

## The PACE Trial did not go unchallenged for five years

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28<sup>th</sup> March 2016

On 21<sup>st</sup> March 2016 Rebecca Goldin, Director of STATS.org and Professor of Mathematical Sciences at George Mason University in Fairfax, Virginia, published her devastating critique of the PACE trial, asking in bewilderment: “How did the study go unchallenged for five years?” ( <http://www.stats.org/pace-research-sparked-patient-rebellion-challenged-medicine/> ); others have been asking the same question.

However, the iatrogenic disaster that is the PACE trial did not go unchallenged for five years.

It is important that there should be an accurate record of the many challenges which were submitted by numerous people, including Professor Malcolm Hooper, but which were either ignored, dismissed, publicly ridiculed, denied outright or denigrated, for example, as in Nigel Hawkes’ feature article in the British Medical Journal: “Dangers of research into chronic fatigue syndrome -- **Nigel Hawkes** reports how threats to researchers from activists in the CFS/ME community are stifling research into the condition” (BMJ 2011;342:d3780 doi: 10.1136/bmj.d3780 Page 1).

Hawkes wrote that publication of the PACE results prompted a: “response to the Medical Research Council (MRC), which part funded the trial, and a shorter 43 page rebuttal to the Lancet. Both were written by Malcolm Hooper, emeritus professor of medicinal chemistry at the University of Sunderland, who branded the trial “unethical and unscientific.” He wrote: “Entry criteria were used that have no credibility; definitions and outcome measures were changed repeatedly; data appears to have been manipulated, obfuscated, or not presented at all (so it cannot be checked) and the authors interpretation of their published data as ‘moderate’ success is unsustainable.” Both the MRC and the Lancet have considered the submission and rejected it, the Lancet commenting that the volume of critical letters it received about the PACE trial smacked of an active campaign to discredit the research.

*‘It is a relentless, vicious, vile campaign designed to hurt and intimidate’, Professor Wessely says....‘These people are sulphurous, vicious, horrible’.*

*“Professor Wessely is not alone. All of those who approach CFS/ME from a psychiatric perspective are the targets of critics who believe the disease has a physical cause that would have been discovered by now if the debate, and the research money, had not been cornered by what they see as a conspiracy of psychiatrists, characterised by them as ‘the Wessely school’.*

*“As for Professor Wessely, he gave up active research on CFS/ME 10 years ago. He now specialises in the problems of war veterans. ‘I now go to Iraq and Afghanistan, where I feel a lot safer’, he says”.*

Such public disparagement is characteristic of how genuine and legitimate complaints about the PACE trial have been treated. All challenges from within the UK were simply buried without trace, even by Ministers of State.

Indeed, on 6<sup>th</sup> February 2013 there was a “debate” on the PACE trial in the House of Lords for which, on his own admission, Professor Peter White (Chief Principal Investigator of the trial) briefed all those who spoke in support of it, with the intended result that the study was enshrined in Hansard as an officially-recorded success story.

It was not until David Tuller from America took up the cause that the whole matter was subjected to world-wide scrutiny by academics, medical scientists and statisticians whose views could not be dismissed or silenced.

It is worth noting that currently there are calls for the involvement of UK’s Royal Statistical Society: the RSS has already been involved but was conflicted, so declined to assist (see below).

Some of Professor Hooper’s challenges about the PACE trial are listed below; most are available at [www.meactionuk.org.uk](http://www.meactionuk.org.uk)

(i) The PACE trial is believed to be the first and only clinical trial that patients and the charities that support them tried to stop before a single patient could be recruited. As long ago as 2007, multiple successful FOIA requests resulted in considerable insight into the workings of the PACE trial.

In February 2010 these culminated in “MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR” ( <http://www.meactionuk.org.uk/magical-medicine.pdf> ). This was sent to Ministers of State and to the MRC itself: it was ignored for almost a year, until on 6<sup>th</sup> January 2011 (ie. before publication of selective results of the PACE trial) Dr Frances Rawle, Head of Corporate Governance and Policy at the MRC, conceded that the reason for the PACE trial was because (quote): *“there was a lack of high quality evidence to inform treatment of CFS/ME and in particular on the need to evaluate treatments that were already in use and for which there was insufficiently strong evidence from random controlled trials of their effectiveness”*

That was an astonishing admission, since the NICE Clinical Guideline on “CFS” of 22<sup>nd</sup> August 2007 relied upon the psychiatric lobby’s “evidence-base” to recommend the use of CBT and GET nationally as the intervention of choice, yet the MRC confirmed – in writing -- that there was insufficient evidence for the implementation of this nationwide programme of CBT and GET recommended by NICE in its Clinical Guideline, so NICE jumped the gun by four years.

(ii) Again before publication of any PACE trial results, on 1<sup>st</sup> March 2010 Professor Hooper submitted a formal complaint to the West Midlands Multicentre Research Ethics Committee, this being the body which had granted ethical approval for the PACE trial. There was considerable concern that the Chief Principal Investigator (Professor Peter White)

had not adhered to what had been approved by the MREC yet the MREC had taken no action ( <http://www.meactionuk.org.uk/MREC-complaint.htm> ).

On 22<sup>nd</sup> March 2010 a response was sent by Janet Wisely, Director of the National Research Ethics Services (which is part of the National Patient Safety Agency). In it, she confirmed that they had been in touch with Professor Peter White and thereafter decided that *"In the case of the PACE Trial I have concluded that there is no likely benefit of a more extensive review of the original decision made by the REC because it was a decision made a long time ago"*.

(iii) Following publication in The Lancet of selective results of the PACE Trial, in March 2011 Professor Hooper submitted a detailed formal complaint to The Lancet ( <http://www.meactionuk.org.uk/COMPLAINT-to-Lancet-re-PAACE.htm> ).

On the instruction of The Lancet's Editor-in-Chief, Dr Richard Horton, the Executive Editor responsible for the fast-track publishing of the selective PACE results that was insisted upon by Professor Peter White (Dr Stuart Spencer) sent an email to Peter White notifying him of Professor Hooper's complaint, and Peter White replied to Stuart Spencer saying that he was not surprised and that (quote) *"We'll deal with it"*.

For the avoidance of doubt, following Professor Hooper's complaint, Zoe Mullan, a Senior Editor at the Lancet, included in her response Peter White's letter to Richard Horton: it was in this letter that Peter White wrote that the PACE trial *"does not purport to be studying CFS/ME but CFS simply defined as a principal complaint of fatigue...."*. That letter was important because in it, Peter White denied in writing carrying out a study for which the MREC had granted ethical approval.

On 18<sup>th</sup> April 2011 Richard Horton spoke on Australian ABC radio about the PACE trial; interviewed by Dr Norman Swan, Horton was openly contemptuous about Professor Hooper's complaint: *"the paper went through peer review very successfully, it's been through endless rounds of peer review and ethical review so it was a very easy paper for us to publish. It was only at the point of publication and just after that we have had this extraordinary negative reaction....We have been deluged with dozens of letters raising serious objections to the conduct and interpretation of the study. Most recently a 43 page diatribe (Professor Hooper's formal complaint) calling for the paper to be retracted based upon the fact that it is entirely invalid and unethical....Pretty much every aspect of the study you can think of has been impugned....I think the criticisms about this study are a mirage..."*

*"The accusations that are being made about (the investigators) is that they have behaved unethically, breached international standards of ethics and indeed...allegations have been made to the professional authorities, the General Medical Council here in the UK about the work of these scientists on the basis of the flimsiest and most unfair allegations...."*

*"One sees a fairly small... very vocal and very damaging group of individuals who have I would say actually hijacked this agenda and distorted the debate so that it actually harms the overwhelming majority of patients"* ( <http://www.abc.net.au/rn/healthreport/stories/2011/3192571.htm> ).

However, of particular note is what Professor Michael Sharpe (a PACE trial Principal Investigator) said in the same broadcast: *“What this trial wasn't able to answer is how much better are these treatments than really not having very much treatment at all”*.

Richard Horton's public display of disdain continues unabated, as exemplified in his support for the persistent refusal by Professor Peter White to release the raw data to legitimate scientists who seek to re-analyse it in accordance with the original PACE trial protocol.

(iv) On 28<sup>th</sup> May 2011 Professor Hooper provided his detailed response to Professor White's letter to Richard Horton ( <http://www.meactionuk.org.uk/Comments-on-PDW-letter-re-PACE.htm> ).

(v) On 30<sup>th</sup> June 2011 Professor Hooper received an unsolicited invitation from the Editor of the magazine of the Royal Statistical Society (“Significance”) to write an article on the PACE Trial for publication in the December issue. He was informed (in writing) that: *“We do publish, among other things, articles exposing unjustified statistical claims. A piece on ME would be specially welcome to us, as ME is a topic of great interest to the public and treatment for it, if unjustified, should be exposed as such....The focus of the article should be on the curious situation that could result in participants being deemed to have attained levels of physical function and fatigue ‘within the normal range’ when they had actually deteriorated on these parameters over the course of the trial....What you describe as the ‘tragedy for patients’ is our main concern”*.

On 12<sup>th</sup> September 2011 the article was duly submitted ( Statistics and ME <http://www.meactionuk.org.uk/Statistics-and-ME.htm> ) but on 28<sup>th</sup> November 2011 Abdel Khairoun, Editorial and Membership Assistant, sent an email saying: *“The Editor was considering the article for an issue but I regret to inform you that after consideration and consultation has now decided against using it. I apologise for my error in not communicating this to you sooner”*.

When he agreed to write the article, Professor Hooper was unaware that the Director of the Board of Straight Statistics, a pressure group whose stated aim is to detect and expose the distortion and misuse of statistical data and to identify those responsible (the Royal Statistical Society's “Significance” being the executive of Straight Statistics), was Nigel Hawkes -- the same Nigel Hawkes who in the same month that the RSS invited <http://www.meactionuk.org.uk/Comments-on-PDW-letter-re-PACE.htm> Professor Hooper to write an article for them (June 2011) had published an attack on him in the BMJ, allying him with “CFS/ME” activists who intimidate researchers because they do not approve of psychiatric research into the disorder, or that Hawkes was also a member of Council of The Royal Statistical Society.

Equally Professor Hooper was unaware that another member of Straight Statistics' Board of Directors was Dr Ben Goldacre, a psychiatrist and former research fellow at the Institute of Psychiatry where Professor Simon Wessely is Vice-Dean of Academic Psychiatry. Goldacre is a regular Guardian columnist in which he *“skewers the enemies of reason. If you're a journalist who misrepresents science for the sake of a headline....then beware: your days are numbered”*. He seeks to promote his opposition to what he regards as “bad science”;

according to Wikipedia, Goldacre claims to be *“devoted to criticism of scientific inaccuracy”* and (somewhat ironically) on 24<sup>th</sup> July 2010 he wrote: *“Even those carrying out academic research are guilty of twisting scientific facts to suit their purposes”* (this being the very subject of Professor Hooper’s article for the RSS).

Yet, as a member of the Board of Directors of Straight Statistics, Goldacre has remained strangely silent about the obfuscatory and clearly contrived statistical analysis of the PACE Trial data and the exaggerated claims for the efficacy of the interventions used.

Could it be that, despite the aims of the Royal Statistical Society being to maintain statistical standards, there was never any chance of Professor Hooper’s invited article being published by the RSS?

It may be worth noting that Professor Goldin’s Sense about Statistics (STATS.org) is a collaboration between Sense about Science USA and the American Statistical Association; its logo also lists Sense about Science UK, so perhaps a word of caution is indicated because in the UK, Sense about Science has been less than supportive of those calling for biomedical research into ME.

On 18<sup>th</sup> June 2005 The Times carried an item by Tracy Brown that promoted a Discussion Paper extolling the virtues of the peer-review system in the protection of the public. Being aware of the extent of published academic unrest about corruption of the peer-review system, this merited further investigation, which revealed that Tracy Brown is Director of Sense about Science, a registered charity whose actions and unstated aim appear to be to “educate” the public so that it unquestioningly accepts its own agenda for ever-tighter control of the nation’s health, thus limiting the scope of public debate about science.

Apart from Tracy Brown herself, other members of the Sense about Science Working Group that produced the Discussion Paper on peer review included Professor Colin Blakemore, then Chief Executive of the Medical Research Council, and Fiona Fox, Director of the Science Media Centre (a sibling organisation of Sense about Science), of which Professor Sir Simon Wessely is a founder member and trustee and on whose Science Advisory Panel he sat.

Causing particular distress to the ME community was not only the fact that Sense about Science promotes Professor Michael Sharpe’s (PACE PI) glowing endorsement of CBT and GET (*“The good news is, the benefits of these treatments is still apparent two years later, and they do not lead to a relapse of the illness. This new finding should reassure patients who want to try these treatments”*) ([http://www.senseaboutscience.org/for\\_the\\_record.php/214/response-to-headlines-suggesting-me-is-all-in-the-mind](http://www.senseaboutscience.org/for_the_record.php/214/response-to-headlines-suggesting-me-is-all-in-the-mind)) but perhaps even more importantly, it was the fact that the initiative for the inaugural award of the John Maddox prize was shared by the journal Nature and Sense about Science and that it was jointly awarded to Professor Sir Simon Wessely specifically for his “courage” in facing opposition to his views about ME and Gulf War Syndrome.

On 6<sup>th</sup> November 2012 it was announced that: *“Two strong-minded individuals are the first winners of an award for standing up for science....The prize rewards individuals who have*

*promoted sound science and evidence on a matter of public interest, with an emphasis on those who have faced difficulty or opposition in doing so". To award the prize to Simon Wessely further entrenches the unfounded notion that ME is a behavioural disorder that is perpetuated by "aberrant illness beliefs", "maladaptive coping" and "hypervigilance to normal bodily sensations".*

For Wessely to have received such an award initiated by Sense about Science was deemed by many to be a travesty.

(vi) On 10<sup>th</sup> December 2012 the Countess of Mar submitted a formal complaint to the now-extinct Press Complaints Commission about The Lancet's failure to correct the Bleijenberg and Knoop Comment of a 30% "recovery" rate which, despite denials by Dr Astrid James, Deputy Editor of The Lancet, was upheld.

(vii) In September 2013 Professor Hooper exposed the involvement of the psychiatric lobby with the Science Media Centre and the harm done by the dishonest promotion of the success of the PACE trial ( <http://www.meactionuk.org.uk/The-SMC-and-its-campaign-against-MECFS.pdf> ).

The above are merely examples of some of the challenges submitted by Professor Hooper, but they demonstrate that it is simply untrue that the PACE trial went unchallenged for five years.

### Further background

There is much more at stake here than the PACE trial fiasco, for example:

(A) In 1994, the ME charity Westcare published a report that was co-funded by the UK Department of Health; it emphasised the organic nature of ME/CFS and did not find it to be a somatoform disorder. Incensed that their input was rejected, in 1996 the psychiatric lobby orchestrated and published the Joint Royal Colleges Report on CFS (CR54) which had such devastating results in the UK, key messages from these august institutions being:

*"The group within CFS with more symptoms, profounder fatigability, greater disability and longer illness duration is the subset with the strongest associations with psychological disorder"*

*"The possibility that abnormalities of immune function play a role in the pathogenesis of CFS has attracted considerable attention. Such abnormalities should not deflect the clinicians from the biosychosocial (psychiatric) approach and should not focus attention towards a search for an 'organic' cause"*

*"No investigations should be performed to confirm the diagnosis".*

(B) During the life of the UK Chief Medical Officer's Working Group on ME/CFS (1998-2002), members were ordered not to discuss the deliberations and were even threatened with the Official Secrets Act.

If the psychiatric lobby which dominated that Working Group was so confident that they were right, why the need to force the suppression of opposing views by resorting to threats of prosecution under the Official Secrets Act in a Working Group that had nothing to do with State security but was supposed to be acting simply in the best interests of sick people?

It is common knowledge that Professor Peter White and four of his close colleagues walked out because they were not getting their own way (they were determined that the Report should categorise "CFS/ME" as a somatoform disorder, but they failed to achieve their objective).

(C) In 2007, Professor Hooper published an article entitled *"Myalgic Encephalomyelitis: a review with emphasis on key findings in biomedical research"* in which he wrote:

*"An ill-founded approach offers a common psychiatric explanation..... The disputed claims of some psychiatrists that all these syndromes are expressions of somatisation or are exemplified by the biopsychosocial theory lack an intellectually sound basis..... There can be little doubt now that ME is correctly described as an encephalitis with up-regulation of pro-inflammatory immune responses, coupled with down-regulation of suppressor cytokines. This, coupled with the association of NTE (neuropathy target esterase) genes, validates the WHO nomenclature and classification under neurology. Undoubtedly, the perverse use of "CFS" to impose a psychiatric definition for ME/CFS by associating it with fatigue syndromes has delayed research, the discovery of effective treatment(s) and care and support for those with (ME/CFS)" (J Clin Pathol 2007;60:466-471).*

Although the paper had been published for over a year (having been peer-reviewed and having satisfied the BMJ Publishing Group lawyers), in 2008 it was announced on the internet that Professor Hooper had retracted his paper. Professor Hooper had not retracted his paper: he had not been contacted by the journal and initially knew nothing about the alleged retraction.

Triumphant and immoderate comment abounded on the internet that it had been retracted because it was flawed and the journal's website did indeed carry a notice that the paper had been retracted, as did PubMed.

Retraction of a published paper is a serious matter because it confers disgrace on the author(s) and is damaging, having global implications on the author's credibility and reputation.

Following detailed investigations and negotiations with the Queen's solicitors (Messrs Farrer & Co, who also act for the BMJ Publishing Group), the following statement was agreed: *"The BMJ Group wishes to inform readers that a series of technical errors resulted in the unjustified retraction of the article 'Myalgic Encephalomyelitis: a review with emphasis on key findings in biomedical research'. The article's citation remains as originally published*

*(J Clin Pathol 2007;60:466-471; doi10.1136/jcp.2006.042408). The Journal of Clinical Pathology offers an unreserved apology to the author of the article, Professor Malcolm Hooper, and regrets any confusion or distress that may have been caused". This was acknowledged by the journal's lawyers to be a very serious and unfortunate incident.*

The truth of what actually happened may never be publicly known, because those who were involved with it had to sign what was effectively a gagging agreement.

(D) It may not have been coincidence that in 2008, Professor Hooper was an expert witness in the High Court challenge to the NICE Guideline on CFS (CG53) in which Professor Peter White was so instrumental, so anything that damaged Professor Hooper's credibility was to the advantage of NICE and its lawyers (Messrs Beachcroft, who act for the Government) and of the Guideline Development Group which formulated the Guideline.

At the 11<sup>th</sup> hour, Messrs Beachcroft threatened the Claimants' lawyers with punitive damages; sadly, the lawyers succumbed to the threats and withdrew about 60% of the Claimants' evidence, with the result that their challenge failed on all counts. Notwithstanding, the Judge fined the Claimants' lawyers £50,000.00.

In summary, all these challenges to the dismissal of ME as a behavioural disorder were unsuccessful.

However, when the full history of the disease is written, it should not be overlooked that the Establishment's position was repeatedly contested.

It can only be hoped that future generations of clinicians may learn from what is undoubtedly a medical scandal of immense proportions.