late death is substantial, the prevalence of secondary cancer is rising, and cardiotoxicity is an increasing problem. Although we accept the hugely beneficial impact of stem-cell transplantation on the lives of many patients with malignant and non-malignant disease, there should still be room for questioning. Indeed, although the EBM T specifically recommend stem-cell transplantation late in second remission in acute lymphoblastic leukaemia, they also state that some of the guidelines in their handbook may be controversial. The wisdom of transplantation beyond second remission may still be in doubt, especially in the very young and for the sake of the child undergoing this procedure, this fact should not be forgotten.

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Is there a Gulf War syndrome?
Sir—Khalida Ismail and colleagues (Jan 16, p 179)1 claim to have approximated the factor analysis of symptoms that I did in US Gulf War veterans and found it unable to detect the same syndromes in British Gulf War veterans. They were sufficiently satisfied with their replication of my work that they referred to their analysis as the Haley model. This analysis, however, does not approximate my factor analysis, could not have identified the same syndromes even if tested in the same sample we studied, and does not test the validity of my findings.

Since publishing my analysis that identified six syndromes,2 linked them to organic neurological dysfunction,3 and identified strong associations (relative risks 4–8) with risk factors of organophosphate and other chemical exposures,2 I have been eager for others to attempt to replicate the findings. In September, 1998, I met with a co-author of the Ismail report1 and others at the British Ministry of Defence and provided full details of my factor analysis to facilitate exact replication. I was never informed that they had undertaken such an analysis.

A comparison of the variables used in the two studies demonstrates five bases for profound differences between the two factor models.4 Of the 23 symptoms that loaded strongly on my three primary syndrome factors, Ismail and colleagues measured only 11—ie, fewer than half. They omitted four of the five most important symptoms for distinguishing my syndrome factor 2.5 Of their 17 symptoms, five (almost a third) were extraneous variables not included in my model. Five of the eight symptoms they used to detect my syndrome factor 2 were not in my model.2 In three instances, they used ambiguous symptoms that would be endorsed by high percentages in most populations. For example, where they asked about “headaches”, I asked a battery of questions to distinguish rarer migraines. Similarly, they used dizziness whereas we measured vertigo attacks (“feeling like the room is spinning”). In nine instances, they failed to disentangle crucial ambiguities in traditional symptom terminology, which is regarded as an important innovation of our work. For example, they used fatigue, whereas we distinguished excessive daytime sleepiness and excessive muscle exhaustion, which have different pathogenetic mechanisms and are loaded on different syndrome factors.3 They used three symptoms in calculations of the wrong syndrome factors.

Besides non-comparable symptom measures, Ismail and colleagues’ mathematical methods of factor analysis were incorrect in at least three important respects, further ensuring a radically different result. Whereas our factor model had six factors justified by clinical as well as statistical criteria, they arbitrarily used a three-factor model, even though their statistical criteria identified at least six. We produced uncorrelated syndrome factors (orthogonal rotation), but they allowed theirs to be correlated (equivalent to oblique rotation). Although we published all factor loadings, they used entirely different factor weights in calculating their factors.

It does not take an expert statistician to see that Ismail and colleagues have misrepresented their analysis as an approximation of my factor model. They should retract their paper.


Authors’ reply
Sir—Robert Haley contends that our factor analysis does not approximate his factor analysis and that our mathematical methods were incorrect. The main objective of our study was to test whether the factor structure of the symptoms reported in a randomly selected UK Gulf War cohort was different from the factor structure of symptoms in two other randomly selected military cohorts. To do this, we obtained a Gulf War reponse rate of 70%, a sample size of 3225, and two large control groups of Bosnia and Era veterans. We emphasise that our major findings are that subjective reporting of symptoms in the Gulf War cohort was similar to that in two military control groups. Three other large scale epidemiology studies have also used control groups and reported similar findings.5,6 At present, there is no compelling evidence for the existence of a unique Gulf War Syndrome.

By contrast, Haley reported results from a single unit, with a sample size of 249, a response rate of 41%, and no control group, military or otherwise. As many commentators have noted,4 Haley’s design does not allow him to address the central question of the existence or otherwise of a Gulf War Syndrome.

It was only a secondary objective for us to examine Haley’s reported factors, since Haley’s work was published after we embarked on our study. Haley’s penultimate paragraph

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demonstrates both his confusion over the differences between exploratory factor analysis and confirmatory factor analysis, and (like many other non-statisticians) a naïve faith in the statistical criteria associated with the former. These criteria, the scree test, and the number of eigenvalues greater than one test, are nothing more than rough guides to the number of factors. And Haley’s appeal to that old favourite clinical interpretability is also not wholly convincing in view of the well known difficulties with the refilcation of factors and the dangers of their over interpretation.

With these points in mind, and noting that the last three of Haley’s factors accounted for only small amounts of variance, we decided to base a model on only the first three of his factors emphasising that this was an approximation.

What we then did was to try to match the symptoms that loaded onto the first three factors he identified to symptoms measured in our study. We found 17 symptoms from our 52 symptoms questionnaire that had face validity with the 23 symptoms that loaded onto his first three factors. Out of courtesy, we labelled this approximation the Haley model and then used it as the basis of one of our confirmatory factor analyses. We also draw attention to the many publications showing the general non-specificity of chronic self-reported somatic symptoms in the general population, as well as the dangers of assuming that each individual symptom can be ascribed to a precise pathological process, as Haley seems to believe.

This Haley model was tested with confirmatory factor analysis on the three cohorts in our data. The loadings of some variables in the model were allowed to be free parameters to be estimated, with the remainder having loadings constrained to be zero. The factor loadings from Haley’s analysis were used only to suggest which variables should have zero loadings, and which should not; their numerical values were never used. The correlations between factors were also allowed to be free parameters to be estimated during the analysis. Haley objects to this procedure since in his own exploratory factor analysis orthogonal factors were derived. His suggestion that what we did was equivalent to an oblique rotation merely underscores his unfamiliarity with confirmatory factor analysis. And since the estimated correlations were all significantly different from zero, constraining them to be zero could only have made the fit of the model worse. The model loosely based on his results did not fit our data well.

In settings where there is good access to haemodialysis, we are yet to see whether therapy with fomepizole is better than prompt haemodialysis. Administration of the drug may obviate the time needed for consultation with the dialysis service and preparation of a dialysis machine, and does not require insertion of a catheter into the femoral vein. The comparative costs and efficacy of these two strategies are not yet clear. Borron’s report shows that a test of the merits of these treatment options is an important next step.

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Fomepizole for ethylene-glycol poisoning

Sir—Stephen Borron and colleagues (Sept 4, p 831) report that fomepizole for treatment of ethylene-glycol poisoning will allow avoidance of haemodialysis for poisonings not complicated by renal insufficiency or severe metabolic acidosis. The investigators suggest that fomepizole might prevent the need for small medical centres to transfer patients to centres with capacity to do haemodialysis, or monitor patients in intensive-care units.

The issue here is whether or not these smaller centres will have the drug available. With the high cost of the drug (about US$1000 per gram), smaller programmes that see only an occasional case of ethylene-glycol poisoning would be unlikely to keep it in stock. Ethanol, though perhaps more cumbersome to administer, is inexpensive and readily available, at least in its well known oral form. If making the decision to have fomepizole in stock, smaller centres should know that the suggested shelf life of the drug is 3 years, and the manufacturer (Orphan Medical, Minnetonka, MN, USA) will replace it at no charge after that period (S W Borron, personal communication). It therefore seems economical for smaller emergency departments to have the drug in their armamentarium.

Soluble thrombomodulin as predictor of incident coronary heart disease

Sir—G Cella and M L Randi,1 L l Menen and colleagues,2 and M R Goldstein3 comment on our article on soluble thrombomodulin (STM).1 Mennen and colleagues ask whether our results differed by sex, and suggest that the inverse association between STM and incident coronary heart disease (CHD) might be explained by their observation that there is an association between STM and fibrinolysis among men but not women. We have analysed our data by sex and, as mentioned in our report, the findings did not differ between men and women. The table shows the adjusted rate ratio of incident CHD in the higher quintiles of STM compared with the lowest quintile in men and women. The overall association between STM and incident CHD was significant for both sexes.

The relation between STM and fibrinolysis is complex and poorly understood. Mennen and colleagues report a positive association between the STM concentration and fibrinolytic activity among men. Other researchers, however, have reported that, at least in vitro, thrombomodulin may actually inhibit fibrinolysis by potentiating the activation of thrombin-inactivatable fibrinolytic inhibitor.4 We included the D-dimer in our analyses, but it showed no significant association with STM and we therefore omitted it from our final version. We are now working on more detailed analyses of