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Give physical symptoms equal prominence

EDITOR,—We read with interest the many articles on the chronic fatigue syndrome or myalgic encephalomyelitis published in the *BMJ* on 19 March.

Our first point is made specifically on behalf of our patient group. We believe that care must be taken with the nature of the current debate to ensure that the patients are not discriminated against and disadvantaged any more than they are already. The difficulties in understanding the difference between the chronic fatigue syndromes and myalgic encephalomyelitis are already creating issues whereby effective comparisons of research are proving difficult. Resolution of "bitter conflict" will never come about until the physical aspects of this illness are given equal prominence in the debate.

Secondly, we challenge the statement by Tony Delamothe about there being a Myalgic Encephalomyelitis Act on the British statute books¹; this is not true. Neither were we, other organisations of patients, or other groups of supporters involved at any level in the World Health Organisation's decision to add myalgic encephalomyelitis to the 10th revision of the *International Classification of Diseases*.

Finally, S M Lawrie and A J Pelosi are clearly confused about our perception of the illness from the patient organisation's point of view. Our advisers are not lay people but qualified medical professionals, who no doubt will resent, as we do, the assumption that any advice is based on speculation and anecdotal reports or even wishful thinking. Perhaps, too, before making statements such as that myalgic encephalomyelitis organisations give "nihilistic" prognoses or implying that we advocate complete rest the writers would be wise to refer to our publications. We advise rest with activity within the limits that the disease imposes, emphasising a balance of rest and activity and patients pacing themselves.

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Conflicts of interest

Drug advertising corrupts journals

EDITOR,—In his editorial on the ethical problem of conflicts of interest and the *BMJ* Richard Smith refers to the *New England Journal of Medicine* leading the way with "its policies on conflict of interest."¹ He states that the editors of the American journal "have said that 'most academic institutions and journals have not gone far enough in dealing with this problem'" and that this may be "still

true on [the British] side of the Atlantic." The 3 March issue of the *New England Journal of Medicine*—a 93 page publication—contained 22 pages of drug advertisements. Notwithstanding the fact that the 2 April issue of the *BMJ*—a 63 page issue—contained 21 pages of pharmaceutical "offerings," the *New England Journal of Medicine* hardly seems to be in a position to be in the vanguard of establishing ethical-categorical imperatives regarding the submission of articles to journals that may be funded or influenced by sources that are not impartial. This strikes me as being akin to the syndrome "do as I say and not as I behave."

Drug companies' advertisements in medical journals may pose an even greater threat to medical practice and education than pharmaceutical funding of medical research because of the industry's use of the latest "technology" in advertising methods. Surely another mechanism to fund medical journals should be investigated.

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Halcion trial wasting valuable resources

EDITOR,—I read the news item on Halcion (triazolam)¹ with some surprise. It seems extraordinary to ventilate this ancient history when the manufacturer, Upjohn, is engaged in a libel trial which centres on the issues reported.

Having read the transcript of Ilo Grundberg's case with particular attention to the psychiatric and drug history, I am astonished at her claims to have been acting "under the influence of Halcion." Even more remarkable was Upjohn's decision to make an out of court settlement without admission of liability. Since this was purported to be a substantial sum there was inevitably a widespread assumption of culpability. It seems, however, that the company feared the adverse consequences of publicity regarding methodological deficiencies in study 321 and the massive costs of defending the case.

The evidence presented to the Persons Appointed Committee of the Medicines Commission made it clear that study 321 of 28 long term prisoners in a high security prison was, though within the acceptable ethical and scientific standards of the day, virtually useless as a means of identifying behavioural abnormalities related to the drug, nor was it intended to do so. Neither study 321 nor other studies showed evidence of serious psychiatric complications attributable to the drug. The millions being expended on these protracted cases and inquiries would be so much better spent on high quality independent safety trials or other medical research.

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**When we asked professor Brandon to declare conflicts of interest we received the following response.

Author considers his conflict of interest

EDITOR,—I have recently read your editorial on conflict of interest.¹ I wrote the above letter to the

BMJ—rather than to the lay press—when I was irritated by the raising of those issues in the middle of the Oswald libel case and with the conviction that Upjohn's money would be better spent on proper clinical trials.

When I was responsible for the "Man in society" course at the University of Leicester's medical school, Upjohn's education department produced an agency placement handbook each year for our new students. Some years later Leicester was a participating centre in the cross national panic disorder study—run by Upjohn—and as director I received sufficient funds to employ a research assistant who, in addition to helping with the cross national (alprazolam) study, was able to undertake an entirely independent study on the community prevalence of panic disorder. During this time either my assistant or I attended the study directors' meeting held in various parts of the world. Upjohn provided our travel and accommodation on these occasions.

Subsequently I was asked by an American legal firm to review the papers on the Grundberg case because a British professor (Ian Oswald) was to give evidence for Grundberg and the lawyers wanted to match him with another "British expert." As a result I made a careful study of the papers and was somewhat taken aback when they informed me that the matter was settled.

Later I was paid for advising the company on their objection to the withdrawal of the product licence on triazolam and represented them at the Appointed Persons Panel. Our arguments to that panel resulted in the recommendation that the licence should be restored, but this advice was rejected by the minister.

About three years ago I requested financial help from the company to enable one of my juniors to undertake a community study on the prevalence of anxiety disorders and the facilities that might be provided in general practice to alleviate them. They gave the department £3000, which was used to provide stationery, postage, and computer facilities.

Last year I was asked by a related legal firm to give evidence against Oswald in his libel suit. With some reluctance I agreed but I subsequently withdrew because I wasn't able to commit the time they required of me.

I have written at some length because it is evident that I do have a conflict of interest but wrote my angry letter with no conscious awareness of the fact. My letter reflected the fact that I had a detailed knowledge of the Grundberg case and was offended at the fact—as I see it—that triazolam played no part in the murder. I also had considerable sympathy with the Upjohn company, whose alleged misdemeanours were in my view a consequence of modest incompetence combined with the use of a powerful retrospectroscope to judge studies that were just about acceptable by the standards of 20 or more years ago.

- 1 Smith R. Conflict of interest and the *BMJ*. *BMJ* 1994;308:4-5. (1 January.)

Blood pressure and myocardial infarction

Low blood pressure can be hazardous

EDITOR,—The study of Ulf Lindblad and colleagues highlights a high risk group of hypertensive patients with evidence on electrocardiography of ischaemia or left ventricular hypertrophy, or both, who experience a greater number of first myocardial infarctions (than those with normal electrocardiograms) if their diastolic blood pressure is lowered to below 95 mm Hg.¹ These new data supplement the findings of the Framingham study,

which showed no J curve relation between diastolic blood pressure and deaths from coronary heart disease for those without coronary heart disease or left ventricular hypertrophy. By contrast, those with either coronary heart disease or left ventricular hypertrophy showed a J point in the high 70s of diastolic blood pressure and those with combined coronary heart disease and left ventricular hypertrophy had a J point shifted to the right at pressures of 85-89 mm Hg.

Lindblad and colleagues indicate that left ventricular hypertrophy is associated with an impaired coronary flow reserve. Left ventricular hypertrophy as such is not associated with low coronary flow reserve, as shown by patients with aortic stenosis and concentric left ventricular hypertrophy who have a normal coronary flow reserve.² However, left ventricular hypertrophy linked to hypertension is associated with an impaired coronary flow reserve, and this is due to coronary artery medial hypertrophy and fibrosis resulting from exposure to high perfusion pressures (high diastolic blood pressure) over the years.³ Such patients, particularly if ischaemic heart disease is also present, have diminished coronary flow reserve and left ventricular functional reserve. Thus hypertensive patients with anginal symptoms and severe left ventricular hypertrophy (echocardiographic)—unlike those with no, or less severe left ventricular hypertrophy—show ischaemia on electrocardiography if diastolic blood pressure is lowered (with nitroprusside) to 80-90 mm Hg⁴ and there is a 25% fall in coronary blood flow accompanied by a 25% increase in myocardial oxygen extraction.⁵ This high risk hypertensive group with combined left ventricular hypertrophy and coronary heart disease also responds abnormally to a fall in diastolic blood pressure (to less than 70 mm Hg) induced by trimetaphan: instead of the usual 20-25% increase in left ventricular ejection fraction there was a mean 8% fall.^{2,6} Thus it may be hazardous to lower diastolic blood pressure to inappropriately low levels in hypertensive patients with ischaemia and left ventricular hypertrophy.

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Caution in left ventricular hypertrophy unjustified

EDITOR,—Ulf Lindblad and colleagues report an inverse relation between diastolic blood pressure and the incidence of myocardial infarction in men in their study, which is mainly confined to those with electrocardiographic evidence of left ventricular hypertrophy.¹ They conclude from this that it may be dangerous to lower the diastolic pressure below 95 mm Hg in this group. They do not,

however, discuss the alternative hypothesis that the low diastolic pressure may be a marker of some other factor, such as left ventricular dysfunction or decreased compliance of the great vessels.^{2,3}

Many studies have shown J shaped and U shaped curves relating blood pressure to myocardial infarction, and these have been found in treated and untreated patients, including the control groups of the European working party on high blood pressure in the elderly trial and in our own study.⁴

In our follow up of 10 732 people aged 60-80, a J curve was found relating baseline blood pressure to coronary deaths.⁵ When we divided the subjects into two groups—those with associated disease (arrhythmias, heart failure, diabetes, previous myocardial infarction, and severe diseases) and those without—the negative relation to myocardial infarction was found only in the former (figure). In nearly all these patients blood pressure was untreated, and therefore this finding cannot be imputed to antihypertensive treatment. From the data given by Lindblad and colleagues it seems likely that the relation they report would apply to baseline blood pressure as well as blood pressure on treatment.

Standardised mortality ratios relating to coronary deaths in "healthy" patients and patients with known medical problems

In the systolic hypertension in the elderly programme trial the diastolic blood pressure was reduced to below 70 mm Hg without any evidence of untoward effects.⁶ As the subjects in that trial were older than 60 many must have had left ventricular hypertrophy.

The only definitive test of these hypotheses would be a study randomising patients to two different treatment regimens, one lowering the pressure more than the other. Until the results of such a study are published it is premature to deliver advice that may dissuade doctors from lowering the blood pressure in this vulnerable group of men.

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- 1 Lindblad U, Råstam L, Rydén L, Ranstam J, Isacson S-O, Berglund G. Control of blood pressure and risk of first acute myocardial infarction: Skaraborg hypertension project. *BMJ* 1994;305:681-6. (12 March.)
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Reactive arthritis

May develop in patients with HIV infection

EDITOR,—B Svenungsson's editorial on reactive arthritis fails to draw attention to the fact that the disease may develop in patients with HIV infection and AIDS.¹ Arthritis in patients infected with HIV is usually septic and caused by a variety of secondary pathogens, although bacterial septic arthritis is more commonly encountered.² Reactive arthritis has also been described in AIDS, with HIV being isolated from the synovial fluid.³ Patients infected with HIV are more prone to acquire several sexually transmitted infections or even enteric infections, some of which could potentially evoke a reactive arthritis. In cases of reactive arthritis clinicians need to be aware of the possibility of HIV infection as this may have implications not only in the management of the arthritis but also for staff handling specimens from these patients.

Another debatable issue is the use of intra-articular steroids to treat sexually acquired reactive arthritis. Since the detection of chlamydial elementary bodies in material from the affected joints in patients with sexually acquired reactive arthritis was reported⁴, many clinicians have become wary of using intra-articular steroids to treat this condition for fear of exacerbating the infection, even though the reported inclusions may not have represented live chlamydia. The implications may be even more severe in HIV infected patients with reactive arthritis. With early, adequate antibiotic treatment for the triggering infection, use of non-steroidal anti-inflammatory drugs, and resting of the affected joints in the acute phase with subsequent mobilisation and physiotherapy, most patients with sexually acquired reactive arthritis cope well without recourse to intra-articular steroids. Although the implications are not clear, the chronic destruction of the joints that was seen in some patients with sexually acquired reactive arthritis decades ago is now fairly rare. One important aspect of management is advice about future avoidance of the triggering infection. In addition to contact tracing and treatment of partners, adequate counselling is mandatory.

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Consider combination treatment

EDITOR,—B Svenungsson's editorial on the treatment of reactive arthritis¹ drew attention to the important fact that large prospective studies are needed to establish the best treatment, as advocated previously.²

In a double blind, placebo controlled study of three months' treatment with lymecycline we found that the combination of lymecycline with a non-steroidal anti-inflammatory drug shortened the duration of reactive arthritis triggered by *Chlamydia trachomatis*, which suggests that *C trachomatis* may persist as prolonged or chronic infection.² In addition, of the 40 patients with reactive arthritis (not only those with chlamydia arthritis), eight patients in the placebo group and