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A response to Professor Esther Crawley's broadcast on BBC Radio Bristol

Margaret Williams **6th November 2016**

It has been said that people like Professor Esther Crawley and those involved in PACE-Gate genuinely don't understand that the whole endeavour of science is predicated on objective and reproducible measurements (private communication: 5th November 2016).

In her broadcast on 5th November 2016 with Dr Phil Hammond on BBC Radio Bristol in which she promoted her FITNET trial (**F**atigue **I**n **T**eenagers on the inter**NET**), Professor Crawley made some very unscientific statements.

The FITNET trial is funded by Health Technology Assessment (HTA) Programme (UK), which claims to fund "independent" research about the effectiveness, costs and broader impact of healthcare treatments; it is the largest of the programmes supported by the National Institute of Health Research (NIHR), which is the research arm of the NHS. The HTA Programme says: "*Our research serves a wide variety of key stakeholders, including decision-makers in local government (and) policy-makers (including NICE)"*.

Its Clinical Evaluation and Trials Board includes Professor Michael Sharpe, one of the PACE Principal Investigators and a staunch supporter of behavioural interventions for ME/CFS.

This NHS support presents a major discrepancy, because whilst one arm of the NHS is funding behavioural interventions to be used in the FITNET trial (CBT and GET), another arm of the same NHS (NHS Plus, a Government-funded project) has condemned graded exercise as it may cause (quote): "*significant deterioration*" (see below).

The "information" leaflets – all headed "**Dealing with Chronic Fatigue (CFS/ME) in Young People….Specialist help for ME"** -- produced by CFS/NHS/PAEDIATRICS/BATH are lacking in any appreciation of what ME/CFS actually is.

The leaflets are deeply concerning because, first and foremost, "Chronic Fatigue" is not "CFS/ME" and they pay no attention to the reality of ME/CFS, for example:

The leaflet "Cognitive Behaviour Therapy" starts off by saying: "*Hassles and problems are part of everyday life…but sometimes…the problems seem to take over and you*

may end up feeling unhappy…People with problems often think in unhelpful ways….CBT will help you find the ***link*** *between what you think, how you feel and what you do…(and) how to face and* ***overcome*** *your problems*".

The "Exercise Chart for Severely Affected" requires one specified exercise **each hour**.

The leaflet entitled "Thinking Traps" says: "*"This leaflet will help you find the negative trap you have fallen into. You will then be able to challenge your negative thoughts and fight back*".

The "Thoughts and Feeling Diary" requires that at the end of each day, the young person must write down what they have done that day, naming the time, who was there, where they were, what was happening before, and what happened afterwards.

The "Managing Feelings and Emotions" leaflet says: "*If we feel angry and frustrated, we might shout or swear at someone….If we feel anxious and worried about something, we might avoid doing it, and make up excuses….****Don't worry – the trick is to just a little bit more each time you do something****."*

The "Activity, Rest and Sleep Diary" is to *"help you use a graded activity programme to record what you do each week. This will help as you gradually increase the amount you do"*.

The "Energy Management" leaflet says: "*We have lots of ways to help you…including charts and cards…When you have managed* ***2 weeks*** *of the same activity daily, you can start to increase it by* ***10% a week***".

In her interview, Crawley said about ME/CFS: "*we know very little about it*" and this was endorsed by Hammond: *"We certainly know very little about it"*.

Such statements are untrue: although the cause remains unknown, much is known about significant pathology in ME/CFS:

- abnormalities of the central nervous system include abnormalities of brain cognition, brain perfusion, brain metabolism and brain chemistry; there is evidence of low blood flow in multiple areas of the brain; neuro-imaging has revealed lesions in the brain of approximately 80% of those tested and according to the researchers, these lesions are probably caused by inflammation: there is a correlation between the areas involved and the symptoms experienced; abnormalities on SPECT scans provide objective evidence of central nervous system (CNS) dysfunction; there is evidence of a chronic inflammatory process of the CNS, with oedema or demyelination in 78% of patients tested; there is evidence of a significant and irreversible reduction in grey matter volume (especially in Brodmann's area 9) which is related to physical impairment and may indicate major trauma to the brain

(which could also explain the low recovery rate); there is evidence of seizures; a positive Romberg is frequently seen in authentic ME/CFS patients

- abnormalities of the autonomic and peripheral nervous systems: there is evidence of dysautonomia in ME/CFS patients

- cardiovascular dysfunction: there is evidence of haemodynamic instability and aberrations of cardiovascular reactivity (an expression of autonomic function); there is evidence of diastolic cardiomyopathy; there is evidence of endothelial dysfunction; there is evidence of peripheral vascular dysfunction with low oxygenation levels and poor perfusion and pulsatilities; there is evidence of abnormal heart rate variability and evidence of abnormal orthostasis; there is evidence of abnormally inverted T-waves and of a shortened QT interval, with electrophysiological aberrancy; there is evidence of abnormal oscillating T-waves and of abnormal cardiac wall motion (at rest and on stress); there are indications of dilatation of the left ventricle and of segmental wall motion abnormalities; there is evidence that the left ventricle ejection fraction – at rest and with exercise – is as low as 30%; there is evidence of reduced stroke volume

- respiratory system dysfunction: there is evidence of significant reduction in many lung function parameters including a significant decrease in vital capacity; there is evidence of bronchial hyper-responsiveness

- a disrupted immune system: there is evidence of an unusual and inappropriate immune response: there is evidence of very low levels of NK cell cytotoxicity; there is evidence of low levels of autoantibodies (especially antinuclear and smooth muscle); there is evidence of abnormalities of immunoglobulins, especially sIgA and $IgG_{3,}$ (the latter having a known linkage with gastrointestinal tract disorders); there is evidence of circulating immune complexes; there is evidence of a Th1 to Th2 cytokine shift; there is evidence of abnormally diminished levels of intracellular perforin; there is evidence of abnormal levels of interferons and interleukins; there is evidence of increased white blood cell apoptosis, and there is evidence of the indisputable existence of allergies and hypersensitivities and positive mast cells, among many other anomalies, with an adverse reaction to pharmacological substances being virtually pathognomonic

- virological abnormalities: there is evidence of persistent enterovirus RNA in ME/CFS patients; there is evidence of abnormalities in the 2-5 synthetase / RNase L antiviral pathway, with novel evidence of a 37 kDa binding protein not reported in healthy subjects or in other diseases; there is evidence of reverse transcriptase, an enzyme produced by retrovirus activity, with retroviruses being the most powerful producers of interferon; there is evidence of the presence of HHV-6, HHV-8, EBV, CMV, Mycoplasma species, Chlamydia species and Coxsackie virus in the spinal fluid of some ME/CFS patients, the authors commenting that it was surprising to find such a high

yield of infectious agents on cell free specimens of spinal fluid that had not been centrifuged

- evidence of muscle pathology: this includes laboratory evidence of delayed muscle recovery from fatiguing exercise and evidence of damage to muscle tissue; there is evidence of impaired aerobic muscle metabolism; there is evidence of impaired oxygen delivery to muscle, with recovery rates for oxygen saturation being 60% lower than in normal controls; there is evidence of prolonged EMG jitter in 80% of ME/CFS patients tested; there is evidence of greater utilisation of energy stores; there is evidence that total body potassium (TBK) is significantly lower in ME/CFS patients (and abnormal potassium handling by muscle in the context of low overall body potassium may contribute to muscle fatigue in ME/CFS); there is evidence that creatine (a sensitive marker of muscle inflammation) is excreted in significant amounts in the urine of ME/CFS patients, as well as choline and glycine; there is evidence of type II fibre predominance, of scattered muscle fibre necrosis and of mitochondrial abnormalities

- neuroendocrine abnormalities: there is evidence of HPA axis dysfunction, with all the concomitant implications; there is evidence of abnormality of adrenal function, with the size of the glands being reduced by 50% in some cases; there is evidence of low pancreatic exocrine function; there is evidence of an abnormal response to buspirone challenge, with a significant increase in prolactin release that is not found in healthy controls or in depressives; there is evidence of abnormal arginine – vasopressin release during standard water-loading test; there is evidence of a profound loss of growth hormone; even when the patient is euthyroid on basic screening, there may be thyroid antibodies and evidence of failure to convert T4 (thyroxine) to T3 (tri-iodothyronine), which in turn is dependant upon the liver enzymes glutathione peroxidase and iodothyronine deiodinase, which are dependant upon adequate selenium in the form of selenocysteine (which may be inactivated by environmental toxins)

- defects in gene expression profiling: there is evidence of reproducible alterations in gene regulation, with an expression profile grouped according to immune, neuronal, mitochondrial and other functions, the neuronal component being associated with CNS hypomyelination

- abnormalities in HLA antigen expression: Teraski from UCLA found evidence that 46% of ME/CFS patients tested were HLA-DR4 positive, suggesting an antigen presentation

- disturbances in oxidative stress levels: there is mounting evidence that oxidative stress and lipid peroxidation contribute to the disease process in ME/CFS: circulating in the bloodstream are free radicals which if not neutralised can cause damage to the cells of the body, a process called oxidative stress: in ME/CFS there is evidence of increased oxidative stress and

of a novel finding of increased isoprostanes not seen in any other disorder; these raised levels of isoprostanes precisely correlate with patients' symptoms (isoprostanes being abnormal prostaglandin metabolites that are highly noxious by-products of the abnormal cell membrane metabolism); there is evidence that incremental exercise challenge (as in graded exercise regimes) induces a prolonged and accentuated oxidative stress; there is evidence of low GSH-PX (glutathione peroxidase, an enzyme that is part of the antioxidant pathway: if defective, it causes leakage of magnesium and potassium from cells)

- gastro-intestinal dysfunction: there is evidence of objective changes, with delays in gastric emptying and abnormalities of gut motility; there is evidence of swallowing difficulties and nocturnal diarrhoea; there is evidence going back to 1977 of hepatomegaly, with fatty infiltrates: on administration of the copper response test, there is evidence of post-viral liver impairment -- an increase of at least 200 in the copper level is the expected response, but in some severely affected ME/CFS patients the response is zero; there is evidence of infiltration of splenic sinuses by atypical lymphoid cells, with reduction in white pulp, suggesting a chronic inflammatory process; there is evidence that abdominal pain is due to unilateral segmental neuropathy; there is significant evidence that people with ME/CFS have increased serum levels of IgA and IgM against the LPS of gram-negative enterobacteria, indicating the presence of an increased gut permeability resulting in the autoimmunity seen in many ME/CFS patients; this indicates that the symptoms of irritable bowel seen in ME/CFS reflect a disorder of gut permeability rather than psychological stress as most psychiatrists believe (gastro-intestinal problems are a serious concern in ME/CFS, and 70% of the body's immune cells are located in the GI tract)

- reproductive system: there is clinical evidence that some female patients have an autoimmune oophoritis; there is evidence of endometriosis; there is evidence of polycystic ovary syndrome; in men with ME/CFS, prostatitis is not uncommon

- visual dysfunction: there is evidence of latency in accommodation, of reduced range of accommodation and of decreased range of duction (ME patients being down to 60% of the full range of eye mobility); there is evidence of nystagmus; there is evidence of reduced tracking; there is evidence of problems with peripheral vision; there is evidence that the ocular system is very much affected by, and in turn affects, this systemic condition.

Recently, Naviaux et al reported that targeted, broad-spectrum metabolomics of plasma revealed a characteristic chemical signature and showed that (ME)CFS is a highly concerted hypometabolic response to environmental stress that traces to the mitochondria (PNAS 2016:113:7).

As world expert Professor Anthony Komaroff said at the IACFSME conference in Fort Lauderdale in October 2016, we know that genes involved in signal transduction are hypomethylated but that genes involved in apoptosis are hypermethylated; that exercise triggers a characteristic gene expression signature involving 15 cytokines/adipokines/growth factor; that there is lower oxygen consumption leading to earlier conversion to anaerobic metabolism and that lactate levels are higher at all work effort; that most of the dysfunctional cytokines are pro-inflammatory and that there is evidence of chronic low-level inflammation. We know there is altered heart rate variability due to reduced cardiac vagal activity.

As a paediatrician with an interest in ME/CFS, why does Professor Crawley ignore this large body of science and persist in testing – yet again — a theory that has comprehensively and unarguably failed, and why did she make such insupportable assertions on BBC radio, demonstrating once again a fundamental lack of understanding of basic scientific principles?

Data from the FINE and PACE trials do not support Crawley's assertions; in fact they vitiate them and, as Komaroff also pointed out, it has been shown in a study of 990 ME/CFS patients that their belief about the cause of the illness did not explain their level of activity, a result that does not support the use of CBT, but Crawley said on air: *"the evidence for cognitive behavioural therapy and graded exercise therapy is good: it's good in adults…and if you're a child with chronic fatigue syndrome, you have a two-thirds chance of recovery at six months with treatment…I'll just say that again – two thirds at six months with treatment"*.

When Hammond mentioned that in the Dutch study upon which Crawley's FITNET trial is based, recovery was not sustained over time, Crawley's response was immediate: "*Oh people have really made a mistake on this…the recovery was still very high*". This appears to demonstrate Crawley's inability to accept that in the Dutch study in question, there was no difference between the active and control groups at long-term follow-up, which is consistent with every other trial of CBT.

Despite many trials that have attempted to cure ME/CFS by incremental physical exercise, none of these has demonstrated sustained objective improvement, let alone a cure for the disease.

Of importance is that by promising even a two-thirds recovery in her FITNET trial, Crawley is in breach of the General Medical Council Regulations as set out in "Good Medical Practice": *"You must not make unjustifiable claims about the quality or outcomes of your services in any information you provide to patients. It must not offer guarantees of cures"*.

Furthermore, Crawley is introducing bias into her own trial by declaring that the active therapy has already been shown to work. Given that the trial relies on subjective endpoints and is unblinded, this is particularly egregious.

In her broadcast, Crawley said of the PACE trial that: *"it was a GREAT, great trial…"*. Even though the PACE trial has been debunked beyond dispute, she seems to be blinkered, as evidenced by the fact that she co-authored a paper which claimed up to 40% recovery in the PACE trial participants (BMC Health Services Research 2011, 11:217 doi:10.1186/1472-6963-11-217) with which even the PACE trial authors disagreed, as they published a 22% recovery rate.

Crawley was dismissive about the biological studies that have produced ground-breaking results, including evidence of hypometabolism, saying: "*We have to stop doing these really small studies, because I think they're just confusing. They don't end up being what's called 'replicated', so they're not reproduced a second time, and I don't think they're adding, at the moment, to the world literature*".

Crawley went on to say about graded exercise therapy: "*the best evidence that you can ever get is what's called the systematic review…and the largest systematic review, of over 1,500 people was absolutely clear, there was no evidence of harm*".

The "evidence" from a systematic review of the literature cannot be taken in isolation (for example, Professor Peter White, whose life's work has been spent on proclaiming the benefits of behavioural interventions in ME/CFS, was involved in the Cochrane Database of Systematic Reviews 2014, Issue 4. "Exercise therapy for chronic fatigue syndrome": Larun L, Odgaard-Jensen J, Brurberg KG, Chalder T, Dybwad M, Moss-Morris RE, Sharpe M, Wallman K, Wearden A, White PD, Glasziou PP, thus potentially compromising the independence of the Review).

Over the years, there is abundant evidence from numerous surveys by ME/CFS charities of almost 5,000 patients that in such patients CBT is ineffective and that GET is unacceptable and sometimes positively harmful.

Those surveys include one sponsored jointly by the ME Association and Action for ME ("Report on a Survey of Members of Local ME Groups". Dr Lesley Cooper, 2000). Cooper found that ***"Graded exercise was felt to be the treatment that made more people worse than any other"*** **and that it had actually harmed patients**.

Another survey of 2,338 ME/CFS sufferers ("Severely Neglected: M.E. in the UK") was carried out in 2001 by Action for ME; its preliminary report stated: "***Graded exercise was reported to be the treatment that had made most people worse"***; in the final report, this was changed to stating that **graded exercise had made 50% of patients worse**.

The 25% ME Group for the Severely Affected carried out a further survey in 2004 which found that **93% of respondents found GET to be unhelpful, with 82% reporting that their condition was made worse**.

In 2005, a report ("Our Needs, Our Lives") published by The Young ME Sufferers Trust found that **88% had been made worse by exercise**.

In October 2006 the ME Association secured an acknowledgement by NHS Plus – a Government-funded project -- that GET (recommended in the NICE Guideline as part of CBT) can be harmful to people with ME/CFS. The NHS Plus Guidance leaflets now say: "*Although some RCTs show evidence of improved functional capacity for work, and reduced fatigue, some patients experience a significant deterioration in symptoms with this intervention*". The ME Association noted: **"*This is a significant acknowledgment by the NHS that GET has dangers to people with ME/CFS*".**

In 2008, Action for ME published a survey of over 2,760 patients ("M.E. 2008: What progress?") which found that **one third had been made worse by GET and that at their worst, 88% were bed/housebound, being unable to shower, bathe or wash themselves, and that 15% were unable to eat unaided**. The Press Release of 12th May was unambiguous: "***Survey finds recommended treatment makes one in three people worse***".

Professor Crawley, a member of the GDG that drew up the NICE Guideline, dismissed the AfME / AYME report's findings, saying the survey was unreliable: "*This survey is based on a biased sample of people who have had an issue with treatment and we cannot deduce who had graded exercise therapy delivered by a specialist, as NICE recommends*". Her dismissal was notable, given that she was -- and still is -- Medical Adviser to the charity AYME.

On 15th May 2008 a Joint Statement about CBT and GET by the ME Association and The Young ME Sufferers' Trust noted their *"serious concern for the safety of patients given this controversial approach to management. Put simply, the illness worsens as a result of physical and mental effort.* ***Advocating progressive exertion is to show a worrying lack of knowledge about the nature of the illness. Any treatment that causes an adverse reaction in 33% - 50% of those using it cannot be recommended as a blanket form of treatment****…. **We consider this is likely to result in iatrogenic damage to some patients".***

In 2009, the Norfolk and Suffolk ME Patient Survey of 225 respondents stated: ***"Respondents found the least helpful and most harmful interventions were Graded Exercise Therapy and Cognitive Behavioural Therapy".***

Hence there is an abundance of patient reports of harm (which are analogous to Yellow Card reporting of adverse drug reactions) from ME/CFS patients and charities (and indeed from NHS Plus) confirming that GET makes people with ME/CFS, including children, worse.

Regarding the economic value of CBT/GET, if an intervention has been shown to fail, how can it possibly be cost-effective?

Prior to the failed PACE trial and the 2012 paper by McCrone et al on the alleged cost-effectiveness flowing from it, as far as GET is concerned, there is no evidence at all of cost-effectiveness.

The single study which attempted to demonstrate that GET is more (or indeed less) effective than CBT was unable to show any difference between CBT and GET (McCrone P et al: Psychological Medicine 2004:34:991-999) and there were only two studies that considered the cost-effectiveness of CBT: one was the flawed (Dutch) study by Prins et al (Lancet 2001:357:841-847) and the other was a study by Wessely et al (BJGP 2001:51:15-18); it showed no cost-effective benefit from CBT.

Given the existing evidence, how can yet more trials of behavioural interventions be justified? Will anyone ever be held accountable for such a significant failure of regulatory and ethical oversight in supporting trials of disproven interventions on children?

Why do those with responsibility continually deny and disregard so much evidence and authorise the waste of public money on trials of interventions that have been shown to be ineffective?

Surely it is time to stop.