lying mechanisms and appropriate treatments. For example, a hallmark of these syndromes is "central" pain, in which pain (whether it be myalgia, arthralgia, or visceral pain or discomfort) is not due to damage or inflammation of peripheral tissues, but to an underlying disturbance in the central processing of pain that can be quantified objectively by using newer functional imaging techniques.[11] (Such findings also call into question some groups' interpretation of abnormal functional imaging results in Gulf war veterans as indicative of neural "damage."[12]) Because the pain in these conditions is not due to damage or inflammation of peripheral tissues, these conditions respond poorly to non-steroidal anti-inflammatory drugs or opioids and instead are more responsive to low night time doses of tricyclic compounds or other centrally acting analgesics. In addition, treatments such as aerobic exercise and cognitive behavioural therapy have been found to be useful.

Make no mistake: ill Gulf war veterans have a very real illness. It is not likely to get better without specific interventions. But we don't serve these or other veterans well by focusing inordinate attention on the specific exposure(s) that may have been responsible for some rare cases of illness. As patients, they deserve far better: the medical and scientific communities need to stop belittling and trivialising them and their illnesses, as well as individuals in the general population who have the same symptom complexes.

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Evening primrose oil for atopic dermatitis

Time to say goodnight

With concerns about using topical corticosteroids for atopic dermatitis sometimes reaching phobic proportions,[1] the emergence of a natural plant oil extract as a possible alternative treatment was well received in the early 1980s.[2 3] Interest was fuelled because evening primrose oil extract (containing 8-10% of gamma linolenic acid (GLA)) appeared to cause few side effects and because there was a very plausible mechanism to explain why supplementation with this essential fatty acid might work in atopic dermatitis.[4] The scene was therefore set for a new treatment, and physicians like myself were delighted to have another option to offer patients with this miserable condition.

Since then many studies have evaluated the efficacy of oral gamma linolenic acid supplementation for atopic dermatitis, with conflicting results. Fifteen studies (10 dealing with evening primrose oil, and five with borage oil, which contains even higher concentrations of GLA) were summarised in a systematic review of atopic dermatitis treatments that I and others conducted for the NHS Health Technology Assessment programmes.[5] Although we could not pool the data because of differences between study participants, GLA doses, and outcomes (which were often clinically meaningless), we found that the largest and best reported studies did not show convincing evidence of any benefit.[6]

Primary care p 1385

The last stone to be turned

One "unturned stone" has been the notion that GLA works only when given in very high doses.[3] In this week's *BMJ*, Takwale et al (p 1385) report the results of a double blind randomised controlled trial of high dose GLA capsules in 151 people with atopic dermatitis.[7] They found no statistically significant benefit for GLA supplementation when compared with placebo (liquid paraffin or olive oil). Although it is difficult to "prove a negative," the 95% confidence intervals surrounding the main effect estimate exclude a difference that is likely to be clinically useful. This most recent study, along with the recent decision of the UK's

BMJ 2003;327:1358–9

Medicines Control Agency's decision to withdraw the product licence, suggests that GLA supplementation for atopic dermatitis has had its day.

Yet many questions surrounding the story of evening primrose oil for eczema remain unanswered: how was this drug licensed in the first place and why have so few data been available in the public domain for open scientific debate?

Unanswered questions

In 1989 Horrobin et al published a meta-analysis in the *British Journal of Dermatology* of the two earliest studies plus another seven small (14-47 participants) company sponsored studies of evening primrose oil (Epogam, Scotia Pharmaceuticals) for atopic dermatitis.[8] They found that atopic dermatitis improvement scores for evening primrose oil were significantly better than placebo, with effects on itch being "particularly striking." Apart from the fact that the seven company trials included in that study have never since appeared in the public domain, the other concern about that meta-analysis was its exclusion of the one other independent and relatively large study (123 participants) by Bamford et al.[9] The company authors of the meta-analysis suggested that active versus placebo treatments became mixed up in the Bamford study, based on an analysis done by the company of fatty acid levels in blood samples taken from study participants.[8] After this meta-analysis was published, others thought it odd that Bamford et al never published a response to the company's serious criticisms of their study.[10] In fact Bamford immediately wrote a lengthy and clear explanation of the steps that were in place to avoid such purported contamination, but he was refused an opportunity to defend his study with a published response because the journal decided that Bamford's response did not add anything to the understanding on the use of evening primrose oil as a supplemental treatment for atopic eczema (J Bamford, written communication 12 Nov 2003). In desperation, Bamford tried to publish his response in other dermatology journals, but without success, so his defence of his original paper (a copy of which is now sitting on my desk) has to this day remained unpublished.

A year later, two British dermatologists wrote a detailed review article on evening primrose oil and atopic dermatitis. Out of courtesy, they showed a copy of the peer reviewed article to the manufacturers, who intimated their intent to pursue the matter legally further if the authors did not withdraw or modify the article substantially. (J Marsden, written communication, 27 November 2003). The article (now sitting on my desk) was never published despite getting to proof stage.

More significantly, in 1995 the Department of Health commissioned me and a colleague to conduct an individual patient meta-analysis of 20 studies of oral evening primrose oil supplementation for treatment of atopic dermatitis, which included 10 unpublished studies held by the company (Li Wan Po A, Williams HC. A systematic overview of clinical trials of Epogam in atopic eczema. Department of Health, 1995). Although it was our view that the report produced a relatively clear conclusion, we were never allowed to share the report in the public domain for reasons that are still unclear to me, even though it was funded by public money. Shortly after we submitted our report to the Department of Health, Searle, the company then responsible for marketing evening primrose oil, expressed concern that the contents of the report had been leaked, and the authors and referees were required to sign a written statement to the company (through the Department of Health) to indicate that this was not the case.

Too little data in the public domain

The Health Technology Assessment systematic review published in 2000 provided an opportunity for the company to hand over its unpublished studies for inclusion in that report.[5] Although Searle wrote back to tell us that they would be "compiling the data," no data have been forthcoming to date. We can only hope that it will be compiled in time for the current Cochrane review on GLA supplementation for atopic dermatitis.[11] Finally, in the autumn of 2002 the Medicines Control Agency withdrew the marketing authorisations for evening primrose oil following a "review of all the relevant information, including new studies," although which information and new studies is unclear from the very limited information available on the agency's website.[12]

In fairness to the innovators of evening primrose oil for atopic dermatitis, they evaluated their product more than many other products used in dermatology. Nobody would have been happier than myself if evening primrose oil had produced a clinically worthwhile benefit for eczema sufferers. But the history of its development has been marred by lack of data in the public domain. As we bid goodnight to the evening primrose oil story, perhaps we can awaken to a world where all clinical trial data, derived from people who are good enough to volunteer for such studies, reach the light of day, where they can be openly debated in the public domain.

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