

CORRESPONDENCE

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Interferons in relapsing remitting multiple sclerosis

Sir—The conclusions of Graziella Filippini and colleagues (Feb 15, p 545)¹ differ from those noted in two previous reviews,^{2,3} especially with respect to the effect of interferon beta on attacks of multiple sclerosis. Methodological differences could account for these discrepancies.

In our report² we assessed seven randomised placebo-controlled studies, involving patients with relapsing remitting and secondary progressive multiple sclerosis, since we believe both conditions represent different stages of the same underlying illness; secondary progressive multiple sclerosis always begins as relapsing remitting multiple sclerosis, and 80–90% of patients with relapsing remitting disease develop secondary progressive multiple sclerosis. Filippini and co-workers, however, included only trials of patients with relapsing remitting multiple sclerosis, suggesting that the two conditions represent distinct diseases. By analysing only this subset of patients, they effectively discard most of the available randomised placebo-controlled evidence on the effect of interferon beta on disease episodes.

With respect to outcome measures, we analysed the effect of treatment with interferon beta on various disease-activity measures (both clinical and MRI);² treatment significantly improved these outcomes in all trials. By contrast, Filippini and colleagues examined only attack-free status; the use of complimentary (confirmatory) outcomes—for example, MRI—would have provided convergent validity⁴ to the clinical findings. Moreover, because attack-free status is the same irrespective of whether a patient has one attack or ten, the use of an outcome—eg, attack rate—that captures such clinically relevant information, might be preferable.

Finally, although drop-out bias is an important consideration, the sensitivity analysis used by Filippini and co-workers is problematic. The most glaring difficulty is in their treatment of the Multiple Sclerosis Collaborative Research Group (MSCRG) trial. This trial was stopped early and Filippini and colleagues treat the large group of non-completers as dropouts in their

worst-case scenario—ie, they assume all placebo dropouts remain attack-free and all treatment dropouts have attacks. Admittedly, a systematic handling of the MSCRG data presents challenges. There was seemingly no a-priori stopping rule and, although this trial was allegedly stopped without knowledge of outcome data, how the stated reason for stopping (a low early dropout rate) shortened the observation-time needed to establish efficacy on the primary endpoint (ie, disability) is difficult to understand. Furthermore, the two subgroups (completers and non-completers) were responding quite differently to therapy when the trial was stopped.⁵ Consequently, I believe that this trial should have been excluded from analyses, rather than giving it undue weight in a worst-case meta-analysis.

Furthermore, analysis of non-completers in a stopped trial as dropouts has serious drawbacks. For example, consider a 2000-patient, 2-year trial, comparing drug X with placebo. Suppose, after an interim analysis (a-priori stopping rule: if $p < 0.001$), the trial is stopped because of a 100% increase in attack-free status on drug X compared with placebo (100% vs 50% at year 1; 80% vs 40% at year 2). Suppose there were no dropouts but that 50% were non-completers when the trial was stopped. Clearly, such a trial provides overwhelming evidence of efficacy. However, for the worst-case scenario (assuming all 500 non-completers in the treatment group, but none of the 250 non-completers in the placebo group, will relapse in year 2) there would be 600 drug X failures compared with only 550 placebo failures. Consequently, even in the face of overwhelming evidence, this worst-case method¹ would cast doubt on the efficacy of drug X. Such a method seems far too stringent to be of any practical use in the assessment of studies.

I have participated (or am currently participating) in several industry-sponsored clinical trials in multiple sclerosis. The sponsoring pharmaceutical companies for these trials have included (or do include) Ares-Serono, Berlex Laboratories, Biogen, Immunex,

and Teva-Marion Partners. I have also lectured at medical conferences and in public on various aspects of the diagnosis and management of multiple sclerosis. In many cases these talks have been sponsored by non-restricted educational grants from one or another of the companies listed above or by Athena Neurosciences. In addition, the clinical operations of the VCSF MS Center (nursing and patient care services) have been supported by non-restricted grants from Ares-Serono, Berlex Laboratories, Biogen, and Teva Neuroscience.

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- 1 Filippini G, Munari L, Incorvaia B, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet* 2003; **361**: 545–52.
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- 4 Groves RM. Survey errors and survey costs. New York: John Wiley and Sons, 1989.
- 5 Biogen. Summary basis of approval: FDA official document for license of interferon beta-1a (Avonex). <http://www.fda.gov/cber/products/ifnbio051796.htm> (accessed April 8, 2003).

Sir—Systematic reviews are thought to be objective and comprehensive meta-analyses based on a sufficient number of comparable trials, thus providing added import to the results of individual studies. Possibly the most difficult part of undertaking a systematic review is deciding whether randomised trials are sufficiently similar to combine their results statistically. Graziella Filippini and colleagues' systematic review¹ does not meet these requirements² and results in flawed conclusions.

First, Filippini and co-workers artificially inflate the available number of trials by including two trials with interferon alfa, a cytokine that has not been approved for treatment of multiple sclerosis.

Second, in view of the ongoing discussion about the effect of dose,

frequency, and route of administration, especially on short-term results of treatment with interferon beta, mixing up so many different approved and non-approved dose regimens can only jeopardise the results of a meta-analysis. Consequently the data of the 1-year analysis were significantly heterogeneous ($p=0.044$).

Third, the decision not to consider relapse rates, although they were the primary outcome in two and secondary outcome in one of the three pivotal interferon beta studies, is not sufficiently justified. Inclusion of this outcome would have yielded more robust results both for the first and the second year on study.

Fourth, Filippini and colleagues state that interferons' ". . . effect beyond one year is uncertain . . .". This conclusion is based on a sensitivity analysis for the 2-year relapse data. Although in the main analysis for the second year the effect on relapses is highly significant and homogeneous for all three studies, interpretation of the alternative scenarios is flawed by significant heterogeneity. The authors note that the study that causes this heterogeneity (interferon beta-1a once a week intramuscularly pivotal trial) had a high rate of patients not completing the second year on study. But they do not take into account that non-completion was nearly exclusively due to early termination of the trial that was decided after an interim analysis, which yielded positive results with respect to the main outcome. Since the decision to stop the trial was based on a recommendation of the external patient safety monitoring board, Filippini and colleagues' calculation based on the worst-case scenario (that all patients who did not complete were treatment failures) does not make sense. The same critique also applies for the 2-year data on progression presented in figure 3 of their report.

Finally, little effort seems to have been made by Filippini and co-workers to obtain additional information from trial investigators or trial sponsors if need be, despite their claims that this would be done. For instance, for table 1 they state that age of included patients is not reported for PRISMS.³ However, two of the authors were leading investigators in this study, and should have direct and easy access to this information.

Doctors and patients should know that interferon beta is only partly effective as a treatment for multiple sclerosis. If Filippini and colleagues'

aim was to emphasise this fact, their chosen approach seems questionable.

L Kappos has received honoraria for participation in clinical studies, advisory committees, and presentations at scientific meetings as well as grants for research projects by several pharmaceutical companies, including those whose products are discussed in this letter.

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- 1 Filippini G, Munari L, Incurvaia B, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet* 2003; **361**: 545–52.
- 2 Laupacis A. The Cochrane Collaboration: how is it progressing? *Stat Med* 2002; **21**: 2815–22.
- 3 PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; **352**: 1498–504.

Sir—Graziella Filippini and colleagues¹ call into question widely accepted results of clinical trials in multiple sclerosis. However, we believe that their meta-analysis confuses the picture. Meta-analysis is a powerful technique, but can lead to erroneous conclusions if important variables such as dose, frequency of dose, and type of therapy are not recognised and accounted for.² The original Cochrane Report³ of treatment of multiple sclerosis with interferon concluded that the "the efficacy of interferon . . . was 'modest' after one and two years of treatment". Filippini and co-workers' conclude that "the clinical effect beyond one year is uncertain".

We disagree with the conclusion that the effects of treatment with interferon over 2 years were inconclusive. As the authors point out, this conclusion rests for the most part, perhaps entirely, on the results of one⁴ of the three pivotal trials that were subjected to a worst-case scenario analysis. The 1-year data from this trial were not included in the published report. However, these data can be retrieved from the FDA summary basis for approval, and indicate that most patients did not choose to stop treatment but that the trial was terminated early.

Furthermore, Filippini and colleagues include alfa and preliminary beta interferon studies in their review. We believe that to lump different types of interferons and clearly ineffective and preliminary dose regimens with

effective ones is inappropriate. This approach biases the results against a true therapeutic effect.

The authors also say that they decided not to do a quantitative analysis of the MRI outcomes. The unwritten suggestion of their summary to us is that the data were no good, which is untrue. The MRI results in the major clinical trials showed great efficacy.

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- 1 Filippini G, Munari L, Incurvaia B, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet* 2003; **361**: 545–52.
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Sir—As PRISMS investigators, we would like to provide commentary on methods used in the analysis by Graziella Filippini and colleagues,¹ and correct some errors related to our study.²

The authors state that 9–10% of patients in PRISMS² were lost to follow-up. These figures refer to patients who did not complete treatment. Several of these patients continued follow-up and the correct proportion of patients lost to follow-up is 5%. Many of the dropouts, however, had the outcome before they discontinued the study. Although not likely to affect greatly the analysis, for the exacerbation-free outcome, using the worst-case analysis, Filippini and co-workers assign five patients on interferon to have a relapse when in fact no patients were lost to follow-up in the treatment group before having a relapse. Similarly, ten relapses have been assigned for patients in the placebo group, when only two patients were lost to follow-up without having a relapse.

For the MSCRG study, the review includes the entire enrolled population as the denominator, but uses only the number of patients who completed 2 years of treatment (57% of total

population) in the numerator for best-case scenarios. Outcomes are then assigned for those who did not complete the study for the likely and worst-case scenarios. Many of the patients who did not complete 2 years on study had had the outcome, and thus more actual data should be available than indicated. This method of analysis leads to great study heterogeneity that has not been adequately addressed and that affects the ultimate conclusions of the review.

Since interferon alfa is not used in multiple sclerosis, and although a type 1 interferon could function via a different mechanism of action, we challenge the validity of including data for interferon alfa in this review. The supposed reduced quality of life attributed to therapy with interferon stems from one small study of interferon alfa in which no treatment benefit on relapses was noted, making conclusions on quality of life of questionable importance.

Combining data on various doses assumes no differential effect on outcomes, an assumption contrary to published data. Results of studies^{2,3} with subcutaneous interferon beta-1a given three times a week show better outcomes relative to placebo than the same product given once a week.⁴ Furthermore, subcutaneous interferon beta-1a 44 µg given three times a week is significantly better than intramuscular interferon beta-1a 30 µg once a week on the outcome prominently discussed by Filippini and colleagues, proportion relapse-free.⁵ To assume that all regimens can be pooled to ascertain an overall estimate of potential efficacy is questionable and does a disservice to patients by concluding that a marginal benefit exists for a treatment regimen that has shown consistent efficacy on disease measures of multiple sclerosis. PRISMS-4³ provides data on 80% of enrolled patients, balanced in accord with original treatment groups, showing treatment efficacy is maintained for at least 4 years without compromising patients' safety.

Finally, the use of the term likely scenario for the combination of worst-case scenario for interferon and best-case scenario for placebo, is in fact doubly punitive for treatment effect and will lead to misunderstanding by many readers of what is indeed the likely outcome for patients with multiple sclerosis treated with interferon.

M Freedman has received consulting fees and honoraria from Biogen, Berlex, Serono, and Teva, and a research grant from Biogen.

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- 1 Filippini G, Munari L, Incurvaia B, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet* 2003; **361**: 545–52.
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Authors' reply

Sir—The comments received on our paper underline the difficulties in interpreting the results of these trials. All four letters contested our inclusion criteria. However, exclusion of the small trials of interferon alfa made little difference to our result (relative risk of exacerbation at 1 year 0.79, 95% CI 0.58–1.07).

With regard to dose heterogeneity, we considered the highest dose in trials that used more than one dose. Neither univariate nor multivariate meta-regression analysis of treatment in the first year showed significant effects for dose ($p=0.222$), type of interferon ($p=0.427$), or duration of treatment ($p=0.260$).

Goodin suggested we should have included trials on secondary progressive multiple sclerosis. Our a-priori inclusion criteria, however, stipulated relapsing remitting multiple sclerosis only.¹ Secondary progressive multiple sclerosis can be assessed in a separate review.

Both Ludwig Kappos and Jörg Kesselring, and Goodin stressed the need to consider relapse rate. We could not undertake a quantitative analysis of relapse rate because it was assessed differently among the trials, and the PRISMS and OWIMS studies did not report relapse rate. We always contacted sponsor companies and trialists for additional details, but the companies did not give sufficient information and the principal investigators did not have access to the primary data. This problem could

be addressed by making the primary data available, as is now required for a study to be published.

Goodin, and Don Paty and colleagues suggested we should have assessed MRI measures. MRI was a secondary outcome in our protocol but MRI measures differed so profoundly between studies—and the reporting of data was so selective—that a meta-analysis was impossible. Studies to show that MRI measures are independent predictors of long-term outcome are urgently needed.

With regard to PRISMS, we abstracted the data from figure 1 in the original article²: five patients on interferon and ten on placebo lost to follow-up at 2 years were included in sensitivity analysis.

We cited Nortvedt's study³ since it was the only one to include quality of life as an outcome measure.

We re-emphasise that sensitivity analysis does not provide a way to analyse or compensate for incomplete results, since it is a tool to assess treatment claims against the effect of missing information. We did a sensitivity analysis at 2 years (when overall 20% of patients were lost to follow-up) because all studies reported efficacy results instead of the intent-to-treat results required by protocol.¹ The sensitivity analysis tells us that information on this 20% is essential to support or reject the efficacy of interferons at 2 years.

Goodin's suggestion to disregard MSCRG was contrary to our protocol.¹ Moreover, MSCRG was used for the registration of Biogen's interferon beta-1a (Avonex), the most widely-used interferon in the USA. Goodin's example to show the drawbacks of sensitivity analyses is a good one, but not applicable to MSCRG because, as he rightly states, the study had no a-priori stopping rules. Evidence of an effect beyond 1 year could be assessed if the individual patient data were made available for new systematic reviews.

G P A Rice has received honoraria from, and participated in clinical trials sponsored by, Biogen.

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Sir—We do not believe that Filippini and colleagues’¹ conclusions are valid. In their worst-case sensitivity analysis, patients judged lost to follow-up in the interferon group were assumed to have one or more exacerbations during the treatment and follow-up periods, or disease progression after 1 and 2 years. Those classified as lost to follow-up in the placebo groups were assumed to have not reached these endpoints. Filippini and co-workers concluded that interferon might have no benefit beyond 1 year, and their abstract suggests that interferon might make multiple sclerosis worse. These results derived from incorrect use of data from the MSCRG study² in which we played key parts.

Filippini and colleagues classified patients enrolled in the MSCRG study who did not complete 2-years on-study as lost to follow-up, resulting in lost to follow-up rates of 46% and 39% for interferon and placebo groups, respectively. Most of these patients were censored because the study was terminated earlier than planned, but they were not lost to follow-up. The circumstances that surrounded early termination of the MSCRG study have been reported^{2,3} and presented numerous times. After Betaseron (interferon beta-1b, Berlex Laboratories, Montville, New Jersey, USA) was approved in spring, 1993, for relapsing remitting multiple sclerosis, the MSCRG investigators presented ethical concerns about continuing a placebo-controlled study to the National Institute of Health-appointed patient safety monitoring board (PSMB) that summer. Study statisticians reported the lost to follow-up rate was less than 3%, and indicated the study had accumulated enough patient time-on-study to ensure adequate power for the primary outcome measure of time-to-sustained disability progression. Because of the nature of the primary outcome measure and the remarkably low lost to follow-up rate, it was possible to stop the study in early 1994, rather than 1995 as planned. Consequently, a group of patients were

followed up for less than 2 years. They should not be classified as lost to follow-up for the purpose of showing that interferon does not work.

Incorrect use of data from our trial led to illogical and erroneous conclusions, which were contrary to findings from three independent randomised controlled clinical trials. This fact should have prompted Filippini and colleagues to check their methods and to undertake further analyses. We believe their review does not adhere to rigorous scientific standards advanced by the Cochrane Collaboration or by *The Lancet*.

R A Rudick was a coinvestigator on the MSCRG study and his institution receives and has received grants for research studies done by Rudick. Rudick is currently an investigator on a Biogen-sponsored study. He has received honoraria from Biogen, Teva, Sero, IDEC, and Berlex. D L Cookfair was the main statistician and director of the MSCRG data management and statistical center. J Griffin was chair of the MSCRG PSMB. S Hauser and S Piantadosi were on the MSCRG PSMB.

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Authors' reply

Sir—In response to Richard Rudick and colleagues’ letter, we did not conclude that interferons might have no benefit beyond 1 year but rather that any effect is uncertain beyond 1 year because of inadequacies in the available data.

We are pleased to have the opportunity to highlight the MSCRG study, since we found it the most unclear of those reviewed. We found no definitive evidence to corroborate therapeutic claims for Avonex. We had to extract key data, known to the investigators but not present in their publications, in order to arrive at this conclusion; which we find an unwelcome development.

With respect to lost to follow-up, an authoritative definition is that these are

patients who “become unavailable for examinations at some stage during the study” for any reason, including “clinical decisions . . . to stop the assigned interventions”.¹ Thus, the patients were lost to follow-up.

The MSCRG study used the Kaplan-Meier model to assess the probabilities of sustained progression (primary outcome) and exacerbation. However, so many patients were unavailable for examination (censored in Kaplan-Meier terminology but lost to follow-up nevertheless) that basic assumptions of the model were undermined.²

In fact, two fundamental assumptions of Kaplan-Meier were violated.³ First, censored patients did not have the same attack (exacerbation) probabilities as those who continued to be followed up, as is made clear in the FDA analysis of MSCRG data.⁴ Second, sustained progression was considered to have taken place when confirmed at examination 6 months later. However, so many patients were censored that confirmation was often not possible. Furthermore, more were censored in the interferon group than in the placebo group—again as the FDA analysis makes clear. In fact, sustained change in the EDSS score at 2 years was analysed on less than 40% of randomised patients, putting into doubt the MSCRG claim that the probabilities of sustained progression were 34.9% for placebo and 21.9% for interferon. The FDA⁴ commented, “patients who withdrew prior to reaching each of the designated time points were eliminated from the attack rate calculation. This may bias the result by elimination of patients who withdrew from disease progression and activity. The sponsors’ analyses eliminate considerable patient experience from each calculation”.

The FDA grappled with the “significant exacerbation reduction” claimed for the 2-year completers by MSCRG. They noted the marginally significant reduction in exacerbation rate⁴ but did not correct for multiple comparisons. The claim stands up neither to this correction nor to the removal of the placebo patient who had nine exacerbations. This individual determined almost 20% of the treatment effect on relapses, a fact only emerging from careful scrutiny of the paper. These observations undo, in our opinion, the claim for exacerbation prevention—in any event unsupported by significant mitigation of attack severity, prolongation of time to first attack on treatment, convincing reduction in steroid use in the

intention-to-treat group, or increase in patients who remained exacerbation-free during the study.

A further serious defect of MSCRG was that there were no stopping rules. In their letter, Rudick and colleagues say the study was stopped when it "had accumulated enough patient time-on-study to ensure adequate power for the primary outcome measure". This statement seems perilously close to admitting the trial was stopped because the p values had become significant, in a context where the number of data peeks was not specified. Nevertheless, Avonex was approved in the USA for a "reduction in disease progression"—despite the trenchant criticisms in the FDA analysis. This reduction implies an effect on unremitting progression of disability, the main prognostic determinant in this 30–40 year disease. However, important facts, omitted from this report, invalidate this MSCRG outcome measure in our opinion. First, for progression to be confirmed it was not necessary that deterioration be confined to one EDSS functional system. Thus, if weak leg at one examination had remitted 6 months later but was replaced by bladder urgency, then progression was confirmed. This is highly misleading, since in such circumstances, progression can be due to remitting changes or simply to noise (blinding efficacy uncertain). Second, as we noted in our original paper, 50% of Avonex-treated patients, who had met the definition of treatment failure in the first year, were indeed better in the second year. Natural history studies show that at least 1 year is needed to confirm progression. Third, the deterioration in EDSS score (1 point) needed to satisfy the study's definition of progression corresponds to the inter-rater variability around 40% of the time for the low disability patients recruited.⁵ There was no stated attempt to correct observer-dependent upward movement on this scale.

Interferons clearly affect MRI outcomes. However, the effect of Avonex on gadolinium after 2 years was only marginally significant ($p=0.051$) with no significant change in the median percentage T2 burden. The effect of Avonex on atrophy was analysed only on data from the second treatment year, in which selected or available scans showed an atrophy-sparing effect ($p=0.03$, no correction for multiple looks).

The MSCRG provides a vivid example of the need for Cochrane reviews undertaken according to rigorous standards. Remaining

ambiguities in this controversy might be clarified by making the primary data of this study publicly available, and we call on Rudick and colleagues to do this to allow an independent audit.

G P A Rice has received honoraria from, and participated in clinical trials sponsored by, Biogen.

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Sir—Graziella Filippini and colleagues¹ assessment of effectiveness, side-effects, and cost of interferons in relapsing remitting multiple sclerosis could be discouraging to patients who are properly managed at specialised treatment centres.

In our 498 patients with relapsing remitting and relapsing progressive disease who did not stabilise on monotherapy with interferon beta or glatiramer acetate, annual relapse rate decreased greatly after addition of immunosuppressants to their treatment regimens, including low doses of prednisone, azathioprine, or cyclophosphamide. For example, in 177 individuals on Avonex (30 µg intramuscularly per week) and prednisone (on average not exceeding 0.15 mg/kg bodyweight daily) for a median of 39 months (range 4–74), the annual relapse rate after a median of 39 months of follow up is 0.11. Their expanded disability status scale rating is also lower than it was at the

start of treatment (mean 2.96 [1.33] vs 2.37 [1.68]; $p<0.0001$; unpublished data).

Because of treatment satisfaction, 97% of patients have so far complied with the regimen. Furthermore, the additional cost of the immunosuppressive medications, particularly prednisone, is low.

Pulse therapy with intravenous glucocorticoids in patients who do not respond to interferon beta does not reduce relapse rate, and has no long-term functional benefits.²

To recognise and prevent side-effects in patients on combined immunomodulatory-immunosuppressive medications, neurological follow-up should be undertaken every 10–12 weeks.

To assess the safety and efficacy of immunomodulatory-immunosuppressive medications, double-blind randomised trials, which compare patients treated with controls chosen only on the basis of age, sex, socioeconomic background, and clinical symptoms of disease, need to be modified to reflect advances in molecular chemistry. With the emerging use of metabolomics,³ to disregard immunogenomics and pharmacogenomics in the individuals studied, including their controls, could lead to misleading conclusions and recommendations, resulting in suboptimum treatment of patients with multiple sclerosis.

Adequately documented, comprehensive clinical follow-up of patients in specialist centres by properly trained staff would be the most promising way to generate practically applicable data for their management.

O Kolar received a grant from Biogen for monitoring serum activation markers in patients with multiple sclerosis given Avonex, prednisone, and azathioprine.

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- 2 Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002; **58**: 169–78.
- 3 Sedlak BJ. Advances in metabolomics: drug evaluation now encompasses physiological outlook. *Genetic Engineering News* 2003; **23**: 1.

Unrelated kidney donors

Sir—In his Viewpoint,¹ Michael Friedlaender stated that “The surgical group of the Rabin Medical Center in Tel Aviv circumvented Israeli law by doing kidney transplants from unrelated living donors in several accessible countries including Estonia, Bulgaria . . .”

Rabin Medical Center is the largest medical centre in Israel, serves as a major tertiary referral centre, and undertakes most of the kidney transplants done in Israel. The association of our name with questionable practices has caused us great concern and upset. We therefore demanded an apology from Friedlaender, who told us that the published version differed from the original manuscript, suggesting that the meaning of his text had been altered during editing.

I would like to make clear that the Rabin Medical Center is not involved in any way with kidney transplants from paid unrelated living donors out of Israel. Furthermore, all transplants done in Israel are undertaken in accordance with Israeli law, follow Ministry of Health guidelines, and take into account ethical considerations.

G Dinari

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- 1 Friedlaender MM. The right to sell or buy a kidney: are we failing our patients? *Lancet* 2002; **359**: 971–73.

Author's reply

Sir—The administration of the Rabin Medical Center persist in their attempts to dissociate themselves from the actions of one of their departmental heads (recently retired) and one of his colleagues. These actions have been the subject of numerous local and international reports, both in the media and in medical journals.

Would it not be more rewarding for them to help seek alternative solutions to present practice, thus alleviating the need for extraterritorial, unregulated surgery on donors and transplant recipients?

The difference between the sentences in my original manuscript “They [the surgical group of the Rabin Medical Center] started performing non-related living donor kidney transplants in several accessible countries [. . .]. These operations, illegal in Israel, were thus out of Israeli jurisdiction” and that published “Therefore the surgical group of the Rabin Medical Center in Tel Aviv circumvented Israeli law by doing

kidney transplants from unrelated living donors in several accessible countries . . .” may need an expert in English to adjudicate whether the meanings are equivalent. I made no claim that Israeli law had been broken. I did see and consent to the editorial changes made to my Viewpoint before publication.

G Dinari's letter, written a year after publication of my Viewpoint, completely ignores the real issues that I raised and is misplaced.

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Potential for sibutramine-yohimbine interaction?

Sir—The serotonin and norepinephrine reuptake inhibitor sibutramine is frequently used as an adjunctive treatment for obesity. The beneficial effect of sibutramine on bodyweight is mainly mediated through an increase in satiety. Inhibition of noradrenaline uptake in peripheral tissues could theoretically exacerbate arterial hypertension and increase the risk of cardiovascular complications. Fortunately, the peripheral stimulatory effect of norepinephrine transporter blockade on the sympathetic nervous system is attenuated by a reduction in sympathetic outflow from the central nervous system.^{1,2}

Animal studies suggest that this sympatholytic effect of noradrenaline reuptake inhibition is in part mediated by stimulation of α_2 adrenoreceptors in the central nervous system (clonidine-like effect).^{3,4} α_2 adrenoreceptor blockade can unmask the peripheral effects of noradrenaline reuptake inhibition with profound sympathetic side-effects, including a substantial rise in blood pressure and tachycardia.

Products that contain the α_2 adrenoreceptor blocker yohimbine are widely available and have been advocated as antiobesity treatments.⁵ Concomitant use of sibutramine and yohimbine or other substances that inhibit α_2 adrenergic transmission could, therefore, unmask the peripheral effect of sibutramine, resulting in untoward cardiovascular effects.

Physicians who prescribe sibutramine should be aware of this potentially life-threatening drug interaction. We suggest that this danger should be pointed out in the product information of

both sibutramine-containing and yohimbine-containing products.

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- 1 Esler MD, Wallin G, Dorward PK, et al. Effects of desipramine on sympathetic nerve firing and norepinephrine spillover to plasma in humans. *Am J Physiol* 1991; **260**: R817–23.
- 2 Birkenfeld AL, Schroeder C, Boschmann M, et al. Paradoxical effect of sibutramine on autonomic cardiovascular regulation. *Circulation* 2002; **106**: 2459–65.
- 3 Eisenhofer G, Saigusa T, Esler MD, Cox HS, Angus JA, Dorward PK. Central sympathoinhibition and peripheral neuronal uptake blockade after desipramine in rabbits. *Am J Physiol* 1991; **260**: R824–32.
- 4 Goldstein DS, Eisenhofer G, Stull R, Folio CJ, Keiser HR, Kopin IJ. Plasma dihydroxyphenylglycol and the intraneuronal disposition of norepinephrine in humans. *J Clin Invest* 1988; **81**: 213–20.
- 5 McCarty MF. Pre-exercise administration of yohimbine may enhance the efficacy of exercise training as a fat loss strategy by boosting lipolysis. *Med Hypotheses* 2002; **58**: 491–95.

The role of the Israel and World Medical Associations

Sir—Yoram Blachar (Feb 1, p 425)¹ claims that “the IMA has been fighting to better the daily existence of the Palestinian population and improve the provision of health care to the innocent civilians suffering as a result of the past 2 years of unceasing terrorism”. These and other passages of his article will ring hollow to those who have read the recent report published by Physicians for Human Rights-Israel (PHR-Israel). To quote: “We believed that the IMA might be able to curb the appalling deterioration in the attitude of Israeli military forces toward Palestinian health and rescue services. Yet despite severe injury to medical personnel and to the ability of physicians to act in safety to advance their patients' interests; despite Israeli shells that have fallen on Palestinian hospitals; despite the killing of medical personnel on duty—IMA has chosen to remain silent. Only after extensive contact between PHR-Israel and global medical bodies, and ahead of the convention of the World Medical Association, was a discussion forum called to discuss IMA's position.”²

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- 1 Blachar Y. Israel Medical Association: response to Derek Summerfield. *Lancet* 2003; **361**: 425.
- 2 Physicians for Human Rights. A legacy of injustice: a critique of Israeli approaches to the right to health of Palestinians in the Occupied Territories. Israel: Physicians for Human Rights, 2002: 74. http://www.phr.org.il/Phr/downloads/dl_145.pdf (accessed March 3, 2003).

Author's reply

Sir—The IMA has, notwithstanding the report of PHR, been involved in several endeavours to improve health care for the Palestinian population. My response to Derek Summerfield mentioned the statement issued by the IMA, and our futile overtures to our Palestinian counterparts to issue a joint statement condemning terror and calling for the assurance of health care. I also referred to our attempt to hold a joint symposium on health care during the current conflict. Both our efforts and those extended on our behalf by neutral, international bodies, were rejected.

The IMA maintains ongoing contact with the Israel Defense Forces (IDF) medical liaison to the coordinator of civilian activities in the territories in an effort to solve existing problems and to ensure the provision of medical services to the civilian population. We are also in contact with the International Red Cross to find mutual solutions to the problems faced.

Israeli doctors have unilaterally undertaken to find ways to examine and treat Palestinian children and pregnant women, and the IMA has taken it upon itself to try to find funding for these activities. The IMA has also intervened to prevent the restraint of Palestinian youths in hospitals and the detention of Palestinians in need of medical treatment at IDF checkpoints.

At the IMA's request, a course on ethics for IDF medical officers has been introduced to better enable them to deal with complex issues, and the IMA has initiated the training and distribution of informative materials to IDF physicians and physicians drafted for reserve duty.

The IMA has offered to assist international organisations that wish to enter Israel to provide purely humanitarian support to the Palestinian population, and it has agreed to serve as an intermediary between these organisations and the Israeli Ministry of Interior in cases where they have difficulty in receiving permission to enter Israel.

The IMA has also contacted the National Health Funds and the Ministry of Health to ensure reportage of ethical problems encountered in the course of treatment, and any instances of unethical treatment of patients.

Finally, it is somewhat disingenuous to quote from a PHR report as proof that the IMA is not engaging in humanitarian enterprises. If PHR were itself a purely humanitarian organisation this might be easier to accept. However, in light of PHR's statement that they will cooperate only with those who oppose "the Occupation",¹ we see that PHR's agenda is political and not merely humanitarian. The IMA, on the other hand, takes no political stance, but simply tries to improve the lot of suffering civilians and to uphold our commitment as doctors to treat all patients without regard to race, religion, or nationality.

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- 1 Physicians for Human Rights-Israel. Clarification. *Haaretz*, Feb 11, 2003: 2.

Sir—Yoram Blachar's response to my challenge of the IMA ethical track record on torture¹ is formulaic—as usual invoking the mantra of World Medical Association (WMA) membership, the Declaration of Tokyo, and the imputation that critics are motivated by anti-Israeli or anti-semitic sentiments. Are Amnesty International and others to be thus dismissed?

He asks for the names of offenders, and I gave him one: Eran Dolev, the IMA's Head of Ethics, for his approval of the breaking of Palestinian fingers during interrogation. At a human rights conference in Gaza in 1997, an Israeli doctor told me that an Israeli medical colleague had confessed to her that he had removed an intravenous drip from the arm of a seriously ill Palestinian detainee and told the man that if he wanted to live, he should co-operate with his interrogators. I immediately sent this to Dolev and asked if he would act. I received no reply, even after reminders. This is the reality behind the rhetoric of the IMA and it is no wonder that Palestinian doctors are suspicious of them.

Delon Human for the WMA² also ignores the nub of my paper. Why does the WMA not act on the findings of authoritative studies in the human rights field? How does Human's claim that WMA is working "tirelessly" against torture globally sit with their inaction over Amnesty International's sober conclusions that Israeli doctors form part of a system of institutionalised torture, and with his scarcely credible public defence of the IMA record and of Blachar's position on the WMA Council? I repeat: if the

WMA takes no action, what is it for? Currently the WMA seems in breach of its own Declaration of Tokyo.

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- 1 Blachar Y. Israel Medical Association: response to Derek Summerfield. *Lancet* 2003; **361**: 425.
- 2 Human D. World Medical Association: response to Derek Summerfield. *Lancet* 2003; **361**: 425–26.

Sir—Derek Summerfield's Health and Human Rights piece¹ and the responses following it^{2,3} failed to present the point of view of PHR-Israel, an independent non-governmental organisation that uses its unique place to struggle against torture and the violation of human rights in the Occupied Territories from within Israeli society. They therefore miss the opportunity to support and indeed encourage fellow Israeli doctors in their struggle against violations of human rights. Many of these doctors pay a personal price for their opposition to official Israeli policies.

PHR-Israel approached IMA in 1992, requesting it to join its opposition to interrogations involving torture, and to protest the participation of Israeli doctors in its mechanism. Since then, PHR-Israel has led a wide-ranging public campaign against the participation of Israeli physicians in torture. Our efforts to recruit IMA into this struggle were in vain.

I recount IMA's support of "moderate physical pressure", only to stress its long tradition of siding with "national Israeli considerations" rather than with universal medical ethics. This position governs IMA's current reaction since the outbreak of violence in our region in September, 2000. PHR-Israel believed that IMA, as the representative of the medical establishment in Israel, might be able to curb the appalling deterioration in the attitude of the Israeli military forces toward Palestinian health and rescue services. We sent dozens of complaints to IMA, protesting the army's conduct and the Israeli policy of siege, which makes it impossible for the Palestinian health system to function. However, IMA has chosen to remain silent.

Only just before the WMA convention in 2002 did they publish a position paper; but even that failed to condemn Israel's shooting on ambulances. On its return from the WMA conference, IMA presented its performance as an Israeli propaganda victory over those who had wished to condemn or even suspend IMA from the WMA. This presentation, together

with the failure—up to this day—to answer even one of our detailed complaints, prompts one to ask whether the IMA is merely an executive arm of the Israeli establishment—one that works very hard to present the face of the “enlightened occupier” rather than striving for universal medical ethics. And indeed with such a view, why should they expect Palestinian doctors, detained and humiliated at every checkpoint in the Occupied Territories, to cooperate gladly with IMA, when IMA does nothing to protect them?

The ongoing joint work of PHR-Israel with our colleagues in the Palestinian medical and human rights community has engendered an alternative to the discourse of occupation, dispossession, and violence; one that is based on human rights. We believe that this different voice, which does exist locally, should be heard and used in international fora today. We urge the WMA to make its stand clear on the issue of occupation and human rights violations in our region.

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- 1 Summerfield D. What is the WMA for? The case of the Israeli Medical Association. *Lancet* 2003; **361**: 424.
- 2 Blachar Y. Israel Medical Association: response to Derek Summerfield. *Lancet* 2003; **361**: 425.
- 3 Human D. World Medical Association: response to Derek Summerfield. *Lancet* 2003; **361**: 425–26.

When does exposure of children to tobacco smoke become child abuse?

Sir—We report an instance of a child aged 2·5 years, who is exposed to tobacco smoke in the home. The child is a participant in a prospective cohort study (ABIS; all babies in southeast Sweden) we are undertaking, on environmental factors affecting development of immune-mediated diseases in children.¹

Exposure to environmental tobacco smoke, known to affect present and future health of children,² is one of the environmental factors being studied. Parents are asked, in questionnaires, if and how much they smoke. A subsample of smoking parents of 2–3 year-old children has been asked about their smoking behaviour at home—ie, what precautions they use to protect their child from tobacco smoke. To validate this questionnaire, we have analysed urine cotinine concentrations (the major urinary metabolite of

nicotine) in specimens provided by children of this age. We recorded that the smoking behaviour of parents at home was significantly associated with cotinine concentrations of their child. Cotinine concentrations were adjusted for creatinine.³

The child we report here had a cotinine/creatinine ratio of 800 µg cotinine/1 g creatinine, corresponding to active smoking of 3–5 cigarettes a day.⁴ The parents reported a joint consumption of 41–60 cigarettes a day. They said they smoke in the kitchen and living room, whereas bedrooms were reported to be smoke-free. The parents reported smoking at the dinner table once a day and in front of the television set several times a day. They also said they smoke near the kitchen fan several times a day and near an open door at least once a week. These comments from the parents indicate that, in their opinion, their child was well protected from exposure to environmental tobacco smoke, since they did not smoke in bedrooms and the windows were almost always open.

Though nicotine and cotinine metabolism is independent probably due to genetic differences,⁵ the cotinine concentration of this child is remarkably high. If active smoking in adults causes lung cancer and other serious diseases, passive smoking from the age of 2·5 years (and probably younger) must be even more deleterious. Since a child at this age cannot, by his or her own will, avoid a smoky environment, we ask ourselves when exposure to tobacco smoke should be regarded as child abuse?

We want to stress the fact that, although most parents are aware of the importance of protecting their children from tobacco smoke, and try in different ways, children can still be massively exposed to this toxic drug. Since to just forbid smoking might be ineffective, nurses and doctors should pay attention to smoking behaviour of smoking parents they meet. Until we know more about effective measures of protection, the recommendation should be never to smoke indoors in homes with children.

We thank the Health Research Council of Southeastern Sweden (FORSS) for financial support, and Pharmacia UpJohn, Helsingborg, Sweden, for support with cotinine analyses.

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- 1 Ludvigsson J, Ludvigsson M, Sepa A. Screening for prediabetes in the general child population: maternal attitude to participation. *Pediatr Diabetes* 2001; **2**: 170–74.

- 2 WHO. Report on tobacco smoke and child health: consultation report. Geneva: WHO, 1999.
- 3 Benowitz NL. Biomarkers of environmental tobacco smoke exposure. *Environ Health Perspect* 1999; **107** (suppl 2): 349–55.
- 4 Willers S, Attewell R, Bensryd I, Schutz A, Skarping G, Vahter M. Exposure to environmental tobacco smoke in the household and urinary cotinine excretion, heavy metals retention, and lung function. *Arch Environ Health* 1992; **47** (5): 357–63.
- 5 Ahijevych K. Nicotine metabolism variability and nicotine addiction. *Nicotine Tob Res* 1999; **1** (suppl 2): S59–62.

Genes for schizophrenia

Sir—In their Rapid review on genes for schizophrenia (Feb 1, p 417),¹ Paul Harrison and Michael Owen make omissions in their presentation of the data in support of the *PRODH* gene being a susceptibility gene for the disorder. They claim that no one has replicated the association, but this statement is incorrect. First, the original paper that described the *PRODH* gene as a susceptibility gene for schizophrenia² included a within-study replication whereby the original positive association seen with the US sample was reproduced in an independent South African sample. Although Harrison and Owen include similar supporting information for other genes (ie, *G72*) in their table, they ignore it in the case of *PRODH*.

Second, they do not mention the study by Jacquet and colleagues,³ in which systematic screening of 23 genes from the 22q11 locus for individual gene deletions revealed deletions of the *PRODH* gene in one family with schizophrenia. *PRODH* was the only one of the 23 genes examined that was deleted in individuals with schizophrenia. Furthermore, the studies by Jacquet and colleagues³ and Liu and colleagues² identified several mutations of conserved residues in their independent samples of patients with schizophrenia. Hyperprolinaemia was correlated with the presence of these coding mutations as well as with schizophrenia in the carrier families. Moreover, both studies presented evidence for a modest to striking (depending on the tested population) enrichment of these mutations in populations of patients with schizophrenia.

Although we understand that Harrison and Owen themselves have not been able to replicate the association between *PRODH* and schizophrenia in their own sample, there are two independent published studies with positive and consistent

evidence in support of *PRODH* as a susceptibility gene for schizophrenia.

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- 1 Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* 2003; **361**: 417–19.
- 2 Liu H, Heath SC, Sobin C, et al. Genetic variation at the 22q11 *PRODH2/DGCR6* locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proc Natl Acad Sci USA* 2002; **99**: 3717–22.
- 3 Jacquet H, Raux G, Thibaut F, et al. *PRODH* mutations and hyperproliferation in a subset of schizophrenic patients. *Hum Mol Genet* 2002; **11**: 2243–49.

Sir—Paul Harrison and Michael Owen¹ draw cautious positive conclusions from genetic linkage studies in schizophrenia and point to pathophysiological implications. One can review the same evidence and reach a different conclusion with respect to the genetic basis of psychosis and the direction of future research.

Harrison and Owen cite two meta-analyses^{2,3} and claim that “replicated linkages to several chromosomal regions are accumulating”. But the striking feature of these meta-analyses is that, despite the fact they include many of the same studies, their summaries agree with respect to only one chromosomal arm (8p) of the nine they highlight. A reasonable conclusion is that the null hypothesis has not been disproved.

Why should this substantial endeavour have revealed so little firm evidence of genetic linkage to psychosis? An alternative to the view adopted by Harrison and Owen (that there are multiple genes of small effect) is that the relevant variation is epigenetic—ie, involves modifications such as methylation of the sequence rather than alterations in the DNA sequence itself. For this reason, the modification is invisible in terms of the linkage strategy.

There are already indications of epigenetic variation in the data from monozygotic twins. Whereas concordance (between 40% and 50%) is greater than that (12–15%) seen in dizygotic twins consistent with a genetic factor, it falls well short of 100%. The discrepancy is often interpreted as evidence for an environmental interaction, but no consistent differences in exposure to putative risk factors between affected and non-affected members of discordant pairs have been identified. The alternative is that discordance reflects a difference in gene expression in the course of development.

These arguments can be placed in relation to the nature of psychotic symptoms—ie, disturbances of human beings’ specific capacity for language. Hallucinations (voices), disturbances of thought processes (thoughts experienced as alien, loss of direction), and even delusions (distortions of meaning) can all be conceived as deviations in the transition of thought to speech (production) or from perceived speech to meaning. Thus the phenomena of psychosis are associated with the core characteristic of the species. The importance is that the relevant genetic variation relates to precisely those changes that distinguish *Homo sapiens* from other great ape species.

Already there is evidence from monozygotic twins that asymmetry of the planum temporale and its relation to handedness is subject to epigenetic variation,⁴ as is the association between psychosis and asymmetry of the posterior segment of the Sylvian fissure that overlies the planum. Thus, the asymmetry that separates human beings from other species, and the substrate of language, is subject to variation within the species that is independent of the DNA sequence. This epigenetic variation transmitted between generations is dependent on an interaction between maternal and paternal genomes and perhaps stochastic processes in the course of development.

These conclusions lead to future strategies that depart from those of Harrison and Owen. Rather than concentrating resources on ever-widening searches for multiple genes of small effect, they dictate a focus on the characteristics that distinguish the course of brain development in *Homo sapiens* from that in other primates, and on the ill-understood interaction of genetic and epigenetic factors in determining the variation associated with this development.

Tim Crow

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- 1 Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* 2003; **361**: 417–19.
- 2 Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol Psychiatry* 2002; **7**: 405–11.
- 3 Levinson DF, Lewis CM, Wise LH, et al. Meta-analysis of genome scans for schizophrenia. *Am J Med Genet* 2002; **114**: 700–01 (abstr).
- 4 Steinmetz H, Herzog A, Schlaug G, et al. Brain (a)symmetry in monozygotic twins. *Cerebral Cortex* 1995; **5**: 296–300.

Authors’ reply

Sir—Maria Karayiorgou and Joseph Gogos take us to task for underplaying the evidence that *PRODH* is a schizophrenia susceptibility gene. The format of a Rapid review inevitably means that issues are covered briefly, without being able to do justice to every aspect of the data or their interpretation. Moreover, we were limited to 30 references, and had to remove mention of unpublished data concerning several of the genes. These factors all affected the way we portrayed the background to, and strength of evidence for, each of the genes. It also led us to omit other candidates worthy of mention, such as *DISC1*, *DRD3*, and *HTR2A*.

Nevertheless, Karayiorgou and Gogos correctly point out that their study¹ includes a within-study replication which, to be consistent with the way we summarised the *G72* data, should have been stated in the table. We apologise; the error arose when we simplified an earlier version of the table, which included more details about replications. Although we acknowledge this upgrading of the evidence, we are still cautious about the evidence for *PRODH*, since some comparisons used two-marker haplotypes whereas others used three-marker haplotypes, and the observation was not significant in a third sample ($p=0.055$, one-tailed)¹ nor in an independent family-based association study.² Lack of space and citations also led us to omit the study by Jacquet and colleagues,³ which certainly provides some additional support for *PRODH* involvement in schizophrenia.

We agree with Tim Crow that epigenetic factors might well be important, and said so in our article. However, we disagree with his negative interpretation of the evidence for any of the loci, and hence for all the genes that we reviewed. The fact that two meta-analyses do not come up with exactly the same result is hardly unexpected, given the emerging methods in this specialty, and variation in the datasets used and approaches adopted. We are more impressed by the similarities than the differences in results between the two meta-analyses, and by the fact that in the larger one,⁴ six loci met genome-wide criteria for significance (including 6p and 8p, harbouring *DTNBP1* and *NRG*, respectively). That three of the other five susceptibility genes are also situated at loci with strong, albeit less conclusive, evidence of linkage, surely increases the likelihood that they are true loci for schizophrenia. Moreover, although the evidence might be incomplete with respect to the multiple susceptibility genes model of

schizophrenia, it compares favourably with the lack of empirical data yet available to support Crow's challenging hypothesis.

The two letters show the divergence of opinion that remains about the genetics of schizophrenia. On one hand we are criticised for underestimating the "positive and consistent" evidence for *PRODH*, while on the other we are criticised for proposing the existence of any autosomal genes at all. This state of affairs encourages us to believe that the opinions we expressed lie somewhere close to the middle ground. Ultimately, data will resolve the uncertainty, and determine whether the protocadherin XY is the epigenetic answer to the puzzle.

*P J Harrison, M J Owen

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- 1 Liu H, Heath SC, Sobin C, et al. Genetic variation at the 22q11 *PRODH2/DGCR6* locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proc Natl Acad Sci USA* 2002; **99**: 3717–22.
- 2 Fan J-B, Ma J, Zhang C-S, et al. A family-based association study of T1945C polymorphism in the proline dehydrogenase gene and schizophrenia in the Chinese population. *Neurosci Lett* 2003; **338**: 252–54.
- 3 Jacquet H, Raux G, Thibaut F, et al. *PRODH* mutations and hyperprolinemia in a subset of schizophrenic patients. *Hum Mol Genet* 2002; **11**: 2243–49.
- 4 Levinson DF, Lewis CM, Wise LH, et al. Meta-analysis of genome scans for schizophrenia. *Am J Med Genet* 2002; **114**: 700–01 (abstr).

Granulocyte-macrophage colony-stimulating factor for Crohn's disease

Sir—Brian Dieckgraefe and Joshua Korzenik (Nov 9, p 1478)¹ report on the efficacy of granulocyte-macrophage colony-stimulating factor (GMCSF) for the treatment of Crohn's disease. However, the authors make no reference to our previous publication² in which we reported the use of granulocyte colony-stimulating factor (GCSF) to treat Crohn's disease in an adolescent boy whose disease was resistant to other forms of treatment.

Our report clearly outlined the rationale for use of GCSF as reiterated by Dieckgraefe and Korzenik—ie, in the presence of Crohn's-like lesions with conditions of neutrophil dysfunction, including glycogen-storage disease type 1B, chronic granulomatous disease, and congenital neutropenia. We postulated at the time, as do Dieckgraefe and Korzenik, that the benefit of treatment with GCSF could be due to an

antibacterial effect with an increase in the number of neutrophils or to an effect on cytokines, including the suppression of tumour necrosis factor α .

Since ours was the first report on the use of colony-stimulating factors in the treatment of Crohn's disease, we were surprised that it was not referenced by Dieckgraefe and Korzenik. Our surprise was accentuated by the fact that the authors had knowledge of our publication; one of us was invited to visit their poster at the American Gastroenterology Association meeting in Atlanta in 2001, which outlined preliminary results of the study published in *The Lancet*. This invitation arose because the authors had been aware of our initial report.

In the conflict of interest statement outlined by Dieckgraefe and Korzenik in their *Lancet* publication, they state that, on the basis of their hypothesis, Washington University has applied for a patent covering the use of "colony-stimulating factors" for the treatment of Crohn's disease. They further state that the technology has been licensed to a commercial firm and that both authors are entitled to royalties. Obtaining a US patent is dependent on being first to invent. In their patent application filed in February, 2000, more than 1 year after our report, Dieckgraefe and Korzenik refer to case reports on the use of colony-stimulating factors to treat Crohn's disease-like lesions associated with defects of neutrophil function. These conditions are not covered by their patent application. By contrast, whereas the first claim outlined in their patent application covers the use of GCSF rather than GMCSF in the treatment of Crohn's disease they do not mention our publication, which remains the only report on the use of GCSF to treat Crohn's disease.

As we stated to Dieckgraefe and Korzenik in Atlanta, we published our report with the intention of stimulating studies such as theirs in the hope that this proposed treatment would be of benefit to patients with intractable Crohn's disease. We did not intend this hypothesis to be subject to patent protection, thereby rendering the treatment less available to many chronically ill patients. Withdrawing their claim for patent protection for GCSF alone, about which they have not published, would be of great benefit to patients if clinical trials confirm the efficacy of colony-stimulating factors in treating Crohn's disease.

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- 1 Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002; **360**: 1478–80.
- 2 Vaughan D, Drumm B. Treatment of fistulas with granulocyte colony-stimulating factor in a patient with Crohn's disease. *N Engl J Med* 1999; **340**: 239–40.

Authors' reply

Sir—Brendan Drumm and David Vaughan are critical of our manuscript for failing to cite their case report,¹ describing GCSF treatment of a rectal fistula. In fact, the first reference we did cite² was for a review that summarised evidence supporting an association between Crohn's disease and impaired innate immune function. Drumm and Vaughan's case report was included in this review (reference 36). The format of research letters in *The Lancet* allows for only five references to be included. The limited references we cited were central to reviewers' questions and details of the clinical trial being presented. If we could have cited additional case reports, we would have chosen the seminal observations of Roe and others^{3,4} who deserve credit for establishing the gastrointestinal phenotype in glycogen-storage disease type 1B. Finally, Drumm and Vaughan's case report describes the use of an entirely different medication; GCSF has vastly different properties to GMCSF used in our trial. Although both medications increase neutrophil counts, these proteins lack structural similarity, they act on different receptors and cell populations, and they have fundamentally different biological activities.

While we commend Drumm and Vaughan on their observation that GCSF may promote fistula closure, their assertion that our trial was inspired by or followed their work is inaccurate. Our study, examining the safety and effectiveness of GMCSF for the reduction of Crohn's disease activity, was well underway at the time of Drumm and Vaughan's case report.

With respect to the issue raised of inventorship, *The Lancet* has a copy of correspondence and a manuscript submission, documenting our hypothesis and research that greatly predates Drumm and Vaughan's report.

We share Drumm and Vaughan's stated desire that new promising therapies be made widely and rapidly available to patients. However, we believe that the most effective way to accomplish this goal is in the form of well designed clinical trials. Results of such clinical trials and other related investigations are precisely the driving forces that stimulate new avenues of

exploration into the mechanisms that underlie the effectiveness of these novel therapeutic agents.

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Use of mobile phones in hospital

Sir—As someone who has helped draft my hospital's mobile communications policy, I take issue with Omer Aziz and colleagues' contention (March 1, p 788)¹ that it is time to reappraise current restrictions against use of mobile phones in hospitals.

They mention a 10-year-old warning from the UK Medical Devices Agency, which they claim has been superseded by the advent of digital global system (GSM) mobile phones. In drafting our policy, we referred to the Medical Devices Agency's bulletin issued in 1997,² which includes GSM phones (in fact, they were as troublesome as the older phones). This bulletin reports many instances of mobile phones interfering with medical equipment at distances from 0 m to 1 m. For example, three infusion pumps went into shut down in the presence of a GSM device and one went into draw back. For those of us trying to draft a hospital-wide policy, our nightmare scenario would be a patient on infusion surrounded by visitors, any one of whom could be using a mobile phone close to the device.

Aziz and colleagues imply that medical staff could be exempt from restrictions on mobile phones. I find this puzzling. Paging systems operate at a far lower power level than mobiles and are known to produce negligible interference. Moreover, most patients and their hospital visitors comply with the mobile phone ban. If medical staff were seen to be operating outwith the restriction, it would not be long before

the average ward was awash with the acoustic and electromagnetic babble that fills every other public space. But, of course, the specific low range dangers would not be known by all.

Our own decision was to create several mobile friendly places where we knew that the nearest electromedical equipment was at least 5 m away.

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Gut flora in health and disease

Sir—We read with interest the Review on gut flora in health and disease (Feb 8, p 512).¹ However, we were disappointed that so little mention was made of the effect of critical illness on gut flora and the potential benefits of probiotics in this group of patients.

In critically ill patients, composition of gut flora changes within a few hours. The reasons for this change are a combination of reduced food intake, gut ischaemia, use of broad-spectrum antibiotics, and the direct effect of critical illness on host immunity.

The subsequent large numbers of potentially pathogenic microorganisms (PPMs) and altered gut permeability have given rise to the notion that the gut acts as the motor for multiorgan failure in critical illness. This idea is not new, and has led to widespread interest in selective digestive tract decontamination (SDD). This treatment was hoped to target aerobic gram-negative organisms and fungi, leaving anaerobes and gram-positive bacteria intact, thereby reducing mortality. In a meta-analysis assessing the efficacy of SDD, benefits in mortality rates were seen in critically ill surgical patients but not in medical patients.²

An alternative approach to gut floral changes is not direct eradication of PPMs with antibiotics but preservation or re-establishment of normal gut flora with probiotics. Intensive-care unit research in this area is in its early stages, but results of several preliminary studies have shown mortality benefit in severe acute pancreatitis, liver transplantation, and abdominal surgery patients.^{3–5} We are presently researching the effects of probiotics on gut floral ecology in a mixed intensive-care unit population.

An adequate supply of enteral

nutrients to the gut is vital if normal immune status in the intestinal tract is to be maintained. Early use of the enteral feeding route and prevention of extended periods of fasting during critical illness are widely believed to be helpful in establishing this status.

As we consider the growing problem of nosocomial infections in the intensive-care unit, perhaps now is the time to change our management strategy: rather than treating effect, we should treat the cause. Will re-establishing a healthy gut flora switch off the multiorgan failure engine?

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- 1 Guarner F, Malagelada J-R. Gut flora in health and disease. *Lancet* 2003; **361**: 512–19.
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- 3 Oláh A, Belágyi T, Issekutz Á, et al. Early enteral nutrition with specific lactobacillus and fibre reduces sepsis in severe acute pancreatitis. *Br J Surg* 2002; **89**: 1103–07.
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What is best for the patient?

Sir—Peter Bogaty and James Brophy's Viewpoint (published online March 25)¹ on treatment for acute coronary syndromes provided a well thought out and powerful argument to keep evidence-based treatment in perspective in an era in which we tend to rigidly misapply data. There are important implications of the data obtained from carefully controlled trials being used to guide practice in day-to-day care of patients, both with respect to individual patients and the allocation of resources.

As a geriatrician, I am constantly battling with adverse drug reactions on the one hand, and compliance on the other. My prescribing for many drugs is limited by local and national rationing constraints. For example, the only selective serotonin reuptake inhibitor I am allowed to prescribe is fluoxetine, which frequently aggravates my patients' anxiety, and I am not allowed to prescribe a serotonin norepinephrine reuptake inhibitor without the consent of an already overworked psychogeriatrician. More than 90% of my in-patient

workload involves the care of individuals with various stages of dementia, though the potential symptomatic benefits of cholinesterase inhibitors are denied my patients through inadequate resourcing of memory clinics and the artificially restrictive constraints of prescribing the drugs; National Institute of Clinical Excellence (NICE) guidelines use a mini-mental state examination as the principle criterion for deciding appropriateness of a therapy, for which the practical benefits are with behavioural improvements and reductions in anxiety.² As a result, a 75 year old with mild dementia is more likely to receive a cocktail including aspirin, an angiotensin converting enzyme inhibitor, a statin, and a β blocker as preventive therapy for their possible angina, than medication with potential symptomatic benefits that could have a great effect on their independence and functional state.

Unfortunately, we will probably continue with the simplistic application of evidence-based medicine through guidelines and misguided rationing. We are now in a position in which we have to justify the withholding of potentially protective cardiac medications, where general consensus and guidelines have that everyone receives them, often despite a fairly small reduction in risk. Guidelines seem to be getting priority over the individual patient, and the problem is compounded through audit and targets. We should focus our limited resources better, though to do so will require a major change to our approach to modern medicine. We are already losing our clinical freedom, and look back fondly to the days when we could use our experiential knowledge and prescribe the treatments felt to be most beneficial to the patient.

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- 1 Bogaty P, Brophy J. Increasing burden of treatment in the acute coronary syndromes: is it justified? *Lancet*. Published online March 25, 2003. <http://image.thelancet.com/extras/02art8093web.pdf> (accessed April 24, 2003).
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SARS—a clue to its origins?

Sir—We detected large quantities of viable microorganisms in samples of stratospheric air at an altitude of 41 km.^{1,2} We collected the samples in specially designed sterile cryosamplers carried aboard a balloon launched from the

Indian Space Research Organisation/Tata Institute Balloon Facility in Hyderabad, India, on Jan 21, 2001. Although the recovered biomaterial contained many microorganisms, as assessed with standard microbiological tests, we were able to culture only two types; both similar to known terrestrial species.² Our findings lend support to the view that microbial material falling from space is, in a Darwinian sense, highly evolved, with an evolutionary history closely related to life that exists on Earth.

We estimate that a tonne of bacterial material falls to Earth from space daily, which translates into some 10^{19} bacteria, or 20 000 bacteria per square metre of the Earth's surface. Most of this material simply adds to the unculturable or uncultured microbial flora present on Earth.

The injection from space of evolved microorganisms that have well-attested terrestrial affinities raises the possibility that pathogenic bacteria and viruses might also be introduced. The annals of medical history detail many examples of plagues and pestilences that can be attributed to space incident microbes in this way. New epidemic diseases have a record of abrupt entrances from time to time, and equally abrupt retreats. The patterns of spread of these diseases, as charted by historians, are often difficult to explain simply on the basis of endemic infective agents. Historical epidemics such as the plague of Athens and the plague of Justinian come to mind.

In more recent times the influenza pandemic of 1917–19 bears all the hallmarks of a space incident component: “The influenza pandemic of 1918 occurred in three waves. The first appeared in the winter and spring of 1917–1918 . . . The lethal second wave . . . involved almost the entire world over a very short time . . . Its epidemiologic behaviour was most unusual. Although person-to-person spread occurred in local areas, the disease appeared on the same day in widely separated parts of the world on the one hand, but, on the other, took days to weeks to spread relatively short distances.”³

Also well documented is that, in the winter of 1918, the disease appeared suddenly in the frozen wastes of Alaska, in villages that had been isolated for several months. Mathematical modelling of epidemics such as the one described invariably involves the ad hoc introduction of many unproven hypotheses—for example, that of the superspreader. In situations where proven infectivity is limited only to close contacts, a superspreader is someone who can, on occasion, simultaneously infect a large number of susceptible individuals, thus causing the sporadic emergence of new clusters of disease. The recognition of a

possible vertical input of external origin is conspicuously missing in such explanations.^{4,5}

With respect to the SARS outbreak, a prima facie case for a possible space incidence can already be made. First, the virus is unexpectedly novel, and appeared without warning in mainland China. A small amount of the culprit virus introduced into the stratosphere could make a first tentative fall out East of the great mountain range of the Himalayas, where the stratosphere is thinnest, followed by sporadic deposits in neighbouring areas. If the virus is only minimally infective, as it seems to be, the subsequent course of its global progress will depend on stratospheric transport and mixing, leading to a fall out continuing seasonally over a few years. Although all reasonable attempts to contain the infective spread of SARS should be continued, we should remain vigilant for the appearance of new foci (unconnected with infective contacts or with China) almost anywhere on the planet. New cases might continue to appear until the stratospheric supply of the causative agent becomes exhausted.

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DEPARTMENT OF ERROR

Donnelly CA, Ghani AC, Leung GM, et al. *Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong*. *Lancet* 2003; **361**: 1761–66—In this Article (May 24), in the sixth sentence in the fifth paragraph of the Results section (p 1763), 48·5 days should be: “4·85 days”, and 10·71² days should be “10·71 days” (p 1764). In the first sentence of the sixth paragraph of Results (p 1764), 572·9² days should be “572·9 days” and 62·1² days should be “62·1 days”.

Ruan YJ, Wei CL, Ling AE, et al. *Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection*. *Lancet* 2003; **361**: 1779–85—In figure 3 of this Mechanisms paper (May 24), the sequence for the Hong Kong CUHKW1 isolate should be, from top to bottom: “TCTGCCCGCAACCCA”.