Digicaylioglu and Lipton propose an alternative mechanism by which JAK-2 leads to the phosphorylation of a tyrosine residue of IkB α, in addition to the standard phosphorylation of two serine residues. Whether both forms of phosphorylation are required for the erythropoietin-mediated activation of NF-κB is not clear, but the sustained activation of NF-κB by erythropoietin in neurons might be explained by the activation of both phosphorylation pathways. NF-κB nuclear translocation then leads to the transcription of NF-κB-dependent neuroprotective genes, including some that inhibit apoptosis (XIAP and c-IAP2). This cross-talk between JAK-2 and NF-κB signaling has not been observed in non-neuronal cells, thus there are likely to be neuron-specific proteins that link the two pathways together. If these observations are confirmed and the proteins linking these two pathways are identified, this previously unappreciated complexity in neuroprotection would present new challenges to the understanding of neuronal signalling and might suggest cross-talk between other divergent signalling pathways. Such observations also present opportunities for identifying novel drug targets. Thus, erythropoietin exerts its potent neuroprotective actions through multiple protective signalling pathways, including the EPOR-Ras-MAPK and erythropoietinR-P13K-Akt/PKB pathways and the EPOR-NF-κB pathways. All the signalling pathways appear to be initiated by activation of EPOR-associated JAK-2.

Although erythropoietin has been proposed to have a prominent role in ischaemic preconditioning, this function has not been shown, nor has erythropoietin been shown to be directly induced by ischaemic preconditioning. Indeed, neuronal expression of erythropoietin is reduced after stimuli that induce ischaemic preconditioning. Lethal stresses and hypoxia/ischaemia clearly induce erythropoietin, but it seems that sublethal preconditioning stimuli are not potent enough to induce substantial concentrations of erythropoietin. Despite the lack of a direct evidence that endogenous erythropoietin mediates ischaemic preconditioning, erythropoietin may be an ideal exogenous preconditioning agent. Pretreatment of neurons with erythropoietin is potently neuroprotective. It is safe, well tolerated, can be administered systemically, and crosses the blood-brain barrier. One possible use of erythropoietin is preoperatively to precondition the brain before neurosurgical procedures and coronary artery bypass surgery or other surgical procedures that put the brain at risk of injury. Erythropoietin might also be beneficial in acute neuronal injury such as stroke or trauma, since erythropoietin reduces injury up to 6 h after the initial insult in animal models. Because the protective action of erythropoietin lasts only about 3 days, it would need to be administered chronically in the treatment of neurodegenerative diseases, so there may be untoward side-effects, since the long-term consequences of lengthy erythropoietin treatment may include polycythaemia. In addition to the potential direct therapeutic actions of erythropoietin, work on elucidating the downstream signalling pathways of erythropoietin-induced neuroprotective actions may offer novel therapeutic interventions that can be harnessed in the future to protect the vulnerable nervous system from injury.

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Chronic fatigue syndrome: a step towards agreement

The 1996 report by the Royal Colleges of Physicians, Psychiatrists, and General Practitioners, Chronic Fatigue Syndrome, received a mixed reception—approved by some, but severely criticised by others, including The Lancet. The patients’ organisations were among the harshest critics, and the report was seen by some as a cogent criticism that patients’ views had not been included within the report.

Now a new report has been published, and we hope that it will mark a turning point in the history of the illness. A working group on Chronic Fatigue Syndrome and Myalgic Encephalomyelitis or Encephalopathy, the name preferred by patient advocate groups in the UK, was set up in 1998 to report to the Chief Medical Officer of England and Wales. The fact that both names for the illness were used symbolises respect for different viewpoints whilst acknowledging the continuing lack of consensus on a universally acceptable name.

The brief of this 16-member working party was to review management and practice with the aim of providing guidance for professionals, patients, and carers, and to make recommendations, including those for research. It attempted to achieve a consensus between patients’ representatives and health professionals. How did it work out?

The good news is that a substantial amount of centre ground was established between medical researchers, practitioners, and patient advocates. However, not surprisingly there were serious and principled disagreements on several issues, which led to six members (all clinicians) deciding that they could not endorse the final report. Not surprisingly there were serious and principled disagreements on several issues. Four clinicians were unable to endorse the final report, arguing that it was insufficiently evidence based and paid too little attention to the biopsychosocial approach. Two patients also declined to endorse the final version,
believing that it paid too little attention to pathological models and portrayed rehabilitation approaches in too favourable a light. Nevertheless, whilst of concern, the disagreements should not detract from what was achieved by all the members.

So where is the centre ground? First, there is agreement with the report’s conclusion that the illness “is a real clinical condition, which can cause profound, often prolonged, illness and disability, and can have a very substantial impact on the individual and family”. It is also agreed that it can affect both sexes, and a wide range of ages, including children. The report makes plain that it will no longer be acceptable for clinicians to state that they do not “believe” in CFS/ME. The report is explicit: it states “inaction . . . due to ignorance or denial of the condition is not excusable”.

The report notes that a significant minority of patients who are very severely affected often receive the least support. Particularly welcome is the conclusion that patients need positive early diagnosis and appropriate management and advice, and that patients’ organisations have an important role to play in this. All parties will also welcome the conclusion that this often disabling and chronic disorder has not been addressed by sufficient research activity and public funding.

What treatments do the report recommend? One of the main polarities has been about rehabilitative treatments such as cognitive behavioural therapy (CBT) and graded exercise therapy (GET). These have been reported as beneficial in trials but have been criticised by the patients’ organisations because of negative reports from some of their members and the still limited evidence base. Furthermore, some have drawn the understandable, but erroneous conclusion that the success of either CBT or GET implies a psychogenic cause of the disorder. The report now signals acceptance of what is an unpalatable fact to some—symptom management and rehabilitative treatments, such as GET and CBT, are for now the best available in terms of evidence-based strategies. But there are key messages that both practitioners and patients need to understand in applying these therapies.

None of the rehabilitation approaches is intended to be curative, no approach has been found to be beneficial for everyone, and all can be tainted by poor practice by therapists lacking proper understanding of the disorder. Furthermore, the systematic review underpinning the report noted that those with the severest disabilities, and the young, have not been included in the randomised controlled trials to date, limiting the conclusions that can be drawn concerning either of these crucial groups.

The report is also correct to draw attention to the myths held by some patients and practitioners surrounding treatments such as CBT or GET that need to be overcome. For example, neither GET nor CBT insists on blind adherence to strict exercise regimens. CBT, for instance, is instead based on the principle that activity, physical or mental, must first be made manageable for the patient; the psychologist or therapist is there to help the patient to pace himself or herself.

Moving beyond the evidence from controlled trials, the report does endorse an additional approach to activity management known as “pacing”, which has been advocated by patients’ organisations and is consistently reported by their members as being helpful. Pacing proposes a balance, both of activity and rest, with the aim of maximising recovery and promoting self-empowerment. However, it has not yet been well defined or evaluated and should also be the subject of research.

Some of the recommendations will be continue to be controversial. Much of this controversy stems from the false view that those therapies pioneered by psychiatrists imply that the illness is, in that awful phrase “all in the mind”, or that failure to respond is the patient’s own fault. There are still too many reports from the field of patients being treated with disrespect or disbelief, and not being true collaborators in treatment. It is vital for the future that practitioners agree that there is no place for “boot camp” ideologies, as in overaggressive attempts at crude exercise regimens. Equally, there is no longer any place for a fatalistic acceptance of the disorder. Finally, those who, despite every effort, still remain severely affected, require service provision and further research.

This has clearly been a difficult and challenging experience for many of the participants in the working group. There is likely to be continuing discussion and even argument about many of its conclusions. Some of those not involved in the report and holding entrenched positions will continue to fire broadsides at its conclusions. However, nothing must detract from perhaps the most important area of progress—namely, that in a complex and controversial field, it is possible to develop dialogue and find centre ground.

We can now endorse the recommendation that better service provision for patients is urgently needed. We agree that not all the answers to this illness are in hand and that there is a need for high-quality research. We agree that ideologies both within and without the health professions have not served patients well in the past, and that both doctors and the patients’ charities need continued humility in this uncertain area. In particular, we believe that the time has come to move on and for patient advocates, practitioners, and researchers to work together to both press for better services and fair benefits for sufferers, as well as for further research into the causes of this complex condition. The ball is now in the government’s court.

C C and A M (a retired medical practitioner and person with M E) were members of the core group of the Working Party and S W was a member of the external reference group. S W is honorary member of the supervisory group of Prismamedicalcare, which provides rehabilitation for patients on permanent health insurance.

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