

CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Screening mammography: setting the record straight

Sir—Reviews of randomised screening trials done earlier than that undertaken by Ole Olsen and Peter Gøtzsche (Oct 20, p 1340)¹ have supported the practice of screening for breast cancer with mammography, particularly for women older than 50 years;^{2,3} Olsen and Gøtzsche challenge this view. Unfortunately, they provided one version of their review to *The Cochrane Library*⁴ and another (which is not an approved Cochrane review) to *The Lancet*.¹ These two reviews, although similar, differ in some important features that may lead to confusion.

In his Oct 20 commentary,⁵ Richard Horton claims the Cochrane Breast Cancer Group (CBCG) attempted to unduly influence the text of Olsen and Gøtzsche's review in *The Cochrane Library*. Since Olsen and Gøtzsche conclude that screening mammography is not justified, Horton implies that we tried to suppress this information, which is not the case.

The Cochrane process of peer review for systematic reviews differs from that for journals. Once a protocol is accepted by a Cochrane group the group undertakes to publish the completed review, if it passes peer-review. Therefore, if there are concerns about rigour, methods, or interpretation of data, extensive efforts are made to collaborate with the researchers to improve the quality and objectivity of the final review and arrive at interpretations that all believe are supported by the data.

Horton claims also that the CBCG editors insisted on changes to the review against the reviewers' wishes. This does not fairly portray the editorial process. The CBCG editors had accepted most of the analyses and conclusions after the initial referee process, which Olsen agreed improved the review. After revision, however, the majority of editors still believed that some of the conclusions remained unsupported by the data. First, the emphasis was on the effects of screening mainly on overall mortality. No included trial, nor the combined trial results, was large enough to detect any plausible reduction in overall mortality reliably. Although Olsen and Gøtzsche contended that there may be misclassification bias in the assessment of breast-cancer mortality, this is the endpoint that the trials were

designed to assess and for which there was adequate power. Consequently, we requested that overall mortality and breast-cancer mortality results be presented in the main findings, together with a discussion of the limitations associated with each outcome.

Second, Olsen and Gøtzsche wished to present overall summary statistics from only two of the eligible trials, which they judged to be of the highest quality. We believed that overall results from all eligible randomised trials should first be provided, together with discussion of the limitations of results. We also judged a presentation of results from these two trials appropriate, as a subsequent sensitivity analysis.

Third, they presented data about the use of more aggressive treatment of breast cancers identified on screening. The editors were happy to include the data that show higher rates of treatment (mastectomy, radiation therapy) in patients undergoing screening. However, we were still concerned that some of the conclusions reached about treatment could not be supported by the data, especially any causal inference that increased use of these treatments must be harmful.

The editorial group went to unusual lengths to help the reviewers with their report. At Olsen and Gøtzsche's request, three editors met with one of them in June, 2001. The meeting was judged by all to be useful and worthwhile, and a plan was decided to try to make the review acceptable to the majority of the editorial committee for publication in *The Cochrane Library*. The reviewers agreed to provide summary results, in the text of the review, of the effects of screening on mortality outcomes based on all eligible trials, with appropriate discussion on the limitations of results to enable readers to assess the findings for themselves.

We all agreed that the standard practice for the management of breast cancer has changed since the mammography trials were done. Thus, information about some treatments (especially mastectomy rather than less-radical surgery) may have become less relevant. Additionally, although extra treatment for breast cancer might be harmful (as implied in the review *The Lancet* published), it might also be

beneficial, an interpretation not excluded by the data. Naturally, the possibility that screening might lead to unnecessary treatment in some women is accepted, and is a potential difficulty with any screening strategy.

After this process, and subsequent revision, the majority of editors still thought the conclusions on the use of more aggressive treatment were misleading. Therefore, they requested further modification of this section before publication. To avoid delay of the full review, the editors suggested publication of the other sections of the systematic review pending completion of the review process. Olsen and Gøtzsche accepted this option and agreed in writing to publication of this version in *The Cochrane Library*. We were, therefore, very surprised to hear of the publication of a variant review in *The Lancet* just before our publication date.

Finally, on the issue of including summary statistics for all eligible trials in the report, we had agreed to this principle in June, 2001, but a test for heterogeneity showed some quantitative interaction of the size of the treatment effect across the eligible trials, raising questions about the validity of combining these studies. However, some trials used cluster randomisation, which may affect the p value if the cluster is not used as the unit of analysis. These tests also need to account for multiple comparisons, making interpretation complex. Furthermore, even if size of treatment effect varies, a qualitative interaction is not necessarily implied, and the overall result still provides an average estimate across the trials. The editors therefore believed the full summary statistic, as well as that limited to the two trials, was important, with appropriate discussion to enable readers to judge whether it is the data as a whole or a restricted subset of the data that should be more persuasive.

We believe the review in *The Cochrane Library* is stronger as a result of this extensive peer-review process. Although it does not represent an official Cochrane view of the usefulness of screening mammography, nor necessarily the views of any particular editor, we stand by the process and the integrity of the editorial group. We also hope to be able to add the section on rates of

treatment for breast cancer in due course. We encourage readers to read both versions and to draw their own conclusions.

Where to from here? A new large-scale trial might help to clarify the effectiveness of screening mammography, but the logistics of such a trial are extremely challenging. Currently, the most useful approach, also advocated by Horton, would be to undertake an additional independent systematic review of the completed trials, with updated individual patients' data and incorporating relevant information from clustered randomised trials into the analysis.

The members of the CBCG editorial team are John Simes and Nicholas Wilcken (coordinating editors), Christine Brunswick, Mike Clarke, Patricia Ganz, Davina Ghersi, I Craig Henderson, Alessandro Liberati, Sue Lockwood, Kathleen Pritchard, and Alan Rodger.

The CBCG editors

NHMRC Clinical Trials Centre, Locked Bag 77, Camperdown, NSW 1450, Australia (e-mail: enquiry@ctc.usyd.edu.au)

- 1 Olsen O, Gøtzsche P. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; **358**: 1340–42.
- 2 Kerlikowski K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography: a meta-analysis. *JAMA* 1995; **273**: 149–54.
- 3 Nyström L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* 1993; **341**: 973–78.
- 4 Olsen O, Gøtzsche PC. Screening for breast cancer with mammography (Cochrane Review). In: *The Cochrane Library*. Issue 4. Oxford: Update Software, 2001.
- 5 Horton R. Screening mammography—an overview revisited. *Lancet* 2001; **358**: 1284–85.

Sir—Richard Horton¹ reminds us that Cochrane reviews are, on average, of higher quality than similar studies published in paper journals. This view reflects the dedication of the Cochrane editorial groups, their thorough editorial processes, and the close working relationships between reviewers and editors within the Cochrane Collaboration.

However, I was disturbed by your allegation that editors in the CBCG have practised censorship in Ole Olsen and Peter Gøtzsche's review² on mammographic screening. Having now had access to much background information, I am aware there has been a complex scientific debate around a very contentious topic, and I think Horton's commentary is unbalanced.

Does this unusual affair suggest a problem with existing Cochrane editorial processes? Cochrane reviews are developed according to rigorous methods that discourage censorship.³ This process culminates in editorial

peer review by internal and external refereeing. As with any editorial process, there is frequently negotiation between editors and researchers to ensure the conclusions are reliable and can be supported by the available evidence. However, Cochrane reviews probably require more negotiation and revision than conventional publications for two reasons. First, Cochrane editorial groups are committed to try to publish reviews—rejection is very much a last resort. Second, because limited resources must be used responsibly there should only be one Cochrane review addressing a particular question. It therefore needs to be comprehensive and balanced.

I recognise that negotiations within the constraints imposed by accepting these principles could raise the suspicion of censorship, but at least the process is transparent. By contrast, traditional journals have certainly exercised what amounts to editorial censorship by simply rejecting reports.⁴ Dispute will inevitably arise sometimes between Cochrane review researchers and editors. Mechanisms for dealing with such disputes exist and have operated fairly well over the few years that the Cochrane Collaboration has existed. These mechanisms may now have to be further developed. Ultimately, if researchers are unhappy with the process, they are free to withdraw their review.

One of the features of Cochrane reviews that distinguishes them from most other forms of research report is that they can be modified in the light of new data and in response to comments and criticisms. The Collaboration will continue to try to take full advantage of the fact that Cochrane reviews are dynamic documents, and thus, hopefully maintain their status as important documents that reflect continuing intensive efforts to reduce biases that may result in misleading inferences about the effects of health care interventions.

PL is chair of the Cochrane Collaboration Steering Group but had no direct interest in or involvement with the systematic review of screening mammography.

Peter Langhorne

Academic Section of Geriatric Medicine, Royal Infirmary, Glasgow G4 OSF, UK

- 1 Horton R. Screening mammography—an overview revisited. *Lancet* 2001; **358**: 1284–85.
- 2 Olsen O, Gøtzsche P. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; **358**: 1340–42.
- 3 Clarke M, Oxman AD, eds. Cochrane reviewers' handbook 4.1.3. In: *The Cochrane Library*. Issue 3. Oxford: Update Software, 2001.

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Author's reply

Sir—The CBCG editors think it is unfortunate that we submitted a version of our Cochrane Review to you. However, the Cochrane Collaboration encourages researchers of Cochrane Reviews to publish their reviews in paper journals. We published the report mainly because we believe it is important for women to know that screening increases their risk of losing a breast. This finding contrasts with the information they get from screening advocates who generally say the opposite, but without reliable data to support their claims.

The Cochrane editors say that they worked diligently with us to produce a work of Cochrane standard, and they remind readers that the review published by you is not a formal Cochrane review. We agree that the editorial comments led to improvements, but they also led to difficulties. I arranged two meetings with some of the editors to get advice on how to proceed in view of the conflicting recommendations we had received. Most of the text is the same in the two versions of our review, but we feel the version printed by you lives up to Cochrane standards better, since it contains no flawed summary analyses and reports on all the data that were envisaged in our published Cochrane protocol. When the Cochrane editors feel confident that the Cochrane Review is the stronger report, they are simply approving of their own changes. Moreover, the review you published has also been extensively peer reviewed.

When the editors, in their third round of comments, insisted on introducing flawed summary analyses on breast-cancer mortality, we felt that, if we were ever to get our review published, we would have to compromise sound scientific principles. With the submission of the third revision, I wrote to the editors that we hoped they would reconsider their approach carefully. The editors did not change their decision, however, and had even included the flawed summary estimate in our abstract in the edited version of the review they sent us in August, 2001, shortly before the deadline for the October issue of *The Cochrane Library*, and 11 months after we first submitted our review.

3 working days before the deadline,

the editors informed us that they had decided by a majority vote to cut out all data on the use of surgery and radiotherapy, and that we had to accept this if we were to publish the review in October. We were told that, in the modern setting, the editors would expect far fewer mastectomies to be done as part of current standard practice. However, we had already discussed this change in practice in our submitted review. Furthermore, epidemiological data strongly suggest that even today there will be more mastectomies in screened women than in non-screened women.¹ The editors now write that they hope that the data on rates of treatment can be added to our review. I would have preferred a promise for a hope.

Despite all of our reservations, the misleading statement about breast-cancer mortality in the abstract has already been misused by screening advocates to claim that we should have shown that screening were effective. The claim is flawed for two reasons. First, breast-cancer mortality is unreliable and biased in favour of screening.¹ Second, the editors requested that we lumped together the results from two medium-quality trials with those from three poor-quality trials, despite the fact that we have shown, first, that the available data from all three poor-quality trials are unreliable and, second, have explained at length why the biggest one, the Two-County study,² is very probably flawed.

We present more than just the results of the two medium-quality trials in our *Lancet* review. We also show the results of the three poor-quality trials, and have shown that there is significant heterogeneity for breast-cancer mortality, the primary trial outcome, between the two groups of trials. The heterogeneity is not driven by the fact that the available data did not allow us to take the clustering into account for the Two-County trial.

When we published our first *Lancet* paper on screening in January, 2000,³ the word Cochrane appeared only as our affiliation and in our search strategy. Nonetheless, the editors of the CBCG received letters of complaint, individuals resigned from some advisory committees, and the editors faced pressures from various people requesting that we should be prevented from completing our Cochrane Review on this topic.⁴ The editors very properly withstood this pressure. However, should a Cochrane researcher become dissatisfied with the Cochrane editorial group he cannot

choose another Cochrane journal for publication to obtain the Cochrane stamp of approval—a quality stamp that, in the case of mammography screening, seems to have been important given that the Cochrane review was eagerly awaited by many policy-makers.

This fact gives power to Cochrane editorial teams and the risk of bias, but this challenge has generally been well met by Cochrane Review groups, and Cochrane reviews seem to be less biased than systematic reviews published in paper journals.⁵ Even so, I believe it is important that the Cochrane Collaboration sets up an effective mechanism to deal with issues between editors and researchers quickly and in line with the evidence, so that conflicts of the type described here can be resolved.

Peter C Gøtzsche

Nordic Cochrane Centre, Rigshospitalet Dept 7112, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
(e-mail: pcg@cochrane.dk)

- 1 Gøtzsche PC. Screening for breast cancer with mammography. *Lancet* 2001; **358**: 2167–68.
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Editor's reply

A quick glance at these letters might mislead a busy reader. Is this exchange all about who published a better systematic review? Members of the CBCG editorial team insist that they did—"we believe the review in *The Cochrane Library* is stronger"—whereas Peter Gøtzsche reports that the version published in *The Lancet* "lives up to Cochrane standards better". There are much bigger issues at stake.

I cannot imagine anybody wishing that screening mammography does not succeed in reducing both breast cancer and overall mortality among women. But the public believes mammography to be far more effective than it really is.¹ Women deserve an accurate assessment of the benefits or harm from screening mammography. That means encouraging an open debate about the issue. Some

senior scientists have said to me that this debate should not be taking place in public. Screening mammography is, they argue, too important for women's health to have its image damaged by questioning the technique's efficacy and safety. Such paternalism assumes that women cannot decide for themselves whether the available evidence supports or refutes the case for mammography. Discouraging a discussion with women about the evidence for and against mammography is more harmful for women's health, not less, if doctors truly believe that patients should be active partners in making decisions about their care.

No study or group of studies is likely to produce a completely certain result, in the sense of absolute statistical precision. What matters, therefore, is the diligence with which investigators eliminate bias, both qualitatively (by providing thorough narrative critiques of studies) and quantitatively (through sensitivity analyses and other standard statistical means).

Here, there is inevitably room for different analytical approaches and nuances of data interpretation; such plural views should surely be supported, provided they are based on sound scientific principles. In this instance, there were serious yet well grounded differences of opinion between the scientists completing the review of mammography trials and the Cochrane editors. The result? Two different reviews in two separate journals, together with confusion, anger, recrimination, bitterness, and a private e-mail exchange that deserves publication in its own right as a study in the socio(patho)logy of science.

But I believe the outcome has been, on balance, a good one. An important debate has been made public, and continues elsewhere in this week's issue of *The Lancet*. Still, there would have been a simple way of preventing the bruises endured by all participants in this encounter. I urge the Cochrane Collaboration to consider this proposal seriously. When Cochrane reviewers produce a review at odds with the opinions of Cochrane editors, the normal process of peer review and negotiation will resolve many of the differences. But if a difference remains, let the scientists doing the review publish what they wish to say—it is, after all, their work. The editors can present their own view as a supplementary discussion or comment. That way, the debate proceeds properly, each side is given its voice, accusations of censorship are avoided, and the public sees science as a truly

collaborative process, in which differences of opinion are not only respected, but also welcomed.

Richard Horton

- 1 Chamot E, Perneger TV. Misconceptions about efficacy of mammography screening: a public health dilemma. *J Epidemiol Community Health* 2001; 55: 799-803.

Sir—No organisation is perfect, not even the Cochrane Collaboration, which is discussed by Richard Horton.¹ We write as consumer contributors to the Collaboration, and we acknowledge that the contribution of consumers is valued. However, the problem with overviews and meta-analyses is that they can deal only with trials that are completed.

If research questions have not been asked, they will not be answered. This difficulty is particularly frustrating for consumers, who notice, for example, side-effects of treatments but are told that there is no evidence on these effects (ie, no evidence from randomised controlled trials). The patients' own experience tells them otherwise.

The controversy about mammography highlighted by Horton illustrates a further issue. The CBCG editors insisted on changes to the review of Ole Olsen and Peter Götzsche, against their wishes. This move implies that Cochrane does not like negative results.

We had a similar experience with the Early Breast Cancer Trialists' tamoxifen overview,² which you published and which was taken over virtually unchanged into *The Cochrane Library*. We thought that the subject of non-life-threatening toxic effects had not been given sufficient weight, but the understanding of Chris Williams, coordinator of the Cochrane Cancer Network, was that the Early Breast Cancer Trialists' Collaborative Group thought they could not add more to their review since the process needed the agreement of all trialists (C Williams, personal communication). A report by Fellowes and colleagues³ lends scientific support to some of the issues we were worried about—eg, hot flushes and weight gain. Will all the trialists agree to mention this report in the next edition of *The Cochrane Library*?

Doctors and consumers need to know the truth about risks and benefits of treatments. Assessment of quality of life in cancer therapy is now routine,⁴ so the Cochrane Collaboration should insist, we believe, that the collection of quality-of-life data forms a criterion for acceptability of trials for inclusion in

reviews. The Collaboration must also be true to the spirit of Archie Cochrane himself, who said (in the context of quality of life for breast cancer treatments) "I do not want to give the impression that [the randomised controlled trial] is the only technique of any value in medical research. This would, of course, be entirely untrue."⁵

*Heather Goodare, Clare Dimmer, Kathy Page

Breast UK, "Solva", Denmead, Waterlooville P07 6LA, UK

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Rapid prenatal diagnosis of aneuploidies

Sir—Matteo Adinolfi and Jon Sherlock, in their Sept 29 Commentary,¹ discuss the use of the QF-PCR assay for the rapid prenatal diagnosis of aneuploidies 21, 18, and 13.

They list some countries (UK, Austria, Spain, and Italy) where this method is used with success. In Turin, we have applied QF-PCR^{2,3} tests since 1998, initially for the detection of trisomies 21 and 18, and later in a multiplex test with markers for chromosomes 21, 18, 13, X, and Y. Since the beginning of 1999, we have analysed 1653 samples: 1302 amniotic fluid from women referred for maternal age (50%), serum screening (38%), and ultrasonography (12%); 61 chorionic samples; and ten fetal blood samples. We have also tested 280 fetal tissues collected from aborted fetuses.

All samples were tested by conventional cytogenetic testing. Overall, we have detected 207 aneuploidies: 110 trisomies 21; 40 trisomies 18; 15 trisomies 13; 17 triploids; 18 patterns 45,X; four samples 47,XXY; and three samples 47,XYY. We noted full agreement between QF-PCR and karyotyping results. False-positive or false-negative cases were not encountered. In

addition, we were able to detect some cases of mosaicism in which trisomy was present in at least 30% of the cells.

By use of the amelogenin and X22 markers, abnormal QF-PCR patterns allowed the detection of two mosaicisms: 45,X/45,X, der (21)t(21p;Yp), and 46,X, idic (Yp)(q11.2)/45,X/46,XY. By comparison of the totality of aneuploidies detected by cytogenetics with those detected by QF-PCR, we showed a sensitivity of 98.9% for QF-PCR, since in more than 1653 samples analysed, the assay did not detect only two cases: 47,XY+15, and 45,XY-22/46,XY r22.⁴

Our experience suggests that the QF-PCR method for the diagnosis of numerical anomalies of chromosomes 21, 18, 13, X, Y is rapid, economic, and efficient, and removes the anxiety of the parents, but it can be applied to confirm the presence of affected fetuses in mothers at risk, as suggested by biochemical and ultrasound tests, thus allowing therapeutic interventions.

*Gianfranco Vogliano, Antonella Marongiu, Marco Massobrio, Mario Campogrande, Tullia Todros

*Molecular Pathology Laboratory, and Department of Obstetrics and Gynaecology, Sant'Anna Hospital, Corso Spezia 60, 10126 Turin, Italy; and University of Turin, Turin (e-mail: gianvol@tin.it)

- Adinolfi M, Sherlock J. Prenatal detection of chromosome disorders by QF-PCR. *Lancet* 2001; 358: 1030-31.
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Sir—In response to the Commentary by Matteo Adinolfi and Jon Sherlock,¹ we have started in Barcelona (Spain) a clinical service for the rapid prenatal detection of aneuploidies by QF-PCR.^{2,3}

Several markers of short tandem repeats (STRs) are included in multiplex assays, allowing rapid identification of copy number for chromosomes 21, 13, 18, X, and Y. Our method has already been applied on 1640 amniotic fluids. We have successfully diagnosed Down's syndrome in 28 fetuses, Eduards' and

Patau's syndrome in 18 and three, respectively, and three cases of triploidy.

Fetal sexing was correctly achieved in all samples by amplification of the X/Y amelogenin marker. Other X/Y chromosome-specific STRs^{4,5} were always included to assess sex chromosomes copy number. By use of this approach, we have correctly identified two 47,XXY fetuses, two with Turner's syndrome and three with Klinefelter's syndrome. We confirmed all detected aneuploidies with a chromosome-specific QF-PCR test (eg, by using only chromosome 21 STRs if the first assay revealed a fetus with Down's syndrome). Parents could be informed about the final result within 24 h of collection of samples. If QF-PCR results and ultrasonography findings were in agreement, therapeutic interventions were made available, if required, without waiting for completion of fetal karyotype.

In nine cases, diagnosis could not be reached for one chromosome because of the homozygosity for all specific STRs. In one case, sex chromosome mosaicism could be suspected because of skewed allelic ratios of all sex chromosome markers used. Fetal karyotype later revealed a 46,XY; 45,X0 mosaic. Two more mosaics for sex chromosome aneuploidies were the only false-negative results in our series; in the first, one QF-PCR was concordant with a normal female but cytogenetic analysis later showed a 45X0;47,XXX chromosome complement. The second, diagnosed as a normal female, was later shown to be mosaic for an Xq deletion in a low percentage (20%) of cells.

Only three parents of the 1640 cases asked not to be informed about the sex of the fetus, but asked to be told if it was affected by an X/Y chromosome disorder.

We agree with Adinolfi and Sherlock that all prenatal samples undergoing QF-PCR should also be tested for sex chromosome copy number. If the rapid test is not done, the abnormal karyotype will later be shown by conventional cytogenetics. Therefore, the time available to the parents for reaching a decision about pregnancy management will be shortened. Sex chromosome markers should also be included in all cases with ultrasonographic indication of sex-chromosome aneuploidy, and the full test should always be done if QF-PCR is used as the only prenatal diagnostic procedure. In view of its accuracy and low cost, we believe that the QF-PCR assay should be done on

all prenatal samples to reduce the anxiety of the parents.

*Vincenzo Cirigliano, Maijo Ejarque, Paz Cañadas Cingliam, Carme Fuster

*Department of Molecular Genetics, General Lab, 08021 Barcelona, Spain; and Department of Cellular Biology and Physiology, Universitat Autònoma, Barcelona

- 1 Adinolfi M, Sherlock J. Prenatal detection of chromosome disorders by QF-PCR. *Lancet* 2001; **358**: 1030–31.
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Fatigue due to hypocalcaemia

Sir—Dominik Alscher and colleagues (Sept 15, p 888)¹ report calcium supplementation to cure fatigue in a patient. The disorder of familial hypoparathyroidism, sensorineural deafness, and renal dysplasia reported is very rare. However, the underlying disorder of hypocalcaemia is a frequent cause of fatigue.

We treated two teenage girls who were dark-skinned asylum seekers from Somalia who had fled to the Netherlands. They presented with limb pains and tiredness that was so extreme that it prevented climbing stairs, carrying schoolbooks, or attending school. Their diet was poor in calcium and vitamin D and they had worn clothing that covered the whole body, except part of the face, since the onset of puberty. The girls had serum calcium concentrations of 1.61 and 1.92 mmol/L (normal range 2.20–2.65), ionised calcium concentrations of 0.85 and 1.01 mmol/L (1.10–1.30), 25-hydroxyvitamin D concentrations less than 10 nmol/L (30–100), and parathormone 59.4 and 51.1 pmol/L (30.0–100.0). We made a diagnosis of vitamin D deficiency because of insufficient dietary intake and lack of exposure to sunlight. They responded rapidly to calcium and vitamin D supplementation, with normalisation of calcium concentrations and striking improvements in energy.

We suggest that fatigue may be caused by hypocalcaemia more frequently than is thought. All muscle fibres use ionised calcium as their main regulatory and signalling molecule.² Reduced sarcoplasmic reticulum ionised calcium release is an important component in skeletal muscle fatigue.³ Even simple causes of hypocalcaemia may give the same symptoms as rare cases such as that reported by Alscher and colleagues.

*A M Oudesluys-Murphy, A C H de Vries

Department of Paediatrics, Medisch Centrum Rijnmond Zuid, locatie Zuider, 3075 EA Rotterdam, Netherlands

- 1 Alscher DA, Mettang T, Kuhlmann U. Cure of lifelong fatigue by calcium supplementation. *Lancet* 2001; **358**: 888.
- 2 Berchtold MW, Brinkmeier H, Muntener M. Calcium ion in skeletal muscle: its crucial role for muscle function, plasticity, and disease. *Physiol Rev* 2000; **80**: 1215–65.
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Levodopa and recovery after stroke

Sir—Klaus Scheidtmann and colleagues (Sept 8, p 787)¹ report on the effect of levodopa on recovery after ischaemic brain infarction. Therapeutics are limited, especially after the first hours and among elderly patients, who make up the majority of admitted patients. We understand the researchers' enthusiasm because levodopa seems to be easy to use and could be introduced late in the course of the disease.

Nevertheless many questions should be elucidated. We agree with the discussion about the possible role of the side affected by stroke in recovery because this parameter is not well balanced between the levodopa and the placebo groups at baseline. Some other baseline characteristics, shown in the table of the report, raise the same question about the comparability of the two groups at baseline: the sex-ratio seems to differ and patients in the placebo group are older and their initial Rivermead motor assessment scores are lower.

Age reliably predicts recovery and outcome,² as does initial clinical deficit and size of infarct,³ which are not mentioned by Scheidtmann and colleagues. The possibility that these differences between the two groups at baseline explain all or a part of the effect of levodopa cannot be totally ruled out. Even if some of these factors remain controversial, all efforts should be made to control consistent

prognostic factors at baseline, to take them into account during the analysis of the results, or both.

Despite these limitations in methods, the study may open a new way in stroke care. Levodopa seems to be effective late in the course of stroke. Brain plasticity plays a key part in recovery and has been described several months after stroke onset, especially in the healthy hemisphere.⁴ By means of bilateral transcranial doppler ultrasonography, this mechanism of recovery could be studied in patients receiving levodopa and controls, in numbers high enough to take into account confounding factors.

Stephane Vinzio, *Bernard Goichot

Hôpital de Haute-pierre, 67098 Strasbourg Cedex, France

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Authors' reply

Sir—Stephane Vinzio and Bernard Goichot point out that some of the variables such as demographic data (sex and age), the side of stroke, and the functional Rivermead motor assessment scores at baseline are not well balanced between the study groups. They argue that these differences might help to explain the described effects of levodopa.

The mean difference of 8 years between study groups is not significant. By contrast to the workers in the studies mentioned by Vinzio and Goichot, other researchers have noted no effect of age on functional motor outcome.^{1–3}

The predominance of right hemispheric lesions in the placebo group could have affected the outcome data, even though in large cohorts¹ a hemispheric preference for outcome was not reported. In a subanalysis comparing the gain in motor function separately for left-sided and right-sided strokes, we noted the same difference between the group treated with levodopa and that given placebo, for each side.

The difference in baseline Rivermead motor assessment scores is not

significant. Furthermore, patients did benefit from the treatment with levodopa in addition to physiotherapy, irrespective of the severity of the initial functional motor deficit shown in figure 3 of the report. Even if outcome in general depends on the severity of the initial clinical deficits, the effect of levodopa on the gain in motor function compared to placebo does not.

We agree that many open questions need to be answered, such as the stability of the achieved effects, the time window during which pharmacological intervention is effective, or the optimum drug dose. This research is on the way.

*Klaus Scheidtmann, Wolfgang Fries

*Neurologische Klinik Bad Aibling, 83043 Bad Aibling, Germany; and Neurologische Neuropsychologische Rehabilitation, Munich (e-mail: Kscheidtmann@schoen-kliniken.de)

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Ethylene glycol poisoning mimicking Snow White

Sir—J Jaffery (Oct 13, p 1236)¹ reports a case of ethylene glycol poisoning complicated by focal neurological signs. We report another case of ethylene glycol poisoning with an even more striking clinical presentation that mimicked brain death and made a remarkable functional recovery.

A factory worker aged 23 years presented in another hospital with a 2-day history of confusion, slurred speech, and somnolence. Physical examination was unremarkable. 2 days before admission he consumed 12 units of alcohol. Blood tests on admission showed: serum creatinine 228 µmol/L, sodium 142 mmol/L, chloride 115 mmol/L, pH 7.21, bicarbonate 4 mmol/L, and anion gap 23 mmol/L. Toxic alcohol ingestion was not considered at that time.

He was referred to our hospital 3 days after presentation for renal biopsy and to start dialysis. Urine analysis showed oxalate crystals, and haematuria without casts. Renal biopsy showed tubular necrosis, glomerular microangiopathy, interstitial haemor-

rhage, and tubular oxalate deposits. Ethylene glycol poisoning was considered as the clinical diagnosis. Retrospective investigation of initial serum samples showed no detectable ethylene glycol concentrations, and glycolic acid could not be measured because of the shortage of sample.

7 days after the first symptoms deafness, dysphagia, and dysarthria developed. The patient was alert, had a bilateral complete external ophthalmoplegia, non-reactive pupillary light reflexes, moderate paresis of bulbar muscles and extremities, decreased myotatic reflexes, and diminished sensory perception in the distal extremities. We inserted an endotracheal tube and he was mechanically ventilated because of hypercapnic respiratory failure.

After 12 days, he was completely unresponsive to any stimulus, all brainstem reflexes being absent, and was unable to cough or to trigger the ventilator. Deep tendon reflexes were absent, and he had a flaccid tetraparesis. Since the CT scan of the brain and the electroencephalography were normal, the clinical diagnosis of brain death was rejected. We concluded that he was awake but fully paralysed. Clinical neurophysiological examination showed a severe axonal polyneuropathy, and sural nerve biopsy findings showed severe axonal degeneration and oxalate depositions. After 2 months, the patient could breath spontaneously and muscle power recovered slowly.

After 16 months, the patient could walk with crutches, and was independent in activities of daily life. He was completely deaf and was being treated with continuous ambulatory peritoneal dialysis. Urinary excretion of oxalic acid was within normal limits (urine oxalate/creatinine ratio 0.04, normal value for adults <0.08),² which suggests that ethylene glycol poisoning was the temporary source of oxalate deposition in the kidney and sural nerve.

This case shows that ethylene glycol poisoning may cause severe neurological deficits, and even mimic a clinical state of brain death. Severe neurological abnormalities eventually proved reversible. Ethylene glycol poisoning should be considered in the differential diagnosis of acute neurological deficits and acute renal failure.

*Tom J M Tobé, G Branko Braam, Jan Meulenbelt, Gert W van Dijk

Departments of *Intensive Care I/Clinical Toxicology, Nephrology, and Neurology, University Medical Centre, PO Box 85500, 3508 GA Utrecht, Netherlands; and National Poisons Control Centre, National Institute of Public Health and the Environment, Bilthoven (e-mail: t.j.m.tobe@digd.azu.nl)

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Multidrug-resistant *Streptococcus pneumoniae* from India

Sir—*Streptococcus pneumoniae* resistant to penicillin, non- β -lactam agents, or both have been reported with increasing frequency worldwide, with some countries in the Asian continent reporting up to 70% resistance to penicillin.¹ There are, however, very few reports of penicillin-resistant pneumococci from India,² and those that do report, present no details on the susceptibility profile to other classes of antibiotics. We report a multidrug-resistant isolate of *S pneumoniae* in India, its susceptibility pattern, and other characteristics.

At our centre, continuing surveillance programmes for monitoring the emergence of drug resistance and serotype pattern of *S pneumoniae* were started in 1993. No multidrug-resistant *S pneumoniae* has yet been isolated in those studies.^{3,4} We identified an isolate of *S pneumoniae* in the throat of a child aged 12 years, admitted to our hospital in 1999. The child presented with high-grade intermittent fever and chills of 3 days' duration, with abdominal pain, diarrhoea, and generalised rashes on the body, palms, and soles. White blood cell count was $18 \times 10^9/L$ with 2% band forms, 89% neutrophils, 7% lymphocyte, 1% eosinophils, and 1% monocytes. Antibodies to streptolysin O were negative.

We isolated coagulase-negative staphylococci from the blood, which we later judged a contaminant. We assumed the penicillin-resistant

S pneumoniae isolated from the throat was a nasopharyngeal coloniser. The strain was identified and confirmed by standard microbiological procedures.⁵ The final diagnosis of the patient was septic-shock syndrome along with toxic myocarditis from an unconfirmed cause. The inability to isolate the causative agent in this case could be because of previous treatment with antimicrobials.

The *S pneumoniae* isolate was further characterised in the laboratory. The table shows the susceptibility profile of the isolate. Minimum inhibitory concentration testing was repeated at the Hershey Medical Center, PA, USA, which was our reference centre, and the results showed 100% concordance. The isolate was multidrug resistant but quinolone susceptible, and is the first confirmed isolate resistant to cefotaxime and erythromycin from our centre. PCR for detection of *erm* gene for macrolide resistance gave a positive result, which suggests inherent macrolide resistance. The isolate belonged to serotype 6B.

Our surveillance programmes have received strains of *S pneumoniae* from different regions of India since 1993. So far, only 5% intermediate resistance to penicillin has been recorded,⁴ with no multidrug resistance. Incidentally increasing minimum inhibitory concentration levels to erythromycin and cefotaxime have been noted in the strains showing intermediate resistance to penicillin, although they were still within the susceptible range.

The emergence of multidrug resistant pneumococcus makes it important to propagate the judicious use of antibiotics, continue surveillance studies, and to focus attention on pneumococcal vaccination, especially in children at high risk, especially in day-care centres and boarding schools.

Kurien Thomas, K N Brahmdathan, and Prabhakar D Moses belong to the CMCH Pneumococcal Study Group.

*M K Lalitha, Rekha Pai, Anand Manoharan, PC Appelbaum, and the CMCH Pneumococcal Study Group

*Department of Microbiology, Christian Medical College and Hospital, Vellore 632 004, India; and Hershey Medical Center, Hershey, PA, USA (e-mail: mkl_micro@yahoo.com)

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Effect of preoperative warming on wound infection

Sir—Andrew Melling and colleagues (Sept 15, p 876)¹ conclude that preoperative warming of the patient or the operative incision site significantly lowers the frequency of surgical infection after clean operations. However the wound infection rate in normothermic patients was 14%, which is much higher than the 2–4% infection rate reported in other large studies done with similar surveillance methods.^{2,3} Even in their treated groups, the reported wound infection rate of 5% seems to be somewhat excessive for clean wounds. Furthermore, only ten (31%) of 32 wounds judged infected in their study were culture positive.

We wonder, therefore, why the background infection rate was raised in this study and question whether the results can be generalised to other centres with lower wound infection rates.

*Dana Saadat, Albert B Lowenfels

Department of Surgery, New York Medical College, Mungler Pavilion, Valhalla, NY 10595, USA

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Authors' reply

Sir—We agree with Dana Saadat and Albert Lowenfels that the infection rate of 14% in patients who did not undergo warming before clean surgery

Antimicrobial	MIC (mg/L)
Penicillin	2.0*
Amoxicillin	1.0†
Co-amoxiclav	1.0†
Cefuroxime	8.0*
Ceftriaxone	1.0†
Cefepime	1.0†
Cefotaxime	2.0*
Clarithromycin	>32.0*
Azithromycin	>32.0*
Erythromycin	>32.0*
Imipenem	0.12‡
Meropenem	0.25‡
Levofloxacin	0.5‡
Chloramphenicol	32.0*
Trimethoprim/sulfamethoxazole	6.0*

MIC=minimum inhibitory concentration. *Resistant. †Intermediate resistance. ‡Susceptible.

Antimicrobial susceptibility pattern of multidrug-resistant *S pneumoniae*

is much higher than the 2–4% reported elsewhere. They state that those workers used similar surveillance methods to us, but we believe there are many differences that may account for the variation in infection rates.

The need for surveillance after discharge is now accepted, but the best method of achieving this is still in question. Reliance on the patient, their surgeon or doctor, or both to diagnose infection via telephone calls or questionnaires has been suggested will underestimate the overall incidence of infection.¹ We interviewed all patients and directly observed wounds at weeks 2 and 6. All patients were discharged with a diary in which to record wound healing, and we did not limit the definition of infection to the presence of a purulent discharge. When similar methods or definitions to ours have been used in other studies, much higher rates of infection have been reported (8–18%).^{2–4} Furthermore, the frequency of administration of post-operative antibiotics for wound complication reflects the high rate of infection. 16% of patients in the non-warmed group were prescribed postoperative antibiotics by their own family doctor or an outpatient-clinic physician for wound healing problems, compared with only 6% in the warmed group.

We do address the reason for the low numbers of positive wound cultures in our report. The difficulties we encountered were due to the logistics of swabbing patients after discharge, in many cases the patients had already started antibiotic treatment after a visit to their family doctor or their wound discharge had stopped, leaving nothing to swab at the time of review.

We recognise the need to standardise wound infection surveillance methods and definitions of infection to allow comparisons between surgeons and institutions. This approach has been achieved by many hospitals in the USA because they have adopted Centers for Disease Control and Prevention guidelines.⁵ However these guidelines are merely for the widespread audit of infection rates. As such, they will not be the most sensitive of tools but represent a simple and achievable method of surveillance.

We intended to use the most sensitive methods of surveillance to try to highlight any differences between randomisation groups and the real problem that infection represents in this type of surgery. We believe the rate of 14% represents a realistic

wound complication rate when intensive methods of wound surveillance, as described above, are used.

*Andrew C Melling, David J Leaper

Professorial Unit of Surgery, North Tees and Hartlepool NHS Trust, University Hospital of North Tees, Stockton-on-Tees TS19 9PE, UK

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Japanese HIV-blood trial

Sir—In his Oct 6 news item, J Watts¹ suggests a brief comment would be of interest on the irony of the dismissal of charges that Takeshi Abe, the Japanese government's leading advisor on blood products in the mid-1980s, had contributed to the death of patients by failing to recognise the risk of non-heat-treated blood products—ie, antihæmophilic factor VIII concentrates.

Under Abe's presidency of the XIIth Congress of the International Society on Thrombosis and Haemostasis in 1989, we presented a report of the immunosuppressive effect of commercially available non-heat-treated factor VIII concentrates, which were grossly contaminated with factor XIII in the purification procedure at the time.² Factor XIII, the lesser-known culprit than the more widely acknowledged HIV-1, is a contributing factor to immunosuppression in AIDS-associated hæmophilia³ and, even today, as reported by Craven and colleagues,⁴ has remained consistently ignored in discussions of the impropriety of the use of factor VIII concentrates.

The clinical importance of factor-VIII-induced immunosuppression to the predisposition to HIV-1 in hæmophiliacs has been borne out by the high frequency of immune aberrations in HIV-1-seronegative compared with seropositive hæmo-

philiacs.³ This finding suggests that such aberrations are due to factors other than HIV-1. Also relevant is the variation in geographical incidence of AIDS-associated hæmophilia in the USA relative to the source (purity) of blood coagulation concentrate received.³ Hæmophiliacs in New York City, for example, an area representative of one of the highest number of AIDS-associated cases in the USA,³ were principal recipients of factor VIII concentrates containing the greatest amount of factor XIII contaminant and suppressive activity.²

The profits for plasma suppliers were, at the time, huge, and entrepreneurs at the time paid little attention to the health status of blood donors and to the purification process for the isolation of factor VIII.⁵

Not limited to Japan, these careless and criminal practices were global and have included France, Germany, Italy, Switzerland, and the USA. In fact, in the case of Japan, it was the US blood suppliers who sold untreated factor VIII concentrates to the Japanese at discounted prices.³ Japanese doctors and hospitals then profited by claiming the higher official price from insurance schemes.³

Attention to the non-viral impurities in factor VIII would not have eliminated AIDS-associated hæmophilia in its entirety. However, dependent on the commercial source of factor VIII received, hæmophiliacs may have received a double whammy—ie, HIV-1-contaminated concentrate and concentrate that suppresses their immunity. In the current age of the use of recombinant factor VIII, if nothing else, let us at least recognise for the individuals who have perished, that HIV-1 was not the only culprit.

Richard J Ablin

Innapharma Inc, 1 Maynard Drive, Suite 205, Park Ridge, NJ 07656, USA (e-mail: rablin@innapharma.com)

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Bad decision NICE

Sir—The perversely named National Institute for Clinical Excellence (NICE) is attempting to ban the use of β -interferon for multiple sclerosis in England and Wales. NICE has issued its Final Appraisal Determination¹ after 2 years of deliberation. NICE is trying to prescribe use of this drug on the basis of a flawed and unreliable cost-benefit analysis. NICE accepts that such estimates are sensitive to assumptions made in the modelling process.

NICE decided not to rely on the cost-effectiveness models that were submitted (cost per quality-adjusted life year down to UK£8100²) but commissioned its own analysis. The appraisals committee then rejected their own analysis' assumption to cost benefits over a 20-year time frame (so raising the cost per quality-adjusted life year from £40 000 to £90 000) for a disease that normally lasts more than 30 years.

The analysis starts with short-term studies (2–5 years) designed primarily to show efficacy, extracts from the expanded disability status scale (non-linear ordinal scale) quality-of-life data, which is extrapolated over decades. This approach might well be construed as a post-hoc, highly speculative, and unreliable hypothesis-generating piece of work, not robust enough to determine the fate of thousands of patients with multiple sclerosis.

Quality-adjusted life years are flawed in that they ask able-bodied people to make judgments about the quality of life of disabled people. They also do not take into account the complex interactions between different features of neurological disability (diminishing marginal value). Quality-adjusted life years, and their inverse disability-adjusted life years, value disabled people less than people without disabilities.

If NICE succeeds in banning the use of β -interferon for multiple sclerosis in the name of equality, it will be forced to ban dialysis for seriously ill patients with renal failure staying in hospital (£95 837 per quality-adjusted life year),³ neurosurgery for malignant intracranial tumours (£95 837 per quality-adjusted life year),⁴ and cardiopulmonary resuscitation (£164 293 per quality-adjusted life year).⁵

The UK Government has already undermined NICE's decision by proposing a risk-sharing scheme that will assess clinical and cost effectiveness. It is difficult to see what scientific merit such a scheme might have since a placebo group would be unethical, and I suspect that the government's

announcement is a delaying tactic using the principle that "a decision delayed is a few grand saved". This dishonourable chapter in the care of neurological patients in the UK is a clear lesson of how not to ration treatment.

Simon J Ellis

North Staffordshire Royal Infirmary,
Stoke on Trent ST4 7LN, UK
(e-mail: Simon@northesk.demon.co.uk)

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Infectious syphilis and importance of travel history

Sir—Margaret Kingston and colleagues (Sept 8, p 808),¹ in their report of genital schistosomiasis mimicking vulval warts, reiterate the importance of recording adequate travel history in patients presenting to sexually transmitted disease clinics with genital manifestations of tropical diseases.

Their message is also relevant to clinics serving rural communities. We saw two patients with infectious syphilis who had moved out of the area then returned.

The first, a man aged 37 years, attended in 1999 with what he described as recurrent herpes infection. He had declared when he first attended in 1989 that he had sex with men and had attended for HIV and hepatitis B screening. Urethral samples were screened for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and serological screening was done for hepatitis B antigen, syphilis, and HIV-1 antibodies, which was negative. Perianal warts were noted and treated. He attended repeatedly between 1989 and 1995 with recurrence of genital warts, but agreed only to serological tests for syphilis and HIV antibody, which were negative. In 1999, he declined infective screening, asserting it had been done in another clinic. He was treated for presumptive herpes. The other clinic confirmed his



Penile ulceration seen on patient one

attendances and negative serological test results for syphilis and HIV-1 and HIV-2 antibodies, and non-isolation of herpes simplex virus from the penile ulcer. He defaulted from his review scheduled in November, 1999.

The second patient, a man aged 30 years, first attended our clinic in December, 1999, with anal soreness and irritation. He declared he had sex with men and mentioned previous attendance in another clinic for treatment of genital warts. On examination, he had four tender shallow perianal ulcers. Infective screening, initially by gram staining of urethral materials followed by culture, was done for *Neisseria gonorrhoeae* from urethral, pharyngeal, and rectal samples, *Chlamydia trachomatis* from urethral samples by ELISA, herpes simplex culture from the perineal lesion, and serological tests for syphilis and HIV-1 and HIV-2 antibodies, HBsAg antibodies, and core antibodies. He was treated as presumptive herpes simplex viral infection. Herpes simplex virus type 2 was isolated from the perianal lesions and syphilis antibodies were detected on ELISA. The other clinic confirmed negative syphilis serology on the occasions he attended. Reference serology confirmed treponemal IgG and IgM antibody, and gave a *Treponema pallidum* haemagglutination assay (TPHA) positive result and a Venereal Disease Reference Laboratory result of 1:16.

The first patient attended as his named contact and still had penile ulceration (figure). Reference serology detected treponemal IgG, and gave a TPHA-positive result, and a Venereal Disease Reference Laboratory result of 1:4. Treponemal IgM was not detected.

The rate of infectious syphilis is rising in England and Wales, as reported in Bristol,² Brighton,³ Manchester,⁴ and London. The greatest rise is among men who have sex with men. Most patients in the Manchester series presented with painful ulcerations suggestive of herpes simplex, as did our two cases. However, our cases reiterate the usefulness of documenting travel

details and always requesting serological tests for syphilis, even in cases suggestive of herpes simplex.

Tubonye C Harry

Bure Clinic, James Paget Healthcare NHS Trust, Great Yarmouth NR31 6LA, UK (e-mail: tcharry@bureclinic.com)

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Two decisions of Japanese court on detained Afghan asylum seekers

Sir—Richard Horton, in his Oct 6 Commentary,¹ projects that the war against terrorism will fail. Therefore, the war against terrorism is not achieving its aim, but is killing innocent Afghan people. They seem, however, to be victims of the war not only in their homeland but also in asylum.

On Oct 3, 2001, nine Afghan applicants for refugee status in Japan were detained by Tokyo Immigration Bureau because of their illegal entry without valid visa. Allegedly, these asylum seekers were oppressed by the Taliban.

According to the international convention of refugees, these people should be protected while applying for refugee status.² Japan's refugee protection system is stretched, as are systems in other more-developed countries.³ During the process of application for refugee status, asylum seekers are ineligible for welfare assistance as well as health-care services and treated as illegal migrants. The refugee application process generally takes several years. Since Japan's refugee protection system does not secure legal status of asylum seekers, it eventually allows the government to arrest them as illegal migrants at anytime at its will, without explanation for their detention.

Lawyers representing the nine detained Afghan asylum seekers took an action, at the Tokyo District Court, to contest the detention by Tokyo Immigration Bureau. As a result two different decisions were made by the court. On Nov 5, four of them were refused release because whether they sought asylum in Japan was unclear. On the next day, a different judge in the

same court made an opposite decision for the remaining five because the detention was deemed to be ignoring the international convention on refugees.

Afghan asylum seekers in Japan are in a very insecure environment. We should, therefore, take into account the possibility of mental harm, especially in asylum seekers who are in detention,³ since they are at great risk of psychological trauma. As the lawyers appeal to the court, we urge the government to adopt a more humane policy for asylum seekers.⁴

*Masao Ichikawa, Junko Okumura, Susumu Wakai

Department of Community Health, School of International Health, Graduate School of Medicine, University of Tokyo, Tokyo 113-0033, Japan (e-mail: masao@m.u-tokyo.ac.jp)

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WHO addresses poverty and bioterrorism

Sir—In Clare Kapp's Jan 19 news item¹ on WHO's campaign for health spending in less-developed nations, we note some erroneous statements.

Some of the statements about a study entitled New Products into Old Systems: the Global Alliance on Vaccines and Immunizations (GAVI) a country perspective are incorrect.

We were involved in the design, methods, data collection, and analysis of this study, which was facilitated, funded, and published jointly with Save the Children UK. The study looked at four countries' experience with the application process for new vaccines from GAVI, and their perceptions about funding for systems support.

The report did not raise concerns about pharmaceutical company involvement in GAVI; this perspective came from a Save the Children press release about which the London School of Hygiene and Tropical Medicine was not consulted. A quotation in Kapp's item about the long-term sustainability of the programme implies that the quote was taken from the study. It was not, although country-level

respondents, especially some donors, did raise this concern.

*Gill Walt, Ruairi Brugha, Mary Starling

Health Policy Unit, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

- 1 Kapp C. WHO executive board addresses poverty and bioterrorism. *Lancet* 2002; **359**: 239.

A cure for anthrax?

Sir—Anthrax is one of the most important life-threatening health problems, and people do not know exactly what to do against this illness. Currently, inhalation anthrax is the most important form of infection, but in the 1950s, cutaneous anthrax was a big problem for my grandmother and the people in her village.

She lived in a village about 35 km away from Ankara, Turkey, called Yaglipinar. Many inhabitants migrated from Caucasus in the time of the Ottoman Empire and were farmers working with animals.

The animals started to become ill, but the farmers did not understand why. The horses and the sheep were especially affected. Some farmers shot the horses and burned the sheep, but others cut up the sheep to use their meat before they died. A daughter, aged 18 years, of one of the farmers who used the sheep meat developed pruritic and itchy lesions on her neck and hand.

There were no doctors in the village. A woman called Habibat was in charge of treating the illnesses with herbal medicines. All the medical problems including tuberculosis, amenorrhoea, allergy, and so on in the village were treated by her. The girl was taken to Habibat, at which time she had a painless red macule surrounded by brawny oedema on her neck and hand. She had skinned an ill sheep 4–5 days previously. Habibat took a wooden spoon, heated it on the fire, and used it to cauterise the wound. After a while, the girl's neck was greatly healed, with a small cauterisation scar, as was her hand, with no scar at all.

The farmer's daughter was my grandmother. She said that the scar had stayed for 50 years and that most of the people in our village had similar scars at various points on their bodies.

I do not know whether Habibat's other treatments were as effective as this one. However, she had cured my grandmother's illness. Who knows, maybe the cure of the inhalation anthrax will be as easy as this one?

Erkin Sönmez

Baskent University, School of Medicine, Ankara, Turkey