CORRESPONDENCE

Long-term outcome of invasive breast cancer

Sir—László Tabár and colleagues (Feb 5, p 429)[1] report striking results about a novel prognostic factor in breast cancers of small size.[1] Currently, the proportion of small breast cancers diagnosed is increasing as a result of large-scale mammographic screening. However, the selection of women who will benefit from adjuvant treatment remains a challenge. Also, prognostic factors for breast-cancer outcome, such as involvement of axillary lymph nodes or high-grade tumours, have not been consistently reported as useful for small tumours.[2]

In their prospective study of invasive breast cancers of less than 15 mm diameter, Tabár and colleagues showed that casting-type calcification, when present on a diagnostic mammogram, was associated with a significantly worse survival. Comedocarcinoma results in casting-type mammographic calcifications and is associated with residual microscopic disease, local recurrence, and high-grade invasive cancer.[3,4] All these features could negatively influence outcome. By contrast, little is known about the influence of host factors on outcome.[5] To address this question, we did an ethnically restricted retrospective study. We studied 85 consecutive pathology blocks from Ashkenazi Jewish women under the age of 65 years, who had been diagnosed between 1986 and 1995 with breast cancers of less than 15 mm diameter. All except one (99%) patient were treated by breast conservative surgery and 29 (34%) patients received adjuvant chemotherapy. After recording histopathological variables, DNA was extracted from tumours and tested for the presence of the three common founder mutations present in Ashkenazi Jewish women in the breast-cancer predisposing genes *BRCA1* and *BRCA2*. Ten (11·8%) *BRCA1* and two (2·4%) *BRCA2* mutation carriers were identified. Breast-cancer-specific survival was assessed after a median follow-up of 88 months. Seven breast-cancer deaths were recorded. As reported by Tabár and colleagues, axillary lymph-node status was not identified as a prognostic factor (p=0·8) and nuclear grade was of borderline significance (p=0·08). The strongest outcome predictor was the *BRCA1/2* mutation carrier status. At the median follow-up, breast-cancer-specific survival for *BRCA1/2* mutation carriers was 60% versus 95% for women without *BRCA1/2* mutations (p<0·0001).

The numbers are small, but these findings suggest that *BRCA1/2* mutation status, which is a risk for breast cancer that is present at birth, has a significant impact on outcome, even when tumours are very small. It is uncertain whether or not *BRCA1/2*-associated breast cancer is associated with ductal carcinoma in situ (DCIS). In our series, none of the 12 *BRCA1/2*-associated breast cancers was associated with comedo-type or had an important component of DCIS, compared with 17 of 73 non-*BRCA1/2* tumours. Our findings suggest that prevention will be particularly important for *BRCA1/2* mutation carriers because mammography is unlikely to detect serious preinvasive disease and the outcome following small invasive breast cancers is surprisingly poor.

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1 Tabár L, Chen H-H, Duffy SW, et al. A novel method for prediction of long-term outcome of women with T1a, T1b, and 10–14 mm invasive breast cancers: a prospective study. *Lancet* 2000; **355:** 429–33 (published errata appear in *Lancet* 2000; **355:** 850 and 1372).

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4 Gupta SK, Douglas-Jones AG, Fenn N, Morgan JM, Mansel RE. The clinical behaviour of breast carcinoma is probably determined at the preinvasive stage (ductal carcinoma in situ). *Cancer* 1997; **80:** 1740–45.

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Sir—László Tabár and colleagues[1] suggest that mammographic classification is an important prognostic indicator in early breast cancer. However, there are several limitations to their data. Theirs was a very small study based on only 35 deaths resulting from breast cancer. As the supplementary tables listed on *The Lancet* website (www.thelancet.com) show, there were 128 deaths from other causes and 180 women still alive at the time of analysis from a total of 343 women. Thus, almost 90% of the observations included in their survival curves come from censored data.

The investigators state that they "assessed significance with proportional hazards regression", but their statement that the "effectiveness of mammographic findings to predict survival was significant (p<0·001), which remained significant after adjustment for tumour size, . . . node status, and malignancy grade" is rather vague. Did they test significance with mammographic findings alone as a variable in a proportional hazards model with death from breast cancer as the outcome? The p value for such a model would have little relevance since confounding would not be addressed. And how were mammographic findings categorised in the model? Did they adjust for the other variables by adding them to the multivariate model? If so, what was the exact model used, and what was the p value? Did the investigators test for appropriateness of the

proportional hazards model? They apparently did not consider the possibility of overfitting, which is a serious concern since the number of events (35) is less than ten times the number of variables modelled (4).[2] The investigators do not even mention hormone-receptor status, which is much too important a prognostic variable to be ignored.[3] Also, it is inappropriate to model long-term survival without including age-at-diagnosis as a variable.[4] Yet, including two additional variables would result in a hopelessly overfitted proportional hazards model.

At best, Tabár and colleagues present an interesting hypothesis-generating study. A much larger study with information on hormone-receptor status and age is needed to test their hypothesis.

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1 Tabár L, Chen H-H, Duffy SW, et al. A novel method for prediction of long-term outcome of women with T1a, T1b, and 10–14 mm invasive breast cancers: a prospective study. *Lancet* 2000; **355:** 429–33 (published errata appear in *Lancet* 2000; **355:** 850 and 1372).

2 Harrel FE Jr, Lee KL, Matchar DB, Reichert TA. Regression models for prognostic prediction: advantages, problems, and suggested solutions. *Cancer Treat Rep* 1985; **69:** 1071–77.

3 Bernoux A, de Cremoux P, Laine-Bidron C, et al. Estrogen receptor negative and progesterone receptor positive primary breast cancer: pathological characteristics and clinical outcome. *Br Cancer Res Treat* 1998; **49:** 219–25.

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Sir—The paper by László Tabár and colleagues[1] is a good illustration of a YAPI (Yet Another Prognostic Indicator). Calcification as a method of prognosis is not as accurate as other methods and has no practical clinical use.

I draw attention to two publications from my own unit. The first, by Kollias and colleagues,[2] was a substantially larger study of 789 small breast cancers (319 ⩽1 cm). This study showed that small, as with larger, tumours are well stratified into groups with significantly differing prognoses by the Nottingham Prognostic Index (NPI), an integration of size, grade, and lymph-node stage. As with larger tumours the patient's NPI is very important in giving individual advice on adjuvant systemic therapies to women with small tumours. Grade and NPI are well validated prospectively.

Clearly, calcification in a tumour is not a primary determinant of tumour behaviour. High-grade invasive tumours were shown in the second study, by Evans and colleagues,[3] to frequently have a surround of high-grade DCIS with calcification. Thus calcification is associated with grade, which is strongly associated with prognosis. Calcification is qualitative and of no clinical use. Grade is quantifiable and of considerable clinical importance.

The paper by Tabár and colleagues also suffers from being a retrospective study and therefore has no validation and seems not to have any correction for multiple comparisons.

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1 Tabár L, Chen H-H, Duffy SW, et al. A novel method for prediction of long-term outcome of women with T1a, T1b, and 10–14 mm invasive breast cancers: a prospective study. *Lancet* 2000; **355:** 429–33 (published errata appear in *Lancet* 2000; **355:** 850 and 1372).

2 Kollias J, Murphy CA, Elstan CW, Ellis IO, Robertson JF, Blamey RW. The prognosis of small primary breast cancers. *Eur J Cancer* 1999; **35:** 908–12.

3 Evans AJ, Pinder SE, Snead DR, Wilson AR, Ellis IO, Elstan CW. The detection of ductal carcinoma in situ at mammographic screening enables the diagnosis of small, grade 3 invasive tumours. *Br J Cancer* 1997; **75:** 542–44.

Sir—The article by László Tabár and colleagues[1] ignores the extreme variations in growth rates. Therefore, length bias sampling and a lead time bias influence the conclusions drawn and negate the significance of the conclusions that earlier diagnosis improves survivorship. The investigators provide no data on the proliferative indices nor other biological characteristics of the cancers.

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1 Tabár L, Chen H-H, Duffy SW, et al. A novel method for prediction of long-term outcome of women with T1a, T1b, and 10–14 mm invasive breast cancers: a prospective study. *Lancet* 2000; **355:** 429–33 (published errata appear in *Lancet* 2000; **355:** 850 and 1372).

Authors' reply

Sir—The findings of Pierre Chappuis and colleagues are very interesting and this work is to be encouraged. In our study the presence of *BRCA1/2* mutations could have accounted for the few patients who died from their breast cancers but did not have casting-type calcifications on their mammograms. However, it seems unlikely that the *BRCA1/2* mutation is responsible for our results, because there was no important intraductal component in the *BRCA1/2*-positive tumours.

Carl Atkins is mistaken. His comment that our study is a small one is quite clearly in error. Ours is a large series of invasive tumours of size 1–14 mm. Because of the small tumour size, the death rate from breast cancer is low. We encourage other researchers with similar data to try to confirm our results. His criticism that our results are inadequately adjusted or a product of overfitting is not justified. We assessed the effect of our mammographic prognostic features on survival alone and adjusted for grade, node status, and size in the Cox regression model. The effect on survival was substantial and significant. Atkins' assertion that the number of variables in the model should be less than one tenth of the number of events is arbitrary. Also, Atkins' belief in oestrogen-receptor status as the fundamental prognostic indicator in these small tumours is likely to be misconceived. Reed and colleagues[1] found oestrogen-receptor status to be unrelated to survival in node-negative breast cancers, which form the majority of the tumours in our study. However, we believe that future research should take place to establish other biomarkers that correlate with casting-type calcifications. The findings by Padmore and colleagues[2] seem to provide confirmation of our observations.

We share R W Blamey's belief in the accuracy of prediction of prognosis in tumours larger than 15 mm diameter with the first-generation prognostic factors: tumour size, malignancy grade, and node status. It would make life simpler for all of us if this were universally the case. However, these factors were not adequate prognostic indicators in the tumours we studied (1–14 mm diameter). We found that the four mammographic prognostic features were significantly predictive of long-term outcome. We are astonished by his assertion that our finding is a product of retrospective study and multiple comparisons: it is neither. Ours was a prospective study and the tables A–D (published by *The Lancet* in electronic form at www.thelancet.com) clearly show that most of the patients who died from their breast cancer and who had casting-type calcifications had no

positive axillary nodes, and that the invasive component had an intermediate histological malignancy grade in most of the cases, expecially in 1–9 mm tumours. The very point of our article is that these first-generation histological prognostic variables would not have predicted the high rate of fatality, nor would the NPI.

Our article did not deal with calcification overall as a method of prognosis, although there is an obvious positive correlation between the histological and mammographic image of different subtypes of DCIS.[3] Instead, we pointed out the prognostic value of the presence of a very specific type of calcification, the so-called casting type, which is strongly correlated with grade 3 DCIS. The substantial prognostic significance of casting-type calcification is shown by our data. Also, Blamey assumes that the associated T1a and T1b invasive carcinoma is frequently poorly differentiated. In the patients in our study these associated invasive tumours more frequently had intermediate malignancy grade, especially the 1–9 mm tumours. The prerequisite for the poor outcome is the presence of extensive grade 3 DCIS and not the tiny invasive carcinoma.[2] There is no reason to believe that it is the tiny invasive carcinoma that leads to a poor outcome, since women with unifocal, grade 2 cancers of similar size (ie, solitary stellate lesions on the mammogram) had an excellent outcome.

In response to John Spratt's comments, tumours with casting-type calcifications are associated with increased fatility. If lead time or length bias were an issue here, which we doubt, they would be expected to dilute the observed association. Thus the effect of this radiological marker might be even stronger than we observed.

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1 Reed W, Hannisdal E, Boehler PJ, Gundersen S, Host H, Nesland JM. The prognostic value of p55 and c-erb B-2 immunostaining is overrated for patients with lymph node negative breast carcinoma: a multivariate analysis of prognostic factors in 613 patients with a follow-up of 14–30 years. *Cancer* 2000; **88:** 804–13.

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Pertussis transmission in England and Wales

Sir—We were surprised by the statement made by Pejman Rohani and colleagues (Jan 22, p 285)[1] that pertussis vaccination is not thought to prevent transmission. In the review of pertussis epidemiology[2] which we did and which was cited by Rohani and colleagues, we concluded that "whole-cell pertussis vaccines can give good protection against both clinical disease and transmission of infection". We showed the impact vaccination has on transmission of infection by investigating the incidence of notified disease in infants aged 0–2 months (figure, with data updated to 1999). These infants are too young to be protected directly by vaccination, so changes in their incidence of disease reflect changes in the level of pertussis transmission in the population.[2] This is a far more direct measure of the level of pertussis transmission than are changes in the spatio-temporal pattern of pertussis epidemics. Rohani's observation of the increased frequency of fade-outs of notifications after vaccination does not necessarily indicate any reduction in transmission, but may simply be the consequence of a reduction in disease.

Although it is clear that pertussis vaccination does reduce transmission of infection, data from recent years suggest that there has been an increase in undetected transmission. In the 1990s the overall notification rate for all ages has continued to show a downward trend, but no such trend is evident in the notification rate in infants younger than 3 months. Significant transmission between infants of this age is unlikely, and the most probable source of these infant infections would seem to be undiagnosed infections in older vaccinated people.

**Nigel J Gay, Elizabeth Miller*

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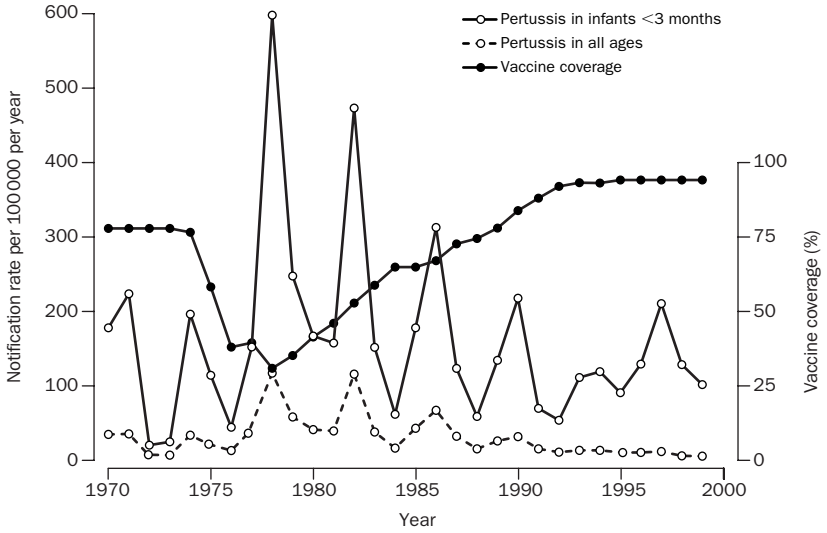
1 Rohani P, Earn DJD, Grenfell BT. Impact of immunisation on pertussis transmission in England and Wales. *Lancet* 2000; **355:** 285–86.

2 Miller E, Gay N. Epidemiological determinants of pertussis. *Dev Biol Stand* 1997; **89:** 15–23.

Authors' reply

Sir—Nigel Gay and Elizabeth Miller raise several important issues. First, they correctly point out that pertussis vaccination does reduce the incidence and transmission of infection.[1] This conclusion is indeed supported by our study and we are pleased to have the opportunity to emphasise this aspect of their paper. However, we seem to be in the minority—as we stress in our paper, most other investigators have concluded that pertussis vaccination is not very effective in preventing transmission.[2–4] It is this conventional wisdom that we, and Miller and Gay are questioning, from different perspectives.



Pertussis notification rate in infants aged less than 3 months and for all ages, and pertussis vaccine coverage at age 2 years in England and Wales, 1970–99

We addressed the highly influential study by Fine and Clarkson,[5] in which they explored aggregate cases of pertussis in England and Wales and concluded that—compared with the pre-vaccine era—the period of pertussis outbreaks in the vaccine era had not increased. Since epidemic frequency is a function of the rate of influx of susceptibles, they argued that a potential explanation for their observation is that pertussis vaccines are more effective in protecting against disease than protecting against infection. By contrast, our analysis of detailed spatial data showed that vaccination did indeed coincide with a striking increase in the inter-epidemic period. This implies an increase in the mean age at infection, consistent with a reduction in pertussis transmission.

Second, Gay and Miller propose that the incidence of pertussis in infants is a direct measure of pertussis transmission. We agree with this statement and are encouraged that these data support the qualitative conclusions of our study. Gay and Miller's use of infant cases represents an important refinement. As well as exploring the dynamic effects of temporal variation in vaccine uptake, it would be interesting to compare these dynamics with cases of pertussis in infants in the pre-vaccination era (pre-1957). As we stated in our paper, the latter comparison is likely to reveal the most dramatic dynamic effects of vaccination.

Finally, Gay and Miller correctly point out that the change in the pattern of pertussis fade-outs during the vaccine era may simply reflect a reduction in disease (and not transmission). In our article, we pointed out that several alternative methods for evaluating the success of pertussis immunisation schemes seem to suggest that transmission is strikingly reduced in the vaccine era. Each method of evaluating success in isolation is by no means conclusive, but the accumulation of evidence seems to point towards a vaccine-induced reduction in pertussis transmission.

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1 Miller E, Gay N. Epidemiological determinants of pertussis. *Dev Biol Stand* 1997; **89:** 15–23.
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Toxicity of old and new antidepressant drugs

Sir—Justine Kent (March 11, p 911)[1] presents an elegant review of four new antidepressant drugs: venlafaxine, nefazodone, mirtazipine, and reboxetine. The antidepressant effects appeared comparable to that of the serotonine reuptake inhibitors (SSRIs), and the older antidepressants—tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). The main advantage of these new drugs is that the adverse effects are mild, and have different side-effect profiles compared with SSRIs. Inadvertent weight gain, sexual dysfunction, and sleep disturbance may limit the use of SSRIs, and so the new drugs offer an alternative. An important consideration, which was addressed in the paper by Kent, is the toxicity of these new antidepressants when taken in overdose. The limited information available suggests that the toxic effects of these new drugs are mild and compared favourably with SSRIs, TCAs, and MAOIs. Antidepressant intoxications are not only a concern for prescribers of these drugs, but they also continue to challenge emergency and intensive-care physicians.[2] Also, the newer antidepressants may be more expensive, but the total cost of treating depression is not necessarily higher with these new drugs. Cost of SSRIs were even less than that of TCAs, because of the increased adherence of patients with the newer agents and lower costs secondary to physician visits, laboratory monitoring, and hospital admission.[3]

Between 1994 and 1998, 258 patients with intoxication were admitted to our 11-bed university-hospital-based intensive-care unit. Significantly more patients with TCA intoxications (n=65) than with SSRI intoxications (n=20) were admitted during this study period, despite the fact that the prescriptions of antidepressants in the community for SSRIs outweighed TCAs. The prescriptions of the various groups of antidepressants in 1993–97 were studied by the Dutch National Health Insurance Board (Ziekenfondsraad), Drugs Information Project.[4] During this period, the SSRI intake increased slightly but not significantly (p=0·06). For TCAs, there was also an increase of the number of prescriptions, though less pronounced. Compared with patients who we admitted to the intensive-care unit because of self-poisoning with SSRIs, TCA-intoxicated individuals needed orotracheal intubation significantly more often (41·5% *vs* 35·0%, respectively, p<0·05), and QRS-complex widening (19 *vs* 1) and tachycardia (14 *vs* 3) were observed significantly more often (p<0·05). To combat the toxic effects of TCA self-poisoning, specific ovine antibody treatment has been proposed.[5] Indeed, such new treatments may be a useful adjunct of general intensive treatment modalities such as mechanical ventilation, gastric lavage, active coal and laxatives to prevent ongoing absorption from the digestive tract, and administration of sodium bicarbonate infusion to correct electro-cardiographic abnormalities.

Continuing medical education programmes should emphasise the risks of TCA prescriptions, and we suggest that physicians are discouraged to prescribe self-administered TCAs to patients with depressive syndromes who are at risk of self-poisoning. The medical community should make an effort to carry out prudent prescription practice for patients with depressive syndromes, to avoid the toxic effects of TCAs in overdose, to reduce the claim for limited resources, including the use of intensive-care beds, and to avoid unnecessary suffering for patients with affective disorders and their relatives.

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1 Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet* 2000; **355:** 911–18.
2 Stoner SC, Marken PA, Watson WA, et al. Antidepressant overdoses and resultant emergency department services: the impact of SSRIs. *Psychopharmacol Bull* 1997; **33:** 667–70.
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4 Ziekenfondsraad. Kengetallen farmaceutische hulp 1997. Geneesmiddelen Informatie Project (GIP). *Gipeilingen* 1998; **8:** 44–46.
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Another look at latex

Sir—It is with dismay that we read the conclusions of Philippa Goulden and colleagues (Jan 22, p 315),[1] that a history of allergy to latex should be a contraindication to voluntary stem-cell donation. Such a broad statement fails to qualify the importance of a proper assessment of suspected allergic disease. We appreciate that the intended donor was a volunteer, but considering the position of the recipient, it is unfortunate that a full risk assessment, based on clinical and investigative methods, seems not to have been done. In the reported case it is unclear whether or not the prospective donor did indeed have a documented IgE-mediated sensitivity to natural rubber latex (NRL). Was the latex sensitivity manifested by contact urticaria, or was it allergic contact dermatitis, which is most commonly caused by thiuram compounds and not latex proteins and with little risk of anaphylaxis? Did the donor have skin-prick tests performed or specific IgE to latex measured to confirm the history? Did the donor have any history of bronchospasm, angioedema, or systemic anaphylaxis on exposure to NRL? Since she had undergone dental treatment and a delivery without any allergic reactions it is highly likely that she would have tolerated non-mucosal exposure to a latex-free operating environment. In addition, systemic anaphylaxis is almost exclusively limited to significant mucosal or serosal exposure to NRL.

In assessing allergic disease and the risk of systemic anaphylaxis one should always consider the nature of the symptoms, the nature and degree of exposure required to produce symptoms, the time between exposure and onset of symptoms, the duration of symptoms, and whether treatment was required. The clinical history should be confirmed by skin-prick tests that can be done with easily obtained high-quality reagents, or by measurement of specific IgE (although this latter test is less sensitive in detecting sensitivity to NRL).[2] When there is a significant risk, elimination of all latex gloves and minimising the use of latex-containing equipment should prevent systemic anaphylaxis in most patients, even highly sensitised ones. In addition, the prophylactic use of antihistamines and corticosteroids may further prevent, or at least attenuate, systemic anaphylaxis. In the case described by Goulden and colleagues these measures would most certainly have prevented significant anaphylaxis associated with surgery of a non-mucosal site. With due consideration, most patients with NRL allergy can safely undergo operations and certainly stem-cell donation, which does not involve manipulation of mucosal or serosal surfaces.

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1 Goulden P, Gravett P, Goldman J. An unfortunate case of allergy to latex. *Lancet* 2000; **355:** 315–16.
2 Frankland AW. Latex allergy. *Clin Exp Allergy* 1995; **25:** 199–201.

Authors' reply

Sir—We have considered the points made by Grant Hayman and colleagues and entirely agree that given a positive history of allergy a full risk assessment and investigation are mandatory before operation can be undertaken. In our case the donor had latex allergy confirmed by skin sensitivity testing, but the physician undertaking pre-operative assessment felt reassured by the successful childbirth and indeed by the patient's own view that this had never been a major problem for her. Specific questioning about the dental procedure on the morning of the proposed bone-marrow harvest led her to admit that there had been some swelling of the lips and mucosal membranes together with an exacerbation of her asthma, which subsided with treatment.

Although a latex-free operating set was available, the operating theatre had not been prepared in accordance with current guidelines and so, at best, it might have been possible to proceed the following day once suitable preparations had been made. However, discussion with other anaesthetist colleagues led us to conclude that for this donor, even with suitable precautions and prophylactic use of antihistamines and corticosteroids, there was a significant extra hazard over and above the usual anaesthetic risk. In this situation it is not sufficient to be giving prophylaxis that may further prevent or at least attenuate systemic anaphylaxis. It may be that most patients with NRL allergy could safely donate stem cells, but what about the minority who cannot safely do so?

As a harvesting team we consider that our first responsibility is for the safety of the donor and that our conclusion that a history of allergy to latex should probably be regarded as an absolute contraindication to stem-cell donation is appropriate when an unrelated donor is volunteering, for purely altruistic reasons, to undergo a procedure that is of no benefit to themselves or a family member. It would be a disaster for all concerned should a significant reaction occur. For this reason we suggested that it is prudent to exclude potential volunteers who have a history of latex allergy and to proceed to a full assessment in case of doubt.

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High-risk behaviour

Sir—John Richens and colleagues (Jan 29, p 400),[1] report how, using the example of seat-belt and condom use, behavioural adaptation may change the influence of safety interventions. Indeed, the effects of these interventions do not necessarily translate into benefits when they are used by whole populations because they can effect the perception of risk.

Another example of a safety intervention that can be studied in a population is sunscreen use. Whereas experiments in rodents and human beings have shown the ability of sunscreens to prevent ultra-violet-induced skin cancers, results from epidemiological investigations do not show that sunscreen use is associated with a reduced incidence of melanoma.[2] On the contrary, most case-control studies of the association between melanoma and sunscreen use found higher sunscreen use in patients with melanoma than in controls,[3] suggesting that sunscreen use could be a risk factor, rather than a protective factor. Since high naevi counts in adults are a strong predictor of melanoma, an epidemiological study was done in European children to assess the number of naevi according to sunscreen use.[4] Results showed that sunscreen use was associated with the development of naevi. It has been suggested that sunscreen may encourage prolonged sun exposure because it delays sunburn occurrence. To test this hypothesis, a double-blind randomised trial was done to assess whether the sun-protection factor could influence recreational sun-exposure duration.[5] Results showed that the use of higher sun-protection factor sunscreens increased the duration of sun exposure of young white Europeans.

To avoid the scenario in which a sunscreen-promotion policy could increase rather than decrease the

incidence of sun-related cancers, communication has to focus on educating the public so that they have a real perception of the risks of prolonged sun exposure. Thus, patients must be asked to decrease their exposure to sunlight and to wear protective clothes, whether they wear sunscreens or not.

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1 Richens J, Imrie J, Copas A. Condoms and seat belts: the parallels and the lessons. *Lancet* 2000; **355:** 400–03.
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Sir—John Richens and colleagues[1] looked at the risk homeostasis (or risk compensation) hypothesis, and explained that the adoption of one or more health risk reduction strategies, such as the use of seat belts, may be offset by compensatory behaviours that increase risk, such as speeding. When applied to sexual risk behaviours, the risk homeostasis hypothesis predicts that some people who reduce their risk of acquiring a sexually transmitted infection (STI) by increasing their use of condoms might compensate by making other behavioural changes, such as having more sex partners or engaging in more frequent sexual activity. The ultimate question is whether these additional changes are sufficient to offset the protection afforded by condoms, resulting in a net increase in the risk of infection.

Richens and colleagues suggest that "increased condom use could reflect decisions of individuals to switch from inherently safer strategies of partner selection or fewer partners to the riskier strategy of developing or maintaining high rates of partner change plus reliance on condoms". But are partner-based strategies "inherently safer" than condom-based strategies? A simple (Bernoullian) mathematical model of STI transmission can be used to examine how the number of acts of intercourse, the number of partners, and the frequency of condom use affect the probability of transmission.[2] For example, the risk of being infected by HIV-1 for a man who engages in n acts of vaginal intercourse—some proportion, f, of which are protected by condoms—with each of m different partners is about:

$$P=1-[(1-\pi)+\pi(1-(1-f\varepsilon)\alpha)^n]^m,$$

where π is the probability that a randomly-selected partner is already infected with HIV-1, α is the per-act probability of transmission, and ε is the effectiveness of condoms in preventing HIV-1 transmission.

Following Richens and colleagues' example, suppose that 1000 heterosexual men have intercourse an average of four times each during 6 months. Because the effect of the number of patients on the risk of transmission is greatest when condom use is low, assume that condoms are not used at all by these men. If the prevalence of infection among their partners is 25%, the effectiveness of condoms is 90%, and the per-act transmission probability is 0·001, then the risk of infection is 0·0009985 if each man has only one sex partner, and 0·0009996 if each has four different partners. Thus, reducing the number of partners from four to one decreases HIV risk by 0·11%. If instead of limiting partners, the men increased their condom use to just 1% of all acts, then the risk of infection would drop to 0·0009906, a reduction of 0·90%. Indeed, using condoms for only eight of the 4000 sexual episodes (a use rate of 0·2%) would reduce the risk as much as would switching from four partners to one partner.

Whether sexual risk homeostasis occurs to a measurable extent is an open empirical question. If it does, then it will be critical to determine how competing changes in behaviour affect overall risk levels. However, modelling analyses suggest that the number of partners is not an especially important determinant of the risk of HIV transmission, except in very high-risk environments.[3,4] In particular, limiting the number of partners is not inherently safer than relying on condoms.

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Post-exposure prophylaxis for HIV infection

Sir—J M Parkin and colleagues (Feb 26, p 722)[1] report results from a cohort of 24 health-care workers who began HIV post-exposure prophylaxis, nine of whom stopped prophylaxis because of side-effects associated with indinavir. The investigators say that indinavir-associated side-effects may make a difference to complete recommended treatment, and that routine use of indinavir in post-exposure prophylaxis regimens is questionable.

We reviewed the data prospectively collected by the Italian Post-Exposure-Prophylaxis Registry. We excluded health-care workers who withdrew or discontinued post-exposure-prophylaxis because the person thought to be the source of infection tested negative for HIV-1. Discontinuation was taken as having stopped prophylaxis before 4 weeks. Statistical analysis was done with Student's *t* test and χ^2 test, when appropriate.

Until December, 1999, 647 health-care workers on zidovudine (1000–1250 mg/day) and 341 on combination prophylaxis were enrolled into the study. Among the latter, 115 received zidovudine (500–600 mg/day) plus lamivudine, and eight other combinations of two nucleoside reverse transcriptase inhibitors (NRTIs). Two NRTIs plus a protease inhibitor were given to 218 health-care workers: 191 received zidovudine, lamivudine, and indinavir; other regimens included indinavir in 14 cases, nelfinavir in six, saquinavir in five, and ritonavir in two. All drugs were prescribed at the standard dose for adults.

No significant differences were found in the proportions of health-care workers experiencing side-effects and discontinuing prophylaxis among zidovudine, zidovudine plus lamivudine, and zidovudine, lamivudine, and indinavir groups (table). However, 20 (10·5%) health-care workers on zidovudine, lamivudine, and indinavir discontinued indinavir because of side-effects after a median of 7 days (mean 8 days), although they completed the 4-week course of zidovudine and lamivudine. If we add these health-care

Drug regimen	Total number	Reports of side-effects			Discontinuing prophylaxis			Duration (days)	
		Number	OR (95% CI)	p	Number	OR (95% CI)	p	Median	Mean
ZDV	647	409 (63·2%)	1		207 (32·0%)	1		8	9
ZDV+3TC	115	67 (58·3%)	0·82 (0·53–1·25)	0·37	33 (28·7%)	0·86 (0·53–1·34)	0·55	7	10
ZDV+3TC+IDV	191	127 (66·5%)	1·16 (0·82–1·66)	0·44	57 (29·8%)	0·90 (0·62–1·30)	0·63	7	10

ZDV=zidovudine; 3TC=lamivudine; IDV=indinavir; OR=odds ratio.

Tolerability of antiretroviral post-exposure prophylaxis in health-care workers

workers to the 57 discontinuations observed in the group, the difference approximates to the significance (zidovudine, lamivudine, plus indinavir *vs* zidovudine odds ratio 1·44 [95% CI 1·01–2·03], p=0·04, and odds ratio 1·68 [0·99–2·86], p=0·055 for the triple therapy *vs* zidovudine plus lamivudine). In nine health-care workers who discontinued indinavir, side-effects persisted and prophylaxis was discontinued after a mean of 4·5 additional days on zidovudine and lamivudine. Among the 35 health-care workers treated with other regimens, 21 developed side-effects; one health-care worker in the indinavir group, one on nelfinavir, and two on saquinavir discontinued prophylaxis. Type and incidence of specific adverse effects were similar to those reported by Parkin and colleagues[1] and in the literature.[2–4]

Although the incremental benefit of a regimen of three versus two drugs is speculative at present, combination prophylaxis is recommended for its higher antiretroviral activity and for overcoming resistance. Although the use of regimens proven to be well tolerated is obviously recommended, we believe that the rate of discontinuation because of indinavir side-effects does not justify the initial use of a less potent regimen. Unless already contraindicated, we recommend beginning prophylaxis with a three-drug regimen and discontinuing the protease inhibitor in the case of adverse effects. Further studies are needed to assess the potential role of non-NRTI agents in prophylaxis regimens.

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Chimeric and humanised—misunderstood

Sir—In the second paragraph of their March 11 Commentary,[1] Sally Bell and Michael Kamm present misleading information based on false scientific logic. They state that chimeric antibodies are only about 75% human and 5% humanised. Although it is true that chimeric antibodies are made by transplanting the whole V-region (about 25%) and that only a fraction (about 5%) of the V-region in humanised antibodies, this does not allow an estimation of how human the final sequence is. The reason is very simple. The sequences of many proteins, and this includes immunoglobulins, are conserved between species, so a sequence could in theory be both 100% mouse and 100% human at the same time. In practice, as can be seen from the Kabat database,[2] mouse V-regions vary in their homology to human sequences by about 60–80%. However, this also means that some chimeric antibodies can be more homologous to some human sequences than some humanised antibodies. The name chimeric or humanised does not provide the relevant information and it is thus necessary to compare the sequences of the antibodies with the human germline genes in the databases to assess the true homology.

Bell and Kamm are also incorrect in their generalised statement that humanised antibodies are less immunogenic than chimeric ones. They are presumably basing this on an assumption that all humanised antibodies are more homologous in sequence to human antibodies than all chimeric antibodies. I would assert that the only valid data that can be assessed from clinical trials at present leads to the conclusion that some therapeutic antibodies are more immunogenic than others. We cannot as yet say definitively what the determining factors are, although I accept that sequence homology still remains one possibility.

Bell and Kamm are not alone in perpetuating these common misunderstandings about chimeric and humanised antibodies within the scientific literature. Indeed some companies with commercial interests in the different approaches to producing therapeutic antibodies might benefit from the general acceptance of these ideas. However, until clear and strong evidence to substantiate these claims is presented they should not be given the weight of scientific fact.

I have started to collect information on sequence homologies of therapeutic antibodies to human germline sequences. My aim is to group antibodies being used clinically according to their sequence homologies and then hopefully this can eventually be used to assess the validity of statements about antibody immunogenicity.

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Measles genotype G2 in Indonesia and Malaysia

Sir—R L de Swart and colleagues (Jan 15, p 201)[1] reported the isolation of a measles virus belonging to a new genotype. This virus was isolated in November, 1997, from an immunocompromised Indonesian child who had been referred to a Dutch hospital for treatment of lymphoblastic leukaemia. Sequence analysis of the N and H genes of this virus, MVi/Amsterdam.NET/49.97, showed that it was most closely related to the reference strain for genotype G.[2] However, this virus was sufficiently different from the reference strain to be considered as a new genotype within clade G. The investigators proposed that clade G should be divided into two genotypes with the previous reference strain for clade G, MVi/Berkely.USA/83, being used as the reference strain for genotype G1, and MVi/Amsterdam.NET/49.97 used as the reference strain for genotyping G2.

Because measles was isolated from the child within 1 week of her arrival from Indonesia, it was assumed that viruses in genotype G2 were circulating in Indonesia in late 1997. We now have direct evidence to confirm that viruses from genotype G2

are circulating in Indonesia and also in neighbouring Malaysia. The sequences of the complete N and H genes of a virus, MVi/Jakarta.INO/32.99, obtained from measles outbreaks in central Java, Indonesia in late 1999, had only five and one nucleotide changes, respectively, when compared with the H and N gene sequences of MVi/Amsterdam.NET/49.97. The sequences of the complete N gene of a viral isolate from Malaysia in November, 1999, MVi/Kuala Lumpur.MAA/45.99 had only two nucleotide changes compared with the Dutch virus and one substitution compared with the Indonesian virus. Phylogenetic analysis (not shown) clearly indicated that the Malaysian and Indonesian viruses were members of the proposed new genotype, G2. The sequences of these viruses from Malaysia and Singapore have been deposited in GenBank under accession numbers AF243851 and AF24852.

Before these viral isolations in the Netherlands, Indonesia, and Malaysia, there had been no viruses belonging to clade G isolated since 1983 and it had been assumed that this clade represented an extinct or inactive lineage of wild-type measles viruses.[3] However, our information provides evidence that viruses from clade G are circulating in at least one region of the world and serves to emphasise the weakness of the current state of virus surveillance. Indonesia has a relatively high incidence of measles and it is surprising that the G2 viruses were not detected in other countries before the importation into the Netherlands in 1997. Clearly, our understanding of the degree of genetic diversity present among wild-type measles strains is still incomplete and greater efforts must be put into the characterisation of viral isolates from all areas of the world.

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Discontinuation of doxazosin arm of ALLHAT

Sir—In his March 11 Commentary,[1] Franz Messerli informs us that the data safety monitoring board advised stopping of the doxazosin treatment arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial. The reason was "that a significantly higher percentage of patients on doxazosin developed congestive heart failure (a secondary end-point) and on the view that doxazosin was unlikely to be better than chlorthalidone in preventing coronary heart disease (primary end-point)". It must have occurred to many clinicians that since diuretics are the cornerstone of treatment for symptomatic heart failure their use in advance of the development of heart failure would mask its subsequent manifestation. By contrast α-blockers have not proved useful in the treatment of chronic heart failure.[2] So what is truly prevention and what is treatment of symptoms in advance of a condition becoming overt? There are other examples in cardiovascular medicine, not least the claims for angiotensin-converting-enzyme inhibitors to prevent heart failure.[3] Large-scale trials alone cannot necessarily distinguish prevention of a condition from its symptomatic treatment.

Myocardial infarction as an outcome of coronary heart disease, on the other hand, would not seem to present the same problem, typical chest pain, electrocardiogram change, and enzyme rise occur or are prevented.

These are not trivial issues since patients and providers might like prescription of a drug only when needed, yet at the same time would prefer prevention to cure. Understanding mechanisms and consideration of the individual remain essential to interpreting and implementing appropriately the findings of large-scale trials.

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Encephalopathy associated with influenza epidemics

Sir—In your Feb 12 editorial,[1] you refer to the encephalitis lethargica epidemic that raged in 1918–30 and the, as yet unsuccessful, attempts to find out whether it was connected to the influenza pandemic of 1918. A study has been done in Japan to investigate the association of encephalitis or encephalopathy with influenza infection.

On the basis of case reports from physicians stating the incidence of mortality as a result of encephalopathy accompanying influenza infection,[2,3] the Japanese Ministry of Health and Welfare decided to do a cross-sectional survey of influenza in all medical facilities. The research was done from Jan 1, 1999, to March 31, 1999—which is the influenza season in Japan. Case reports of patients who developed encephalitis or encephalopathy during this time were gathered. The cases of influenza included: cases that met the clinical case definition; cases that met the clinical case definition and were epidemiologically linked to laboratory-confirmed cases; and cases that met the clinical definition and were laboratory-confirmed. The clinical definition used in this study is the sudden onset of a fever over 39°C, respiratory symptoms, myalgia, and headache. Diagnosis of encephalopathy was based on clinical symptoms. Cases of meningitis, myelitis, or severe febrile convulsions were excluded.

In total 217 cases were reported, 179 (82·5%) of them were children younger than 5 years. 58 patients died and 56 had neurological sequel. There were no differences in prognosis or incidence by sex. Furthermore, when observing the cases and their progress, neurological complications—eg, seizures and unconsciousness—developed within 1·5 days of the first symptoms of influenza. For patients who died, death occurred 1·1 days from the onset of influenza symptoms.

We inquired about the use of salicylic acid and found that aspirin was given to three patients. Two patients met the definition of classical Reye's syndrome. The number of reported cases of Reye's syndrome has been, as in the USA,[4] with the exception of ten cases reported in 1987–88, less than ten since the use of salicylic acid as an antipyretic has been stopped in Japan.[5]

According to the data on school closures, there were about 860 000 cases of influenza-like illnesses reported during the 1998–99 season. The scale of the epidemic was within the range of

expectation. An H3N2-Sydney-like strain was primarily isolated during that season. Because of the nature of the cross-sectional study, however, the association between strain and neurological complications remains unclear. Likewise, although vaccinations were not reported as having been done in any of the reported cases, the effect of vaccination and possible prevention of encephalitis or encephalopathy also remains unclear.

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Black people's red faces and AIDS prevention

Sir—My mother was the only person who could tell when I blushed. The rush of blood to the face which gives a white person's blushes is only discernible by very close relatives or friends of the black person. *Zo gbe ler* (shame killed her/him) is the Krobo for she/he blushed. In translation literal meaning must always give way to true meaning and context.

Michael Phillips' dream in which "The Dean turns scarlet with rage" (Feb 19, p 660),[1] would in my Krobo language be translated as *Dean-or mimi fu saminya* (the Dean's stomach swelled up to bursting point). To translate Krobo literally back into English would cause hoots of laughter. Some expressions in my mother tongue are "quite without aesthetic parallel in any other language of mortals".[2] Much health material written in English presented to Africans is quite useless. I had to shake my head in disbelief 10 years ago, in the early days of the AIDS epidemic, when, on my African tour,[3] I visited Kenya and saw a poster heralding a campaign to prevent the spread of AIDS—a large fist holding some crumbling material, with the slogan "Help Crush AIDS!" printed above it. How ridiculous, I thought, and guessed the campaign was being run by a non-Kenyan. How on earth does one stop the march of AIDS with a slogan like that? When I pointed out the absurdity of the whole thing to a Kenyan public-health doctor, shame killed him (he blushed), and he agreed that the AIDS prevention strategy in Kenya needed to be in his hands, not in those of foreigners. "But," he pondered, "it is they who bring the money for AIDS prevention. What can we do?"

I saw this doctor in Nairobi just 3 months ago on the day President Moi placed a national alert on AIDS prevention. When I said to him, "How come AIDS incidence in Kenya had quadrupled since the Help Crush AIDS! programme started?", he remembered our discussion 10 years earlier,[3] and shame killed him. He complained about at least two "very sad things". He had been advised from abroad (he did not say who by) that blood transfusion was not a significant means of AIDS propagation in Africa, so there was no need to test every single unit of blood in the country before transfusion. With a shrug of the shoulder he said again, "But what can we do? It is they who bring the money for AIDS research and prevention". The same advisory source impressed upon him that if a polygamous man is found to be HIV positive, he should not be told because he would commit suicide. When I asked him for how many of the 32 Kenyan languages he was carrying out the AIDS prevention campaign in, and he replied "only English, I am sorry to say," I shook my head and looked him straight in the eyes. Shame killed him again.

I am in the process of producing a method of writing tonal African languages to improve upon what the Swiss-German Basel missionaries did when they first wrote our languages in 1828, but they did this without any indication of how the words should be pronounced. For instance, the Krobo word written *ta* has six meanings (chew, war, giant-ant, fish out, narrate, and palm tree) depending entirely on the tonal pronunciation. Teachers and health workers in my tribe in south-east Ghana where I am at present involved in a health-education project, will be delighted when my tadka phonation technique is complete sometime this year, God willing. They will then be able to read Krobo-Dangme/Ga as fast, if not faster, than they can English.

Tribal slogans for AIDS prevention would be much more hard hitting than national ones, which are often in English or French, and sometimes miss the point.[4]

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Forecasting disease risk with seasonal climate predictions

Sir—Once again anomalous weather has caused a humanitarian disaster in Africa. As well as major infrastructral damage in Mozambique, excess rainfall and flooding have increased the risk of malaria epidemics in the region, particularly in vulnerable groups. Forecasting epidemic risk is a prerequisite to effective epidemic intervention and the greater the lead-time available the better. Where diseases have a strong climate component it should be possible to incorporate weather monitoring or even weather forecasting into the health surveillance processes.[1]

Seasonal climate forecasting (up to 6 months ahead) has developed rapidly with several atmospheric climate modelling groups showing evidence of skill and reliability in their systems. The European Union (EU) funded PROVOST (PRediction Of climate Variations On Seasonal and interannual Timescales) project was set up to study the predictability of seasonal to interannual atmospheric variability as a function of season, location, and meteorological variable (notably cumulative rainfall and temperature).[2]

Because of the chaotic nature of the atmosphere, seasonal forecasts are necessarily probabilistic. These probabilistic predictions are defined from multiple integrations of deterministic climate models. A multi-model system (in which results from four quasi-independent models were integrated) has been found to be superior to any individual model system in terms of skill and potential economic value.[2] Further developments that have led to atmospheric-ocean coupled models allow real-time prediction of the sea-surface temperatures around the globe. These models successfully predicted the

onset and demise of the 1997/1998 El Niño event and its impact on weather in Africa.[3] However, only limited validation of the climate models has been undertaken. Nonetheless the excess rainfall correctly predicted from these models in East Africa in 1997–98 were associated with devastating malaria epidemics.[4]

The EU DEMETER (Development of a European Multimodel Ensemble system for seasonal to inTERannual prediction) project is aimed at developing a seasonal climate forecasting system for operational use by different sectors, including health services in the tropics, particularly Africa.[5] Over the next 3 years the six global ocean-atmospheric models available in Europe will be installed on a single supercomputer at the European Centre for Medium Range Weather Forecasting, Reading, UK. Standardisation of the archive format and model outputs will mean that intermodel differences can be assessed, systematic errors removed, and, most significantly, the final 54 (six models, nine ensembles) outputs (eg, precipitation, temperature, and humidity) integrated into a multimodel system. The outputs will be tested by end-users to assess the potential for improved resource allocation. The MALSAT research group (see www.liv.ac.uk/lstm/malsat.html) will test these model outputs in statistical and rule-based models of climate-change-associated diseases (eg, malaria and epidemic meningococcal meningitis).

The disease model outputs will represent a probability distribution of disease risk. In years and regions where the probability distribution is broad there will be little predictability in the system. However, where there is a sharp probability distribution, predictability will be stronger and the information may be used by decision makers for taking precautionary action. The main advantage of using a probabilistic system is that users should not be misled by overconfident erroneous forecasts in situations where predictability is small.

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Pliny, Galileo—and the late Bill Hamilton

Sir—During the eruption of the Vesuvius, which destroyed Pompeii and Herculaneum, Pliny the Elder (AD 23–79) left the small boat from which he was observing the volcano's activity for a fleet of quadriremes to rescue people forced to the shore by the lava. Pliny was killed during his "combined scientific and humanitarian" efforts.

Had Galileo's (1564–1642) astronomical theory been erroneous, his judges would not have been less wrong. His judges, the Vatican's ecclesiastic hierarchy insisted that they possessed truth and refused scientific debate.

William Donald Hamilton (1936–2000), died of complications of malaria contracted in the Congo jungle while seeking indirect evidence for the controversial theory that HIV origin can be traced to the oral poliovaccine developed in Africa in the 1950s. He was collecting samples of chimpanzee faeces to see if they contained a virus related to HIV.

Like Pliny, Hamilton died a victim of his scientific determination. Could the judges of the vaccine theory—never mind if right or wrong—be blinded, like Galileo's inquisitors, by that very faith in modern medicine's infallibility which Hamilton challenged?

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A shocking case of diabetic neuropathy

Sir—A man aged 43 years came to the diabetes clinic at the National Institute of Health, Phoenix, Arizona, USA, complaining of polyuria, polydipsia, blurred vision, and weight loss of about 11·8 kg in 3 months. He had no other symptoms and no pertinent medical history. On physical examination, he weighed 99·8 kg and his blood pressure was 128/72 mm Hg. Except for a mild erythematous rash in his groin, his physical examination was normal. In particular, there was no evidence of retinopathy or sensory neuropathy. Laboratory results showed blood glucose (random sample) of 23·0 mmol/L, no ketones, and an HbA_{1c} of 12·1%. He was treated with insulin and given a prescription for oral glyburide 5 mg to be taken twice a day. 1 months later his polyuria and polydipsia had stopped. His fasting blood glucose was 5·7 mmol/L.

The patient returned to the clinic 3 months later for a routine follow-up, accompanied by his wife. He felt well, in general, and had resumed work as a carpenter. His only complaint was of paresthesia in his hands and feet that he described as "kind of like an electric shock". He worried that these symptoms might be an early sign of diabetic nerve damage. Sensing an opportunity for patient education, his physician proceeded to outline the benefits of strict glucose control in the prevention of diabetic neuropathy.

After listening intently for several minutes the patient seemed convinced. "I didn't know whether or not I should be worried" he said. "After all, I only get the tingling when I'm taking a shower. When I reach up and adjust the shower head, I feel it in my hand—and it feels like its coming out my feet."

"You know, I've felt the same thing" volunteered his non-diabetic wife. The patient and his wife were immediately referred to a specialist—an electrician—who found that the grounding of the electrical system in their house was dangerously faulty. The defect was promptly repaired and their symptoms completely resolved.

As physicians, we are constantly reminded that things are not always as they seem to be. Taking a careful history can often sort it out.

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DEPARTMENT OF ERROR

Role of microvascular decompression in trigeminal neuralgia—In this Correspondence letter by G Broggi and colleagues (March 11, p 929), the seventh sentence of the first paragraph should be, "Moreover, aborted percutaneous procedures unfortunately never result in pain relief, even as a result of the placebo effect".

Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya—In this Article by J A G Scott and colleagues (April 8, p 1225), the first sentence of the interpretation section of the summary on page 1225 should be, "We suggest that tuberculosis is a sufficiently common cause of acute pneumonia in Kenyan adults to justify routine sputum culture, and that, with monitoring for clinical failure due to *M tuberculosis*, intermediate-resistant pneumococci, and other bacterial pathogens, treatment with benzylpenicillin remains appropriate".