the above motion - and this is from 1988!

The sad fact is that the above motion could have been brought before parliament today.

In fact, this motion from thirty years is far more advanced than some recent motions that have been brought before parliament.

And what was the request from this bill from 30 years ago?

“The Bill is a simple measure which merely requires the Secretary of State to make an annual report to Parliament describing the progress that has been made in investigating the causes, effects, incidence and treatment of ME.”

An annual report into progress!

Logical, simple, coordinated.
Something that any health department of chief medical officer might well see as common sense for a disease that affects so many and costs so much.

Yet thirty years on we have nothing of the sort. We can wonder how things may have been if this request had been enacted. Thirty years have passed since the above motion was made, and very little has changed, and the scale of the failure of those chosen to deal with ME is apparent. So many false starts and disingenuous actions by those in influential positions!

Since the CMO report on ME from 2002 people in positions of influence have had adequate opportunity to support biomedical research into ME. Instead, we witness dead-end “expert” panels and collaboratives formed – coming and going every few years, ending in failure, before another dead end initiative is set up. This pattern of stalling tactics is there to be seen and should fool no one.

It is tempting for some to believe those who perform a 180° change of direction to embrace “biomedical research” into ME, or issue statements that CBT and GET should not be offered as treatments – despite having promoted these views for decades. We do not believe in these epiphanies. After years of collaborating or supporting those proponents of the biopsychosocial theories of ME, the motives for changing of views has more to do with self-interest and less than the good of mankind at heart.

Continually offering second chances to organisations that repeatedly failed people with ME is a perverse form of Stockholm syndrome. As we stated in our letters to NICE we would advise people not to believe these statements and only give trust when one sees concrete action and permanent change.

Research into ME

But what of research into ME? This brings us on to our cover image – which sums up the state of current research into ME.



Are we any closer today to joining the pieces together and creating the bigger picture than we were twelve years ago when the Gibson Inquiry of 2006 suggested that “£11 million should be made available for research to redress the balance in an illness where too much emphasis had been put on psychological ‘coping strategies’ ”?

Yes and no.

liMER were probably one of the first to begin discussing the idea of international collaboration in research into ME many years ago as the way forward. We embedded this concept in all we do following the 2007 conference. Now this term is being used more and more. Yet, if we are honest, it is still not how we wished things to be.

If we discount the doubtful areas of research that have received large funding in the past – what liMER refers to as the “Wrong Stuff” – then rather than real coordinated collaboration what we see at the moment is still largely sets of disparate research threads and “territories” which continue to be, to a great extent, competing rather than joining together.

Perhaps it is just the phase we are going through where everyone is finding their place in the new world

following the decimation of the flawed PACE Trial and glimpses of realisation by the establishment that things must change.

IiMER were arguably the first to develop the idea of a Centre of Excellence for ME in UK – started almost a decade ago – a while after the Gibson inquiry and after that charity had sat in interminable meetings with the NHS for years and which had achieved nothing by the time we walked out in disgust. Those senseless meetings are still going on with no sign of any progress.

The Gibson Inquiry recommended an investigation of those vested interests in ME that have so manipulated the research and treatment services. Dr Gibson suggested a standards committee because too often patients had to live with the double burden of fighting for both their health and their benefits. This has not occurred. Instead, it has been left to an independent journalist from outside the UK to expose the flawed PACE Trial and all of its underlying intrigue. Yet, compared to even five years ago there are changes which have occurred.

Thanks to leading organisations, such as Invest in ME Research, a great deal of international collaboration has been initiated, some more funding has been found (though still mostly from philanthropic and charitable sources).

The recent NIH award is encouraging but far less than Invest in ME Research suggested in our response to [IOM and P2P Reports](#) (\$250 million dollars for the next five years).

However, our cover image shows the reality of the state of research into ME today – lots of pieces to a puzzle, without anyone really knowing what the bigger picture will look like, even though there are hints.

The landscape for ME still seems like a jigsaw puzzle with an historical lack of funding meaning that relatively few players have been able to start to create the big picture.

In research it is common for false starts to occur when attempting to find the cause(s) and treatment(s) for a disease. The fact that ME has had far fewer false starts, let alone breakthroughs, than other areas of research is also an indication of the pitiful attention that has been given to it by successive governments and health

departments and by disingenuous establishment representatives.

Biomedical research into ME has not been well served in UK or elsewhere for a generation. Patients are (literally) sick of the biopsychosocial approach to ME and fatigued by the constant false belief that exercise will make them better.

The reasons for lack of funding have been political for the main part, and more to do with reasons disassociated from researching this disease.

This has had consequences in scaring off new research interest, in avoiding ME being brought into mainstream biomedical research and lacking any sort of strategy.

Progress from seed funding research from occasional philanthropic means has largely failed.

At best, all this has done is to create more puzzle pieces and nothing has been joined together.

So many disparate pieces of research – uncoordinated, using precious funds raised mainly by patients and poor use of the comparatively small research capacity available.

Until very recently nobody has been looking at the whole puzzle, with genomics technologies now assisting.

This is why Invest in ME Research has been developing a strategy since 2010 to develop the UK/European Centre of Excellence for ME – where a hub of research, based in Norwich Research Park, can be created to build up the bigger picture and then add research onto to it as knowledge develops.

To create hypotheses to establish how things may link up.

Already, in recent discussions on research, we can see that our Centre approach is functioning and addressing other missing aspects of the big picture that have been allowed to be ignored – such as overall standards and outcome measures which can be used by all. The basics are still lacking and there is an urgent need to raise the standards.

This is why Invest in ME Research has spent so much effort in facilitating international collaboration between trustworthy biomedical researchers who wish to work together – such as the European ME Research Group (EMERG) concept.

This is why common data elements is required and why the recent NIH work on that may be crucial to move forward.



This is why we need a specialism in ME – a clinical consultancy attached to the research. And this is why we need up to date information that is not serving the biopsychosocial ideology or some careers.

These are all elements that Invest in ME Research have been developing for years, with few resources and with little support other than from the great supporters that we have.

It is why we need to complete the establishment of the foundation for the Centre of Excellence that we have started - to join research and create the future rather than rely on the status quo that benefits some organisations and individuals – but not patients.

We need momentum and international collaboration in research – and this is what Invest in ME Research provides with its cpd-accredited Colloquiums that are designed to bring together researchers, clinicians, patient groups and patients/carers in order to make progress in research into ME.

This year's Colloquium has almost one hundred biomedical researchers from around the world, from all of the main centres of research into ME and the CDC and NIH, binding these research elements together and creating new ones.

The Colloquiums are created by a small charity with great supporters without support from large establishment organisations or paid employees doing the work.

But then the Colloquiums are the real thing – not carrying any baggage from the wrong stuff or weighed down by affinities to the BPS lobby. Moreover, they are successful – often even helping those who choose not to support the charity.

It is five years since we began funding the first biomedical research project at Norwich Research Park.

An organisation can achieve a lot in five years – or it can achieve nothing. The difference is often down to individuals – those who have the passion and dedication to make change - or those who fail to do anything and are comfortable with seeing no change, merely making disingenuous platitudes aimed to assuage patient opinion.

We have been reminded in recent times of how fragile life is and how healthcare is so important for a just society. Even “established” diseases that have comparatively large research funding and correct

perception amongst health departments are not without issues. We have seen examples of this close up. The negative early results from the Norwegian Phase III trial has created a vacuum in research into ME. It directly affected the charity's plans for research and forced a major reassessment of our strategy and that of our supporters.

We were recently grateful to learn that the pledge that was provided for the rituximab trial from the Hendrie Foundation has now been granted for use by the charity in other, future biomedical research. The Hendrie Foundation has been an incredible supporter showing not only advice and support but also huge integrity – a particular attribute that we appreciate.

The NIH initiative is along the lines we foresaw when we initiated our proposal for a Centre of Excellence.

The liMER concept and development is based on a sound foundation and trusted biomedical researchers who are not serving their own agendas and has no baggage associated with it that can cause harm to people with ME.

The key to making ME a disease that receives the highest priority is an objective that we need to attain by establishing basic building blocks and a foundation on which to progress – funding for proper, high-quality biomedical research; education about the disease; and correct perception of the disease. These aforementioned building blocks happen to be the basic objectives of the charity.

We do believe that a corner has been turned and more good news is coming – some from liMER.

However, time will tell if we are heading for a new dawn – or watching the stars circle.

An organisation can achieve a lot in five years – or it can achieve nothing.



National Institute for Health and Care Excellence Guidelines for ME

Correspondence with Professor Mark Baker Centre for Guidelines Director

Whilst preparing for the planned NICE Stakeholders' Workshop in January to review the NICE guidelines for ME it was, in our opinion, necessary to make one request to NICE which we felt could not be delayed.

We requested that NICE remove the recommendations for Cognitive Behaviour Therapy (CBT) and Graded Exercise Treatment (GET) immediately from the existing guidelines due to the possible deleterious effects on people with ME.

All of the correspondence can be seen on our website here - <http://www.investinme.org/IIMER-Newslet-1801-01.shtml>.

We felt that it must have now surely been realised by all that CBT and GET are inappropriate for treating ME and in many cases have proven to be deleterious to the health of patients.

The PACE Trial, which was supposed to prove the efficacy of CBT and GET for ME, has been shown to be flawed and a complete waste of taxpayers' money. Reanalysis of PACE Trial results by Matthees et al (once the data was forced to be released from the authors following a legal challenge) stated -

"This re-analysis demonstrates that the previously reported recovery rates were inflated by an average of four-fold."

The PACE Trial is now being used as an example of how not to perform research – and it is widely seen as flawed and is ridiculed. Several articles by David Tuller academic coordinator of the concurrent masters degree program in public health and journalism at the University of California, Berkeley, have exposed these flaws and demonstrated that the PACE Trial cannot be considered valid.

We believe that a full review of the NICE guidelines, that may take two years or more, will leave patients exposed to these harmful treatments (CBT and GET) and it is not acceptable.



National Institute for Health Research

By removing the recommendations for CBT and GET from the existing guidelines now, with an addendum or correction of some sort, it could go a long way to establishing some trust in NICE from patients that was forfeited when the previous guidelines were published and the views of patients were ignored.

Thus began an exchange of letters between Professor Mark Baker of NICE and Invest in ME Research. The final letter from Professor Baker and our summary are illustrative of a system that has failed people with ME in the past and risks continuing to fail them in the future

By retaining CBT as a recommendation then this only helps those organisations and individuals who continue to promote biopsychosocial theories about ME for their own vested interests and will continue the threat to the welfare of ME patients.

CBT in the existing NICE guidelines is tightly connected to GET as it asserts that fear of exercise and false illness beliefs perpetuate the condition.

If the treatments mentioned (CBT and GET) are already accepted to be "inappropriate", "unacceptable" or "unsuitable" as recommended by the existing guidelines then your (and NICE's) duty and obligation to sick and vulnerable patients is to remove them immediately.

There is no other logical course to take.

Summary from Invest in ME Research 9th February 2018

Following the exchange of letters with Professor Baker we have summarised our views on the statements we have received.

The replies we have received force us to be very concerned about influences still affecting NICE guideline development for ME.

- *Professor Baker believes withdrawal of the guidelines would result in the entire support structure being removed. He has said that the services that are now provided to patients will be withdrawn if the existing guidelines are withdrawn immediately.*

- ◇ We have said we disagree with that.
The reality is that the services offered currently are sparse at best and detrimental to patients' health at worst and rarely meet the needs of patients.
It now must surely be recognised that, in fact, there is a distinct lack of services for ME patients, then we do really think it again illogical to worry about services disappearing.
- ◇ As all doctors will be told that a new set of guidelines will appear then new services will result from that.
CCGs still have a responsibility to patients.
In addition, we have suggested that NICE has a choice of action – if NICE does not wish to remove the existing guidelines then just adding the addendum that CBT and GET are no longer valid recommendations would be appropriate.
The extremely poor or inappropriate services currently offered should not be a reason to retain flawed guidelines that harm patients.
- *Professor Baker stated that "the actions of some service agencies (health care commissioners, children's services, schools and benefits agency amongst others) "...is not something which NICE has direct influence over".*
- ◇ Professor Baker claims that NICE guidelines are responsible for services being provided because they will disappear without them – whilst at the same time claiming that NICE has no direct influence over those services using them.
It is hard to follow this reasoning.
- ◇ The actions of some service agencies (health care commissioners, children's services, schools and benefits agency amongst others) are the direct result of the NICE guidelines and the recommendations therein and NICE must be held accountable and take responsibility.
- *Despite admitting the unpopularity of the guidelines with patients, which Professor Baker and NICE state they "clearly now empathise with", Professor Baker states that the majority view has been that they have done some good.*
- ◇ The guidelines must surely be created to benefit patients.
Professor Baker admits that they are unpopular with patients. Yet patients are only offered empathy - not action.

To what majority view is Professor Baker referring? Is the majority view that of doctors? We doubt it!

Is the "majority view" that of the lobby of psychiatrists who have so dominated the debate regarding what guidelines are imposed on people with ME, and what research is to be funded?

This seems a very odd conclusion in the circumstances.

Mere words being thrown around without any substantiation or detail is not just careless - in this situation it is disingenuous and maybe even dishonest.

If Professor Baker and NICE state that a majority view supports the retention of the existing guidelines then they must provide details of whom that majority consists of.

For it is not amongst patients.

- *Professor Baker believes that the guidelines legitimise the diagnosis.*

- ◇ Yet how could that be when few services have been offered, when the services that are offered are inappropriate and when Professor Baker acknowledges the horror stories confronting him where patients are not treated seriously?
- How can it be when the diagnosis of ME is so unreliable and unclear?
- ◇ In short, we contend that the NICE guidelines have done nothing to legitimise the disease.
- ◇ In fact, they have maintained an ignorance of the disease and allowed patients to be harmed - and continue to allow patients to be harmed.
- ◇ Legitimation is not what patients feel.
- ◇ We also contend that doctors have been ill served by these existing guidelines and cannot help their patients.

After two or three decades of seeing this disease mishandled and starved of funding for proper research then we can attest to the fact that it has been anything but legitimised.

Even the main protagonists of the BPS ideology, an ideology that has so completely raped this illness with its misinformation and vested interests, have stated that they do not see ME as being a disease – but instead a behavioural illness that can be cured by quack treatments.

- ◇ The existing NICE guidelines have done nothing to legitimise or help ME patients and the services that are on offer are mostly inappropriate or sparse – influenced totally by the existing NICE guidelines.
 - *Professor Baker has stated that the existing guidance is carefully worded with the implication that doctors are somehow not only aware of the “nuances” mentioned by Professor Baker, but are also understanding them.*
 - ◇ We have to disagree. If NICE recommend CBT and GET and if these therapies harm patients then no amount of crafted wordsmanship in the world will avoid the situation where patients are harmed.
 - ◇ We have stated that the “nuances” and “craftsmanship” of the wording in the existing NICE guidelines to which Professor Baker refers are lost on doctors, and on almost everyone, except NICE.
 - *Professor Baker states that the (existing) guidance is very carefully worded to protect patients and is “deeply concerned” at the actions of some service agencies (health care commissioners, children’s services, schools and benefits agency amongst others) which clearly do not represent the wording and intentions of the guidance. Professor Baker then states that this is not something which NICE has direct influence over and can only suggest that we direct our ire on those responsible for irrational decisions and the misquoting of our guidance.*
 - ◇ This is an astonishing statement to make - and far from true.
 - ◇ Of course NICE directly influences what doctors prescribe.
 - ◇ It is NICE who are responsible for the recommendations which doctors are compelled to take into account.
 - ◇ This statement demonstrates that NICE still really has no idea at how much damage these existing guidelines have done, and no idea of what damage they continue to do.
 - *Professor Baker suggested that we direct our ire on those responsible for irrational decisions and the misquoting of our guidance.*
 - ◇ Our “ire” is actually directed at those responsible for irrational decisions or decisions that make ME patients worse.
- Professor Baker admitted that the guidelines would be replaced entirely.
Professor Baker has agreed that CBT and GET are perceived and experienced by patients as harmful.
We believe that Professor Baker accepts the claims that patients have been harmed by CBT and GET
- It therefore defies logic to retain harmful recommendations for two more years or more- when it is clearly understood that patients are being harmed by these recommendations.
- *Professor Baker stated that the PACE Trial has had no effect on the recommendations of NICE (despite last summer the surveillance review quoting the PACE Trial).*
 - ◇ In our letter to Professor Baker we did not refer to PACE as being the base of evidence for NICE guidelines.
We only intended to refer to PACE in case Professor Baker came back to us to deflect our argument that CBT and GET need to be dropped by referring to PACE.
 - ◇ Yet NICE did use it to base its decisions in the surveillance review of 2017
 - We have stated it is illogical, and harmful to patients, that NICE retain the existing guidelines when it is admitted they are not fit for purpose, are not what patients want and potentially harm patients, and will be discarded in any case.
 - NICE must follow the USA and remove recommendations for using CBT and GET as treatments for ME with an addendum to the existing guidelines.
 - We have requested that this addendum is communicated to other healthcare agencies around the world who have misguidedly used the existing NICE guidelines as any basis for their own treatment of ME patients.
 - We began this series of letters to Professor Baker due to the comments attributed to him and NICE. These comments have made us wonder how these would be translated into action.
 - Professor Baker’s reply to us – a few hours before the stakeholder meeting – clearly seemed to be contradictory to the comments that Professor Baker made to the participants in the stakeholder meeting and raised major concerns for us as to the actual way NICE were intending to proceed.

- This, and further replies to our initial request to remove CBT and GET from existing guidelines, baffled us.
- The fact that Professor Baker has stated that the existing NICE guidelines will be torn up indicates this realisation that NICE and the existing guidelines have failed.
- What patients have said has proven to be true. Yet NICE did not listen.
- We detect even now that these messages still have not been taken on board.
- Comments such as “we will tear up” the existing guidelines need to be translated into immediate action.
- We have words from NICE - but no action.
- NICE must separate the decision on the continuation of the existing guidelines from the review of them.

These are two separate matters – linked by the fact that NICE has already decided to tear up the existing guidelines and that Professor Baker accepts that CBT and GET are harmful to ME patients.

- The existing guidelines must be withdrawn or NICE must add an addendum that CBT and GET are no longer recommendations.
- The refusal to add an addendum to existing guidelines to remove BOTH CBT and GET is illogical in the context of the remarks made by Professor Baker/NICE.

The refusal to withdraw the existing guidelines whilst they are torn up and new guidelines are developed carries a level of illogical reasoning.

Professor Baker has admitted the existing guidelines are unfit, he has accepted the horror stories of patients being coerced into trying CBT and GET and being harmed by them, he has heard of insurance companies denying benefits when people refuse to agree to try these flawed theories recommended by NICE.

In all of this how can it be logical, or moral, or safe, to retain these existing guidelines, and especially the disastrous and damaging recommendations for CBT and GET?

If a drug is recommended by NICE for a disease and some time later the drug is found to be harming patients then surely NICE would take steps to remove that drug.

They would not retain it as a recommendation, to be in use for two years whilst they developed a new guideline for the disease.

To avoid further harm to patients they would remove the drug immediately.

- This is the same situation that NICE now face with CBT and GET for ME.
- Professor Baker has written to IIMER that he “will discuss at the highest level at NICE what remedial action to help patients we can take in the meantime.”

We hope that this will result in issuing the addendum to the existing guidelines that removes CBT and GET as recommendations for ME – or otherwise the withdrawal of the existing NICE guidelines for ME immediately.

- We do not share the euphoric tributes to NICE for arranging a workshop where the audience is told everything that they want to hear.

- Years of experience of establishment tactics involving wasting several years on initiatives that are already designed to deliver nothing of consequence have made us wary of the corrupt systems in place.

Our recommendation to ME patients and their families is not to trust comments by NICE and not to trust NICE at all – until the day arrives that NICE actually deliver and operationalise guidelines for ME that really do reflect the reality and needs of ME patients and their families.

- Based on their track record NICE do not yet deserve any such trust.

- ME patients have had very little bargaining power over the last decades thanks to the insidious and immoral network of BPS protagonists who have influenced all policies on ME in

the UK and taken over decision making in weak and apathetic research councils and government departments.

- What patients have been able to retain is the ability to give or withhold their trust in new initiatives that promise change to improve their lives. In the world of social media, where the playing field has been levelled in recent times and allowed patients to challenge biased research, this provision of trust by the patient community can be a useful commodity.
- We therefore do not give NICE our trust.

Our recommendation to ME patients and their families is not to trust comments by NICE and not to trust NICE at all – until the day arrives that NICE actually deliver and operationalise guidelines for ME that really do

reflect the reality and needs of ME patients and their families.

Currently that date would be somewhere in two years time.

NICE can bring forward that date by acceding to our request to add an addendum immediately to the existing guidelines to remove recommendations for BOTH CBT and GET - or by withdrawing the existing guidelines for ME immediately, and issuing a press release to doctors in UK and abroad that NICE has found the existing guidelines to be unsatisfactory, that they are going to be torn up and completely revised.

If NICE do this then trust will surely be given by ME patients.

Sir Andrew Dillon might even find it within himself, on behalf of NICE, to issue an apology to ME patients for the wasted years and the distress and the harm which the existing guideline recommendations have caused.

If NICE do not take this eminently logical and fair decision immediately then there is no reason to give that trust.

We really do hope that NICE now act in a logical and fair way with the patients in mind - uninfluenced by the evil of the BPS network that has been allowed to flourish over the last decades.

Add the addendum to remove CBT and GET – or Tear It Up! Now!

Finally, look at a communication below, from a patient, that has come to Invest in ME Research in the last month - a letter which neatly describes the appalling consequences of recommending CBT and GET - something for which Professor Baker and NICE cannot pass on responsibility to others.

This is the result of NICE's recommendations in their existing guidelines - and this just underlines everything we have been trying to make Professor Baker, and NICE, understand.

This letter alone is a testament to the failure of NICE to help people with ME and their families - and a decade on from the creation of the existing guidelines there is enough of an indication that no lessons have been learnt - or any real intent is underway to correct the failings.

Throughout our correspondence it seems clear that Professor Baker is oblivious to the elephant in the NICE room - no matter how much damage it is doing to patients.

NICE must serve the needs of patients.

Unfortunately, we fear that NICE will not do as we suggest and will not act for the interests of patients. We can only surmise that more influential forces are still present, continuing to force more CBT and GET on to patients.

If that were so it would be shameful.

NICE, and those deciding on the future for people with ME, must be held accountable if more people are harmed by retaining the existing damaging recommendations for using CBT and GET for another two or more years.

Further Reading

1/ [NICE Campaigning](#)

2/ [Notes on BPS Model](#)

From a Patient: To Invest in ME Research

I have been closely following your continuing correspondence in relation to the call for revision of the NICE guidelines.

In particular the removal of CBT/GET.

I have had M.E. for almost four years and am quite severely affected.

I am housebound most of the time and often bedbound.

I was previously a 'high flyer' (my neurologists' words) and a civil servant with a social work background.

Due to my illness I am no longer able to work, and have just been through the very painful process of applying for ill health retirement.

My pension provider (through the (name provided) pension scheme) has a two tier system for pension awards in the circumstance of ill health retirement.

I have undergone five medical assessments during the process and have been assessed as permanently incapacitated in terms of employment.

However, as I have not completed the treatment, as recommended in the NICE guidelines, I cannot obtain the higher rate pension. The treatment namely being CBT and GET.

I have engaged with the specialist M.E. service in (location provided) but was unable to continue as attending sessions made me more unwell.

I tried CBT through my local mental health service, attending three out of six sessions, this made me more unwell and put me back into bed for weeks. I am in receipt of the highest rate of both ESA and PIPS.

These were both awarded following the first medical assessment, which I understand is not the position for far too many M.E. sufferers.

I have taken my ill health retirement case to appeal within my pension service. The position of the original decision not to award me the higher rate pension has been upheld on the grounds that I have not completed CBT and GET.

My pension provider will now escalate my appeal to stage two of the process.

However, the decision makes it clear that, in order to succeed, I need to prove that I have completed CBT and GET.

I am faced with a position that is unfair and takes away any right I have not to undergo treatment that exacerbates my illness.

I have had support from my union (name provided), however they aren't familiar with the fight that M.E. suffers like myself face.

I have previously had a life where i travelled up and down the country for my career, helping to make a difference in the lives of vulnerable children.

I had authority and was very much a professional.

I have always worked within the public sector, both local and central government.

I had a lively social life, always on the go with my partner and family.

Now my life revolves around my bedroom. I rely on pillows, blackout curtains and strong medication to try and control my pain. If I journey out, it is to visit my G.P.

which takes around three hours to get me ready for, with lots and lots of assistance from my wife, who is also my carer and carer to our 18 year old disabled son.

Please please continue the fight for those of us struggling to do it for ourselves

I often find it difficult to construct challenges around my illness as i simply can't find the words due to my diminished cognitive functioning. This is one of the hardest symptoms to deal with. The loss of intellect. It's in there somewhere, I'm in there somewhere, but I just can't get the words to make sense.

It is imperative that someone listens to our voices and I am so thankful for your determination in challenging the medical profession around our treatment options.

It will probably be too late to make any difference to my case.

I hope that in the future no one will be penalised for not undergoing treatment that is harmful to their health as a result of your campaigning; that CBT and GET will be removed from the guidelines with immediate effect, rather than waiting for years while the guidelines are revised.

Please please continue the fight for those of us struggling to do it for ourselves

Little more needs to be said.



IiMER Conference DVDs

The Invest in ME Research conference DVDs are professionally filmed and authored DVD sets consisting of four discs in Dolby stereo and available in PAL (European) or NTSC (N. America) format. They contain all of the presentations from IiMER International ME/CFS Conferences (2006 – 2013). Also included in the DVD sets are interviews with ME presenters, news stories and round-table discussions. The Invest in ME Research conference DVDs have been distributed to more than 20 countries and are available as an educational tool – useful for healthcare staff, researchers, scientists, educational specialists, media, ME support groups and people with ME and their carers/parents. Full details can be found at <http://www.investinme.eu/IIMEC13-pastconferences.shtml> or via emailing Invest in ME Research at info@investinme.org

Research News from Katharine Seton

“Defining autoimmune aspects of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)”

I would like to introduce myself to you all. I am Katharine Seton, a 22-year-old PhD student and I have just begun the second year of my PhD.

I originally came from Cumbria and studied Biomedical Sciences at Newcastle University before starting my PhD funded by Invest in ME Research. I have always had a strong interest in the immune system and ME research.

I have a personal investment and interest in ME research, because in January 2009 I was diagnosed with ME, when I was just 13 years old.

It was both physically and emotionally challenging to make the transition from a very active and musical child, regularly competing in basketball, swimming, orienteering, hockey, netball and athletic events, to a child too ill to attend school more than 9 hours a week. Up until my ME diagnosis, I had always dreamt of being a stunt woman and having a very active career. When I developed ME, I had to cut out sport, music and socialising, which meant I became focussed on my education.

I realised after I managed to achieve 11 GCSE's grades A* to A whilst attending school on a part time basis that I am academically able, something I did not realise prior to my ME diagnosis because I was always so focussed on sport.

It was only once I was at University, studying my undergraduate degree, that I came to the realisation that I could contribute to the ME research field. In the summer of my second year, I had a Wellcome Trust funded Vacation Studentship, researching the heritability of ME with Professor Julia Newton at Newcastle University.

I loved every minute of this placement, although it was computer based, and after this valuable work experience I realised that I would love to contribute to laboratory research into the cause of ME.

I aspire to help find a cure for ME ... so watch this space! The research that I am focussing on in my PhD is the immune system and its interaction with gut microbes, specifically, whether there is an inappropriate immune response triggered by bacteria that has leaked across the gut wall.

There is current evidence of an inappropriate immune response and gastrointestinal involvement in ME



patients and I endeavour to find out whether there is a link between the two, and if this link is blocked, would it lead to symptom improvement.

As ME patients experience a wide range of symptoms, and have different onset patterns, it is a scientifically challenging area of research to study, often yielding different results between different research groups. The first year of my PhD was focussed on creating a plan for recruitment, sample collection and sample analysis. This study has received ethical approval from the Health Research Authority, and participant recruitment is underway.

It has been agreed that this study will focus on the recruitment of severe ME patients and their household controls, recruited through East Coast Community Healthcare Centre and through Dr Bansal at Epsom and St Helier CFS Clinic.

As this is a longitudinal study, blood and stool samples will be collected on up to six occasions.

Now that we have received ethical approval for this study, the second year of my PhD will be focussed on participant recruitment, sample collection and processing, and sample analysis, hopefully leading to the generation of some interesting, valuable, results.

Katharine Seton

- Quadram Institute, Norwich

A Study Update

Posted by: Katharine Seton Post Date: 8 February 2018
With regards to the human study being undertaken at the Quadram Institute, “Defining autoimmune aspects of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome” progress has been made, despite hold ups. 50% of the target number of patients have volunteered to participate in the study.

The main study obstacle was identifying a trained person for blood sample collection.

A trained person has been identified at the Quadram Institute to take blood.

An amendment application and approval from the Health Research Authority has been obtained, and a contract delegating study responsibilities between the University of East Anglia and the Quadram Institute is underway.

Once this is in place, home visits and sample collection can commence.

Despite not being able to collect samples yet, major progress in method development and optimisation has been made.

This was done using banked samples from Daniel Vipond's PhD.

Between (fellow PhD students) Fiona Newberry, Shen-Yuan Hsieh and myself we have optimised the following: isolation of virus particles from stool samples, viral identification based on unique sequences, and a method to screen for antibody responses to gut microbes.

I have recently had a review with my PhD supervisors, the purpose of which is to identify how much progress has been made.

I received positive comments that have given me some added motivation: "The quality of the work undertaken to date is also very good with considerable careful and detailed effort being put into evaluating multiple experimental variables to optimise the assay".

Looking forward, the next couple of months entail home visits, sample collection and sample processing, all of which take a considerable amount of time.

While this is occurring, method development will be continued and progressed.

In addition, we have also been very kindly invited to give a presentation at the Shropshire ME Group Conference in May.

This is a great opportunity to communicate our research to the public, and to engage with the public to hear their thoughts.

The move in date to the new Quadram Institute building is now August 2018.

This provides us with plenty of time to do the first round of sample collection.

On a finishing note, I would really appreciate those who received a study invitation, and are interested in participating in the study to please contact myself soon to register your interest.

Bye for now –

Katharine

Katharine Seton - Quadram Institute, Norwich

A New Paper from Fiona Newberry et al

liMER-funded PhD student Fiona Newberry has recently had a paper published - "**Does the microbiome and virome contribute to myalgic encephalomyelitis/chronic fatigue syndrome?**" – with an interesting observation

"..as the number of microbiome studies increases, the need for greater consistency in study design and analysis also increases. Comparisons between different ME/CFS microbiome studies are difficult because of differences in patient selection and diagnosis criteria, sample processing, genome sequencing and downstream bioinformatics analysis. It is therefore important that microbiome studies adopt robust, reproducible and consistent study design to enable more reliable and valid comparisons and conclusions to be made between studies. "



<https://ueaeprints.uea.ac.uk/66615/>

Thinking the Future - Young/Early Career Researchers for ME Research into Myalgic Encephalomyelitis

Prior to the conference Invest in ME Research organised the inaugural meeting of a new international network to encourage young and early career researchers to this field.

Despite the seriousness of this disease still very little biomedical research is funded or performed on ME.

An international family of researchers working together has been facilitated by the Invest in ME Research Biomedical Research into ME Colloquiums.

However, the charity felt that we needed to do more to attract and encourage new, younger researchers or those at the early stages of their careers.

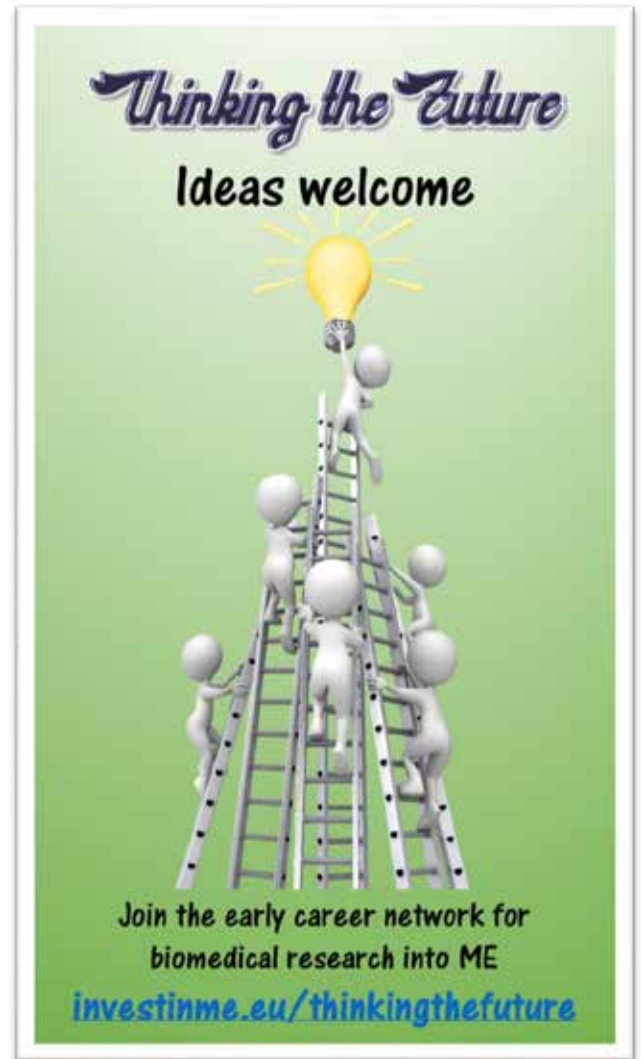
To ensure that a foundation of biomedical research into ME can be sustained and to encourage new ideas from new areas then we cannot rely just on the family of researchers that has been built up from all parts of the world. We need to draw in knowledge and expertise from other areas – as we have been doing for many years with our Colloquiums and international conferences. Importantly, we also need to encourage new researchers – and young researchers. Now in its eighth year we wish to introduce another level to the Biomedical Research into ME Colloquium to address these points.

As part of the European ME Research Group (EMERG) concept - which is building a network of close European biomedical research collaboration to make rapid advances in research and funding for ME - we introduced a new idea. Thinking the Future.

An Early Careers Researcher is defined an individual who is within a few years of the award of their PhD or equivalent professional training, or their first academic appointment.

IIMER has created this additional event to encapsulate the need to bring in new faces and new ideas to the field of ME research - and initiate a network for new research talent.

The charity made this event free for young/ecr researchers in order to facilitate the establishment of these links and it is open to postgraduate students and postdocs involved in biomedical research, and also medical students with an interest in biomedical research into ME.



We will establish this international forum where research into ME can be discussed, ideas can be generated and a network built to allow opportunities for those young or early career researchers who are already involved in research into ME, or involved in another research area which may be of relevance to understanding ME. Importantly, it will provide more awareness of the exciting possibilities of researching this disease – for the betterment of patients and carers.

To make this an international group with events being held elsewhere, and in other countries, we have contacted research groups and our friends in other like-minded charities and organisations who have the same objectives as us.

We welcome all support for this and hope that more early career researchers and research departments will begin to appreciate the interesting and challenging opportunities that exist for biomedical research in this field.

Help us Think the Future - for ME

Quadram Institute Bioscience News

Opening fully in mid-2018, the Quadram Institute will be at the forefront of a new era of food and health research, working at the interface between food science, gut biology and health.

It will develop solutions to worldwide challenges in food-related disease and human health, with a lifelong focus from establishing optimum health at birth through to ensuring we age healthily. The Quadram Institute is assembling interdisciplinary teams and working with appropriate international organisations to address these major issues. Scientists and clinicians working together under one roof will deliver innovative new healthcare solutions.

Based on the Norwich Research Park, it is a partnership between Quadram Institute Bioscience, the University of East Anglia (UEA) and the Norfolk and Norwich University Hospitals NHS Foundation Trust. This brings together excellent research, teaching and patient care, synergising collaborations between the 3,000 scientists and clinicians working in six world class organisations clustered on the Norwich Research Park.

This concentration of interdisciplinary expertise is needed if we are to solve complex health problems facing society. The Quadram Institute, supported by the charity Invest in ME Research, has established a programme of biomedical research addressing the complex causes of Myalgic Encephalomyelitis (ME). Our ME studies are led by Professor Simon Carding, who leads QI's Gut Microbes and Health research programme, and is also Professor of Mucosal Immunology at the Norwich Medical School at the University of East Anglia. The research builds on recent evidence that ME/CFS has a basis in the immune system. Our focus is on the interactions between the immune system and the microbiota in the gut. Many ME

sufferers also have gut-related conditions and several studies have recorded altered microbiota communities.

The gut is a major focal point of the body's immune system. It must deal with a constant barrage of potentially harmful microbes taken into the body with our food, whilst also supporting a large community of microbes that benefit health – the microbiota. Part of the Quadram Institute's mission is to understand how this balance is maintained, and how changes in this balance lead to diseased states. One aspect of this includes the study of what happens when the lining of the gut, the intestinal epithelium, fails to act as a barrier and members of the microbiota are able to cross. This is known as leaky gut syndrome and may be important in a number of conditions, including ME/CFS, as it abnormally presents microbes to the immune system and potentially triggering an autoimmune response. With partners at University College London, we are looking at the nature of autoimmune reaction in patients with ME.

An important aspect of our research into links between the microbiota and ME/CFS is to understand better the role played by viruses in the microbiota. Much research

has focused on the bacterial populations, but the microbiota contains many other organisms, including fungi and viruses, as well as bacteriophages (viruses that infect bacteria). Viruses in particular are of interest in the study of ME/CFS as there has been evidence suggesting a viral role in triggering ME/CFS without being able to identify specific causes. Working with

colleagues at UEA, we are looking to fully study the viral component of the microbiome, the virome, and its relevance to ME/CFS.

Much of our work to date has been supported by the charity, Invest in ME Research, who, as well as raising funds for biomedical research are working to raise awareness of the condition and supporting collaborative efforts across the EU to tackle ME. One target is to establish a Centre for ME Research, building on excellent biomedical research, to act as a hub for European research and treatment of ME.



UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age

Cathie Sudlow^{1,2}, John Gallacher³, Naomi Allen^{2,4}, Valerie Beral⁴, Paul Burton⁵, John Danesh⁶, Paul Downey⁷, Paul Elliott⁷, Jane Green⁴, Martin Landray⁴, Bette Liu⁸, Paul Matthews⁷, Giok Ong⁹, Jill Pell¹⁰, Alan Silman¹¹, Alan Young⁴, Tim Sprosen⁴, Tim Peakman², Rory Collins^{2,4*}

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The challenge of understanding the determinants of common life-threatening and disabling conditions is substantial. These conditions are typically caused by a combination of lifestyle, environmental, and genomic factors, with individually modest effects and complex interactions, the detection and quantification of which require studies with large numbers of disease cases. While retrospective case-control studies of particular diseases [1] or existing prospective studies of particular risk factors can help to address this challenge [2,3], a complementary approach is to establish large prospective cohorts designed to study a much wider range of known and novel risk factors for a wide range of diseases [4]. Prospective studies can assess exposures before the onset and treatment of disease, diseases that are not readily investigated by retrospective studies, and both the adverse and beneficial effects of a specific exposure on the lifetime risks of different diseases.

UK (United Kingdom) Biobank is a very large, population-based prospective study, established to allow detailed investigations of the genetic and nongenetic determinants of the diseases of middle and old age [5,6]. It aims to combine extensive and precise assessment of exposures with comprehensive follow-up and characterisation of many different health-related outcomes, as well as to promote innovative science by maximising access to the resource. Recruitment of

Summary Points

- UK Biobank is a very large and detailed prospective study with over 500,000 participants aged 40–69 years when recruited in 2006–2010.
- The study has collected and continues to collect extensive phenotypic and genotypic detail about its participants, including data from questionnaires, physical measures, sample assays, accelerometry, multimodal imaging, genome-wide genotyping and longitudinal follow-up for a wide range of health-related outcomes.
- Wide consultation; input from scientific, management, legal, and ethical partners; and industrial-scale, centralised processes have been essential to the development of this resource.
- UK Biobank is available for open access, without the need for collaboration, to any bona fide researcher who wishes to use it to conduct health-related research for the benefit of the public.

500,000 participants and the collection of an unprecedented wealth of baseline data and samples were completed in 2010. Activity is now focused on further phenotyping of participants and their health outcomes and on providing access to researchers from around the world.

Cohort Size

The large size of the cohort was based on statistical power calculations for nested case-control studies [7], showing that 5,000–10,000 cases of any particular condition would be required for the reliable detection of odds ratios (ORs) for the main effects of different exposures of 1.3–1.5 (the upper end of the range reported from genome-wide association studies of various conditions [8]), and around 20,000 cases for detection of interactions with ORs of at least 2.0. To observe such large numbers of cases of particular diseases within a reasonable follow-up period, prospective cohorts need very large numbers of participants. Projected numbers of cases of a range of common conditions expected to occur among 500,000 UK Biobank participants during 20 years of follow-up (Table 1) suggest that reliable assessment of the main determinants of most of these conditions (and others that are similarly common) should be possible during the current decade [6,9]. The age range for inclusion of 40–69 years represented a pragmatic compromise between participants being old enough for there to be sufficient incident health outcomes during the early

Table 1. Approximate numbers of incident cases of some exemplar conditions expected to accrue during the first 20 years of follow-up in UK Biobank.

Condition	2012	2017	2022	2027
Diabetes mellitus	10,000	25,000	40,000	68,000
MI and coronary death	7,000	17,000	28,000	47,000
Stroke	2,000	5,000	9,000	20,000
COPD	3,000	8,000	14,000	25,000
Breast cancer (female)	2,500	6,000	10,000	16,000
Colorectal cancer	1,500	3,500	7,000	14,000
Prostate cancer	1,500	3,500	7,000	14,000
Lung cancer	800	2,000	4,000	8,000
Hip fracture	800	2,500	6,000	17,000
Rheumatoid arthritis	800	2,000	3,000	5,000
Alzheimer's disease	800	3,000	9,000	30,000
Parkinson's disease	1000	3,000	6,000	14,000

Based on UK age- and sex-specific rates with adjustment for healthy cohort effects and losses to follow-up [6].

MI: myocardial infarction; COPD: chronic obstructive pulmonary disease or chronic bronchitis/emphysema

doi:10.1371/journal.pmed.1001779.t001

years of follow-up and young enough for the initial assessment to occur before incipient disease had a material impact on exposures.

Data Availability

Data from the Baseline Assessment

The 500,000 participants were assessed between 2006 and 2010 in 22 assessment centres throughout the UK, covering a variety of different settings to provide socioeconomic and ethnic heterogeneity and urban–rural mix. This ensured a broad distribution across all exposures to allow the reliable detection of generalisable associations between baseline characteristics and health outcomes. The assessment visit comprised electronic signed consent; a self-completed touch-screen questionnaire; brief computer-assisted interview; physical and functional measures; and collection of blood, urine, and saliva (Table 2). Multiple aliquots of different sample fractions are stored in UK Biobank's automated laboratory, allowing for a wide range of future assays [10].

Data from Additional Assessments to Enhance Phenotyping

UK Biobank is conducting a range of additional phenotyping assessments in all (or large subsets) of the participants. Data are already available both from a detailed dietary web questionnaire [11], completed up to four times by over 200,000 participants, and from the first repeat of the entire baseline assessment in around 20,000 participants [12]. Over the coming months and years, further data will become available from: a range of biochemical assays and

genome-wide genotyping of baseline samples from all participants; Web-based questionnaires to assess specific characteristics in more detail (e.g., cognitive function, occupational history); and, in subsets of 100,000 participants, collection of data from physical activity monitors and multi-modal imaging (Table 3).

Data from Longitudinal Follow-Up for Health-Related Outcomes

Follow-up is conducted chiefly through linkages to routinely available national datasets. Data are already available on over 8,500 deaths, over 75,000 prevalent and incident cancers, and over 600,000 hospital admissions, while linkages are planned to a range of other datasets, including primary care, cancer screening data, and disease-specific registers. In addition, to reduce misclassification and increase biological specificity of health outcomes, UK Biobank is developing methods for accurate identification and detailed phenotyping of outcomes in a range of disease areas. Initial ascertainment of outcomes with electronic and semi-automated sources will be supplemented by more intensive methods (e.g., retrieval of case records, imaging data, or banked tissue samples) for validation and subclassification (Table 3).

Online Open Access to Researchers

Many cohort studies have mechanisms for sharing data with external researchers on a collaborative basis, but relatively few have arrangements for open access to the data without any need for collaboration, and even fewer have been established from the outset with the intention of making the entire resource available to the

global research community. The development of open access arrangements for data from cohort studies is an important step in maximising their impact with respect to scientific publications, policy making, and understanding of health and disease. Examples of resources whose impact has been enhanced in this way include the UK 1958 birth cohort study [13] and the Australian 45 and Up cohort study [14].

UK Biobank aims to encourage and provide as wide access as possible to its data and samples for health-related research in the public interest by all bona fide researchers from the academic, charity, public, and commercial sectors, both in the UK and internationally, without preferential or exclusive access for any user. UK Biobank's publicly available Data Showcase (<http://www.ukbiobank.ac.uk/>) presents the univariate distributions and methods used for collection of all the

contact are subject to a more rigorous process of scrutiny and scientific review. Following initial assessment by the executive team, all applications are assessed and either approved or rejected (with right of appeal) by an independent Access Subcommittee. Advice is sought on any applications raising potential ethical issues from both the University of Oxford's Ethox Centre and the Ethics and Governance Council. Only de-identified data are provided to researchers, who must sign a material transfer agreement, undertaking not to attempt to identify any participant, to keep the data secure, and to use it only for the purposes of the approved research. Researchers must also undertake to publish their results and to return details of their methods, derived data, and/or sample assay results for incorporation into the UK Biobank dataset so that they can be made available to other approved researchers (see

Table 2. Data collected at the baseline assessment.

Questionnaire and interview

Sociodemographic	Social class; ethnicity; employment status; marital status; education; income; car ownership
Family history and early life exposures	Family history of major diseases; birth weight; breast feeding; maternal smoking; childhood body size; residence at birth
Psychosocial factors	Neurosis; depression (including bi-polar spectrum disorder); social support
Environmental factors	Current address; current (or last) occupation; domestic heating and cooking fuel; housing; means of travel; shift work; mobile phone use; sun exposure
Lifestyle	Smoking; alcohol consumption; physical activity; diet; sleep
Health status	Medical history; medications; disability; hearing; sight; sexual and reproductive history
Hearing threshold	Speech reception threshold*
Cognitive function	Pairs matching; reaction time; prospective memory*; fluid intelligence*; numeric memory†

Physical measures

Blood pressure and heart rate	two automated measures, one minute apart
Grip strength	Left- and right-hand grip strength
Anthropometrics	Standing and sitting height; weight and bio-impedance; hip and waist circumference
Spirometry	Up to three measures
Bone density†	Calcaneal ultrasound
Arterial stiffness¶	Pulse wave velocity
Eye examination§	Refractive index, intraocular pressure; acuity; retinal photograph; optical coherence tomography
Fitness test§	Cycle ergometry with electrocardiogram (ECG) heart rate monitoring

* assessed in 170,000 participants;

† assessed in 50,000 participants;

‡ measured in one heel for 170,000 participants and in both heels for 320,000 participants;

¶ measured in 170,000 participants;

§ measured in 100,000 participants

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variables available for health-related research, enabling potential research users to explore what data are available and plan research applications. An online access process, launched in April 2012, aims to be fair, transparent, and streamlined. Applications for data only are approved so long as the proposed research is in the public interest and the data required are, or will become, available. Applications involving the use of depletable samples or requiring participant re-

www.ukbiobank.ac.uk/scientists/ for details). UK Biobank encourages, but does not mandate, publication of results of research based on the resource in open access journals. Ensuring that the resource and its access arrangements are widely communicated is

Table 3. Current and planned future data available in the UK Biobank resource.

Data type	Number of participants	Details	Date of data acquisition	Date first available for research [‡]
Baseline assessment	Whole cohort	Questionnaire, physical measures, samples (see Table 2); haematological assays done on fresh blood samples	2006–2010	Q2 2012
Repeat of baseline assessment	20,000–25,000	As above every few years, to allow correction for regression dilution due to measurement error and within person fluctuations in exposure levels [12].	2013–	Q3 2013
Biochemical assays (of baseline samples)	Whole cohort	Biomarkers with known disease associations (e.g., lipids for vascular disease), diagnostic value (e.g., HbA _{1c} for diabetes), or ability to characterize phenotypes not otherwise well assessed (e.g., renal and liver function tests).	2014–2015	2015
Genotyping (of baseline samples)	Whole cohort	Dense genotyping chip with >800,000 markers including: approximately 250,000 SNPs in a whole-genome array; approximately 200,000 markers covering CNV, loss of function, insertions, deletions, and previously identified risk factor or disease associations; approximately 150,000 exome markers covering a high proportion of non-synonymous coding variants with allele frequency >0.02%.	2013–2015	2015
Dietary Web questionnaire	210,000	Automatically coded dietary recall questionnaire, providing estimates of nutrient intake. 80,000 respondents completed it ≥ three times.	2011–2012	Q2 2013
Other Web questionnaires	350,000 to be approached	Participants invited by email to provide additional information via Web questionnaires about exposures (e.g., occupation) and health outcomes (cognitive function, depression) that are not readily identified from health record linkages.	2014–	2015
Accelerometry	100,000	Wrist-worn tri-axial accelerometers record information on type, intensity, and duration of physical activity.	2013–2015	2015
Multimodal imaging	100,000	MRI brain, heart, and abdomen (for lipid distribution); ultrasound of carotid arteries; whole body DXA scan of bones and joints	Pilot phase: 2014–2015 Main phase: 2016–2019	2015
Health record linkage	Whole cohort			
Death registrations		ICD-coded cause specific mortality	2006–	Q2 2013
Cancer registrations		ICD-coded cancer diagnoses	1971–*	Q2 2013
Hospital inpatient episodes		ICD-coded diagnoses, OPCS-coded procedures	1997–*	Q4 2013
Hospital outpatient episodes		Limited ICD and OPCS coding	2003–*	2015
Primary care		Read-coded information including diagnoses, measurements, referrals, prescriptions	Variable	2015
Other		UK Biobank will obtain data from national mental health care, residential history, laboratory and disease audit datasets and is considering the value of further linkages (e.g., imaging, cancer screening, dental).	Variable	Not yet determined
Adjudicated health outcomes	Whole cohort	Expert-led confirmation and subclassification of outcomes in a range of disease areas, including cancer, diabetes, heart disease, stroke, mental health, musculoskeletal, respiratory, neurodegenerative, and ocular disorders.		2015

Hb: haemoglobin; SNPs: single nucleotide polymorphisms; CNV: copy number variations; MRI: magnetic resonance imaging; DXA: dual-energy X-ray absorptiometry; ICD: International Classification of Diseases; OPCS: Office of Population Censuses and Surveys Classification of Interventions and Procedures

[‡] Future dates are estimated. Data available may be all or part of the relevant dataset.

* available from an earlier date from health record systems in Scotland

an important task, requiring a dedicated communications team to manage UK Biobank's website, scientific meetings, and other methods for communication with the scientific community, including emails, newsletters, and other social media. In the first two years after the launch of open access to UK Biobank, over 1,000 researchers successfully registered, and over 200 applications were submitted (see www.ukbiobank.ac.uk/approved-research/ for a summary of research that is currently underway). Over 80% of registered researchers were from the UK and over 95% from academic rather than commercial institutions. Approximately 85% of applications

were for data only, with few as yet requesting use of samples or participant recontact.

UK Biobank has now started to receive notifications of submitted abstracts and manuscripts based on the first few completed research projects. UK Biobank reviews its access procedures regularly, revising them in the light of experience and user feedback to make the process as streamlined as possible while remaining consistent with participant consent.

Running UK Biobank

Success so far in developing and enhancing the resource has relied on public willingness to participate

in prospective research studies; close engagement with funders, government health departments, and the UK National Health Service; extensive consultation with the public, scientists, and a wide range of regulatory, legal, and ethics bodies; and the development of cost-effective and efficient methodological approaches. The most significant challenges to be overcome are the implementation of scientifically rigorous processes on a very large scale, sustaining the funding required to ensure the benefits of the resource are fully realised, obtaining approvals from multiple regulatory bodies in a frequently changing political and healthcare environment, and ensuring as wide as possible communication of the non-preferential, open access nature of the resource.

Interactions with Participants

Participant recruitment, retention, and engagement with enhancement projects has benefited from the willingness of very large numbers of British people to take part in observational research without the prospect of direct personal gain [15]. Participants spent an average of about two and a half hours at the recruitment visit. All gave broad consent to use of their anonymised data and samples for any health-related research, to be re-contacted for further substudies, and for UK Biobank to access their health-related records. Large subsets have subsequently completed Web-based questionnaires, agreed to wear a physical activity monitor, and repeated the entire baseline assessment. Of those who attended the first repeat assessment visit and provided feedback, 92% reported that they would be willing to travel for up to two hours for an imaging assessment visit lasting half a day. UK Biobank keeps its participants involved through providing progress updates via its website, with annual newsletters, and through its dedicated Participant Resource Centre (PRC), enabling them to continue to support the project and participate in research over the years ahead.

Interactions with Funding Bodies

Having established UK Biobank as a charitable company over a decade ago, the UK Medical Research Council and Wellcome Trust have provided the vast majority of its funding so far.

These major funders have had the long-term vision to continue to invest substantially in its ongoing development as a global research resource, coordinating both the scientific review of major proposals for developments to the resource and contributions from other funding bodies, including the Department of Health, Scottish and Welsh Governments, North West Development Agency, British Heart Foundation, and Diabetes UK. Long-term funding is not guaranteed, but depends on UK Biobank working

in close partnership with its funders towards the common goal of facilitating high-quality, cost-effective research that will improve the public's health. Crucial to this partnership is provision and joint discussion of regular updates on progress against challenging milestones, new strategic goals, scientific opportunities, financial plans, and use of the resource to generate new scientific knowledge.

Interactions with the UK's Publicly Funded National Health Service

Participant recruitment relied on invitations being mailed to 9 million people whose contact details were obtained from National Health Service (NHS) central registers. Large-scale epidemiological studies in the UK benefit from the fact that 98% of the population is registered with the NHS, which keeps detailed records on all of them from birth to death. Linkages to NHS datasets provide the principal means of follow-up for health-related outcomes.

Industrial Scale, Centralised Processes

A key step in achieving the cost-effective recruitment, characterisation, and follow-up of 500,000 participants was the creation of an executive and advisory team with complementary scientific and management skills and a coordinating centre dedicated to the generation of a resource for the scientific community. This facilitated the development of a centralised infrastructure, bespoke information technology (IT) systems, and industrial approaches to collection and processing of data and samples. For example, inviting potential participants via individual general-practice groupings (an approach used by smaller UK population-based studies) would have been impractical for a study of UK Biobank's scale, so appropriate approvals were obtained to allow direct mailing of invitations using contact details held centrally by the NHS. The recruitment process itself was coordinated centrally, with up to six assessment centres being active at any one time during the recruitment phase. Staffing and equipment needs were carefully configured to ensure the smooth flow of around 100 participants per day through each assessment centre for six days per week. Biological samples were also processed and handled centrally, requiring the development of bespoke laboratory information management and automated robotic systems to facilitate rapid, error-free sample storage in, and extraction from, the freezers (at rates of up to 1,500 samples per day) according to particular sample and participant characteristics [16]. Each step of the recruitment, assessment, and sample handling process was first piloted, modified as necessary and monitored centrally, using statistical methods to identify potential performance issues. Similar industrial-

scale, centralised processes have been or are being developed for the repeat assessment and imaging visits.

Governance Structure

UK Biobank's Board of Directors has overall responsibility for its direction and management. An Executive Management Team, with epidemiology, clinical, management, laboratory, legal, and communications expertise, oversees the development and day-to-day management of the resource and is responsible for the staff working on the study, most of them based at its coordinating centre near Manchester, with others at the Universities of Oxford, Edinburgh, Cardiff, and London. The executive team receives guidance from a Steering Committee of leading UK scientists, supported by specialist working groups advising on baseline data collection, enhanced phenotyping, follow-up and outcomes adjudication, and an international perspective is provided by an International Scientific Advisory Board (see [S1 Consent Form](#) and www.ukbiobank.ac.uk/governance/). This governance structure has facilitated effective working between scientific and management disciplines, allowing UK Biobank to respond to advice from a wide network of scientists on the most scientifically valuable design and development of the PLOS Medicine | DOI:10.1371/journal.pmed.1001779 March 31, 2015 7 / 10 resource, with project management and implementation being the responsibility of UK Biobank's Executive Management Team and dedicated staff.

Robust Ethics and Governance Framework

UK Biobank has consulted widely not only with the scientific community but also with the public, its participants, and other interested parties [17,18]. This has informed the development of its Ethics and Governance Framework, which lays out its principles and policies [19], as well as its access procedures [20]. UK Biobank's research ethics committee and Human Tissue Authority research tissue bank approvals mean that researchers wishing to use the resource do not need separate ethics approval (unless re-contact with participants is required). An independent Ethics and Governance Council oversees adherence to the Ethics and Governance Framework and provides advice on the interests of research participants and the general public in relation to UK Biobank.

In keeping with the informed consent given by its participants, UK Biobank does not generally provide feedback to individual participants about information derived from analyses of data or samples made following their assessment visits. Participants receive limited individual feedback in two areas. First, they

receive a summary of standard measures (e.g., blood pressure, body mass index) at the end of each assessment visit and are encouraged to seek medical advice for results outside the normal range. Second, potentially serious incidental findings (i.e., those likely to threaten life span or have a major impact on quality of life) observed by study staff during these assessments (e.g., possible melanoma on exposed areas of skin) are brought to the attention of participants with encouragement to contact a relevant health professional. Similar feedback is occurring in the imaging substudy, with participants and their general practitioners informed of potentially serious incidental findings noticed by radiographers and confirmed by formal radiologist review. In addition, the overall findings and implications of results that derive from research using the UK Biobank resource are made available to researchers, participants, and the wider community so that they can influence public health strategies.

Interactions with Regulatory Bodies

The wide consultation, rigorous Ethics and Governance Framework, and Ethics and Governance Council oversight role have been essential in paving the way for UK Biobank to accomplish obtaining the multiple ethical and regulatory approvals required for participant recruitment, sample and data storage, linkages to routine health care data, enhancement studies, and the provision of access to data and samples for approved researchers. Substantial amounts of time, resources, patience, tenacity, and evidence of feasibility and/or acceptability from smaller scale pilot studies have also been required to provide regulatory bodies with the reassurance that they need of UK Biobank's rigorous approach and commitment to protecting the interests of its participants within an acceptable legal and ethical framework.

Conclusions

The key lessons learned from establishing UK Biobank are that such large-scale studies require not only a clear scientific focus but also streamlined governance; effective working between academic and management disciplines; centralised infrastructure with industrial approaches to collection and processing of data and samples; close partnership with major funders; a wide network of scientific advisors; high-quality, pragmatic legal and ethical advice; and widespread public support [21]. The resource is now facilitating research by scientists from around the world who wish to investigate how different diseases are caused by the combination of lifestyle, environment, and genes, leading to improvements in prevention, diagnosis, and

treatment. Perhaps unsurprisingly, early use has been mainly, but not exclusively, by UK-based scientists. A major aim for the immediate future is to encourage applications from outside the UK. To facilitate this, UK Biobank is further developing its communications strategy to increase awareness of the resource and its access procedures worldwide.

Supporting Information

[S1 Consent Form.](#)

(PDF)

[S1 Text. UK Biobank Committees and Working Groups.](#)

(PDF)

Author Contributions

Wrote the first draft of the manuscript: CS JG NA GO RC. Contributed to the writing of the manuscript: CS JG NA VB PB JD PD PE JG ML BL PM GO JP AS AY TS TP RC. ICMJE criteria for authorship read and met: CS JG NA VB PB JD PD PE JG ML BL PM GO JP AS AY TS TP RC. Agree with manuscript results and conclusions: CS JG NA VB PB JD PD PE JG ML BL PM GO JP AS AY TS TP RC.

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Farewell to a Friend

In February we received the very sad news that Anne Örtegren from Sweden had passed away.

We considered Anne a dear friend - although we had never met Anne in person, one of the sad things we carry with us.

Yet we instinctively trusted and liked Anne from the very first time we communicated and counted her as a true friend.

When we look at the correspondence with Anne we can see it had started in 2007 - a year after we were formed as a charity.

In all the correspondence that we had with Anne one always admired the resilience, the articulate nature of her commenting, her strength of character, her dedication and her determination to continue to battle this disease, and her kindness in helping others and being there to make progress.

She was a rock – somebody whose opinion we valued and whose help and support we greatly appreciated - and she was generous with her support.

Anne's determination to help us and to encourage Swedish researchers to participate was a shining light for us.

Her help behind the scenes led to real collaborations between researchers who met at our Colloquiums. All of this despite the huge suffering that she endured for years.

Yet she rarely referred to this.

Anne was never one to promote herself or seek the limelight for the sake of it – a refreshing example in this age.

She was irreplaceable.

Her spirit was just an inspiration.

Though we knew Anne was suffering, and had been for such a long time, we were still communicating with her until very recently and had no knowledge of what was to transpire.

It is very difficult to read Anne's last post (below).

Not just because of the suffering and pain and hopelessness that she describes – but because Anne was so articulate in describing her situation – never with self-pity, always displaying the same courage that she showed in her life.

Her story and her life should be seen as an inspiration and she shames those who pretend to be interested in getting change for ME but who do nothing of consequence.

One loses a friend, one loses a part of oneself. Yet there are those who leave footprints in one's memory whom one will always remember.

Anne Örtegren is such a person.

Anne's facebook page is here
<https://www.facebook.com/anne.ortegren>

Extract from “Farewell – A Last Post from Anne Örtegren”

Nobody can say that I didn't put up enough of a fight. For 16 years I have battled increasingly severe ME/CFS. My condition has steadily deteriorated and new additional medical problems have regularly appeared, making it ever more difficult to endure and make it through the day (and night).

Throughout this time, I have invested almost every bit of my tiny energy in the fight for treatment for us ME/CFS patients. Severely ill, I have advocated from my bedroom for research and establishment of biomedical ME/CFS clinics to get us proper health care. All the while, I have worked hard to find something which would improve my own health. I have researched all possible treatment options, got in contact with international experts and methodically tried out every medication, supplement and regimen suggested. Sadly, for all the work done, we still don't have adequately sized specialized biomedical care for ME/CFS patients here in Stockholm, Sweden – or hardly anywhere on the planet.

We still don't have in-patient hospital units adapted to the needs of the severely ill ME/CFS patients. Funding levels for biomedical ME/CFS research remain ridiculously low in all countries and the erroneous psychosocial model which has caused me and others so much harm is still making headway.

And sadly, for me personally things have gone from bad to worse to unbearable.

I am now mostly bedbound and constantly tortured by ME/CFS symptoms. I also suffer greatly from a number of additional medical problems, the most severe being a systematic hyper-reactivity in the form of burning skin combined with an immunological/allergic reaction. This is triggered by so many things that it has become

impossible to create an adapted environment. Some of you have followed my struggle to find clothes and bed linen I can tolerate.

Lately, I am simply running out. I no longer have clothes I can wear without my skin “burning up” and my body going into an allergic state.

This means I no longer see a way out from this solitary ME/CFS prison and its constant torture. I can no longer even do damage control, and my body is at the end of its rope. Therefore, I have gone through a long and thorough process involving several medical assessments to be able to choose a peaceful way out: I have received a preliminary green light for accompanied suicide through a clinic in Switzerland.

When you read this I am at rest, free from suffering at last. I have written this post to explain why I had to take this drastic step. Many ME/CFS patients have found it necessary to make the same decision, and I want to speak up for us, as I think my reasons may be similar to those of many others with the same sad destiny. These reasons can be summed up in three headers: unbearable suffering; no realistic way out of the suffering; and the lack of a safety net, meaning potential colossal increase in suffering when the next setback or medical incident occurs.

Important note

Before I write more about these reasons, I want to stress something important. As for most other ME/CFS patients who have chosen suicide, depression is not the cause of my choice. Though I have been suffering massively for many years, I am not depressed. I still have all my will and my motivation. I still laugh and see the funny side of things, I still enjoy doing whatever small activities I can manage. I am still hugely interested in the world around me – my loved ones and all that goes on in their lives, the society, the world (what is happening in human rights issues? how can we solve the climate change crisis?) During these 16 years, I have never felt any lack of motivation. On the contrary, I have consistently fought for solutions with the goal to get myself better and help all ME/CFS patients get better. There are so many things I want to do, I have a lot to live for. If I could only regain some functioning, quieten down the torture a bit and be able to tolerate clothes and a normal environment, I have such a long list of things I would love to do with my life!

Three main reasons

So depression is not the reason for my decision to terminate my life. The reasons are the following:

1. Unbearable suffering

Many of us severely ill ME/CFS patients are hovering at the border of unbearable suffering. We are constantly

plagued by intense symptoms, we endure high-impact every-minute physical suffering 24 hours a day, year after year. I see it as a prison sentence with torture. I am homebound and mostly bedbound – there is the prison. I constantly suffer from excruciating symptoms: The worst flu you ever had. Sore throat, bronchi hurting with every breath. Complete exhaustion, almost zero energy, a body that weighs a tonne and sometimes won't even move. Muscle weakness, dizziness, great difficulties standing up. Sensory overload causing severe suffering from the brain and nervous system. Massive pain in muscles, painful inflammations in muscle attachments. Intensely burning skin. A feeling of having been run over by a bus, twice, with every cell screaming. This has got to be called torture.

It would be easier to handle if there were breaks, breathing spaces. But with severe ME/CFS there is no minute during the day when one is comfortable. My body is a war zone with constant firing attacks. There is no rest, no respite. Every move of every day is a mountain-climb. Every night is a challenge, since there is no easy sleep to rescue me from the torture. I always just have to try to get through the night. And then get through the next day. It would also be easier if there were distractions. Like many patients with severe ME/CFS I am unable to listen to music, radio, podcasts or audio books, or to watch TV. I can only read for short bouts of time, and use the computer for even shorter moments. I am too ill to manage more than rare visits or phone calls from my family and friends, and sadly unable to live with someone.

This solitary confinement aspect of ME/CFS is devastating and it is understandable that ME/CFS has been described as the "living death disease". For me personally, the situation has turned into an emergency not least due to my horrific symptom of burning skin linked to immunological/allergic reactions. This appeared six years into my ME/CFS, when I was struck by what seemed like a complete collapse of the bodily systems controlling immune system, allergic pathways, temperature control, skin and peripheral nerves. I had long had trouble with urticaria,



hyperreactive skin and allergies, but at this point a violent reaction occurred and my skin completely lost tolerance. I started having massively burning skin, severe urticaria and constant cold sweats and shivers (these reactions reminded me of the first stages of the anaphylactic shock I once had, then due to heat allergy). Since then, for ten long years, my skin has been burning. It is an intense pain. I have been unable to tolerate almost all kinds of clothes and bed linen as well as heat, sun, chemicals and other everyday things. These all trigger the burning skin and the freezing/shivering reaction into a state of extreme pain and suffering. Imagine being badly sunburnt and then being forced to live under a constant scalding sun – no relief in sight.

At first I managed to find a certain textile fabric which I could tolerate, but then this went out of production, and in spite of years of negotiations with the textile industry it has, strangely, proven impossible to recreate that specific weave. This has meant that as my clothes have been wearing out, I have been approaching the point where I will no longer have clothes and bed linen that are tolerable to my skin. It has also become increasingly difficult to adapt the rest of my living environment so as to not trigger the reaction and worsen the symptoms.

Now that I am running out of clothes and sheets, ahead of me has lain a situation with constant burning skin and an allergic state of shivering/cold sweats and massive suffering. This would have been absolutely unbearable. For 16 years I have had to manage an ever-increasing load of suffering and problems. They now add up to a situation which is simply no longer sustainable.

2. No realistic way out of the suffering

A very important factor is the lack of realistic hope for relief in the future. It is possible for a person to bear a lot of suffering, as long as it is time-limited. But the combination of massive suffering and a lack of rational hope for remission or recovery is devastating. Think about the temporary agony of a violent case of gastric flu. Picture how you are feeling those horrible days when you are lying on the bathroom floor between attacks of diarrhoea and vomiting. This is something we



all have to live through at times, but we know it will be over in a few days. If someone told you at that point: “you will have to live with this for the rest of your life”, I am sure you would agree that it wouldn’t feel feasible. It is unimaginable to cope with a whole life with the body

in that insufferable state every day, year after year. The level of unbearableness in severe ME/CFS is the same. If we knew there were relief on the horizon, it would be possible to endure severe ME/CFS and all the additional medical problems, even for a long time, I think. The point is that there has to be a limit, the suffering must not feel endless.

One vital aspect here is of course that patients need to feel that the ME/CFS field is being taken forward. Sadly, we haven’t been granted this feeling – see my previous blogs relating to this here and here.

Another imperative issue is the drug intolerance that I and many others with ME/CFS suffer from. I have tried every possible treatment, but most of them have just given me side-effects, many of which have been irreversible. My stomach has become increasingly dysfunctional, so for the past few years any new drugs have caused immediate diarrhoea. One supplement triggered massive inflammation in my entire urinary tract, which has since persisted. The list of such occurrences of major deterioration caused by different drugs/treatments is long, and with time my reactions have become increasingly violent. I now have to conclude that my sensitivity to medication is so severe that realistically it is very hard for me to tolerate drugs or supplements.

This has two crucial meanings for many of us severely ill ME/CFS patients: There is no way of relieving our symptoms. And even if treatments appear in the future, with our sensitivity of medication any drug will carry a great risk of irreversible side-effects producing even more suffering. This means that even in the case of a real effort finally being made to bring biomedical research into ME/CFS up to levels on par with that of other diseases, and possible treatments being made accessible, for some of us it is unlikely that we would be able to benefit. Considering our extreme sensitivity to

medication, one could say it’s hard to have realistic hope of recovery or relief for us.

In the past couple of years I, being desperate, have challenged the massive side-effect risk and tried one of the treatments being researched in regards to ME/CFS. But I received it late in the disease process, and it was a gamble. I needed it to have an almost miraculous effect: a quick positive response which eliminated many symptoms – most of all I needed it to stop my skin from burning and reacting, so I could tolerate the clothes and bed linen produced today. I have been quickly running out of clothes and sheets, so I was gambling with high odds for a quick and extensive response. Sadly, I wasn’t a responder. I have also tried medication for Mast Cell Activation Disorder and a low-histamine diet, but my burning skin hasn’t abated. Since I am now running out of clothes and sheets, all that was before me was constant burning hell.

3. The lack of a safety net, meaning potential colossal increase in suffering when the next setback or medical incident occurs

The third factor is the insight that the risk for further deterioration and increased suffering is high. Many of us severely ill ME/CFS patients are already in a situation which is unbearable. On top of this, it is very likely that in the future things will get even worse. If we look at some of our symptoms in isolation, examples in my case could be my back and neck pain, we would need to strengthen muscles to prevent them from getting worse. But for all ME/CFS patients, the characteristic symptom of Post-Exertional Malaise (PEM) with flare-ups of our disease when we attempt even small activities, is hugely problematic. Whenever we try to ignore the PEM issue and push through, we immediately crash and become much sicker. We might go from being able to at least get up and eat, to being completely bedbound, until the PEM has subsided. Sometimes, it doesn’t subside, and we find ourselves irreversibly deteriorated, at a new, even lower baseline level, with no way of improving.

PEM is not something that you can work around. For me, new medical complications also continue to arise, and I have no way of amending them. I already need surgery for one existing problem, and it is likely that it will be needed for other issues in the future, but surgery or hospital care is not feasible for several reasons:

One is that my body seems to lack repairing mechanisms. Previous biopsies have not healed properly, so my doctor is doubtful about my ability to recover after surgery.

Another, more general and hugely critical, is that with severe ME/CFS it is impossible to tolerate normal hospital care. For ME/CFS patients the sensory overload

problem and the extremely low energy levels mean that a normal hospital environment causes major deterioration. The sensory input that comes with shared rooms, people coming and going, bright lights, noise, etc, escalates our disease. We are already in such fragile states that a push in the wrong direction is catastrophic. For me, with my burning skin issue, there is also the issue of not tolerating the mattresses, pillows, textile fabrics, etc used in a hospital.

Just imagine the effects of a hospital stay for me: It would trigger my already severe ME/CFS into new depths – likely I would become completely bedbound and unable to tolerate any light or noise. The skin hyperreactivity would, within a few hours, trigger my body into an insufferable state of burning skin and agonizing immuneallergic reactions, which would then be impossible to reverse. My family, my doctor and I agree: I must never be admitted to a hospital, since there is no end to how much worse that would make me.

Many ME/CFS patients have experienced irreversible deterioration due to hospitalization. We also know that the understanding of ME/CFS is extremely low or non-existent in most hospitals, and we hear about ME/CFS patients being forced into environments or activities which make them much worse. I am aware of only two places in the world with specially adjusted hospital units for severe ME/CFS, Oslo, Norway, and Gold Coast, Australia. We would need such units in every city around the globe.

It is extreme to be this severely ill, have so many medical complications arise continually and know this: There is no feasible access to hospital care for me. There are no tolerable medications to use when things get worse or other medical problems set in. As a severely ill ME/CFS patient I have no safety net at all. There is simply no end to how bad things can get with severe ME/CFS.

Coping skills – important but not enough

I realize that when people hear about my decision to terminate my life, they will wonder about my coping skills. I have written about this before and I want to mention the issue here too:

While it was extremely hard at the beginning to accept chronic illness, I have over the years developed a large degree of acceptance and pretty good coping skills. I have learnt to accept tight limits and appreciate small qualities of life. I have learnt to cope with massive amounts of pain and suffering and still find bright spots. With the level of acceptance I have come to now, I would have been content even with relatively small improvements and a very limited life. If, hypothetically,

the physical suffering could be taken out of the equation, I would have been able to live contentedly even though my life continued to be restricted to my small apartment and include very little activity. Unlike most people I could find such a tiny life bearable and even happy. But I am not able to cope with these high levels of constant physical suffering.

In short, to sum up my level of acceptance as well as my limit: I can take the prison and the extreme limitations – but I can no longer take the torture. And I cannot live with clothes that constantly trigger my burning skin.

Not alone – and not a rash decision

In spite of being unable to see friends or family for more than rare and brief visits, and in spite of having limited capacity for phone conversations, I still have a circle of loved ones. My friends and family all understand my current situation and they accept and support my choice. While they do not want me to leave, they also do not want me to suffer anymore.

This is not a rash decision. It has been processed for many years, in my head, in conversations with family and friends, in discussion with one of my doctors, and a few years ago in the long procedure of requesting accompanied suicide. The clinic in Switzerland requires an extensive process to ensure that the patient is chronically ill, lives with unendurable pain or suffering, and has no realistic hope of relief. They require a number of medical records as well as consultations with specialized doctors.

For me, and I believe for many other ME/CFS patients, this end is obviously not what we wanted, but it was the best solution to an extremely difficult situation and preferable to even more suffering. It was not hasty choice, but one that matured over a long period of time.

A plea to decision makers – Give ME/CFS patients a future!

As you understand, this blog post has taken me many months to put together. It is a long text to read too, I know. But I felt it was important to write it and have it published to explain why I personally had to take this step, and hopefully illuminate why so many ME/CFS patients consider or commit suicide.

And most importantly: to elucidate that this circumstance can be changed! But that will take devoted, resolute, real action from all of those responsible for the state of ME/CFS care, ME/CFS research and dissemination of information about the disease. Sadly, this responsibility has been mishandled for decades. To allow ME/CFS patients some hope on the horizon, key people in all countries must step up and act.

If you are a decision maker, here is what you urgently need to do:

You need to bring funding for biomedical ME/CFS research up so it's on par with comparable diseases (as an example, in the US that would mean \$188 million per year).

You need to make sure there are dedicated hospital care units for ME/CFS inpatients in every city around the world.

You need to establish specialist biomedical care available to all ME/CFS patients; it should be as natural as RA patients having access to a rheumatologist or cancer patients to an oncologist.

You need to give ME/CFS patients a future.

Anne ended her letter with –

Take care of each other.
Love, Anne

Anne's Swedish ME/CFS newsletters, distributed via e-mail to 2700 physicians, researchers, CMOs, politicians and medical journalists
<https://mecfsnyheter.se/>



To Prime Minister Erna Solberg and any other relevant recipients An Appeal for help to a seriously ill child

My name is Nicoline and I will soon be 14 years old. The last half year I have been too ill to go to school. For 2 years before this I was often sick with many infections. I really like school and I am what one would probably call a conscientious pupil. For me it has been awful not to be able to go to school. This is my first year in secondary school and I had really looked forward to beginning to get marks.

My plan is to study law in the future. Luckily I have had extremely good help from PPT (Norwegian educational psychology service) and the school. I have received a robot that makes it possible for me to take part in lessons at school when I am able to. I also have home tuition up to two hours a week. This has



meant that I have managed to keep up with the most important subjects and this means a lot to me. The reason I am writing is that, unfortunately, I have met with a part of the system designed to help which does not function at all. I suffer from exhaustion and many other awful symptoms which mean that I am bed bound and isolated at home. I am mostly too ill to meet

any friends and rarely manage to talk on the phone. My mother and many close family members have ME and we are afraid that I have inherited the disease.

A little over a week ago I met my doctor at the paediatric clinic. It was an ugly experience for me. The doctor we met would not allow me or my parents to explain my situation and my symptoms. They only talked about psychiatry and how I should be «forced back to life». It was clear that they did not believe in me being physically ill. They did not want to hear about my symptoms because they did not want to «encourage me to be sick». They were totally against the school robot and home tuition because there are local children sick with cancer who do not receive such help.

I think that is very wrong because I think it is equally bad for me to be too sick to go to school as it is for other sick children independent of the diagnosis. I am very confident in that I do not have a psychological problem. The PPT have also tested me quite thoroughly since last October and they confirm that there is nothing pointing to school refusal or my having something psychologically wrong. Despite this the doctor had decided even before seeing me that I was mentally sick.

So I think that it is very hurtful and bad when a doctor «makes it sound like» I am missing school for the rest of my life because I myself want to, and things will sort themselves out if only I push myself a bit.

If the doctors had listened to me they would have known that I had pushed myself for two years until I collapsed. Just a month ago I was so sick that I just slept for many weeks. My mother had to wake me up regularly to get me to eat and drink. Luckily my mother has a lot of knowledge about exhaustion and I am a little bit better now even though I am still bed bound.

I am fearful of going back to see this doctor. My next appointment is in a month's time. My mother has explored possibilities of getting a referral elsewhere but it looks like children with exhaustion are treated in the same manner in most hospitals in the country. I think this is dreadful.

When one gets sick as I did then it should be obvious to be met in a positive manner whilst in hospital. At least it

should clearly be so that one is not disbelieved the moment one meets the doctor.

I choose to give the doctor the benefit of the doubt and I think they would have treated me in a different manner had they had more knowledge. There is after all no doubt any longer that ME is a physical illness. Nevertheless, children with exhaustion, when there is a reason to suspect ME, are being treated as mentally ill. It is like rubbing salt in the wounds of children and their families who have it bad enough as it is.

In my case the doctor has already, after the first appointment, gone as far as phoning my case officer at PPT and asked them to force me back to school. That will most probably make me even sicker. To become sicker does not only mean that I will be more exhausted.

It also makes all of the other symptoms worse, such as extreme pain all over the body, nose bleeds, nausea, head ache, flu like feeling, sore throat, dizziness and much more. If it turns out that the symptoms were due to ME, as we suspect, then the chances of getting better will be reduced. It means that if I get pushed into using too much energy now then it may lead to my chances of never getting better or healthy - this is frightening when one is only 13 years old and has numerous plans for one's life.

I therefore think it is strange that the doctor will do this, long before I have a diagnosis – as the doctor is taking a huge risk on my behalf.

I have been frightened ever since I came home from the hospital. I am worried that I shall miss all lessons at school now as I am not allowed to receive home tuition or use the school robot.

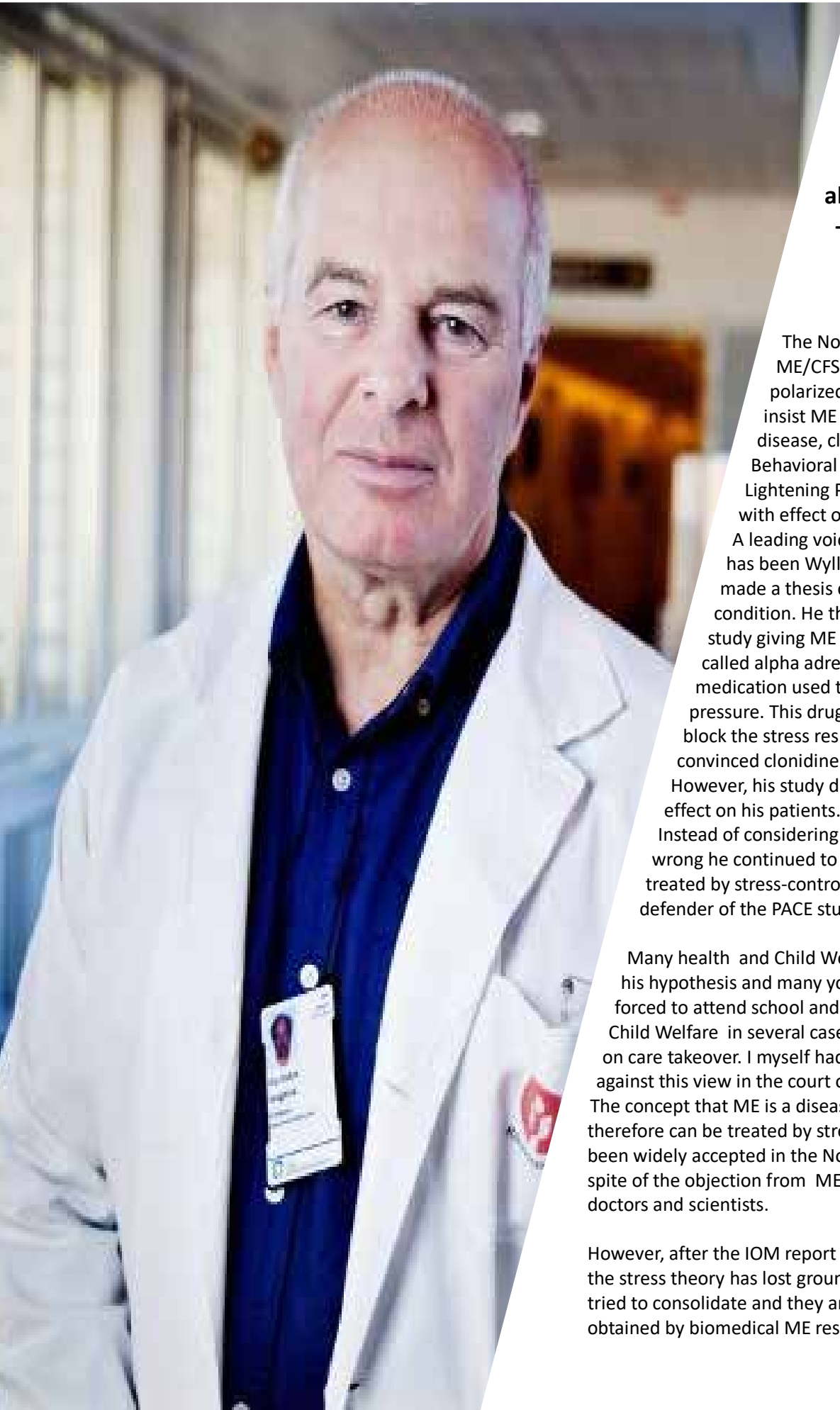
I am also terribly scared of getting sicker than I am already, especially now that I have finally had some improvement.

I know that you have previously engaged with ME patients. I think that is wonderful. Unfortunately, the situation for us children being investigated for ME and children who already have the diagnosis is critical – there is no expertise and no help available. It is urgent to improve our situation.

I therefore ask you to address this so that we can get help soon. I am happy to contribute if there are any questions.

With kind regards,
Nicoline





Ola Didrik Saugstad

A harsh debate about ME in Norway – A personal view from one of the participants

The Norwegian debate on ME/CFS has for many years been polarized between those who insist ME is a psychosomatic disease, claiming Cognitive Behavioral therapy (CBT) and Lightening Process (LP) are therapies with effect on this condition.

A leading voice supporting this view has been Wyller, a paediatrician who made a thesis concluding ME is a stress condition. He therefore performed a study giving ME patients clonidine, a so-called alpha adrenergic agonist which is a medication used to treat high blood pressure. This drug theoretically could block the stress response and Wyller was convinced clonidine would cure ME patients. However, his study did not show any positive effect on his patients.

Instead of considering his hypothesis might be wrong he continued to preach ME could be treated by stress-control and he was a firm defender of the PACE study.

Many health and Child Welfare workers believed in his hypothesis and many young ME patients were forced to attend school and other activities, and the Child Welfare in several cases requested court orders on care takeover. I myself had to appear as a witness against this view in the court on several occasions. The concept that ME is a disease caused by stress and therefore can be treated by stress control, has therefore been widely accepted in the Norwegian community, in spite of the objection from ME organisations and a few doctors and scientists.

However, after the IOM report was published in 2015 the stress theory has lost ground and its defenders have tried to consolidate and they argue against results obtained by biomedical ME research.

In September 2017 a new public ME debate was kicked off in Norway's largest newspaper, Aftenposten. During the years there have been many discussions and articles about ME in Norwegian media. However, this time it was different. The debate became intense, lasted for several weeks and was flavoured with the most hatred personal attacks on those who referred to recent biomedical research and were advocating the view that ME is a somatic disease.

It all started when a new group of 71 persons called "Recovery Norway" wrote an article with the message: "we know how to be cured of ME. Listen to our message". The network consisted of previous patients or relatives, and some health personnel who recommend CBT and LP to cure ME. By mind control ME patients are able to control their disease the Norwegian public was told by this group. Not only ME could be cured by such mental exercise, a number of other diffuse conditions as fatigue, pain and tinnitus should be treated with these alternative methods. Why doesn't anyone listen to us and why do so many doubt we previously have had ME and are now cured? the group asked rhetorically.

Four days later September 22nd I wrote as a response with the title: Listen to the ME patients:

"In Aftenposten September 18th there is an interesting article by a group of former ME patients who are now recovered. Why not take advantage of their experience using untraditional and alternative therapies such as LP and CBT? It is unfortunate that the group feel they are disbelieved both regarding their previous ME diagnosis and that they today are cured. We are grateful for every patient who have been healed and obliged to try to learn from their experience and what made their improvement."

I continued:

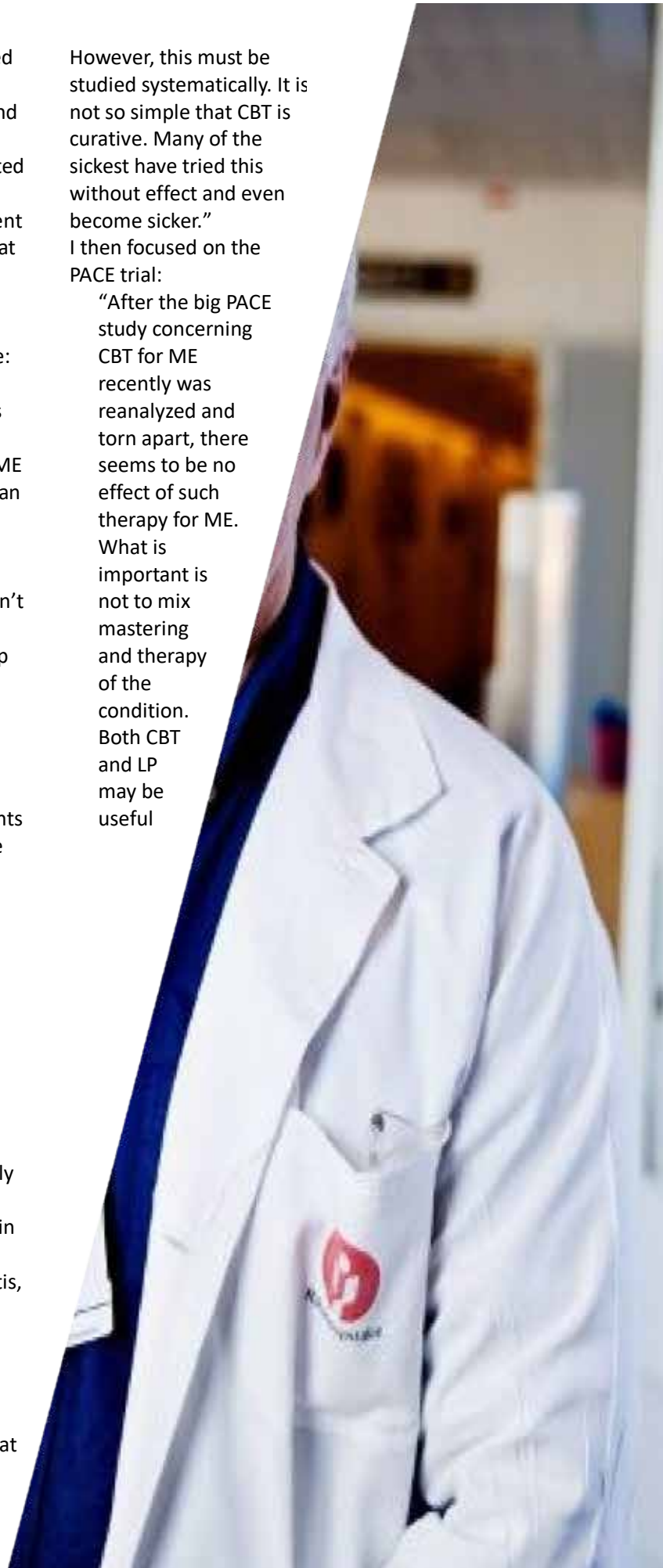
"When we discuss ME it is, however, important to know that ME follows phases. Persons who previously were very active and healthy may quickly deteriorate. I have myself the last 10 years or so visited many of the sickest ME patients in Norway in their homes and probably seen more than most. Many have a condition compatible with encephalitis, and this is exactly what modern research seems to reveal.

ME is an inflammatory condition affecting several organs, also the brain. The immune system is activated. Some patients improve spontaneously while others are bedridden through years with great pain. This is where those who claim to have improved from ME may contribute with valuable information.

However, this must be studied systematically. It is not so simple that CBT is curative. Many of the sickest have tried this without effect and even become sicker."

I then focused on the PACE trial:

"After the big PACE study concerning CBT for ME recently was reanalyzed and torn apart, there seems to be no effect of such therapy for ME. What is important is not to mix mastering and therapy of the condition. Both CBT and LP may be useful



techniques to master challenging life conditions and diseases without curing these.

The authors (Recovery Norway) are wrong and not up to date when they write: "The debate regarding these problems is often about whether the disease is physical or psychosomatic. Lack of knowledge dominates this field."

After the report about ME from Institute of Medicine (IOM) in USA was published in 2015, there has been a paradigmatic change in the view regarding ME. It was concluded that ME is a serious physical, chronic and complex multisystem disease which is strongly debilitating and the misconception that the disease is psychogenic or a form of somatization must stop."

I then referred to a recent study (2016) from the USA with Maureen Hanson as senior author:

"In one study from the Cornell University in the USA the researchers were able to identify biochemical and biological deviations in ME patients, which resulted in the following statement:

"Furthermore, our detection of a biological abnormality provides further evidence against the ridiculous concept that the disease is psychological in origin." (quote by Maureen Hanson in Medical News Today, Tuesday 28 June 2016).

I continued:

"It is the supporters of the concept that ME is psychogenic who maintain to underline the lack of knowledge regarding ME. I agree with the Norwegian Research Council which supports biomedical ME research in line with the US effort to find treatment for the disease. Psychosomatic research has not brought us closer to understanding of ME and may have contributed to a prevention of development through years."

I did not, however want to disregard the Recovery Norway group and therefore added:

"I belong to those who welcome the initiative of the group. It is useful to obtain information on why some were cured and others not. At the same time the group's credibility is weakened by lumping together several poorly explained conditions such as fatigue, pain and tinnitus. One problem for ME patients has been that the health care system has not listened to the sickest, nor even cared to examine them. We must listen to the advice both from those who have improved and from those who still have not".

This article from me resulted in an outcry from those who supported the concept of ME as a psychogenic disease. Two neurologists from the University Hospital

in Bergen, one even a professor, wrote that I was misusing my professor title." Saugstad is exploiting his medical authority to oppress patients who have been cured and want to share their experience." These two neurologists told us they had treated ME patients for years and never or at least only very rarely, seen any trace of inflammation in the central nervous system. I replied by referring to Mady Hornig and co-worker's recent article (2017) showing ME patients have an immune signature in Cerebrospinal fluid reflecting the central nervous system and the study of Nakatomi Y et al (2014) indicating ME patients have activated immune-cells in the brain. I also quoted Harvard Professor Komaroff who commented that if these findings were reproduced it indicates that ME patients have a low graded inflammation in the brain. A Norwegian professor of immunology confirmed that my comments were relevant. The two neurologists never replied. Wyller wrote a commentary: "Saugstad's claims are misleading. That the immune-system is activated in ME does not mean ME is an inflammatory process. The immune-system is also activated in depressions, social stress and loneliness. Does Saugstad mean these are inflammatory conditions as well?".

Wyller is a firm supporter of the PACE study and wrote: "The PACE study showed that CBT has positive effect on ME. The study has been criticized but the main conclusion has not been disproven. Another recent study shows equivalent good effect of LP. That mental conditions may contribute to ME is documented well for instance by MRI pictures of the brain. This does not mean that the disease is psychogenic, but that the mechanisms are complex and both mental and somatic factors may play a role."

And Wyller continued: "Professor Saugstad introduces himself as an ME expert but has never carried out ME research himself. He is stuck in an old fashioned distinction between "body and mind" and is followed by a small but vocal group of ME patients who are fighting frantically against the concept that "the mind" has anything to do with this matter." Wyller concluded his article: "I beg new patients, relatives, health workers – don't listen to this pessimistic outdated message! Instead listen to the majority of patients - many have been completely cured – who make use of modern and documented therapies."

At this stage of the debate a number of doctors, ME patients and relatives had contributed to the debate with their own opinions and experiences. Wyller did not receive much support.

In my reply I underlined I have never pretended to be an ME expert. But I wondered why some people became so emotional because I mentioned recent publications in

the field. Nobody dared to attack the IOM report, instead they attacked me, a “messenger” informing the public about this ground breaking report. I was worried of the fact that those who went against me seemed to be frightened of new data and not willing to discuss recent international research results. I argued that the PACE study had not shown significant improvement for CBT and the recent Smile study concerning LP had profound weaknesses, only 30% of the eligible patients were enrolled in the study and the sickest ME patients had not been included.

I also wrote I was surprised that Wyller characterized ME patients as a small and vocal group. After all, the Norwegian ME association has 4000 members and few of these support Wyller.

“Fortunately it is rare for such disrespect from a doctor for the patients he is supposed to care for is uttered so clearly”, I wrote.

Further, I wondered how Wyller could characterize international research in the field as old-fashioned and outdated.

“Perhaps these new findings are threatening to his psychosomatic position Wyller is basing his academic career, a paradigm which is quickly losing ground? However, for the ME patients this development gives hope for the future” was my conclusion.

Wyller’s next move came a few days later:

“False information about ME may scare patients from documented treatment”.

His article illustrated his views. I therefore refer extensively to parts of it:

“Saugstad is a highly recognized researcher in neonatal medicine. It is therefore surprising that he, in the ME debate, breaks several rules for scientific reasoning and dissemination. That inflammation detected in the central nervous system of ME patients does not prove that inflammation is the cause of fatigue. To illustrate this point from another area: That patients with lung cancer often have yellow fingers does not implicate that yellow fingers are causing cancer (both yellow fingers and cancer may be caused by smoking).

Saugstad has not published his research findings. Saugstad writes that he has in the last years built up a strong research group on ME. Why have the findings not yet been published? Wyller then continued to inform that he had published 25 research articles in the field with a holistic approach to the complex disease that ME is. He then indicated I am biased due to having a close relative with ME. Two Norwegian professors of medicine gave me their support against his emotional

attack. In his next reply he continued to attack these two.

As mentioned Wyller is a firm defender of the PACE study and when the results from the SMILE study came he embraced these results – he had for years supported LP and CBT for ME. Why not try them - they do not have any adverse effects, he suggested. I replied this is wrong. “Several ME patients report adverse effects of these two regimes. The major distinction in the understanding of ME is perhaps between those who understand this and those who do not”. Recovery Norway also attacked me claiming that I told ME patients they have an inflammation in the brain. This is definitely wrong I replied, I never diagnose ME patients I only refer to the scientific literature when I am asked. In my final statement I informed that unfortunately Recovery Norway had “forgotten” to disclose that several of their members were heavily involved financially in LP as LP instructors.

This debate probably represents a watershed in the Norwegian ME debate and understanding. The psychosomatic ME wing had previously given the impression that they often are harassed by aggressive patients and relatives. They have also spread the information that those who support biomedical findings are afraid of new results. The debate demonstrated that the opposite is the case. The psychosomatic lobby’s reaction to new biomedical information was by resorting to personal and emotional attacks on us who had a different view. Their disrespect for the patients they are supposed to serve shocked many of the neutral bystanders.

The debate was probably initiated due to the psychosomatic wing rapidly losing ground after the publication of the IOM report, the new emphasis on biomedical ME research by NIH and also the Norwegian Research Council, the CDC’s change in attitude to CBT, and the reanalysis of the PACE study showing minimal if any effect of CBT. Several of the psychosomatic supporters had invested their prestige and based their whole career on findings that supported their view. I understand it must be painful to see how the basis of their theory quickly eroded. This also explains their uncritical embrace of the Smile study.

During the debate which lasted many weeks I received overwhelming support from more than 1000 persons in the newspaper and on social media.

Ola Didrik Saugstad, MD, PhD, FRCPE
Professor (em) of Pediatrics
University of Oslo

Letter from America

Trial By Error: A Q-and-A with Leonard Jason, on Case Definition

<http://www.virology.ws/2018/05/02/trial-by-error-a-q-and-a-with-leonard-jason-on-case-definition/>

MAY 2018

By David Tuller, DrPH

A Brief Update: Berkeley's crowdfunding period closed on April 30th—Monday night. I ended the campaign with \$87,580. After Berkeley's 7.5% in fees, the funds will cover my salary/benefit from July 1, 2018 to June 30, 2019, and some travel costs. I really, really appreciate the fantastic support. Thanks to everyone! I've taken a few days to regroup from my Australia trip and catch up on my time zones.

Leonard Jason is a professor of psychology at DePaul University in Chicago. He has served as vice president of the International American Association of CFS/ME and as chairperson of the Research Subcommittee of the U.S. Chronic Fatigue Syndrome Advisory Committee. Professor Jason began investigating chronic fatigue syndrome almost 30 years ago. Much of his work has focused on the epidemiology and prevalence of the illness and on the impact of using various case definitions. He has long been concerned that the lack of a uniform set of criteria for identifying study participants has hindered progress in the science. Dr. Jason recently shared his thoughts about these issues. (This Q-and-A has been edited for clarity and length.)



How common is fatigue?

If you were to ask people right now if they are "fatigued," which means feeling weak, tired, or lacking energy, about 25% of the population would say yes, so this symptom is very common. In contrast, "chronic fatigue" means that a person has had fatigue for 6 or

more months. Only about 4-5% of the population has chronic fatigue.

There are multiple reasons for people to be fatigued—for example depression, anxiety, over-exertion, people working three jobs, medications, sleep deprivation, weight problems, poor diet, inactivity, and deconditioning. These are just a few of the many causes of fatigue and chronic fatigue.

Physicians see lots of people coming into their practices, where the patients are seeking help for their fatigue, and in fact it is one of the most common reasons for seeing a doctor. But it's very hard for many physicians to differentiate complaints of general or chronic fatigue versus the illness known as ME [myalgic encephalomyelitis]. Yet it is of critical importance to make a differential diagnosis between those with purely chronic fatigue versus those who have ME. In fact, it is this failure to differentiate these two conditions that has caused so many problems, and the culprit is a flawed and imprecise case definitions as well as failures to gain an international consensus for one research case definition.

So what is a case definition, and why are there different research and clinical definitions?

A case definition is a set of rules that helps a researcher or a clinician make a decision about whether someone has a particular illness or does not have the illness. It's that simple. A good case definition is critical for the assessment process, to identify those people who actually have an illness or disease. It is the cornerstone of medicine.

A research case definition tries to identify a homogeneous group of people who have the illness and can be recruited for research purposes. In contrast, a clinical case definition is used to identify or diagnose a broader group of patients for treatment purposes, and many of these wouldn't qualify for research studies. For

example, if someone is very obese, a research case definition might exclude that person because the weight issue could be causing the person's problems. In other words, for research purposes, we want to select only patients who do not have other psychological or medical conditions that could be causing the illness we are studying.

For science to progress, the research case definition is critical, as it can standardize the selection of patient samples so that research groups around the world are all studying the patients with the same disease. So gaining consensus among international scientists for a research case definition is a most critical task, and one that unfortunately has still not been accomplished for our field.

One of the parameters that's important for a research case definition for this illness, in your view, is that psychiatric co-morbidities should be excluded. Can you explain the reason for that?

Yes, and let me give an example that illustrates this issue. A patient with a major depressive disorder with melancholic features would probably have fatigue, aches and pains, as well as sleep and cognitive problems. Yet these are also symptoms of ME, so some clinicians and researchers could easily confuse these two conditions. But they are very different illnesses, as people with a major depressive disorder feel self-reproach, whereas those with ME do not. If you ask people with a major depressive disorder what they would do tomorrow if they were well, they would not be sure. In contrast, if you asked people with ME what they would do if they were well, they'd give you a long list of all the things they have wanted to do but been unable due to their illness.

If you are studying ME, you need to exclude people who have a primary psychiatric disorder from your study. If researchers misclassify people with a major depressive disorder as having ME, this will have serious negative consequences for identifying biomarkers, estimating prevalence rates, and determining outcomes of treatment trials. The issue of selecting patients who really have ME is the most important issue facing our field. In a sense, the lack of a consensus on a ME research case definition is like building a pyramid of playing cards with a very shaky bottom, and then everything built on top of this foundation is vulnerable to collapsing.

Let's start with what is the broadest case definition that has been used, the so-called Oxford criteria for

CFS. Can you describe that and explain why it presents a problem?

If you have six or more months of fatigue, then you meet this case definition, so it's a very broad category. Clearly, as I mentioned earlier, a lot of people who meet this criteria have medical or lifestyle reasons causing their fatigue. One of my students, Madison Sunnquist, just published her master's thesis that indicated how the CBT theoretical model only works if you identify people with a very wide case definition, but when you have a better and more restricted case definition that requires core symptoms of ME, then the CBT model no longer works. In contrast to the CBT approach, my research group for the past 20 years has been doing research on what we call the energy envelope. But this pacing approach is not a cure, just a strategy to help better cope with ME. Our approach involves helping patients to better monitor their energy levels, learn how to stay within their energy envelope, and sustain lifestyle changes that involve reprioritizing activities.

So how did the CDC come up with the Holmes and then the Fukuda case definitions?

The Holmes case definition came out in 1988. The CDC investigators had gone to Incline Village and ultimately named this illness CFS. Their first case definition included too many symptoms. In fact, to meet their case definition, a patient would have needed to have eight or more symptoms out of a list of 11. But here is the problem that soon emerged—if you develop a case definition that requires so many unexplained somatic symptoms, you have a very high probability of unwittingly selecting people who have a somatoform disorder. And you don't want to select people who have a purely psychiatric condition.

So in 1994, the Fukuda case definition was developed to replace the Holmes definition. For the 1994 case definition, the authors selected eight of the symptoms that had been listed in the Holmes criteria, and a patient needed to have any four of those eight symptoms to meet the new Fukuda case definition.

But here is the problem with the Fukuda CFS case definition—patients are not required to have post-exertional malaise, cognitive problems and unrefreshing sleep, and as we know, these are core symptoms of ME. So, a person could have four of the eight Fukuda symptoms and be diagnosed with CFS, and not have any of the three critical symptoms. In that case, you would be including in your sample a person who does not have the core elements of the illness.

From 1994 and on, I have been doing research that shows some of the diagnostic problems with the Fukuda case definition. And remember, the Fukuda case definition is the research case definition that has been used throughout the world for the past 25 years. But this Fukuda case definition identifies a heterogeneous group of patients, because core symptoms are not required of all patients. So, as a consequence, samples of patients with CFS based on Fukuda case definition vary widely in different research groups and labs.

What is the impact of the case definitions on prevalence rates?

In the late 1980s and early 1990s, the CDC conducted a prevalence study where they started by asking physicians in four cities to identify patients they thought had CFS. At that time, a lot of physicians didn't believe CFS existed, so putting physicians as gatekeepers in the selection of patients for this study resulted in a prevalence rate that was very low. Also, many people in the US do not have the financial resources to have a physician, so relying on primary care doctors to identify patients was another reason for low prevalence rates. The study suggested that CFS was a rare disease that affected fewer than 20,000 people in the US.

At that point, a group of researchers in Chicago began working on a study that involved finding patients from a random community sample, rather than a sample referred from physicians. In 1995, with NIH funding, our Chicago research team conducted a community-based prevalence study, which found that about a million people in the US had CFS. We also found that CFS affected all ethnic and socioeconomic groups, and thus we helped shatter the myth that CFS was a "Yuppie Flu" disease.

What did William Reeves [then-head of the CDC division in charge of the illness] do with the so-called "empiric" criteria? And why did this increase the CDC's estimate of disease prevalence by a factor of 10?

In the early 2000s, Bill Reeves felt there was a need to operationalize the Fukuda case definition. For example, he tried to standardize the way we measure a patient's disability or a substantial reduction in functioning. He used one instrument that has been referred to as the SF-36. According to Reeves, if a patient met criteria for one of several sub-scales within the SF-36, the patient would meet the disability criteria for having CFS.

But one of these domains was "role emotional" functioning. It turns out that every person with a major depressive disorder meets the criteria for "role

emotional" functioning. So you can't just specify instruments such as the SF-36; you have to specify which sub-scales of the instruments you are going to use, and what are the cut-off points. And if any of these choices are wrong, you will identify people who have another illness. My team gathered data on this point, and we conducted a study that assessed people with major depressive disorder, and found that over one-third of them could be inappropriately classified as having CFS under the so-called Reeves empiric criteria.

So, I think in the attempt to operationalize the Fukuda criteria, Reeves made mistakes, and I believe that is one of the reasons the estimated CDC prevalence estimates increased ten-fold, from .24% in a 2003 sample to 2.54% in 2007. They operationalized the Fukuda criteria in a way that classified many people as having CFS when they really had other illnesses.

At that time, many thought this increase in prevalence figures that Reeves proposed was constructive as it suggested that far more people had the illness, and thus these findings could be used to argue for more attention and funding due to this illness being so widespread. But if you use a very broad criteria, and bring into the illness case definition people who don't have the disease, then the entire research effort is seriously compromised. Fortunately, over the past decade, few researchers have used the Reeves way of operationalizing CFS.

What about the CCC and ICC criteria?

The CCC case definition for ME/CFS in 2003 was better because it specified key symptoms such as PEM. It was developed as a clinical case definition, and now it's being used by several teams as a research case definition. With the 2011 ME-ICC, I have noticed problems, and in part this is due to them once again requiring too many symptoms that could, as with the Holmes criteria of 1988, bring into the ME category some individuals who have a primary psychiatric disorder. In addition, the ME-ICC criteria is complicated to use, and many clinicians and scientists will have a difficult time reliably using it with patients.

What is the problem you see with the IOM case definition, apart from the name?

Well, it is true that Systemic Exertion Intolerance Disease (SEID) is a name most patients dislike. However, the IOM report was correct in requiring several core symptoms, such as PEM. But I believe these authors made a mistake in indicating that a patient could have either cognitive impairment or orthostatic intolerance—

one or the other. Cognitive impairment should have been required for all patients to have. But a more serious problem is that they inadvertently expanded the case definition by having just about no exclusionary illnesses, such as primary psychiatric disorders. My team recently conducted a study where about half the people with a variety of medical and psychiatric illnesses met the IOM criteria.

Now the IOM criteria was developed as a clinical case definition, but there was no federal effort to develop a research criteria that selects a more homogenous group of patients. The failure to develop an international consensus on a research case definition means that many researchers will continue to use the problematic Fukuda case definition, or they might use the IOM clinical criteria to select patients for research purposes, and this process has already begun.

To summarize, for research purposes, if a person has the core symptoms of the IOM definition, it would be important to exclude those with a primary medical or psychiatric condition, but this is not what the IOM authors recommended. So, the clinical IOM case

definition once again over-identifies people as having the illness. That means what occurred with the Reeves criteria of a decade ago has once again occurred with the IOM, as these criteria broaden the types of patients identified as having the illness.

What is at stake in this debate?

The stakes are high, for if you have an inappropriately wide case definition for research purposes, you will bring into your studies many fatigued people with a variety of conditions. In other words, if you identify the wrong patients, then your study will make conclusions about people who do not have ME, and you will have significant barriers to engaging in critical scientific activities such as estimating accurate prevalence rates or identifying biological markers. Also, if you bring in lots of people who don't have this illness but lifestyle issues and/or a solely depressive disorder, a good percentage of them will respond favorably to psychogenically oriented treatments. As I have been writing about for many years, this will ultimately lead to some researchers making conclusions about CBT and GET that are not true for patients with ME.

My case is simple. You need to have one research case definition that is used by scientists throughout the world. The clinical case definition can be broader, but the research case definition has to be tightly focused on those with the illness so that results can be replicated in different laboratories. This scientific achievement has been accomplished with every illness or disease except for ME.

We can do better. After working in this area for almost three decades, I am confident that we have the tools and methods to use psychometrically sound procedures to develop a consensus on one research case definition. I am optimistic that one day this will occur, and for me, there is literally nothing as important for our scientific field.



Harry Potter

AND THE DEATHLY HALLOWS



Some may not have noticed but Invest in ME Research has its very own film star supporting the cause.

Jon Campling is an actor, known to many Harry Potter fans as the 'Trainstopping Death eater'.

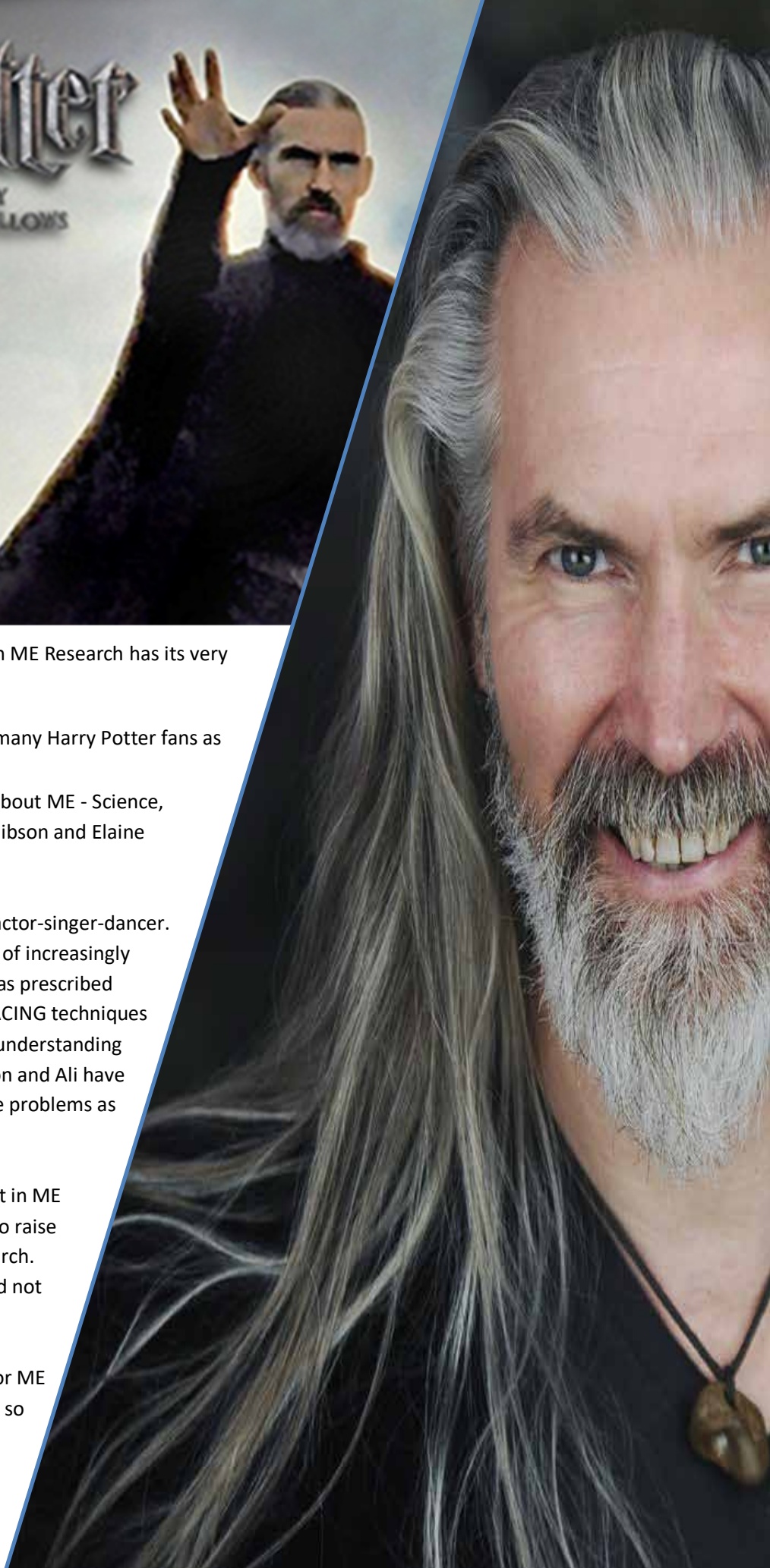
He wrote the introduction to the book about ME - Science, Politicsand ME - written by Dr Ian Gibson and Elaine Sherriffs.

Jon is married to Ali, also an actor – an actor-singer-dancer. Ali was diagnosed with ME after 2 years of increasingly debilitating symptoms. Like many, Ali was prescribed 18 months of CBT and advised to use PACING techniques – but realised that there was little real understanding of this illness and no ongoing care. So Jon and Ali have found themselves dealing with the same problems as all people with ME have to deal with.

Jon has been a staunch support of Invest in ME Research and constantly uses his fame to raise awareness and valuable funds for research. Jon could have just hidden this away and not raised the issue. He didn't.

He uses immense time for fundraising for ME earning the admiration and thanks from so many families where ME has struck.

Jon's fundraising page is here -



<https://www.justgiving.com/fundraising/walktall4me>

Conference Abstracts

Conference Chair

Dr Ian Gibson

Former Dean of Biological Sciences, UEA



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

Dr Elizabeth R. Unger

Chief of Chronic Viral Diseases Branch, National Center for Emerging and Zoonotic Infectious Diseases, Division of High Consequence Pathogens and Pathology, Centers for Disease Control and Prevention



Elizabeth (Beth) Unger, PhD, MD, received an undergraduate degree in Chemistry at Lebanon Valley College, Annville, PA. She then earned her PhD and MD in the Division of Biologic Sciences at the University of Chicago where she also began a residency in pathology. Her

residency and fellowship was completed at Pennsylvania State University Medical Center. During this time, Dr. Unger developed a practical method of colorimetric in situ hybridization. This work led to interest in tissue localization of HPV and ultimately to her initial appointment to CDC in 1997 to pursue molecular pathology of HPV and CFS.

Dr. Unger has served as the Acting Chief of CVDB since January 2010 and has 13 years of experience in CVDB, where she has participated in the design and implementation of CFS research and HPV laboratory diagnostics. During this time, she was co-author on 25 peer-reviewed manuscripts related to CFS, including the often-cited descriptions of the Wichita and Georgia population-based studies. In addition, Dr. Unger has been instrumental in efforts by WHO to establish an HPV LabNet and serves as lead of a WHO HPV Global



Reference Laboratory. She is co-author of 142 peer-reviewed publications and 24 book chapters and serves on the editorial board of six scientific journals. In 2008, for her HPV research accomplishments, she received the Health and Human Services (HHS) Career Achievement Award.

Dr Unger has been selected to serve as the Chief of the Chronic Viral Diseases Branch (CVDB) in the Division of High-Consequence Pathogens and Pathology (DHCPP), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC).

Abstract: Abstract not available at time of printing.

Dr Vicky Whittemore

Program Director in the National Institute of Neurological Disorders and Stroke at the National Institutes of Health in the United States.



Dr. Whittemore is a Program Director in the Synapses, Channels and Neural Circuits Cluster. Her interest is in understanding the underlying mechanisms of the epilepsies including the study of genetic and animal models of the epilepsies.

The major goal is to identify effective treatments for the epilepsies and to develop preventions. Dr. Whittemore received a Ph.D. in anatomy from the University of Minnesota, followed by post-doctoral work at the University of California, Irvine, and a Fogarty Fellowship at the Karolinska Institute in Stockholm, Sweden.

She was on the faculty of the University of Miami School of Medicine in The Miami Project to Cure Paralysis prior to working with several non-profit organizations including the Tuberous Sclerosis Alliance, Genetic Alliance, Citizens United for Research in Epilepsy (CURE), and the National Coalition for Health Professional Education in Genetics (NCHPEG).

She also just completed a four-year term on the National Advisory Neurological Disorders and Stroke Council.

Abstract: Abstract not available at time of printing.

Dr Avindra Nath

NIH National Institute of Neurological Disorders, Bethesda, Maryland, USA

Dr. Nath received his MD degree from Christian Medical College in India in 1981 and completed a residency in Neurology from University of Texas Health Science Center in Houston, followed by a fellowship in Multiple Sclerosis and Neurovirology at the same institution and then a fellowship in Neuro-AIDS at NINDS.



He held faculty positions at the University of Manitoba (1990-97) and the University of Kentucky (1997-02).

In 2002, he joined Johns Hopkins

University as Professor of Neurology and Director of the Division of Neuroimmunology and Neurological Infections.

He joined NIH in 2011 as the Clinical Director of NINDS, the Director of the Translational Neuroscience Center and Chief of the Section of Infections of the Nervous System.

His research focuses on understanding the pathophysiology of retroviral infections of the nervous system and the development of new diagnostic and therapeutic approaches for these diseases.

Abstract: Abstract not available at time of printing.

Professor Simon Carding

Research Leader, Quadram Institute Bioscience

Upon completing postgraduate work at the Medical Research Council's Clinical Research Centre in Harrow,



Simon Carding took up a postdoctoral position at New York University School of Medicine, USA, and then at Yale University as a Howard Hughes Fellow in the Immunobiology Group at Yale University with Profs Kim Bottomly and Charlie Janeway Jr.

While at Yale an interest in gamma-delta ($\gamma\delta$) T cells was acquired working closely with Adrian Hayday on molecular genetics and then with Prof. Peter Doherty to establish their role in (viral) infectious disease. He left Yale after five years to take up a faculty position at the University of Pennsylvania in Philadelphia where he developed a research interest in mucosal and GI-tract immunology, performing studies in germfree mice with Prof John Cebra that helped establish the role of gut microbes in the aetiology of inflammatory bowel disease (IBD).

After 15 years in the USA, he returned to the UK to take up the Chair in Molecular Immunology at the University of Leeds where he established a new research programme on commensal gut bacteria and Bacteroides genetics leading to the development of a Bacteroides drug delivery platform that is being used for developing new interventions for IBD and for mucosal vaccination.

In 2008 he was recruited by UEA and IFR to develop a gut research programme, taking up the Chair of Mucosal Immunology at UEA-MED and the position of head of the Gut Biology Research Programme at IFR, which later became part of the Gut Health and Food Safety (GHFS) Programme. GHFS research covers a broad area of gut biology including epithelial cell physiology, mucus and glycobiology, mucosal immunology, commensal microbiology, foodborne bacterial pathogens, and mathematical modelling and bioinformatics. The success of this programme has led to the establishment of the Gut Microbes and Health research programme that is integral to the research agenda of The Quadram Institute.

Within these programmes, much of the work undertaken in his research group builds upon that carried out in the USA and latterly in the UK with a major focus on understanding the mechanisms of intestinal microbial (bacterial and viral) tolerance. In particular, identifying the pathways and mediators of microbe-host cross talk and the role they play in establishing and maintaining gut health and in diseases that not only affect the gut but other organ systems.

This has led to the development of new research projects relating to the gut-microbiome-brain axis and understanding how the intestinal microbiome impacts on mental health and the development of neurodegenerative diseases, and the intestinal virome and the role that prokaryotic and eukaryotic viruses play in microbial homeostasis and dysbiosis.

Abstract: Abstract not available at time of printing.

Dr Peter Johnsen

University Hospital of North Norway, Harstad, Norway
- Internal Medicine

Dr Johnsen works in the medical department at the



University of Northern Norway in Harstad.

He is currently involved in the clinical trial of FMT which is being funded by the Norwegian Health Council. Five million Norwegian kroner has been awarded for the trial.

Together, it will include 80 participants who either receive treatment with FMT from a

healthy donor or placebo.

The study is double blinded, which means that neither participants nor scientists will know who received the treatment from donor or placebo before the study ends. Startup with the inclusion of participants begins during Summer 2018.

Abstract:

The Comeback study – a double blinded randomized placebo-controlled trial testing the efficacy of faecal microbiota transplantation (FMT) in CFS/ME

Earlier published data suggests that a dysbiotic gut flora may be an important factor in the pathophysiology of CFS/ME. Differences in host metabolism and immune activation pointing to a leaky gut are found in the context of at gut flora that is less diverse with an altered composition when CFS/ME is compared to healthy controls. In addition, an open label study has shown persistent relief in CFS/ME after transplantation of enteric bacteria.

To test the gut dysbiosis hypothesis in CFS/ME we will launch a double blind randomized, placebo-controlled, parallel-group, single-centre trial to test FMT as treatment for CFS/ME. Eighty CFS/ME participants will receive either donor transplant or placebo FMT, with 12 months follow up period. Primary endpoint is the efficacy of FMT at three months. We will use a patient

reported outcome by the Chalder Fatigue Scale to determine efficacy.

Recently we performed a trial with the same study design testing the effect of FMT in irritable bowel syndrome (IBS). In the primary endpoint three months after treatment there was significant improvement on gastrointestinal complaints. Preliminary results also show a significant effect on fatigue, which is a common complaint in irritable bowel syndrome. Conversely, gastrointestinal complaints are common in CFS/ME. Because of our previous experience with FMT for functional disease, the symptom overlap between IBS and CFS/ME, and the evidence for an involvement of the gut microbiome in both, we are eager to launch our trial in August 2018. We expect to have the final results ready by August 2020.

UK charity Invest in ME Research has provided us with a network of great collaborators that may help us to establish a true cause and effect relationship by performing analysis of immunological markers and the gut metagenome.

Biobanking of feces, blood and urine is an important asset to this study and will allow for tandem characterization of the immune response, metabolome and metagenome in CFS/ME. In outlining the study protocol we found the lack of consensus on symptom severity assessment challenging. We are hoping for input on how we can optimize the use of our biobank for insights in CFS/ME pathophysiology and discussions on what are the most relevant endpoints in efficacy studies for CFS/ME. We are thankful for the possibility the Invest in ME Research Foundation has given us to meet and network with the world leading expertise on CFS/ME.

There is great interest in and a commercialisation of FMT treatment, including FMT for CFS/ME. However, this enthusiasm needs to be balanced with a need for caution with the use of FMT. The screening regime for FMT donors is just as extensive as the regime for donors of blood, cells and live tissue. Our main aim is to provide physicians and other caregivers to CFS/ME patients' evidence-based advice regarding the efficacy of FMT. Thereby, this study will fulfil its intention regardless of the conclusion. However, there is a greater potential in this trial. Participants may serve as their own control pinpointing which mechanisms change if they transcend from sick to healthy or improved. In conjunction with the intervention any hypothesis can be tested in silico against the clinical outcomes to identify new therapeutic targets and biomarkers for improving diagnosis or personalizing FMT treatment.

Professor Karl Johan Tronstad

Professor Institute for Biomedicine , Tronstad Lab,
Bergen, Norway



Prof. Tronstad completed his graduate studies in biochemistry at the University of Bergen (UiB) in 2002. As postdoc at the Haukeland University Hospital, he studied bioactive compounds with the potential to modulate mitochondrial functions in cancer cells. In 2005 he was recruited to the Department

of Biomedicine, UiB, where he started his research group to investigate metabolism and mitochondrial physiology. His laboratory seeks to better our understanding of how defective mitochondrial homeostasis may disturb cell physiology, and how this may be involved in mechanisms of cancer and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Karl was involved with the recent paper to come from Bergen - Journal of Clinical Investigation Insight. The Tronstad Lab investigates cell metabolism and mitochondrial biology and we are very fortunate that he can spare time to participate in the Colloquium.

Abstract: Cellular energetics in ME/CFS

Irregularities in cellular energy metabolism have been linked to many human diseases, including metabolic disorders, mitochondrial diseases, cancer, neurodegeneration and ME/CFS. The possible consequences of cellular energy failure caused by a metabolic defect are context-dependent, and may range from mild cellular stress to cell death. An energy-depleted cellular state may theoretically be counteracted by metabolic rewiring, but if this is not sufficient to re-establish the energy level, additional (patho)physiological responses are activated. The consequences may include elements of cellular fatigue, but the mechanisms involved under such conditions are often poorly understood.

Recently we found changes in amino acid levels and gene regulation consistent with altered regulation of the central enzyme pyruvate dehydrogenase (PDH) in patients with ME/CFS compared with healthy individuals. Further, the presence of serum from ME/CFS patients changed energy metabolism in healthy human muscle cells in culture. These findings combined with the anticipated role of dysimmunity in ME/CFS, suggest the presence of an immuno-metabolic

pathomechanism. We are now investigating potential mechanisms involved, and characterizing contextual consequences of cellular energy failure, with particular focus on the mitochondrial oxidation machinery. Defects in this machinery are likely to cause energy deficiency and excessive lactate production, which are hallmarks of fatigue and post-exertional malaise (PEM).

By using a translational research approach, we investigate whether impaired energy metabolism may be linked to ME/CFS symptoms, which could provide support for the development of new biomarkers and treatments. Our research strategy is to build on existing knowledge that has recently emerged concerning metabolic changes in ME/CFS, and to adopt new methods and strategies for studying the mechanisms at the cellular level. This presentation will discuss our current approaches and recent data.

Professor Don Staines

The National Centre for Neuroimmunology and
Emerging Diseases (NCNED), Griffiths University,
Australia



Professor Staines has been a public health physician at Gold Coast Population Health Unit. He has worked in health services management and public health practice in Australia and overseas. His interests include collaborative health initiatives with

other countries as well as cross-disciplinary initiatives within health. Communicable diseases as well as post infectious fatigue syndromes are his main research interests. A keen supporter of the Griffith University Medical School, he enjoys teaching and other opportunities to promote awareness of public health in the medical curriculum. He is now Co-Director at The National Centre for Neuroimmunology and Emerging Diseases (NCNED), Griffiths University in Australia

Abstract not available at time of printing.



Invest in ME Research Conference Events 2018
#BRMECB 30-31May2018 #IIMEC13 1 June 2018

IIMEC13 - the Anne Örtegren Memorial Lecture

Remembering the Influence of Anne Örtegren



Professor Theoharis Theoharides

Professor of Pharmacology and Internal Medicine,
Tufts University, Boston, USA



Theoharis Theoharides is Professor of Pharmacology and Internal Medicine, as well as Director of Molecular Immunopharmacology and Drug Discovery, in the Department of Immunology at Tufts University School of Medicine, Boston, MA. He was born in Thessaloniki, Greece, and graduated with Honors

from Anatolia College. He received all his degrees with Honors from Yale University, and was awarded the Dean's Research Award and the Winternitz Prize in Pathology.

He trained in internal medicine at New England Medical Center, which awarded him the Oliver Smith Award "recognizing excellence, compassion and service." He also received a Certificate in Global Leadership from the Tufts Fletcher School of Law and Diplomacy and a Fellowship at the Harvard Kennedy School of Government. He has been serving as the Clinical Pharmacologist of the Massachusetts Drug Formulary Commission continuously since 1986. In Greece, he has served on the Supreme Advisory Health Councils of the Ministries of Health and of Social Welfare, as well as on the Board of Directors of the Institute of Pharmaceutical Research and Technology, and he is a member of the International Advisory Committee for the University of Cyprus School of Medicine. He first showed that mast cells, known for causing allergic reactions, are critical for inflammation, especially in the brain, and are involved in a number of inflammatory conditions that worsen by stress such as allergies, asthma, chronic fatigue syndrome, eczema, fibromyalgia, migraines, mastocytosis, multiple sclerosis, psoriasis, and most recently autism spectrum disorder.

He has also shown that corticotropin-releasing hormone (CRH), neurotensin and substance P, peptides secreted under stress, act together, and with the cytokine IL-33, to trigger mast cells and microglia to secrete inflammatory molecules. These processes are inhibited

by the novel flavonoids, luteolin and tetramethoxyluteolin that he has helped formulate in unique dietary supplements and a skin lotion. He has published over 400 scientific papers (JBC, JACI, JPET, NEJM, Nature, PNAS, Science) and 3 textbooks with 29,887 citations (h-factor 84) and he is in the top 5% of authors most cited in pharmacological and immunological journals. He has received 37 patents and trademarks, including three patents covering the use of luteolin in brain inflammation and autism: US 8,268,365 (09/18/12); US 9,050,275 (06/09/15); US 9,176,146 (11/03/15).

Acting as Advisor, he was instrumental in the development of ibuprofen (Upjohn), Cetirizine (UCB) and Niaspan (Kos). He is also the Scientific Director of Algonot, LLC, as well as President of Theta Biomedical Consulting and Development Co., Inc., of BiomedAdvice, LLC, and of the nonprofit Brain-Gain.org. He is a member of 15 academies and scientific societies. He was inducted into the Alpha Omega Alpha National Medical Honor Society and the Rare Diseases Hall of Fame. At Tufts, he served on the Curriculum, Students Promotion, Grievance, Faculty Promotion and Tenure, as well as Strategic Planning Committees. He received the Tufts Excellence in Teaching ten times, the Tufts Distinguished Faculty Recognition Award twice, the Tufts Alumni Award for Faculty Excellence, Boston Mayor's Community Award, and the Dr. George Papanicolau Award, as well as Honorary Doctor of Medicine from Athens University and Honorary Doctor of Sciences from Hellenic-American University. He is "Archon" of the Ecumenical Patriarchate of Constantinople.

Abstract: Brain mast cell involvement in Myalgic Encephalopathy/Chronic Fatigue Syndrome

Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS) affects about 1-2% of the US population and is characterized by debilitating fatigue of six months in the absence of systemic diseases. Many ME/CFS patients also have fibromyalgia and skin hypersensitivity, which worsen with stress. We hypothesize that stimulation of mast cells (MC) in the hypothalamus activate microglia leading to secretion of pro-inflammatory mediators that disrupt normal homeostasis and adversely affect mitochondrial function. Corticotropin-releasing

hormone (CRH), neurotensin (NT) and substance P (SP) are secreted under stress and can stimulate MC, necessary for allergic reactions, to release inflammatory mediators that could contribute to ME/ CFS symptoms directly or via activation of microglia. We showed that CRH and NT act synergistically to stimulate MC to secrete VEGF, which increases permeability of the blood-brain-barrier (BBB) and would allow entry of toxins in the brain. We also showed that NT can activate microglia to secrete IL-1 β . Moreover, we showed that the combined action of SP and the alarmin IL-33 lead to impressive amounts of TNF secretion from human MC. We further investigated the effect of combining ip injection of polyinosinic:polycytidylic acid [poly(I:C)], to mimic a viral infection, with 15 min forced cold swim stress, to mimic exercise and stress, on female C57BL/6 mice locomotor activity, as well as brain gene expression and serum levels of inflammatory mediators. Treated mice showed decreased locomotor activity over 72 hrs, while serum levels of TNF, IL-6 and KC (IL-8/CXCL8 murine homologue), as well as their gene expression in the brain, were increased. When other mice were provided with chow high in isoflavones for 2 weeks prior to treatment, this intervention reversed the reduced locomotor activity and minimized the increased serum levels and gene expression of the pro-inflammatory mediators. Moreover, the unique natural flavonoid, tetramethoxyluteolin potently inhibited both human cultured MC and microglia activation. We are presently seeking funding to measure these neuropeptides and cytokines in the blood of ME/CFS patients before and after exercise, as well as develop an intranasal tetramethoxyluteolin formulation for direct delivery to the hypothalamus through the cribriform plexus (Funded by an Anonymus grant).

References from this article will be in the online version of the journal.

Associate Professor Mady Hornig

Associate Professor, Center for Infection and Immunity (CII), Columbia University Mailman School of Public Health New York, USA



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 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.

Abstract: Abstract not available at time of printing.

Professor Maureen Hanson

Director, Center for Enervating Neuroimmune Disease
Liberty Hyde Bailey Professor, Department of
Molecular Biology and Genetics, Cornell University,
USA



Maureen Hanson is Liberty Hyde Bailey Professor in the Department of Molecular Biology and Genetics at Cornell University in Ithaca, NY. Previously she was on the faculty of the Department of Biology at the University of Virginia in Charlottesville and an NIH NRSA postdoctoral fellow at Harvard, where she also completed her Ph.D.

degree. While most of her prior research has concerned cell and molecular biology in plant cells, she began a research program on ME/CFS after noting at a 2007 IACFS meeting the paucity of molecular biologists studying the illness. Her lab was part of the 2012 multicenter study organized by Ian Lipkin's group at Columbia University to assess the actual role of XMRV in ME/CFS.

Abstract:

Research at the Cornell Center for Enervating Neuroimmune Disease

The Center for Enervating Neuroimmune Disease (ENID Center) encompasses a number of projects, including research carried out by the Cornell NIH ME/CFS Collaborative Research Center (CRC). The CRC has undertaken 3 projects, all unified by performance of an exertion challenge by subjects, who will perform two-day cardiopulmonary exercise tests (CPETs) using the protocol developed by the Workwell Foundation and Prof. Betsy Keller (Ithaca College). To ensure that all subjects meet the criteria for ME/CFS or for healthy sedentary controls, Drs. Susan Levine, Geoffrey Moore, and John Chia will diagnose and screen volunteers. In a project led by Professor Dikoma Shungu at Weill Cornell Medicine in New York City, subjects will undergo Magnetic Resonance Spectroscopy (MRS) and Positron Emission Tomography (PET) of their brains in order to evaluate oxidative stress and neuroinflammation. The neuroimaging will occur before performing an initial CPET and before performing a second one the next day, in order to determine the effect of exertion. Blood will be collected before and after each CPET at Weill Cornell Medicine, and before and after CPETs supervised by Dr. Keller at Ithaca College and supervised by the Workwell Foundation at Dr. John Chia's clinic in Los Angeles. Blood will be fractionated and sent to Cornell University in Ithaca. There, my lab group will analyze extracellular vesicle number, size, and content in plasma, and Dr. Andrew Grimson's lab will isolate individual white blood cells to sequence and identify genes that are expressed. The molecular data, neuroimaging, and subject survey data will be examined by a Data Analysis Core headed by Dr. Fabien Campagne (Weill Cornell Medicine) for correlations to identify relationships specific to diseased or healthy status, or pre- or post-exertion state. By examining patients when at baseline and after post-exertional malaise has been induced, we hope to gain insights into the factors that cause this disabling symptom, which also should shed light on the biological basis of the disease.

The Center also has an active outreach program, facilitated by Executive Director Susi Varvayanis and our Patient Advocate Committee. More information about

activities can be found here:

<http://neuroimmune.cornell.edu/news/> or by following us on twitter: @DrMaureenHanson or @CornellMECFs. The Center also has several other ongoing studies, including comparisons of gene expression, oxidative phosphorylation, and glycolysis in B, T, and NK cells from patients vs. controls. We have begun pilot studies to examine plasma metabolites and extracellular vesicles using an existing set of samples collected from patients at baseline.

Information from these studies will be presented.

Professor Markku Partinen

University of Helsinki, Finland

Prof Markku Partinen is a neurologist and an



internationally well-known opinion leader and expert in sleep research and sleep medicine.

Professor Partinen is currently Director of the Helsinki Sleep Clinic, Vitalmed Research Centre, and Principal Investigator of Sleep Research at Institute of

Clinical Medicine, Clinicum, University of Helsinki, Finland.

He has been the coordinator of the NARPANord Narcolepsy Consortium.

He became interested in sleep research while studying medicine at the University of Montpellier, France. He obtained his medical degree (DrMed) from Montpellier in 1976 (Supervisor Prof Pierre Passouant). He received his PhD in 1982 (epidemiology of sleep disorders), and degree of a specialist in neurology in 1982, in Helsinki, Finland.

He has worked as a postdoc researcher at Stanford University, USA in 1985-86 and in Bologna, Italy in 1987. In addition, he has had several shorter visits as visiting researcher or visiting Professor at different Universities in Europe.

His main interests in sleep medicine have been narcolepsy, excessive daytime sleepiness and fatigue (including ME), sleep apnea, and parasomnias. He has published more than 330 original articles in peer reviewed Journals in addition to writing many book Chapters and editing several books.

His Hirsch factor (H-factor) is 59 in ISI Web of Sciences and 64 in Scopus.

He has served in the Editorial Boards and as Assistant Editor in Sleep, Journal of Sleep Research and Sleep Medicine.

He has had many International positions in different research societies including Member of the Scientific Board and Vice-President of the European Sleep Research Society (ESRS), President of the Scandinavian Sleep Research Society, President Elect and President of the World Association of Sleep Medicine (WASM), Coordinating Secretary of the World Federation of Sleep Research Societies (WFSRS) and President and Member of the Board of the Scandinavian Sleep Research Society.

He has been President of the ESRS congress in 1992 (Helsinki), the World Congress of Sleep Apnea in 2003 (Helsinki), and the WASM congress in 2007 (Bangkok). In addition, he has organized several smaller meetings and symposia in the field of narcolepsy, RBD and different sleep disorders.

Currently he is a Member of the Board in the ESRS EU-Narcolepsy Network (EU-NN) and Chair of Scientific Board of the EU-NN, President of the Finnish Parkinson Association and President of the Finnish Sleep Research Society.

Abstract: Abstract not available at time of printing.

Professor James Baraniuk

Professor of Medicine at Georgetown University Medical Centre, Washington, USA



James N. Baraniuk was born in Alberta, Canada, south of Banff. He earned his honours degree in chemistry and microbiology, medical degree, and unique bachelor's degree in medicine (cardiology) at the University of Manitoba, Winnipeg,

Canada. Thereafter, he moved to Akron, OH, USA, for his internship and internal medicine residency at St Thomas Hospital. After another year of internal medicine residency at Duke University Medical Center, Durham, NC, he trained with Dr C.E. Buckley, III, in allergy and clinical immunology. He moved to the laboratory of Dr Michael Kaliner at the National Institute of Allergy and Infectious Diseases, Bethesda, MD, and there began his long-standing collaboration with Dr Kimihiro Ohkubo. After 2 years studying neuropeptides, he joined Dr Peter Barnes' laboratory at the National Heart and Lung Institute, Brompton Hospital, London, UK. Dr Baraniuk

returned to Washington, DC, and Georgetown University, where he is currently Associate Professor with Tenure in the Department of Medicine.

Abstract: Abstract not available at time of printing.

Professor Ron Davis

Professor of Biochemistry and Genetics at the Stanford School of Medicine in Stanford, California, USA



Ronald W. Davis, Ph.D., is a Professor of Biochemistry and Genetics at the Stanford School of Medicine in Stanford, California.

He is a world leader in the development of

biotechnology, especially the development of recombinant DNA and genomic methodologies and their application to biological systems.

At Stanford University, where he is Director of the Stanford Genome Technology Center, Dr. Davis focuses on the interface of nano-fabricated solid state devices and biological systems.

He and his research team also develop novel technologies for the genetic, genomic, and molecular analysis of a wide range of model organisms as well as humans.

The team's focus on practical application of these technologies is setting the standard for clinical genomics.

The genomic revolution has been spurred by technological advances that made nucleotide sequencing inexpensive, high-throughput, and accessible. The next phase in this revolution to pave the way for personalized health entails similar breakthroughs in biosensor technologies for personal molecular monitoring. Just as with DNA sequencing, the key features to optimize are accuracy, sensitivity, cost, and accessibility. Through close collaboration between engineers, biochemists, geneticists, and clinicians, our team has developed several such technologies and devices. The technologies target the biophysical properties of the cells and molecules, and therefore do not rely on introducing labels or other complex sample preparation techniques. We have successfully applied these technologies to detecting drug resistance, resolving cells and molecules in bodily fluids and

tissues, and engineering advanced, multiparametric, wearable biosensors. We have begun applying these methods to understand chronic fatigue syndrome, one of the last major diseases about which almost nothing is known. We anticipate that these technological breakthroughs coupled with data integration of personal molecular profiles will play an instrumental role in the realization of personalized health regimens and disease prevention strategies.

Abstract:

Revolutionizing biomedical research through technology development

The genomic revolution has been spurred by technological advances that made nucleotide sequencing inexpensive, high-throughput, and accessible. The next phase in this revolution to pave the way for personalized health entails similar breakthroughs in biosensor technologies for personal molecular monitoring. Just as with DNA sequencing, the key features to optimize are accuracy, sensitivity, cost, and accessibility. Through close collaboration between engineers, biochemists, geneticists, and clinicians, our team has developed several such technologies and devices. The technologies target the biophysical properties of the cells and molecules, and therefore do not rely on introducing labels or other complex sample preparation techniques. We have successfully applied these technologies to detecting drug resistance, resolving cells and molecules in bodily fluids and

tissues, and engineering advanced, multiparametric, wearable biosensors. We have begun applying these methods to understand chronic fatigue syndrome, one of the last major diseases about which almost nothing is known. We anticipate that these technological breakthroughs coupled with data integration of personal molecular profiles will play an instrumental role in the realization of personalized health regimens and disease prevention strategies.



The European ME Alliance

Patient groups and charities from fourteen European countries working together for ME



Campaigning in Europe for people with ME and engaging with health agencies, governments, professionals, the media, patients and public



Working closely with researchers and organisations and researchers interested in finding treatments and cures for ME



IIMEC13 AGENDA

Start	Presenter	Presentation
07.45	<i>Registration</i>	
08.55	IiMER	Opening
09:00	Dr Ian Gibson	Welcome to IIMEC13
09:05	Dr Beth Unger	CDC update
09:25	Dr Vicky Whittemore	NIH Common Data Elements
09:45	Dr Avindra Nath	Challenges in study design and identification of patients with post-infectious ME
10:00	Panel Session CDC/NIH	Panel discussion with CDC and NIH
10:15	Professor Simon Carding	Gut Microbiota in ME – Student Panel
10:45	<i>Break</i>	
11:15	Dr Peter Johnsen	Double blinded, single center, placebo controlled, randomized clinical trial treating ME with FMT
11.40	Prof Karl Johan Tronstad	Cellular Energetics
12:05	Professor Don Staines	Emerging TRP pathology: the way forward in pharmacotherapeutics and treatment
12.30	<i>Lunch</i>	
13.30	Professor Theoharis Theoharides	Anne Örtegren Memorial Lecture
14.05	Associate Professor Mady Hornig	Parsing heterogeneity in ME/CFS to accelerate discovery of tractable disease phenotypes
14:30	Professor Maureen Hanson	Research at the Cornell Center for Energating Neuroimmune Disease
14.55	<i>Break</i>	
15:25	Professor Markku Partinen	ME/CFS from a sleep medicine perspective
15:50	Professor James Baraniuk	Cerebrospinal fluid miRNA & metabolomics
16.20	Professor Ron Davis	Revolutionizing biomedical research through technology development
17.00	Dr Ian Gibson	Plenary Session
17.30	Adjourn	



liMER

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Conferences

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Young/ECR Researchers

Research

European ME Research Group

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Let's  research!

Myalgic Encephalomyelitis (ME) is a serious, chronic neurological disease. UK Charity Invest in ME - Research (IMER) are establishing a Centre of Excellence for ME - a hub for research activity in Europe - enabling a strategy of high-quality biomedical research projects to follow, coordinated and collaborating with other institutes. Please support our C of E for ME. Let's Do It for ME. Let's C research into ME. See <http://www.investinme.org/research#CofEforME> #LetsCresearch @LetsDolt4ME

Invest in ME - Research (UK charity nr. 1153730)

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