CORRESPONDENCE

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Triptan medications to treat acute migraine

Sir—The effectiveness of the triptan medications in the acute treatment of migraine has been thoroughly established through many well controlled clinical trials. Although Michel Ferrari and colleagues' study (Nov 17, p 1668)[1] is statistically interesting, we question the methods, validity of results, and conclusions.

First, we note that the main body of clinical evidence presented in the meta-analysis was inappropriately derived from indirect comparisons of absolute effects. The analysis is based on pooled triptan response rates and therapeutic gain calculations derived from different sets of placebo-controlled trials. Such measures are influenced by placebo response rates that vary notably in triptan trials. Because such absolute effects are altered by inherent variability among patients, guidelines recommend that in assessment of drugs from separate placebo-controlled trials, only proportional effects (eg, response-rate ratios) from each drug should be compared.

Second, the triptan meta-analysis can be added to the examples of widely discussed flawed meta-analyses that have produced results discrepant to those of individual trials.[2,3] For instance, the sumatriptan 50 mg dose was numerically better than the 100 mg dose, results that have never been produced in clinical trials comparing these doses. The results contradict those of adequately powered head-to-head clinical trials, the gold standard for investigating true differences between medicines. In webtable 3 provided by Ferrari and colleagues, rizatriptan has not consistently, and almotriptan has never been, better than sumatriptan in such trials.

Contrary to the only two head-to-head studies,[4] Ferrari and colleagues conclude that almotriptan is 24% better than sumatriptan for pain-free efficacy. They acknowledge that eletriptan head-to-head trials are biased because of the encapsulation of sumatriptan tablets,[5] which lowered the efficacy of sumatriptan in these trials, but neglect to address the impact of encapsulation on the entire dataset for sumatriptan or their conclusions. Given these evidence-based examples that call into question the results and conclusions, it is unclear how Ferrari and colleagues can draw such definitive conclusions from the data.

Finally, we also question the clinical relevance of the minor significant differences reported. How does the meta-analysis help a practitioner select treatment for an individual patient? No clear subgroups benefiting from one triptan over another are identified. Ferrari and colleagues acknowledge that patients' individual characteristics, preferences, and responses cannot be predicted. Although the meta-analysis may be viewed as a statistical exercise, it does not improve the overall understanding of migraine and its treatment. The most important issue is that migraine is under-diagnosed, highly debilitating, and under-treated.

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1 Ferrari MD, Roon KI , Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358:** 1668–75.
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4 Spierings ELH, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, Jirgens KJ. Oral almotriptan vs oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. *Arch Neurol* 2001; **58:** 944–50.
5 Fuseau E, Petricoul O, Sabin A, et al. Effects of encapsulation on absorption of sumatriptan tablets: data from healthy volunteers and patients during a migraine. *Clin Ther* 2001; **23:** 242–51.

Sir—Michel Ferrari and colleagues'[1] conclusion on which specific triptans they see as having the highest likelihood of consistent success, in our opinion, begins to depart from standard evidenced-based conclusions, given the data in the text.

Eletriptan 80 mg was associated with the highest likelihood of adverse events, in which case the assumption that tolerability is benign or without clinical consequence is presumptive. Most migraine investigators know that adverse events are one of the primary reasons for withdrawal from clinical studies and non-adherence to treatment.

Data available for frovatriptan were assembled from abstracted data, which is not a comparable method. Therefore, statements on its efficacy and tolerability are not relevant.

Ferrari and colleagues' conclusions relate to agents with the highest likelihood of achieving consistent success, yet there was no consistency data presented for zolmitriptan 2·5 and 5·0 mg, rizatriptan 5 mg, and sumatriptan 25 and 50 mg. This omission may mislead readers to assume that comparisons on consistency included all treatments.

There seems to be a mismatch between the section entitled statistical analysis, in which Ferrari and colleagues talk about comparison with placebo, and the results that are compared with sumatriptan 100 mg. Since the only treatment common to all studies was placebo, the only evidence-based conclusions should be active treatment compared with placebo. However, the investigators use non-overlapping 95% CI to infer differences between active treatments from this collection of clinical trials. The statement that no endpoint showed homogeneity for all triptans suggests that Ferrari and colleagues themselves realised that it is statistically inappropriate to combine and compare these trials.

Differences between the selected studies in terms of design, size, and scope (multiple doses, active comparators, small placebo groups) and in sampling of patients (eg, triptan-naïve *vs* non-naïve, ratio for moderate to severe migraine) may invalidate the conclusions. The US Food and Drug Administration has recognised this issue and requires the statement "Comparisons of drug performance based on results obtained in different clinical trials are never reliable" be included on most triptan labels.

Lastly, the larger challenge lies with

the ability to translate these results to improve the clinical care of migraine patients. The results of this meta-analysis show that all triptans are clinically effective, and differences among them are small. For the practising physician, a common treatment plan for all patients is unlikely to result in best clinical practice. A more appropriate approach may be that treatment strategies should be tailored to individual patients' needs and preferences.

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1 Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT$_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358:** 1668–75.

Sir—Michel Ferrari and colleagues[1] report that 100 mg rizatriptan, 80 mg eletriptan, and 12·5 mg almotriptan are better than 100 mg sumatriptan. I have two comments on this meta-analysis.

The investigators state that they collected raw data for patients from the pharmaceutical companies that marketed triptans and from principal investigators of triptan trials. Being a principal investigator of such a clinical trial,[2] I was approached and agreed to let the company, Synthelabo France, provide the data requested. The data requested were not, however, real raw data but those such as number of patients in each treatment group and number of patients in each group with sustained pain-free response, as defined by the study researchers. Therefore, Ferrari and colleagues give the impression that they calculated all the parameters for all patients, which is, thus, somewhat misleading.

Ferrari and colleagues rightly note that we need meta-analyses to supplement head-to-head comparative clinical trials with triptans, mainly because all triptans will never be compared in comparative clinical trials. In addition, selection bias in comparative trials can partly be overcome by meta-analyses. They mention that the remarkable similarity of the results from the meta-analysis and from the comparative trials, summarised in webtable 3, reinforces the validity of the conclusions.

They seem, however, to favour the results from their meta-analysis and report that 12·5 mg almotriptan was significantly better than 100 mg sumatriptan for pain-free and for sustained pain-free time in the meta-analysis. However, in one direct comparative trial they included, the drugs did not differ: 6% (95% CI −4 to 15) more patients were pain-free and 3% (−11 to 6) fewer patients had sustained time pain-free after 100 mg sumatriptan than after 12·5 mg almotriptan. In addition, in a large clinical trial,[3] in which 50 mg sumatriptan and 12·5 mg almotriptan were compared, the pain-free responses were 25% and 18%, respectively (p=0·005). In conclusion, I doubt Ferrari and colleagues' conclusions for almotriptan. Firm recommendations should only be taken if a meta-analysis and comparative clinical trials show the same results.

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1 Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT$_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358:** 1668–75.
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3 Spierings EL, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, Jirgens KJ. Oral almotriptan *vs* oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. *Arch Neurol* 2001; **58:** 944–50.

Sir—In their report, Michel Ferrari and colleagues[1] claim that physicians need evidence-based guidelines to select treatment with the highest likelihood of success. In doing so they reflect an academic preoccupation with efficacy at the expense of the unmet need of patients and pragmatic requirements of physicians.

The trials reviewed are undertaken in circumstances that bear little relation to the real world. Patients do not take their medication according to the well-defined criteria of migraine trials, and their headaches are frequently mixed. Migraine attacks and their management do not conform to the restricted protocols of clinical trials. The studies reviewed by Ferrari describe the aggregated impact of treatment on large groups of patients and overlook the heterogeneity of response of the population under study in a therapeutic area that is characterised by a high level of placebo effect.

The research process itself has an opportunity cost. Rather than spending time on identifying marginal differences in benefit between five agents, the research effort should be focused on improving service delivery in the headache area: finding out why patients are reluctant to consult their family physicians, why their expectations are so low, and why the disorder is so poorly handled when they do so.

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1 Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT$_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358:** 1668–75.

Sir—I find Michel Ferrari and colleagues' report[1] very unbalanced. The benefits of treatment for sumatriptan are reported in the abstract without subtracting the placebo rates, making them seem much larger than the adverse events that are reported as placebo-subtracted rates.

There is a serious danger that the results of the almotriptan comparison from the meta-analysis are spurious because the placebo group rates have not been subtracted. Figure 3 in the report shows that the placebo rates for some outcomes in the almotriptan trials are higher than average. The more robust, randomised, head to head comparison of almotriptan with 100 mg sumatriptan has CI that exclude the differences noted in the meta-analysis for short-term and sustained pain-free responses. The investigators make no reference to this disparity.

Clinical similarity between the trials does not justify a meta-analysis that only pools the results of the active treatment groups, and thereby abandons the safeguards against bias afforded by randomisation in the individual trials.

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1 Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT$_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358:** 1668–75.

Sir—We are surprised by James Palmer and Reijo Salonen's comments, since GlaxoSmithKline agreed to the objectives and design of our study, and did not comment on our methods on review of our results for their drugs, sumatriptan and naratriptan, before publication.

They say guidelines recommend use of active-to-placebo response-rate ratios rather than placebo-subtracted rates. However, the cited guidelines by McAlister and colleagues do not set a level at which a drug can be claimed to

be better than others, but review the prevention of rare events for which statistical models different than in migraine apply.

Contrary to Palmer and Salonen's claim, there is no consensus on which strategy is best to compare results from different trials.[1] The rate-ratio approach assumes a multiplicative relation between active drug and placebo; the placebo-subtraction approach assumes an additive relation, which is more intuitive for most clinicians. The multiplicative model has at least two disadvantages. First, commonly used statistical models overestimate the prevalence ratios when the rare disease assumption is violated, as it is in migraine. In addition, as placebo rates increase (approaching 50%) the maximum ratio is limited (only 2). In the context of placebo-subtracted values, GlaxoSmithKline has promoted early treatment of migraine with sumatriptan on the basis of pain-free rates being better than those in studies with traditional treatment protocols.[2] The placebo rates were, however, also higher (29 *vs* 8% for the traditional treatment protocol),[3] which actually make the rate ratios worse.

As explained in the statistics section, we analysed the data by four strategies: absolute values, ratios, placebo-subtracted values, and number needed to treat (NNT). Results were similar for all. The homogeneities for outcome measures were good and virtually identical for ratios and placebo-subtracted rates. Because most clinicians in pain management are familiar with placebo-subtracted rates (or NNT) we presented the additive model.[4]

Palmer and Salonen question the validity of the meta-analysis by raising minor issues. The difference between sumatriptan 50 mg and 100 mg was only marginally not statistically significant (within the CI), and not seen for time pain-free. GlaxoSmithKline did not object to this finding before publication. Interestingly, Palmer and Salonen dismiss rizatriptan as not being consistently better than sumatriptan, on the basis of one study in which a numerical superiority of rizatriptan just missed significance. The difference for the pooled data of the comparator trials however was significant.

Palmer and Salonen comment on the effects of encapsulation on sumatriptan's efficacy and the dataset. Fuseau and colleagues' study, sponsored by GlaxoSmithKline, showed no reduced clinical efficacy for encapsulated sumatriptan. Similarly, the mean overall headache response rates in our meta-analysis were not altered by encapsulation. If encapsulated sumatriptan is omitted, results are similar: absolute response 59·0 included, 59·3 omitted; placebo-subtracted responses 31·0 and 31·1; absolute pain-free 28·9 and 29·8; and placebo-subtracted pain-free 20·5 and 20·8.

In response to Peer Tfelt-Hansen, we calculated all parameters from the number of patients for each outcome category rather than from the patients' record forms. We also noted the discrepancy for some of the efficacy results in the almotriptan head-to-head comparator trials. Hence, we assigned equal efficacy to almotriptan and sumatriptan in the concluding table. We did not include Spierings and colleagues' trial because it was not placebo-controlled and was completed after the database was closed.

Despite Andrew Dowson and Shaun Kilminster's doubts about meta-analytic pooling of data, most experts agree that meta-analysis is useful for summarising evidence.[1,4] We do recognise that meta-analysis also has limitations.[3] We did not receive the raw trial data for frovatriptan; we therefore reviewed the results available in the discussion section. Controlled consistency data were not available for some of the doses and agents. Because all these doses had reduced 2 h relief rates, their absence cannot alter which drugs show the highest likelihood of repeated relief when treating multiple attacks.

D Kernick touches on translation of results from clinical trials to individual patients. Despite the potential for individual differences in treatment response, a 38% difference in pain-free rates between triptans might offer useful guidence for clinicians making treatment recommendations.

We recognise the issues raised by Christopher Cates around the reporting of adverse events.[3] Total adverse-effects rates combine many minor side-effects and a few important adverse-events. Unfortunately, there is no validated alternative to aid more informative reporting. The efficacy differences in the comparator trials also have CI that overlap with the CI from the meta-analysis.

In summary, the trials we included all had similar designs, populations of patients, and placebo responses. Furthermore, the profiles of the triptans and the differences among them were quite consistent in our analysis of the head-to-head comparative studies and using all four meta-analytic approaches. We are, therefore, confident in the validity of these results.

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Cardioprotection of trimetazidine and anthracycline-induced acute cardiotoxic effects

Sir—Anthracyclines are widely used antineoplastic agents that can induce selective cardiotoxic effects. These effects can be acute, leading to cardiac failure and decrease of the ejection fraction within 48 h, or can be chronic, according to dose, with high mortality rates (30–50%).

The mechanisms have been related to free-radical formation with peroxidation of the cell-membrane lipids and interference with sarcoplasmatic reticulum function and cardiomyocyte apoptosis. In addition, the myocardial high-energy phosphate metabolism can be impaired after treatment with anthracyclines. In an attempt to circumvent these toxic effects, various antioxidants have been used in cell culture, animal, and human studies without consistent beneficial effects.[1,2] The cardiotoxic side-effects are currently treated with dexrazoxane, which works as a chelator agent.

Trimetazidine, a 3-keto acyl coenzyme A-thiolase inhibitor, which acts in the myocyte cell metabolism, raising the ATP content in hypoxic conditions and preventing oxygen free-radical cell-membrane damage,[3] has

been introduced in ischaemic cardiovascular syndromes.

We describe a case of acute anthracycline-induced cardiotoxic effects resistant to dexrazoxane, which improved after treatment with trimetazidine.

A woman aged 76 years who had had total right mastectomy for breast cancer in 1995 and a secondary lesion in L3 in 1998 treated with formestane and pamidronic acid, was referred to our division because of a new bone lesion. Electrocardiography was normal and the echocardiogram showed normal cardiac diameters, 58% ejection fraction, normal regional wall motion, and slight aortic insufficiency. We started 90 mg epirubicin intravenously, and dexrazoxane 100 mg.

1 week later she developed dyspnoea with orthopnoea. A new electrocardiogram showed widespread negative T waves and medium-apical segments were strikingly hypokinetic, with a 38% ejection fraction and mitralic insufficiency. Treatment with diuretics and intravenous nitroderivates was ineffective. We purported that trimetazidine could be useful in the acute anthracycline-induced cardiotoxic effects. We began treatment with oral trimetazidine 20 mg three times daily; the patient's signs and symptoms rapidly improved, and T waves normalised on electrocardiography; 24 h later we did another echocardiogram and noted an increase in systolic function, with a 53% ejection fraction and no mitralic insufficiency. The chemotherapy was discontinued. After 5 months the treatment with trimetazidine was stopped. The patient had no further chest pain or dyspnoea.

Trimetazidine maintains cellular homoeostasis, preserves electrical and contractile function activity, and limits cytolysis; these effects have been ascribed to a protective action on energy metabolism, limiting intracellular acidosis. There is a protective effect on lipid peroxidation and potassium permeability induced by oxygen free radicals.[4] The prevention by trimetazidine of doxorubicin-induced myocardial toxic effects has been studied in rats; it could not prevent the development of long-term effects, but improved substantially the early cardiotoxic signs.[5] These data need to be confirmed by clinical trials.

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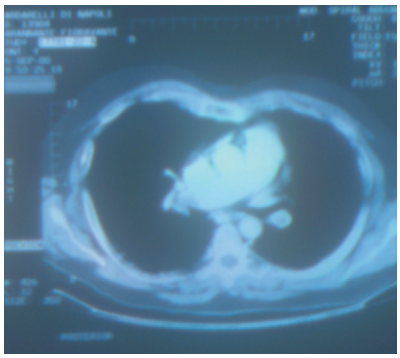
Central venous pressure monitoring during pulmonary embolism

Sir—We report a patient who had severe pulmonary embolism and in whom thrombolytic therapy by central venous line was successful.

The patient developed a severe pulmonary embolism 15 days after surgery for femur rupture, and was admitted in a critical condition. He was dyspnoeic (respiratory rate 35 breaths per min), sweaty, and confused. Arterial blood pressure was 70/40 mm Hg, heart rate 150 beats per min, and arterial blood gases (fractional concentration of oxygen in inspired gas 0·21) showed a partial arterial pressure of oxygen of 6·65 kPa, and of carbon dioxide 3·2 kPa. pH was 7·20 and arterial oxygen saturation 82%.

We confirmed pulmonary embolism by CT spiral scan. We immediately started thrombolysis with 10 mg alteplase in bolus followed by infusion of 90 mg in 2 h (figure), preceded by the insertion of a central venous line through the right internal jugular vein. Central venous pressure was monitored throughout treatment. Dobutamine was started at 10 γ kg^{-1} min^{-1}. Oxygen and air (50% each) were given via facial mask.



Thrombolysis of pulmonary embolism on CT spiral scan

The patient improved immediately. At the end of thrombolytic therapy, the patient was no longer sweaty or dyspnoeic, and was no longer confused. Arterial blood pressure was 120/75 mm Hg; heart rate was 98 beats per min; arterial blood gases (fractional concentration of oxygen in inspired gas 0·5) were partial arterial pressure of oxygen 14·0 kPa and carbon dioxide 4·5 kPa; pH was 7·35; and arterial oxygen saturation 95%. Central venous pressure was 12 mm Hg. Spiral computed tomography scan with contrast 24 h later showed a complete resolution of pulmonary embolism. He was discharged home after 14 days.

The monitoring of central venous pressure is useful during thrombolysis for pulmonary embolism in critically ill patients. This procedure should be done through the internal jugular vein by experienced medical staff to avoid haemorrhage.

Pulmonary embolism is a frequent and complicated chest disorder for which treatment is a great challenge.[1] In randomised controlled trials, thrombolysis alone has not reduced morbidity or mortality.[2] Thrombolysis can have adverse events, such as intracranial or gastrointestinal-tract haemorrhage or vessel puncture. The incidence of haemorrhage is reported to be 6·3–11·9%.[3]

There are no guidelines for central venous monitoring during use of coagulation pathway drugs.[4] Central venous catheterisation is frequently necessary for administration of drugs and the monitoring of central venous pressure. Use of the internal jugular vein, is judged safest because, in the event of accidental arterial puncture, direct compression of soft tissue can be done.

Research of the efficacy of thrombolytic therapy in pulmonary embolism and research into guidelines for placement are needed.

We thank the Department of Radiology, "A Carderelli" Hospital, for technical support.

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Study of genes and environmental factors in complex diseases

Sir—David Clayton and Paul McKeigue (Oct 20, p 1356)[1] thoughtfully review epidemiological methods for studies of genes and environmental factors with ideas about trade-offs between case-control and cohort studies. We would like to augment this review from our perspective as cancer epidemiologists who have worked on these issues for some time.[2,3]

Case-control studies are cheaper and quicker from planning to completion than cohort studies. They allow more thorough ascertainment of disease and standard collection of biospecimens, such as frozen tissue at diagnosis.[2] To ensure that a study is "correctly designed"[1] and done is not always easy, given difficulties in case ascertainment, control selection, and participation.[3] In addition, biospecimens that are markers for exposure might be affected by treatment, limiting the usefulness of case-control studies.[2]

Self-report or proxy reports on exposure obtained after diagnosis in case-control studies can lead to differential misclassification with important consequences. Multiplicative interaction is attenuated rather than exaggerated by differential misclassification of exposure;[1,4] this is small comfort when we realise that this property does not hold for the exposure main effect, the joint effects, the effect of one factor in subgroups defined by the other, the effect of genotype adjusted for exposure, or for assessment of additive interaction.[5] Seriously misclassified exposure, whether differential or non-differential, undermines Clayton and McKeigue's goal of testing hypotheses about causal pathways amenable to intervention.

Much of the economic and ultimate public-health importance of cohort studies arises from their ability to study multiple endpoints in the same base population. Even if the cost is substantially higher than for case-control studies, the attendant gain in efficiency over time is substantial if the cohort is maintained.[3] Also, cohorts allow case-cohort or case-control studies to be nested within, providing an appropriate roster from which to select one or more controls per case, effectively eliminating the problems of control selection and participation in stand-alone case-control studies, which Clayton and McKeigue downplay by assuming that they are well designed. With control-to-case ratios as low as 4 or 5, the power of these efficient nested designs can approach that of the full cohort.

Of course, there remain many circumstances in which case-control studies are indicated, such as when the outcome is rare, information on a specific exposure is not collected in sufficient detail in cohort studies, or when biospecimens that cannot be readily obtained in cohort studies are needed. However, 1 000 000 people were enrolled in prospective cohort studies with blood-sample collections and questionnaire data on important chronic disease risk factors by 1999, and there may be more than 2 000 000 enrolled within 5 years.[3] These studies should provide important information on the environmental and genetic contributions, and their inter-relations, to common sources of mortality and morbidity, at least in adults in developed and in some developing countries.

The presence of these resources, particularly when collaboration is encouraged and analyses are coordinated, should allow investigators to focus case-control efforts where they can provide unique and not duplicative information.

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Sir—We agree with most of David Clayton and Paul McKeigue's points,[1] but differ on certain crucial issues.

The potential distortion that can arise from systematic bias in the retrospective assessment of exposure status in case-control studies is important. Clayton and McKeigue argue that the simple test for an interaction representing a departure from an otherwise multiplicative model may be robust to such biases, provided that errors are independent of genotype, but this latter point is a crucial assumption.[2] Furthermore, such biases could seriously distort other features of the joint effect of an environmental and a genetic determinant.

We believe the extent to which the targeting of interventions in accordance with genotype will ultimately prove useful is as yet unclear. The appropriate action will depend on the multifactorial nature of the disease in question, and on the severity of its consequences for individuals, families, and society; the costs, risks, and unrelated benefits associated with the intervention being considered; and the costs and risks associated with genetic and other screening to detect high-risk individuals. Targeted therapeutic intervention sometimes may provide maximum health benefits and keep costs to a minimum. At other times, the whole-population approach may be preferred,[3] irrespective of individual genotype.

A key issue is the contest between the benefits of prospective exposure assessment (before disease onset) embodied in a cohort design, and the benefits accruing from the greater efficiency of a case-control design. This brings us to the fundamental purpose of BioBank UK.

If the sole aim were to study several specific causal hypotheses (possibly interactions) over 10 years, Clayton and McKeigue's case would be strong. However, the BioBank UK initiative is really about setting up a foundation for various bioscience projects over the next 20–30 years. Many projects will be nested case-control studies that will benefit from the prospective (and potentially repeated) exposure assessment and the ability to undertake detailed additional assessment in cases and a limited number of controls.

We share Clayton and McKeigue's reservations about the interpretation of statistical interactions, particularly when the correct scale of analysis is unknown. However, the current emphasis is more on being able to describe the joint effects of causal determinants.

We share Clayton and McKeigue's belief that a large prospective cohort would be an inefficient approach for a 10-year initiative. However, we believe that BioBank UK's originators had a

vision that extended well beyond one decade. Nevertheless it is obviously important to have potential outputs at a maximum in the first 10 years, and the collection of additional intermediate phenotyping data at baseline in a subset of the cohort could prove invaluable in this regard.

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1 Clayton DG, McKeigue PM. Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet* 2001; **358:** 1356–60.
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Sir—David Clayton and Paul McKeigue[1] show the feasibility of case-control studies, but argue that the scientific usefulness of studying gene-environment interactions may be limited. Instead they suggest a candidate-gene approach, involving genetic association studies to test hypotheses about causal pathways. I suggest an extension to this approach.

Among other limitations and complexities of interaction, Clayton and McKeigue cite the fact that interaction in many situations depends on the model on which absence of interaction is defined. Model dependency is present whenever the environmental and genetic factors have an effect on disease in the absence of the other study factor. On the other hand, whenever at least one of the two study factors does not have an effect on disease in the absence of the other study factor, presence of interaction according to one model, such as the additive model implies interaction on another model, such as a multiplicative model. In other words, the question of presence or absence of interaction is not model dependent.

In relation to their discussion of potential gain in statistical power when the effect of the environmental factor is restricted to a subgroup of individuals with a particular genotype, Clayton and McKeigue state that in practice, such extreme situations are unlikely to be frequently encountered in the study of complex disease. This latter statement may be correct, but I suspect this is partly because most early attempts to study gene-environment interactions have involved genes or genetic markers and environmental factors that are already known to be associated with the disease in question.

If a polymorphism known to affect a certain biochemical pathway does not show association to a disease in question, I suggest that the next logical step would be to test whether there is a statistical interaction between this polymorphism and an environmental factor that is thought to affect the biochemical pathway of interest. This extension requires, of course, that the environmental exposure can be measured with reasonable validity and precision. Such an approach would be based on hypotheses with biological plausibility, and the test of interaction would not suffer from the fundamental issue of model dependency.

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Sir—It has long been apparent that an individual's risk of disease relates to exposure to various factors (including lifestyle, physiological, and environmental factors), personal susceptibility, and chance. Advances in genetics have made large-scale studies incorporating information on exposure and genotype feasible and the logical next step in understanding the factors determining health.

We agree with David Clayton and Paul McKeigue[1] that the usefulness of statistical interaction between genotype and exposure is unclear. Instead, assessment of the effect of exposures on disease risk within specific genotypic subgroups and the effect of genotype within subgroups of exposure would be more useful.

The Wellcome Trust and the Medical Research Council have funded several large case-control studies specifically to investigate genetic associations. In recognition of the pressing need for high-quality large-scale data on exposure, genotype, and a range of outcomes, they and the UK Department of Health have started to develop a prospective study of 500 000 men and women in the UK, called BioBank UK, aiming to investigate the separate and combined effects of genotype and exposure on the risk of common multifactorial diseases of adult life.

Questionnaires, interviews, physical examinations, and blood sampling will be done to gather extensive information on exposure and genetic markers. The main means of examining the relation between genotype, exposure, and disease will be through nested case-control studies, but the cohort is designed to provide a broad framework for various other studies.

To assess combined genotype and exposure effects, prospective studies have several advantages over stand-alone case-control studies.[2] They allow consideration of multiple endpoints, and assessment of the risks and benefits of specific genotypes and exposures. Effects on all-cause and cause-specific mortality as well as features such as dementia can be investigated; this is not generally possible retrospectively. Recall bias is avoided and prior measurement of variables (including blood-based molecular and proteomic factors) affected by disease or awareness of having disease (eg, weight, blood pressure, diet, lipoproteins, hormones, antibodies, &c) is accurate. Genetic and exposure data are available irrespective of disease outcome or severity, and are not limited to survivors. Prospective studies also allow the straightforward selection of suitable controls. Furthermore, the higher the number of endpoints, the more cost efficient the cohort design.

After 10 years of follow-up, BioBank UK is expected to yield around 11 000 incident cases of diabetes mellitus, 8000 of myocardial infarction, 4500 of stroke, and 6000, 5500, and 3000, respectively, of breast, colorectal, and prostate cancer. For these six important disorders, comparable stand-alone case-control studies would probably cost more than the cohort study and data on prior exposures would be less reliable.

Given the complex challenge of studying relations between exposure, genotype, and risk, and the clear importance of exposure in assessing risk, we disagree with Clayton and McKeigue's statement that epidemiologists should focus on use of genetic associations to test hypotheses about causal pathways amenable to intervention. Although the usefulness of this approach is undisputed, such a restricted focus, will probably provide only some of the insights necessary to improve health in the postgenome era.

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2 Albert PS, Ratnasinghe D, Tangrea J, Wacholder S. Limitations of the case only design for identifying gene environment interactions. *Am J Epidemiol* 2001; **154:** 687–93.

Authors' reply

Sir—Shalom Wacholder and colleagues and Paul Burton and colleagues miss our main point about misclassification. In case-control studies of genetic associations, misclassification of genotype can be eliminated as, with care, can the effects of selection bias and confounding. Existing causal relations can then be shown convincingly. By contrast, when studying environmental exposures such as diet, even the most carefully done cohort studies have difficulties with measurement error and confounding.

For genetic associations, the case for cohort designs rests mainly on their supposedly being better for studying the joint effects of genotype and environment. As pointed out, there is more to the quantitative description of joint effects than simply testing for lack of fit to a multiplicative model. We agree. However, as we argued, these are seriously distorted by misclassification of exposure, whether differential (as is likely in case-control studies) or non-differential (as is likely in case-control and cohort studies). Even if, as Burton and colleagues suggest, biological knowledge advances to the point where specific hypotheses can be formulated for models of joint effect, the ability to test these in the presence of exposure misclassification will be limited.

Elimination of non-differential misclassification of exposure in cohort studies would require the exposure to be measured accurately and repeatedly over participants' lifetimes, and this is generally impossible. Although lack of fit of a multiplicative model can still be tested, here cohort studies have no clear advantage over case-control studies.

A separate issue is whether, as Lars Stene suggests, effects of genotype in an exposed subgroup are detectable even when the average effect of genotype is not detectable. Detection does not require a quantitative model for joint effects, only a combined test of the null hypothesis of no effect of genotype in any subgroup. In comparison with testing the average effect of genotype, such combined tests generally yield only a slight gain in statistical power. The rationale for targeting interventions in accordance with genotype, as advocated by Burton and colleagues, is not contingent on the effect of an environmental exposure being subgroup specific.

Emily Banks and Tom Meade note that cohort designs facilitate sampling of controls, and Wacholder and colleagues suggest that this keeps selection bias to a minimum. However selection bias will not affect genetic associations unless there is population stratification. Where population stratification exists, it may be possible to control for it in the statistical analysis.[1,2]

We did not specifically address the design of the proposed BioBank UK cohort, but our arguments apply to this project. Long-term follow-up will certainly be necessary to yield sufficient cases for nested case-control studies to have any power. However the restriction to individuals older than 45 years at baseline severely limits the possibilities for studying lifetime environmental exposures, and weakens the ability to measure exposure before it is affected by the disease process.

Burton and colleagues argue that effects of the disease process on exposure measurements are lessened with longer follow-up. However exposure measurements become less relevant with time as participants' exposures change and biological knowledge moves on.

Wacholder and colleagues and Banks and Meade assert that cohort designs are an economical means of studying multiple outcomes. We find it difficult to envisage how a case-control collection covering multiple diseases, possibly requiring 50 000 individuals to be studied on one occasion, would not be cheaper than the proposed BioBank study of 500 000 individuals over 10 years. We agree with Burton and colleagues that, for testing causal hypotheses, better value for money could be obtained from case-control collections than from the cohort design proposed for the BioBank UK project.

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Vasopeptidase inhibitors: a bradykinin link

Sir—Michael Weber (Nov 3, p 1525)[1] discusses some possible mechanisms of action for vasopeptidase inhibitors.

The primary sites of action of these new pharmacological agents are the inhibition of two enzymes: neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). Weber's focus is mainly on the natriuretic peptides, which are metabolised by NEP, and to the angiotensin-renin system, in which ACE has a key role. Weber mentions only briefly that ACE and NEP also metabolise bradykinin and other kinin peptides, which theoretically could be important mediators of the effects of vasopeptide inhibitors.

Bradykinin, the most studied peptide of the kallikrein-kinin system, is a well known vasodilator and hypotensive agent, and is mainly degraded by ACE. In several studies, researchers show that a substantial part of the antihypertensive action of ACE inhibitors, and other effects of these drugs, is mediated by kinin peptides, via a dual mechanism: increase of bradykinin concentrations by the inhibition of ACE, and increasing the effects of bradykinin on the kinin B2 receptor by a complex interaction between ACE, the ACE inhibitor, and the receptor.[2]

The effectiveness of the ACE inhibitors may, however, be limited by the action of NEP, which can take over the degradation of kinin peptides when ACE is blocked.[3] Thus, in our laboratory, we have noted that the perfusion with 300 μmol/L of the ACE inhibitor captopril raises the concentrations of a kinin peptide (arg-bradykinin) in rat muscle, which is halved after 40 min continuous perfusion of the drug (unpublished results). This finding suggests a rise in the peptide breakdown by other metabolising enzymes, such as NEP.

In support of the mediating role of kinin peptides, Dumoulin and colleagues[4] have reported that omapatrilat induces a higher degree of inhibition of bradykinin degradation than the administration of ACE or NEP inhibitors separately. Thus, the higher efficacy of the vasopeptidase inhibitors on the physiological inhibition of kinin degradation can be an explanation of its better effect than with classic ACE inhibitors. It would be interesting to find out whether these new drugs are also able, as are ACE inhibitors, to

increase the bradykinin action at the kinin B2 receptor level.

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Leflunomide in treatment of rheumatoid arthritis

Sir—In his Oct 13 commentary, F Breedveld[1] discusses the place of leflunomide in the treatment of rheumatoid arthritis. We believe, however, that several important issues were not raised.

There is widespread concern among rheumatologists about this drug's toxic effects and persistent uncertainty as to its place in the hierarchy of disease-modifying antirheumatic drugs (DMARDs).

First, we suggest that the potential contribution of non-steroidal anti-inflammatory drugs to toxic effects is substantial. These drugs are prescribed for most patients taking DMARDs, and the hepatotoxic effects are well documented. Furthermore, like leflunomide, they are highly protein-bound with notable potential for interactions and adverse effects.

Second, controversy surrounds the appropriate dose of leflunomide. A loading dose of 100 mg daily for 3 days is recommended, followed by maintenance therapy of 20 mg daily. In the event of toxic effects or intolerance, the maintenance dose may be reduced to 10 mg daily. Many observers have questioned this approach in the light of the data presented in the original dose-ranging study by Mladenovic and colleagues.[2] They compared leflunomide at three different doses (5, 10, and 25 mg daily) with placebo to treat active rheumatoid arthritis. They reported slightly higher response rate (defined as ≥20% improvement according to American College of Rheumatology criteria) in the 25 mg group compared with the 10 mg group. However, these groups did not differ when assessed on the basis of objective markers such as C-reactive protein (median reduction 14·9 *vs* 9·5 mg/L in the 10 mg compared with the 25 mg group). The currently recommended dose might, therefore, expose patients to a higher risk of toxic effects with no clear evidence of improved efficacy over the lower better tolerated dose.

Third, Breedveld implies that for rheumatologists who prefer monotherapy, leflunomide is the only option in patients for whom methotrexate and sulphasalazine have been unsuccessful. We suggest that D-penicillamine and gold remain useful alternatives. These drugs have well-defined toxic-effect profiles and similar efficacy to methotrexate and sulphasalazine.

Finally, we agree that the addition of leflunomide to methotrexate should be avoided until further long-term efficacy and adverse-effect data are available. In a study of 33 patients with rheumatoid arthritis receiving methotrexate and leflunomide, raised transaminase concentrations were recorded in 19 (63%), and 11 (33%) had concentrations more than twice the upper limit of normal.[3] Clinical benefit is hard to assess in an open study.

Breedveld rightly calls for well-planned epidemiologically sound studies to address the issues surrounding DMARD toxic effects and their efficacy. In the meantime, leflunomide remains a viable option for patients with rheumatoid arthritis who have not responded to the more established treatments.

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Author's reply

Sir—The number of topics that can be explored in a brief commentary is limited. I share David McCarey and colleagues' worry about the contribution of NSAIDs to the toxic effects of DMARDs.

The efficacy and safety of leflunomide was reported to be similar to that of methotrexate in large groups of patients that did not differ with use of NSAIDs.[1] However, the cases of severe hepatotoxic effects from leflunomide noted in post-marketing surveillance might still be due to interaction with NSAIDs. This issue should also be included in studies on the frequency of hepatotoxic effects during antirheumatic treatments.

The recommended dose of leflunomide is not controversial, although it is still being studied. A loading dose of 100 mg for 3 days followed by maintenance therapy of 10–20 mg daily was officially endorsed at the time of marketing approval. In the original dose-ranging study of 5, 10, and 25 mg leflunomide, 5 mg did not differ from placebo. Results in the 25 mg group were consistently significantly better than those in the placebo group for all primary and secondary efficacy parameters. In the 10 mg leflunomide group, several secondary criteria, although numerically better than placebo, did not reach significance. Efficacy variables did not differ significantly between the 10 mg and 25 mg groups, and there were more side-effects in the 25 mg groups.

It can be assumed that the 20 mg dose was chosen for phase III studies to achieve high efficacy and a better safety profile than with a 25 mg dose. 20 mg is now recommended. However, when there is an increased toxic-effect risk, a choice of 10 mg with possible increase to 20 mg if needed is compatible with the European Union summary of product characteristics. A study directly comparing 10 mg with 20 mg daily is currently underway.

In our practice, methotrexate, sulphasalazine, and leflunomide are the first-line DMARDs for rheumatoid arthritis. D-penicillamine and gold have a late onset of action, and their toxic-effect profiles, although defined, have been judged worse than those of other DMARDs.[2] Pharmacoepidemiological data from many countries suggest decreases in the number of patients with rheumatoid arthritis selected for gold or D-penicillamine treatment.

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Parental attitudes towards passive smoking in Japan

Sir—Michael McCarthy, in his Oct 27 news item,[1] reports that the US Environmental Protection Agency has launched a campaign to persuade smokers to smoke outside if they live with small children to protect them from the second-hand tobacco smoke injury.

Much of the public-health burden from passive smoking falls on children in the home, with clear evidence of causal effects for several diseases, including asthma.[1–4] Since the smoking rate among Japanese is the highest in developed countries,[5] we did a survey of the prevalence of asthma in preschool and school-age children whose parents are current smokers or non-smokers. We also investigated to what extent smoking parents have adopted policies to protect their children from exposure to tobacco smoke at home.

Respondents were parents of 1596 non-smoking schoolchildren aged 6–12 years and 545 preschool children aged 3–5 years living in Sendai and Fukushima, Japan. We sent questionnaires to ascertain the presence of recent onset of asthma in the children by school or nursery-school doctors in October, 2001. Recent asthma was defined as having been diagnosed with asthma and wheezing in the past 12 months. We asked each parent about the total number of cigarettes smoked and the number smoked at home per day in the past 12 months. We also asked if they had attempted to lessen the smoke exposure to their children.

The total prevalence of parents' cigarette smoking was 61%, which is extremely high compared with other developed countries.[5] However, the prevalence of children's asthma did not differ significantly between the smoking parents and the non-smoking parents in the preschool and the school-age children (table). The number of cigarettes the parents smoked each day at home was not significantly different in the asthma and non-asthma groups. Importantly, 96% of smoking parents, irrespective of whether they had asthmatic children, answered that they had been advised since 1998 not to expose their children to smoke by the school doctors. They attempted to avoid doing so by smoking outdoors, in another room, or using manoeuvres such as blowing their smoke into exhaust fans or using air conditioners. As a result, parents smoked very few cigarettes in their children's presence (table).

Increase of ventilation is important. If we smoke three cigarettes consecutively, the carbon monoxide (CO) concentration, an indicator of the magnitude of environmental tobacco smoke, measured by a CO analyser in a 24 m^3 room rises to a mean of 14 ppm (SD 1), which rapidly decreases to zero if an exhaust fan or an air conditioner is used.

In contrast to previous reports,[3,4] we noted no significant association between asthma prevalence and parents' smoking habits. This finding might be partly explained by the parents' avoidance of smoking in their children's presence. Since it is very difficult to stop smoking, reduction of children's exposure to passive smoking might be important. A nation-wide campaign and school-based education might be effective in lowering risks of respiratory diseases in preschool-children and schoolchildren.

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	Preschoolchildren		School-age children	
	With asthma (n=39)	Without asthma (n=506)	With asthma (n=102)	Without asthma (n=1494)
Parental smoking status				
Non-smokers	16 (8%)	197 (92%)	43 (7%)	589 (93%)
Smokers	23 (7%)	309 (93%)	59 (6%)	905 (94%)
Odds ratio (95% CI)	0·93 (0·48–1·78)*	..	0·90 (0·61–1·32)*	..
Mean (SD) number of cigarettes smoked per day				
Total	23·2 (0·8)	21·6 (0·1)	22·7 (0·6)	21·3 (0·1)
At home	5·2 (0·7)	4·9 (0·1)	5·4 (0·4)	5·2 (0·1)
In room with child	0·2 (0·1)	(0·1) (0)	0·2 (0·1)	0·1 (0)

*Adjusted for age, sex, family history of asthma, and number of older siblings.

Frequency and risk of asthma and parental smoking habits for preschool and school-age children

Advanced trauma life support courses

Sir—The current shortage of advanced trauma life support (ATLS) courses available in the UK led us to undertake provider training abroad.

ATLS training provides clear protocols for the initial management of major trauma and is essential for medical staff required to deal with such patients, especially in accident and emergency departments.[1] However, the waiting lists for provider courses remain long, many more than 6 months, by which time most trainees would have completed their accident and emergency attachment. Physicians in non-surgical training posts are frequently given lower priority.

Since the principles of ATLS are universal, we sought a course in the USA.[2] Our 2-day provider course in California cost US$550, which was covered by our local trust; flight and accommodation expenses were self-funded.

The course adhered to the doctrine of ATLS, and with a few amusing pronunciations from both sides, was an exhilarating and highly educational experience. Taught mainly by trauma surgeons and emergency physicians, it reflected the local workload and geography, with emphasis on triage, penetrating trauma, and transfer. The instructors and students were interested in our practice and its differences.

This experience has greatly increased our confidence in managing trauma patients, allowing these skills to be put into practice during our current posts and has proved of interest at interviews.

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1 Price A, Hughes G. Training in advanced trauma life support. *BMJ* 1998; **316:** 878–80.
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Adaptation of bone to mechanical loads

Sir—It is proposed that bone adapts to mechanical loads through control of bone strength and mass by bone strain.[1] By contrast, little is known about bone quality (bone material properties), although bone strength is measured by bone mass and other factors such as bone quality. On the basis of this theory, bone quality could explain some discrepant results in bone.

Bone mass in the radius is low, whereas that in the lumbar is high in children with X-linked hypophosphataemic rickets (XLH) characterised by hypomineralised bone (poor bone quality),[2] but the mechanism remains unclear. In a girl aged 7 years with XLH, we noted that a rope-skipping vertical jumping exercise, 50 jumps once every 2–3 days for 6 months, strikingly increased the bone mass on the lumbar bones by 17·0% but by only 1·5% on the radius. Serum intact osteocalcin concentration increased by 34·5%, and urinary deoxypyridinoline concentration decreased by 29·6% (unpublished data). Serum concentrations of calcium, inorganic phosphorus, and alkaline phosphatase did not change.

Poor bone quality increases bone strain from mechanical loads, and impairment of bone quality could be compensated by raising bone mass in weight-bearing bone, as in XLH patients—ie, the increased total bone volume with low mineral content per unit in histology and the increased bone area with low bone mineral density in CT measurement. The compensation mechanism could explain the difference in lumbar and radius bone mass in patients with XLH, because lumbar bone is weight-bearing.

This concept could explain the controversial effects of warfarin, a vitamin K antagonist, on fracture risk. Vitamin K seems to lower fracture risk through improvement of bone quality resulting from an increase of osteocalcin carboxylation.[3] By contrast, the increased fracture risk due to chronic use of warfarin seems to be limited to the rib and vertebra, and the risk for the hip does not change.[4] Warfarin decreases osteocalcin carboxylation and could, therefore, induce impairment of bone quality, but the bone strength at the hip might not be weakened by the compensation mechanism because degree of bone strain from mechanical loads in daily life is higher at the hip than at the rib or vertebra.

Patients with type 2 diabetes have a normal or high bone mass and simultaneously have an increased fracture risk. This apparent paradox could be explained partly by poor bone quality. The high bone mass may be associated with the compensation mechanism between bone mass and quality. Furthermore, the faster bone loss in the hip of these patients[5] may be related to their lowered physical activity, which leads to a decrease of bone strain level, because a gain of bone mass induced by the compensation mechanism is lost because of decreased physical activity.

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Position of cardiac monitor and defibrillator

Sir—It is a pity that a journal held in such high esteem by many in the medical profession should resort to using a stock and frankly incorrect photograph (Dec 8, Talking Points).

The defibrillator is in use, presumably for a cardiac arrest, since the patient is intubated. The UK Resuscitation Council teaches that the cardiac monitor and defibrillator should be on the left of the patient, and not have the wires draped across their chest. In addition, the oxygen should be disconnected when defibrillation is about to occur.

I would hope that your editorial staff are not so far removed from the shop floor that they no longer realise the importance of proper form, especially during such an acute incident as a cardiac arrest.

I am a UK Resuscitation Council advanced life-support course instructor.

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DEPARTMENT OF ERROR

Predictors of mortality in acute myocardial infarction—In this Commentary by C Varma and S J D Brecker (Nov 3, 2001, p 1473) some of the details given in the figure were wrong. The correct figure is printed below.