Guildford ME/CFS Support Group
(& West Surrey)

Newsletter

September 2019

Baby sloth

Future dates

Open to all members and carers

For details of upcoming meetings please contact us:

GuildfordME@hotmail.co.uk

The cellular equivalent of chronic fatigue found in ME/CFS

Source: www.healthrising.org/blog/2019/07/18/cellular-equivalent-chronic-fatigue-mitochondria-found

Paul Fisher is an Australian specialist in neurodegenerative diseases and the mitochondria, who is known for well-published and funded for work into Parkinson's disease by the Michael J. Fox Foundation. Fisher said he's been knocking on ME/CFS's door, trying to get in for over ten years. Only recently did he get his opportunity – and he's made the best of it.

Fisher is studying the mitochondria outside of the plasma – where some sort of inhibiting factor may reside. If anything in the blood is interfering with mitochondrial production – as Ron Davis and Oystein Fluge have suggested – Fisher's tests will not pick it up.

On the other hand, there's a purity to Fisher's examination of just the mitochondria. No outside influences allowed; that is, unless the mitochondria came into the experiment already damaged by something in the blood – a possibility.

Fisher immortalised ME/CFS lymphocytes so that he could grow them in vitro (in the lab) and test (i.e. torture) them again and again and again. Fisher put ME/CFS mitochondria through the wringer so many times that one almost ends up feeling sorry for them.

The first thing Fisher wanted to get across is that mitochondrial respiration – the act of producing energy – is VERY complex, involving numerous pathways. The act of measuring the mitochondria's ability to produce energy, however, is actually quite simple. Since they run on oxygen, you simply need to measure the amount of oxygen they consume in order to determine how much energy they're producing.

You might think that producing energy would be – should be – must be – a clean process. After all, you are dealing with something that could potentially go "boom". (Look at Chernobyl.) Energy production, however, is inherently volatile, and like any volatile situation, it's a bit hard to control.

Some of the electrons involved in the energy production process inevitably leak out of the mitochondria, create reactive oxygen species (ROS), and attempt to tear apart any cell they come into contact with. Energy production is essential, but it's also the biggest producer of free radicals in our bodies.

Fisher was merciless in his efforts to torture, er test, the mitochondria of the immortalised ME/CFS white blood cells in every which way he could. He inhibited every complex (there are five of them) of the Krebs cycle possible; plus, he assessed how well glycolysis – the process of turning glucose into ATP for the mitochondria – was doing.

Results

As expected, the mitochondrial mass and the number of mitochondrial genome copies was normal: there was no drop in number or mass of mitochondria in ME/CFS. The surprise came in the glycolysis findings – all normal! Glycolytic rate, glycolytic production, capacity, reserve – all perfectly fine. That, of course, bucks with Neil McGregor's recent findings and hypothesis that ME/CFS begins and ends with glycolytic issues. I asked McGregor what was up with this? He believes that Fisher's inability to use plasma (the Seahorse will not accept it) could account for the different results.

Fisher also found that the rate of ATP synthesis and production and ROS production were within normal limits. The cells appeared to be producing normal amounts of ATP and were not being slammed, as has been suspected, by reactive oxygen species or free radicals.

Major mitochondrial complex hit hard
However, then the results began playing a familiar tune. Complex V highlighted – Electron transport chain in mitochondria. Note that this appears to be the only complex where ATP is actually created.

ATP production was normal, but once Fisher began stressing the energy production systems strange things began happening. In particular, Fisher found that Complex V – the last of the five complexes and arguably the most important – responded poorly. Complex V transfers protons through the inner mitochondrial membranes to the mitochondria. That process, which involves ATP synthase, releases the energy used to drive ATP synthesis.

The complex looked fine at baseline, but when put under stress it pooped out – suffering a 25% drop in production compared to healthy mitochondria.

That drop caused the other four complexes to spring into action. ME/CFS patients' mitochondrial membranes became packed with extra copies of the mitochondrial complexes. Complex I – the main electron gradient producing complex that provides electrons to Complex V – went gangbusters in an attempt to provide Complex V with as many electrons as possible. ME/CFS patients' proton pumps worked overtime to pump protons out of the mitochondria en masse in order to increase the membrane potential and get more electrons into the cell. Enzymes that consumed O2 were jacked up as well.

The NIH reports that Complex V Deficiency can produce a wide variety of symptoms including extreme fatigue, low muscle tone (hypotonia), increased levels of lactic acid, rapid breathing, cognitive issues, etc… The Complex I upregulation detected by the Seahorse was validated when a proteomic analysis demonstrated that a huge increase in Complex I proteins had taken place. The end result was that the ME/CFS mitochondria were working harder than ever. They were able to get the cells' ATP production up to normal – at rest – but this was not enough to handle stressful conditions. Fisher cleverly noted that he had uncovered important aspects of mitochondrial function with ME/CFS.

The fact that mitochondrial measures generally correlated significantly with disease severity in ME/CFS (i.e. were worse in the patients with the most severe disease) was encouraging.
While Fisher did not find problems with glycolysis, he did find that the energy stressed ME/CFS patients' cells had moved from breaking down glucose to breaking down the more ATP-rich fatty acids in order to squeeze out as much energy as possible. That fatty acid switch – which was similar to what McGregor found (but which McGregor extended to proteins) – was demonstrated by an increase in levels of the six enzymes that break down the fatty acids, as well as the proteins that import fatty acids into the cells.

Ten years ago, Fisher's intuition was correct. ME/CFS patients' mitochondria are having problems producing energy. Something that's gone wrong in one mitochondrial complex is throwing off the rest of the complex. The good news is that the problem is not subtle: Fisher appears to be seeing major problems across the mitochondrial pathways. The bad news is how complex the mitochondria are. Fisher doesn't think he's going to find a single cause that responds to a single, simple fix. He also left open the possibility that the Complex V problems could be a consequence of another as yet unknown problem.

Mitochondrial results starting to add up
We haven't had a lot of mitochondrial studies, but the results are beginning to add up. Tomas's 2018 results could have been taken word for word from Fisher's presentation. Using a Seahorse machine, the U.K. group found that the mitochondria pooped out when put under stress as well. Tate recently reported getting similar results in his New Zealand cohort as well.

"Maximal respiration was determined to be the key parameter in mitochondrial function to differ between CFS and control PBMCs….The lower maximal respiration in CFS PBMCs suggests that when the cells experience physiological stress they are less able to elevate their respiration rate to compensate for the increase in stress and are unable to fulfill cellular energy demands."

We need more and larger studies, but three studies thousands of miles apart getting similar results using the same machine is pretty darn good. It should be noted that Myhill also found mitochondrial dysfunction in every patient tested.

A 2016 Stanford study, which did not use the Seahorse machine, might seem to be an outlier, but maybe not. It found increased ATP respiration – but from non-mitochondrial sources – and increased mitochondrial membrane area and increased number of cristae in ME/CFS, two findings which might be compensatory mechanisms as well.

Plus, in 2015 an in-silico model of ME/CFS showed how problems with mitochondrial functioning could potentially explain the post-exertional problems and long recovery periods needed. The authors suggested a number of issues, including mitochondrial deletions, Epstein-Barr virus-induced alterations of mitochondrial gene transcription, pro-inflammatory cytokines and increased levels of oxidative stress, that could result in an inability to ramp energy levels up in ME/CFS.

With Solve ME's Ramsay award and other studies underway that are measuring energy production in immune cells, expect more results soon. Meanwhile, Fisher is engaged and on the hunt. His next step – which he stated he is taking now – is to manipulate one thing at a time in an attempt to identify the core problem in the mitochondria. His first ME/CFS paper should be published soon.

ME/CFS article rocks top medical journal

Source: www.healthrising.org/blog/2019/07/11/jama-chronic-fatigue-syndrome-article-tony-komaroff-unifying-model/

It took Tony Komaroff over thirty years to get this done but it may have been worth it. Komaroff, Harvard doctor, researcher and ME/CFS advocate, has been studying, writing about and advocating for ME/CFS research since at least 1987 when he was the senior author on no less than four studies.

Over his long research history, he's examined pathogens, the immune system, brain scans, hormones, the autonomic nervous system, cognition and others. His huge 1996 "health status" study demonstrated that people with ME/CFS were more functionally inhibited than people with congestive heart failure, type II diabetes mellitus, heart attack, multiple sclerosis, and depression. All in all, Komaroff has co-authored over 80 studies on ME/CFS.

Only three times has he been able to get something published in JAMA. Ironically, his first "ME/CFS" study – on chronic Epstein-Barr virus – way back in 1987 landed in JAMA. Except for a comment he got published in 1997, that was it until this year when he got "Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome" article published.

It took Tony Komaroff over thirty years to get another ME/CFS paper published on JAMA. This new paper, though, is a hit…

Komaroff's been doing overviews of ME/CFS for years. In 2015, he scored a coup when he got "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Real Illness" published in the most widely read general internal medicine journal – the Annals of Internal Medicine.

This is different – this is JAMA, the flagship journal of the American Medical Association – "the professional organisation for physicians in the United States." Reportedly "the most widely circulated general medical journal in the world", JAMA is not a specialty journal; it doesn't focus on neurology or immunology – it's a general medical journal aimed primarily at doctors and medical students.

It gets around. JAMA states that its Impact Factor (51.3) is one of the highest in medicine and science, that its website gets almost 25 million visits a year, and that it has more than 750,000 followers on Twitter and Facebook.

Getting this article published in JAMA means more than quite a few doctors and medical students are getting a new view of ME/CFS. It also means the editorial staff of JAMA believes Komaroff's message – that ME/CFS is a real disease – has merit and that doctors should be exposed to it – a good sign. Komaroff wrote:

JAMA's "published very little about ME/CFS over the years, but are warming to the subject. They probably are the most widely read English language medical journal in the world, and so their interest is important. The implicit message of the article is that there is a complex underlying biology to ME/CFS and that health authorities are taking it very seriously—which will probably come as a surprise to many readers."

JAMA now knows that it has good reason to "warm" to ME/CFS. Komaroff's article is not just beating the competition – it's blowing it away. The 27,000 plus views it's had over the past four days are far and away the most of any recently published article. Right now, Komaroff's article is about 10,000 page views ahead of its closest competitor with most JAMA articles getting around 3-5K views.

• Update: as of July 19th 2019 the article has received over 57,000 page views, which according to an analysis of the articles appearing on JAMA in 2018, would – just two weeks after its publication- would put it in the top ten most viewed articles of that year. This is despite the fact that the article is not easy to find. It was published online on July 5th (not in the official JAMA editions on July 2nd/9th) yet readers are still flocking to it. The article is now highlighted in a box marked "trending" – which will undoubtedly get it more views.

The article

The article is not long but it is impactful. Komaroff smartly refers to the 2015 Institute of Medicine report on ME/CFS, produced by an institution that the doctors/medical students reading this article will know, appreciate and presumably trust. Komaroff has the doctors and medical students know that this report concluded that "ME/CFS is a serious, chronic, complex systemic disease" that affects up to an estimated 2.5 million people in the United States, and causes from $17 billion to $24 billion in economic losses annually in the U.S.

As to the idea that ME/CFS is not a real disease – well, many of the tests doctors used in the 1980's when ME/CFS first leapt onto the scene in a big way (and the tests that doctors still use today) couldn't find anything wrong. Many doctors concluded that meant there really was nothing wrong, but Komaroff asserts that the results of the next 3 decades indicate that it was the tests that were wrong (and the doctors who put too much faith in them) – not the patients.

The overwhelming weight of scientific evidence over the past three decades suggests that something has gone wrong biologically in ME/CFS. Most of the tests, which have done that, though, cannot be accessed in doctors' offices. Komaroff then quickly spins through the abnormal findings – the autonomic and central nervous system, metabolic, immune, hormonal and exertion findings. Thankfully, he includes the inability to repeat energy production levels on the second day of a two-day exercise test. (Unfortunately, the uniqueness of that finding did not make it into the paper.)

Unifying models

Komaroff presents two models of ME/CFS – both of which result in a hypometabolic state.
It's in the Unifying Model section that things gets really interesting. Komaroff has always been conservative. He's careful, he doesn't go out on limbs – and that's been helpful at times and at times not.

Komaroff, for instance, signed off on the chronic fatigue syndrome name in 1988 (it was called chronic Epstein-Barr virus syndrome), he voted against approving Ampligen for ME/CFS (he wanted more studies – which he must have known were not likely to happen – and six years later, haven't happened and aren't likely to), and his support of Bill Reeves and the CDC when they were under attack all showed just how conservative he can be. That innate conservatism, however, has also probably enabled him to be a bridge to the outside research world. It's possible Komaroff is the only figure that could have gotten this paper into JAMA.

That made the first part of the first sentence in the unifying hypothesis section really surprising: "What if ME/CFS reflects the activation of biologically ancient, evolutionarily conserved responses to injury or potential injury, a pathological inability to turn these responses off, or both?"

Komaroff – our conservative liaison to the medical community – has clearly bought into Naviaux's dauer hypothesis. Two paragraphs later, he devoted a full paragraph to it, and overall, about 10 percent of this short paper – Komaroff's outreach to the medical community – is focused on it. He clearly wants doctors to know it's possible ME/CFS patients are stuck in some kind of hypometabolic, hibernation-like state.

The other model Komaroff presents ends up in a similar state. In that model, neuroinflammation activates a fatigue nucleus in the brain which basically tells the body to shut down. That neuroinflammationwell could be triggered by any number of things – a herpesvirus infection in the brain, autoimmunity, neurotoxins, a breached blood-brain barrier, inflammation in the periphery that's tweaking the vagus nerve (aka VanElzakker), gut inflammation and/or chronic stress. Each of these may be present in ME/CFS but in different individuals.

Or, the worm may be in play. Komaroff suggests people with ME/CFS may have gotten stuck in the ancient biological state of metabolic shutdown seen in the state of dauer that the Caenorhabditis elegans worm enters into, or the state of hibernation that some animals enter into during times of stress. Functionality flies out the window as the animal hunkers down and simply tries to survive.

(As the same end point is reached in both the neuroinflammation and the dauer hypothesis, who's to say (other than perhaps Bob Naviaux :)) that the activation of the fatigue nucleus that Komaroff presents in the first model doesn't also occur when humans, if they do, enter into a dauer state.)

If Komaroff was aiming at perking up some eyebrows, he surely succeeded. His neuroinflammation hypothesis will undoubtedly ring bells with many of the doctors, etc. who've read Komaroff's article over the past couple of days. Few, on the hand, will have heard of dauer, or will have ever thought to possibly connect ME/CFS with a state of hibernation. (Compare the 27,000 plus views Komaroff's article has had to the 4800 views the last JAMA publication on ME/CFS in August, 2018 had.)

The article's Altmetric social media score shows that Komaroff's ME/CFS JAMA article is scoring in the top 5% of all research articles. JAMA, like all medical journals, likes to know that its articles are being read. The more attention given to a subject, the more likely JAMA will revisit it again – and, of course, with its wide reach into the probably the most ignorant branch of our medical establishment – doctors – JAMA is one place that we really want ME/CFS studies to show up on. Please visit the original article here (no need to read it if you don't want to) and share it via tweets, Facebook and other social media outlets.

In another sign that JAMA is coming around, on July 9th in its Biotech Innovations section, JAMA also published a short review of the ME/CFS nanoneedle study "Biomarker Test for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome" that was recently published in Proceedings of the National Academy of Sciences. Please visit that article and pass it around as well.

#MEAction responds to attacks on ME community in the Guardian and Psychology Today

Source: www.meaction.net/2019/08/01/meaction-responds-to-attacks-on-me-community-in-the-guardian-and-psychology-today

1st August 2019

In the past two weeks, The Guardian/The Observer and Psychology Today US have published articles portraying the myalgic encephalomyelitis (ME) community as an angry, misguided mob using social media to denigrate scientific research.

Both articles focus on the criticism that Dr. Michael Sharpe, one of the key authors of the PACE trial and the Oxford disease criteria, has received from the patient community for his work researching ME. The article laments how activist ME patients are using social media to stall the progress of research simply because they are unhappy with research results. Both articles portray Dr. Sharpe – and science – as a victim of these unwarranted attacks at the hands of the online ME community.

The Guardian article headline reads, “ME and the perils of internet activism,” with the subhead: “Research into the chronic illness, which affects 250,000 people in the UK, may be stalling because of online criticism and abuse.” The headline for Psychology Today article reads “The Dark Side of Social Media Activism in Science: Scientists are targeted when results do not align with activist views.”

The context of both articles distorts the truth and seriousness of the situation, and further stigmatises our community. These are hit pieces on the ME community to distract from the serious concerns over the methodological errors of Dr. Sharpe’s PACE trial. The Guardian and Psychology Today articles completely **fail to mention**:

- The scientific community has resoundingly criticised the PACE trial (100+ researchers and academics signed a letter calling for an independent re-analysis of the PACE trial data), concerned about serious methodological errors in the study that have skewed the outcomes.
- Two patient surveys with more than 3,000 patient participants in total show people with ME consistently report deterioration in their health after undergoing graded exercise therapy.
- Research shows people with ME experience physiological abnormalities in their response to exercise.
- The current ME research happening around the world, including at the U.S. National Institutes of Health, the U.K Biobank, and at Harvard, Stanford, Cornell and Columbia increasingly shows the science does not support Sharpe’s beliefs about the illness.

The PACE Trial (short for “Pacing, graded Activity, and Cognitive behavioural therapy) was a large-scale trial of treatments that compared Adaptive Pacing Therapy (APT), Cognitive Behavioural Therapy (CBT), or Graded Exercise Therapy (GET) for people with ME and Chronic Fatigue Syndrome (CFS). The Lancet published the results in 2011. The experimenters hypothesised that the CBT and GET groups would do best, and reported that this is what the trial’s results showed. However, the claim has proved controversial among researchers and patients, largely due to serious methodological errors in the design and execution of the study, and patient experience that finds graded exercise therapy is often harmful.

Similarly, the Oxford criteria — the broad diagnostic criteria used to recruit people for the PACE trial designed by Dr. Sharpe — is widely seen by the scientific and research community as overly broad, drawing in patients who have other conditions that could benefit from exercise and talk therapy, thus skewing the results of a study focused on people with ME.

The U.S. Agency for Healthcare Research and Quality downgraded the evidence for GET and CBT for people with ME and recommended that the Oxford criteria be retired.

How should the community respond
#MEAction has emailed the letters below to the writers and editors at the Guardian and Psychology Today.

We encourage the community not to engage this toxic narrative online, which would give this false, damaging narrative oxygen and attention by sharing it across social media. At the same time, we encourage people to comment below the articles drawing on points from our letter pasted below.

At the same time, we encourage the community to share on social media the many projects of scientists and people with ME, including the recent JAMA article outlining the abnormalities found in people with ME. Share the research focused on epidemiology, etiology, and treatment at Harvard, Stanford, Cornell and Columbia with all-star scientific teams. Share information and stories about the UK Biobank so that people can see the good work being done in the UK. Share stories about the NIH's new Collaborative Centers for research. Share good articles about PACE's flaws, but also about the very real progress we're making in understanding the science of myalgic encephalomyelitis. And use the hashtag #ShareGoodScience so that others can find what you recommend.

#MEAction letter to Psychology Today
Dear Dr. Camarata,
We are writing with serious concerns regarding Psychology Today's July article, "The Dark Side of Social Media Activism in Science." The article stigmatises a disabled population as anti-science and anti-truth, an angry mob unable to understand what is good for us. This is a highly distorted and damaging portrayal of the myalgic encephalomyelitis (ME) community.

In the article, Dr. Camarata writes, "from my point of view, treatments that pass the rigors of evidence-based research and peer review should be welcomed with open arms and with gratitude." The fact of the matter is that Dr. Michael Sharpe's research has not passed the rigors of evidence-based research and peer review.

Dr. Camarata's article fails to mention that the scientific community has resoundingly criticised Dr. Sharpe's design of the PACE trial for containing multiple, serious methodological flaws. More than 100 scientists in the field have called for an independent re-analysis of the PACE trial data.

The Centers for Disease Control and Prevention has removed graded exercise therapy (GET) and cognitive behavioural therapy (CBT) – the therapeutic approach endorsed in the PACE trial – from its recommendations for treatment, and stated that graded exercise may cause harm. The Agency for Healthcare Research and Quality downgraded the evidence for GET and CBT and recommended that Oxford — the broad diagnostic criteria used to recruit people for the PACE trial designed by Dr. Sharpe — be retired.

Meanwhile, patients consistently report deterioration in their health after undergoing graded exercise therapy. A 2017 survey from the UK with over 1000 respondents reported that over 80% experienced worse health outcomes following GET. A recent Oxford

Brookes survey of 2,274 respondents shows the majority reported deterioration or no change in symptoms and health after undergoing GET and CBT. More than two thirds (67.1%) of those who underwent GET reported deterioration in their physical health.

There is also growing evidence that people with ME experience physiological abnormalities in their response to exercise, including reduced blood flow to the brain and heart, reduced oxygen uptake in haemoglobin, reduced oxygen utilisation, and abnormal gene expression.

Patients have been outspoken about the flaws of the PACE trial because we have the most to lose from the propagation of poor science that promotes harmful or ineffective treatments.

It took the Lancet 12 years to retract the paper supporting a link between autism and the MMR vaccine, which has done inestimable damage. The methodological flaws of the PACE trial have likewise done irreparable damage to people with ME: stalling biomedical research, quashing funding, contributing to stigma in the clinic and at home, and leading to dismal health outcomes for people with ME. The PACE trial paper is now flagged by PLoS One with an 'expression of concern'.

Robust research continues into ME. JAMA recently published an article outlining the abnormalities found in people with ME, including in the central and autonomic nervous system, immune system and metabolic systems. Exciting projects focused on epidemiology, etiology, and treatment push forward at Harvard, Cornell, Columbia and Stanford, with all-star scientific teams. The US National Institutes of Health funded its first research centres to study ME, and hosted its first national conference on ME and a Young Investigators Workshop to entice promising young researchers to enter the field. And the UK Biobank to study genetics of ME launched, gathering the data of thousands. You can read more about ME research here.

There can be no question that Dr. Sharpe's current media campaign flies in the face of a modern understanding of ME. Moreover, it bears the distinct flavour of a personal affront countered with a personal attack, simply because Sharpe's treatments make patients worse and people with ME continue to say so.

The history of scientific and medical progress is marked by self-correction. Sharpe's claim that patients belong outside of the conversation for their own good — and about the issues that most closely affect their own lives — is archaic and misguided.

We urge Psychology Today to remove the "The Dark Side of Social Media Activism in Science" from its website. Its presence stigmatises a vulnerable patient population. Articles such as this one cause genuine harm to patients, their families, their clinicians, and their communities.

We hope that in the future you will reach out to us and the ME community with any questions you have about ME's history, the science behind the condition, and developments in research groups around the world. Please find attached our latest ME research summary (July, 2019) for your information.

Sincerely,
Adriane Tillman on behalf of #MEAction

Relevant links:

- #MEAction's ME Research Summary, July 2019: http://www.meaction.net/wp-content/uploads/2019/06/19_MEA_Revised_2019_Research_Summary_190610.pdf
- 100+ scientists call for independent re-analysis of PACE trial:http://www.virology.ws/2018/08/13/trial-by-error-open-letter-to-the-lancet-version-3-0/
- Patient survey showing patients with ME deteriorate after GET: https://journals.sagepub.com/doi/10.1177/1359105317726152
- Oxford Brookes survey of 2,274 respondents shows the majority reported deterioration or no change in symptoms and health after undergoing GET and CBT.
- NPR article, "For People With Chronic Fatigue Syndrome, More Exercise Isn't Better:" https://www.npr.org/sections/health-shots/2017/10/02/554369327/for-people-with-chronic-fatigue-syndrome-more-exercise-isnt-better
- JAMA article: Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome: https://jamanetwork.com/journals/jama/fullarticle/2737854?resultClick=1

#MEAction letter to The Guardian

Dear Mr. Webster and Mr. Anthony,

We are writing with serious concerns regarding The Observer's 28 July article, "ME and the Perils of Internet Activism." The article lacks context regarding Dr. Sharpe's work, and contributes to the harmful stigmatisation of a highly vulnerable population of disabled people.

The reality of the PACE trial is that Dr. Sharpe has produced poorly-designed research that has been resoundingly criticised by the scientific community. Patients have been outspoken about the flaws of the PACE trial because we have the most to lose from the propagation of poor science. It took the Lancet 12 years to retract the paper supporting a link between autism and the MMR vaccine, which has done inestimable damage. The methodological flaws of the PACE trial have likewise done irreparable damage to people with ME: stalling biomedical research, quashing funding, contributing to stigma in the clinic and at home, and leading to dismal health outcomes for people with ME. The PACE trial paper is now flagged by PLoS One with an 'expression of concern'.

The Guardian article fails to mention:

- 100+ scientists have called for an independent re-analysis of the PACE trial data due to serious concerns about methodological flaws in the study.
- 40+ researchers and academics support the temporary withdrawal of the Cochrane review of graded exercise therapy for ME/CFS based on concerns about methodological flaws in cited studies, explicitly stating that their decision was in no way due to "patient pressures".
- Patients consistently report deterioration in their health after undergoing graded exercise therapy (GET), the therapeutic approach endorsed in the PACE trial. A survey from the UK with over 1000 respondents reported that over 80% experienced worse health outcomes following GET.

In the US, the Centers for Disease Control and Prevention has removed GET and cognitive behavioural therapy (CBT) from its recommendations for treatment and stated that graded exercise may cause harm. The US Agency for Healthcare Research and Quality downgraded the evidence for GET and CBT and recommended that Oxford — the broad diagnostic criteria used to recruit people for the PACE trial — be retired.

There is growing evidence that people with ME experience physiological abnormalities to exercise, including reduced blood flow to the brain and heart, reduced oxygen uptake in haemoglobin, reduced oxygen utilisation, and abnormal gene expression.

In the UK House of Commons, 40 MPs passed a motion to support increased funding into biomedical research, and the suspension of graded exercise therapy. The Danish Parliament recently announced that it will unanimously support using the World Health Organization (WHO) classification of ME as a neurological disease.

A sea-change in science has led to a shift in the way researchers and clinicians understand ME. And it goes without saying that this is an unsettling situation for people who have staked their careers on recommending GET and CBT for people with ME.

Robust research continues into ME. JAMA recently published an article outlining the abnormalities found in people with ME, including in the central and autonomic nervous system, immune system and metabolic systems. Exciting projects focused on epidemiology, etiology, and treatment push the forward at Harvard, Cornell, Columbia and Stanford, with all-star scientific teams. The US National Institutes of Health funded its first research centres to study ME. And the UK Biobank to study genetics of ME launched, gathering the data of thousands. You can read more about ME research here.

We urge The Guardian Media Group to carefully consider how articles about ME are approached going forward to minimise any damaging bias.

We hope that in the future you will reach out to us and the ME community with any questions you have about ME's history, the science behind the condition, and developments in research groups around the world. Please find attached our latest ME research summary (July, 2019) for your information.

Sincerely,
Espe Moreno on behalf of #MEAction UK

Attachments and links:

- #MEAction's ME Research Summary, July 2019: http://www.meaction.net/wp-content/uploads/2019/06/19_MEA_Revised_2019_Research_Summary_190610.pdf
- 100+ scientists call for independent re-analysis of PACE trial: https://www.thetimes.co.uk/article/call-for-review-of-flawed-me-research-in-lancet-letter-l75rvcprh
- Patient survey showing patients with ME deteriorate after GET: https://journals.sagepub.com/doi/10.1177/1359105317726152
- NPR article, "For People With Chronic Fatigue Syndrome, More Exercise Isn't Better:" https://www.npr.org/sections/health-shots/2017/10/02/554369327/for-people-with-chronic-fatigue-syndrome-more-exercise-isnt-better
- JAMA article: Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome: https://jamanetwork.com/journals/jama/fullarticle/2737854?resultClick=1

ME/CFS fecal transplant study suggests the treatment holds promise

Sources:

http://simmaronresearch.com/2019/08/fecal-transplant-chronic-fatigue-study-promise/?fbclid=IwAR0vliN3euDo5Sxx8n8JxJEj3wbf9mMVi-58IUmqDiD-0qNRbA59Xrw2qoQ

www.cidrap.umn.edu/news-perspective/2019/06/fda-issues-alert-after-fecal-microbiota-transplant-death

https://search.informit.com.au/documentSummary;dn=119626231492520;res=IELHEA

We covered FMT (Fecal Microbiota Transplant) in our March 2014 newsletter (pages 9 to12). There has been a recent relatively small study showing improvement in 70% of ME/CFS patients using the international consensus criteria for diagnosis. However, there has also recently been a FMT related death in America causing the FDA to issue a warning and suspend FMT clinical trials. The aforementioned study claims to be the first of its kind but there was a similar study in 2012. As such, below are three articles. The 2nd and 3rd are abbreviations of the full articles:

- **1) 2019 fecal transplant study**
- **2) FDA issues alert after fecal microbiota transplant death**
- **3) 2012 the GI microbiome and its role in Chronic Fatigue Syndrome**

1) 2019 fecal transplant study

This first stab at a fecal transplant study isn't a big statistically rigorous, randomised, placebo-controlled trial. Far from it; it's more a series of case reports from a physician's practice over time with a smattering of statistics. It does give us, though, our first data -in rather vivid detail – on the possible efficacy of fecal transplants in ME/CFS.

Ten studies now indicate that the bloom is off in the gut flora of people with ME/CFS. With a 2018 review taking ME/CFS researchers to task for the usual suspects: lack of standardisation in patient selection, sample processing, genome sequencing and data analysis, it's not clear what has gone wrong.

As papers just pour out implicating the gut flora in a wide range of diseases the question becomes more and more what to do about it. While pre and probiotics can help, it's possible that fecal transplants – the direct transfer of stool (or portions of the stool) from a healthy person into the gut of an ill person – may provide a larger, more lasting impact.

The study

Dr. Julian Kenyon runs The Dove Clinic for Integrated Medicine, in the U.K. which uses both an oral (pre and probiotics, diet, etc.) and fecal transplant approach to gut improvement. In this study – A Retrospective Outcome Study of 42 Patients with Chronic Fatigue Syndrome, 30 of Whom had Irritable Bowel Syndrome. Half were treated with oral approaches, and half were treated with Faecal Microbiome Transplantation – he compared the results of the two. Kenyon divided his patients into two groups of 21; one was treated with nutritional remedies, probiotics, prebiotics, and dietary and lifestyle advice. The second group, most of whom had failed the first treatment approach, were given 10 fecal implants over ten days.

As seventy percent of the group also had irritable bowel syndrome (IBS) this may have been a more gut impacted group. In an effort to deliver a maximum diversity of flora, each of the implants came from a different, "carefully screened" donor.

The Taymount Laboratory provided the implants. The laboratory runs a 10-day gut flora transplant (FMT) program which starts off with a colon cleanse and includes dietary advice. While it's not possible to test donors for all possible pathogens (some of which may be undetectable), the donors' blood was screened for the following pathogens: Human Immunodeficiency Virus (HIV) 1/2, Hepatitis A. IgM, Hepatitis B (HBsAg), Hepatitis C antibody, Syphilis, IgG/IgM, Full Blood Count, Urea and Electrolytes, Ferritin, C-Reactive Protein, Tissue Transglutaminase, CMV, H-Pylori.

Their stool samples were screened for: Campylobacter (Jejuni, Coli and Upsalliensis), Clostridium Difficile (A/B), Salmonella, Yersinia Enterocolitica, Vibrio (Parahaemolyticus Vulnificus and Cholera), Diarrhoea-causing E-Coli/Shigella, Enteroaggregative E-Coli (EAC), Enteropathogenic E-Coli (EPEC), Enterotoxigenic E-Coli (ETEC), Shiga-like toxin-producing E-Coli (STEC), E-Coli 0157, Shigella/Enteroinvasive E-Coli (EIEC), Cryptosporidium, Cyclospora Cayetanesis, Entamoeba Hystolitica, Giardiolambia, Adenovirus, Astrovirus, Norovirus GI/GLL, Rotavirusa, Sapovirus.

The Taymount Laboratory website reports that there's no documented evidence infections being passed via fecal transplants. As of this month, though, that's no longer true. The FDA recently reported on two multi-drug resistant infections passed via fecal transplants.

Different kinds of transplant techniques are used. Some clinics use a tube to insert the transplant through the esophagus and into the stomach or the duodenum. This clinic uses a rectal catheter to deliver the goodies into the large bowel or colon. Others use something called a colonoscope. Some companies are creating pills that can be swallowed.

Results

The study reported on past patient outcomes (retrospective case-control) using a vague metric indeed, "% improvement", to assess results. While the statistics were crude, the data presented – in short statements describing how the patients improved or didn't improve – provided vivid reading indeed. The statistics (Mann-Whitney test of "% improvement: $U=111.5$, $p=.003$) indicated dramatically increased improvements in the fecal transplant group compared to the "oral" (probiotic, nutritional supplements, etc.) group.

The fecal transplant group

As noted above the fecal transplant group were tough cases: they hadn't responded to Dr. Kenyon's normal treatment regiment of supplements, pre and pro-biotics etc.
Dr. Kenyon's data suggested that little grey area existed: the fecal transplants either hit or missed: when they hit, they tended to work quite well; when they missed, they pretty much missed entirely.

In quite a few cases, the transplants were associated with some striking increases in energy. Kenyon reported that the energy levels of 7 of the fecal transplant group returned to normal, practically normal or almost normal. (In one case she simply said “chronic fatigue syndrome resolved”.)

The increases in energy did not come in the newly ill either. Six people who’d had ME/CFS “for many years” either totally recovered or were dramatically improved. One 66 year old person who apparently got ill following an amoebiasis infection in the Himalayas over 30 years ago returned to normal health. The energy levels of six others were “significantly improved”, “much improved”, “improved dramatically” or “consistently improved”.

In a few cases, it was impossible to determine if improvements in energy had occurred. For instance, Dr. Kenyon reported that the gut problems of a person with severe vaginal thrush, recurrent abdominal bloating, IBS and ME/CFS largely disappeared but didn’t assess her energy levels. The same occurred with another person with IBS: their IBS disappeared but we weren’t told if her energy levels improved as well. Four people (@20%) were either unable to tolerate the implants (n=2) or showed no improvement (n=2).

Table 1. Chronic Fatigue Syndrome Patients treated with FMT

Patient:		%Improved
(F)Age 36	Severe Chronic Fatigue Syndrome with Irritable Bowel Syndrome for three years, following multiple antibiotics for Quinsy. Severe debilitating Irritable Bowel, with lack of energy. She had FMT in February 2018, following this the Irritable Bowel cleared up, energy significantly better. Has always had many food sensitivities, they are gradually beginning to resolve. A further course of FMT is under consideration.	70%
(F)Age 40	Polycystic Ovary Syndrome, also Irritable Bowel and a Chronic Fatigue. She had FMT in October 2017, following the FMT her energy is much improved and is practically normal, has remained so ever since. Also, her mood is more stable.	90%
(F)Age 59	Severe Vaginal Thrush for five years, recurrent abdominal bloating, Irritable Bowel Syndrome and Chronic Fatigue Syndrome. Clostridium Difficile in 2013. She had FMT in May 2017, two months after FMT the Irritable Bowel cleared up completely, her skin is significantly better than it was prior to treatment, Vaginal Thrush is still something of a problem, but not as bad as it was. She finds she is no longer craving sweet foods.	90%
(F)Age 73	History over many years of Irritable Bowel Syndrome and Chronic Fatigue Syndrome, also overweight. We treated her with FMT in December 2017, the Irritable Bowel Syndrome cleared up during the two months following the FMT and has remained normal. She is still having difficulty in losing weight.	60%
(F)Age 43	Several years history of Chronic Fatigue Syndrome. Also, Irritable Bowel Syndrome. We carried out FMT in January 2017, since that time the IBS has cleared up, energy significantly improved and has remained so.	70%
(F)Age 42	8-year history of Chronic Fatigue Syndrome. Also, Irritable Bowel Syndrome. We treated her with FMT in November 2018, I first saw her in May 2018. Since the FMT her persistent Oral Thrush has cleared, her digestion has improved, and the Irritable Bowel has settled down. She is no longer constipated. Her energy improved almost to normal following the FMT but has had a bit of a relapse since significant family upset, which has been draining on her energy reserves.	95%
(F)Age 73	Insomnia, persistent Nausea, poor energy due to Chronic Fatigue Syndrome, lack of appetite. Has lost a great deal of weight over several years. Complains of bad body odour. We carried out FMT in February 2017. Since then the Nausea has disappeared, the appetite has returned, and she is now putting on weight.	95%
(F)Age 46	I first saw her in 2016 with a history of Chronic Fatigue Syndrome and Fibromyalgia for several years. We carried out FMT in January 2017, no significant response to the FMT. We are thinking of repeating the FMT.	0%
(F)Age 66	At the age of 26 this patient contracted amoebiasis in the Himalayas, then she had lots of antibiotics for various indications and has had Irritable Bowel Syndrome and Chronic Fatigue Syndrome since the age of 30. Also, she has been diagnosed with SIBO and had developed multiple food sensitivities. We carried out FMT in July 2017, her Irritable Bowel Syndrome normalised over the next four weeks, her energy improved and became normal, then she had exposure to contaminated water, probably containing parasites, then she relapsed to some extent and had to have a second course of FMT in December 2017. Since that time, she has been completely normal.	95%
(F)Age 47	This patient has had regular courses of antibiotics since the age of 12 for a range of reasons. She has had many years of Chronic Fatigue and Irritable Bowel Syndrome. We carried out FMT in August 2018, since then the Irritable Bowel has settled down and the Chronic Fatigue has resolved.	90%

(F)Age 73	This patient has had a history of recurrent Candidiasis over many years, including Oral Thrush. She has many years history of Irritable Bowel Syndrome and Chronic Fatigue Syndrome. We carried out FMT on her in November 2018. Since that time, she has had no more Candidiasis, the Irritable Bowel has settled down, and there is significant maintained improvement in her energy levels.	85%
(F)Age 70	This patient has had a history over many decades of a Chronic Fatigue Syndrome. We used FMT in April 2017, there was no improvement in her energy levels since the FMT.	0%
(F)Age 70	Chronic Fatigue Syndrome for 20 years, also Addison's Disease, Fibromyalgia and Irritable Bowel Syndrome. FMT carried out in August 2018. She reacted to several of the Implants with Diarrhoea, so we had to stop the Implants. Clinically, no change.	0%
(F)Age 61	20-year history of Chronic Fatigue Syndrome and Fibromyalgia, also Irritable Bowel Syndrome. Oral treatment did not work. FMT was carried out in April 2018. Following FMT her energy improved dramatically and has remained improved. The Irritable Bowel Syndrome has cleared up and she also lost one and a half stone in weight.	90%
(F)Age 41	Many years history of Chronic Fatigue Syndrome, multiple food sensitivities and Irritable Bowel Syndrome. FMT carried out in September 2018. She managed to tolerate half of the Implants and then temporarily had to stop. No clinical improvement yet.	0%
(F)Age 44	Eight-year history of Chronic Fatigue Syndrome getting significantly worse. Also, Irritable Bowel Syndrome. We carried out FMT on her in October 2018. Her Irritable Bowel Syndrome has cleared up completely, energy is beginning to recover.	75%
(F)Age 56	History of Chronic Fatigue Syndrome, Irritable Bowel Syndrome for many years. Resistant to oral approaches for treating both of these conditions. We carried out FMT in May 2018. Since that time her energy is significantly better, and remains better, bowel function is now normal.	80%
(F)Age 70	Chronic Fatigue Syndrome for many years, also Irritable Bowel Syndrome. We treated her with FMT in October 2017. Bowel habit is now normal, resistance to intercurrent infections has now returned to normal, energy was consistently improved and remains so.	95%
(M)Age 65	Chronic Fatigue Syndrome for many years. We treated him with FMT in November 2017. Energy has returned to normal.	95%
(F)Age 52	This patient has had Chronic Fatigue Syndrome for many years. Also, Irritable Bowel Syndrome. We treated her with FMT in July 2018. Since then, her energy has returned to normal and she has now been able to return to work, her gut has also returned to normal.	95%
(F)Age 48	History of Chronic Fatigue Syndrome and Irritable Bowel for many years. We carried out FMT on her in March 2018. Since then her Irritable Bowel Syndrome has cleared up completely and also her energy has returned to normal.	95%

The standard or oral approach group

The other group treated with nutritional remedies, probiotics, prebiotics, and dietary and lifestyle advice generally did improve – but not nearly to the extent that the fecal transplant group did. Dr. Kenyon reported that most had improved by 30-40% (N=10), two people – one who had had ME/CFS for decades but improved rapidly on Dr. Kenyon's regimen – improved by 90%, two by 50-75% and the rest with lesser improvements.

Dr. Kenyon, not surprisingly, concluded that fecal transplants are more effective at repairing gut flora than pre and probiotics. While two people responded poorly to the transplants, Kenyon reported they generally provide a safe and potentially effective approach to ME/CFS.

Fecal transplants

That begs the question – just exactly what is a fecal transplant? It turns out that a variety of transplants are done. Some transplants transfer all the fecal matter while others filter out other components and only transfer the bacteria.

The Taymount Clinic reported that they implant only bacterial matter. People who go the home route obviously transfer everything: get poop from a healthy donor, and then use saline solution and an enema to get the poop in (which they hold for as long as possible).

As might be imagined raw fecal matter contains all sorts of substances of which bacteria make up just one component. Generally about 75% water and 25% solid matter, bacteria make up between 25-55% of the solid matter and 6-13% of the total matter. That's a lot of bacteria – approximately one hundred billion per gram of wet stool – although only 3.0%–6.6% of total fecal matter may be composed of viable bacteria.

Some history
Other components found in fecal matter include significant numbers of epithelial cells that have flaked off the colon (colonocytes), single-celled organisms call archeae and other primitive organisms, viruses, fungi and metabolites.

A Clostridium difficile outbreak in the U.S. caused doctors to search for alternative treatments In the U.S.. fecal transplants have mostly been used to battle life-threatening Clostridium difficile infections. Transplants got a boost in early 2000's after a particularly virulent form of C. difficile hit the U.S., causing gastroenterologists and patients to scramble for more effective treatments. Six hundred and twenty-five thousand C. difficile cases are believed to occur in the U.S and Europe every year.

One women's unstoppable C. difficile infection prompted her gastroenterologist to tell her, after seven months, to get her affairs in order. She ended up using her daughter as a donor in 2014. She reported:

"My gut drank up the infusion as if it were dying of thirst. My colon, after five months of near-constant spasms, recovered in one transformative instant. Overnight, I went from having 30 bowel movements a day to having one. For breakfast the next morning, I ate a quesadilla loaded with black beans, cheese, salsa, lettuce, and guacamole. I've had no recurrence of C. diff. since."

Four pharmaceutical companies in the U.S. reportedly provide stool donors to doctors – mostly for C. difficile infections. In 2016 the FDA's decision to require stool banks to provide an expensive investigational new drug application (IND) in order to provide stool resulted in the agency being accused of erecting barriers to treatment which would result, among other things, in more unregulated, home use. Other less restrictive measures were proposed.

Although it's believed that tens of thousands of fecal transplants have been done safely, the FDA recently reported for the first time that multi-drug resistant infections were transferred via fecal transplants to two people one of whom had died. The death occurred in a man with a compromised immune system who had been given a transplant which had not been screened for a type of resistant E. coli,. As a result, as of July 15th of this year, the FDA is requiring stool transplant companies to screen their poop for a variety of multi-drug resistant organisms.

Conclusion
The first stab at a fecal transplant study in ME/CFS was weak in statistics and strong in vivid detail. Dr. Kenyon's fecal transplants – used mostly in ME/CFS plus IBS patients – used only bacterial matter and were done in bulk – ten transplants over ten days – from different donors to ensure that a wide variety of flora was transmitted. With seven of the 21 treatment resistant patients reportedly returning to full or near normal health, and six receiving significant improvements in energy, the results were surprisingly good.

While the results were promisingly we need more rigorous studies and one, funded by Invest In ME and lead by Peter Johnsen, a Norwegian researcher is underway. Data collection from the 80 person, randomised, placebo-controlled study at the University Hospital of North Norway started in February of this year and is slated to wind up in February of next year. I couldn't tell how many fecal transplants would be given but changes in gut microbiome, metagenome, metabolome, gut barrier integrity and immune functioning will be assessed at three time points during the year long study.

Johnsen's 2018 (n=86) study found that fecal transplants "provided significant symptom relief for people with IBS. (In a nice bit of collaboration Maureen Hanson will be testing some of Johnsen's samples for gut dysbiosis.)

2) FDA issues alert after fecal microbiota transplant death

Yesterday the Food and Drug Administration (FDA) issued a safety alert after one patient died and another suffered an invasive infection, with both illnesses caused by extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli after receiving fecal microbiota transplants (FMTs) from the same donor.

The donor stool used in both patients had not been tested for ESBL-producing gram-negative organisms prior to use, and subsequent testing has showed the stool to be positive for ESBL-producing E coli. The FDA, which has not approved FMT for clinical use, said both patients were immunocompromised. The FDA is also pulling the plug on several ongoing clinical trails using FMT, the New York Times reported, until investigators can demonstrate they are screening stool for harmful organisms. "FDA is informing members of the medical and scientific communities and other interested persons of the potential risk of transmission of MDROs by FMT and the resultant serious adverse reactions that may occur," the FDA said in its safety alert.

3) 2012 the GI microbiome and its role in Chronic Fatigue Syndrome

Journal of the Australasian College of Nutritional and Environmental Medicine

Chronic Fatigue Syndrome (CFS) has a complex and multifactorial etiology making treatment and definitive diagnosis, currently made through exclusion, difficult. Current therapies, such as cognitive behaviour therapy and graded exercises, are inadequate and targeted to address symptoms, rather than the underlying disease pathology. Increasing evidence implicates the microbiota of the gut in a number of conditions previously thought distinct from the gastrointestinal system. Previous work with bacteriotherapy in CFS has suggested a link between the condition and the composition and health of the gut microbiota.

Here, we review and further examine a larger cohort of CFS patients who had undergone bacteriotherapy for their CFS. Method: A total of 60 patients from the Centre for Digestive Diseases presented with CFS. Of these, 52 patients had concurrent IBS and 4 patients additionally had constipation. All underwent initial transcolonoscopic infusion of 13 non-pathogenic enteric bacteria. 52/60 patients undertook an additional rectal infusion a day later and 3/60 undertook an additional 2 rectal infusions. Results: 35/60 patients who underwent initial bacteriotherapy responded to treatment. 10/15 patients who failed this course were offered a secondary transcolonoscopic infusion followed by a rectal infusion or an oral course of cultured bacteria. Of these 7/10 responded, giving a total of 42/60 (70%) patients who responded to treatment. Contact was achieved with 12 patients after 15-20 year follow-up.

Complete resolution of symptoms was maintained in seven of the twelve patients and 5/12 did not experience recurrence for approximately 1.5-3 years post bacteriotherapy.

Conclusion: Bacteriotherapy achieves initial success rate of 70% in CFS and a 58% sustained response. Given that manipulation of the colonic microbiota improved CFS symptoms, bacteriotherapy for CFS warrants further investigation and may provide further insight into a possible etiology of CFS.