

# CORRESPONDENCE

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## Iraq: harm reduction through health

Sir—Your Editorial (Oct 5, p 1031),<sup>1</sup> does not reflect the whole truth about the current health problem in Iraq and what might happen after the downfall of the present regime.

The WHO figures you mention are provided by Iraqi officials, the only source of information there. Distortion of figures is a well known policy of the regime. It tries to put the blame on Western countries for the suffering of ordinary Iraqis during the past 11 years. The regime has deliberately been denying proper health provisions to achieve its goals and, as a recent programme on BBC television showed,<sup>2</sup> the bodies of dead children are kept in mortuaries until such a time when there are enough bodies to organise a mass funeral, to which foreign media are invited to watch and film.

The *Telegraph* reported last year<sup>3</sup> how Iraqi medicines, with a UN stamp, were found sold in the black markets of Amman and Beirut, and Iraqi doctors fleeing Iraq tell horrendous stories about how drugs are kept in stores in hospitals until they expire, leaving children to die in order to satisfy the government's propaganda machine. We must also remember that there is in reality no limit or sanctions on what food and medicines Iraq wants to import if it so wishes.

Your conclusion: "A war whose goal is regime change is no solution to the crisis facing Iraq" is therefore too naive, simplistic, or at worst, politically motivated. We Iraqis who have the privilege of having the freedom to speak in a Western democracy feel that it may be unfortunate, but there is no other way to achieve the proper standard of health we all wish for the helpless people of Iraq without a regime change. If war is the only way, it will be a war of freedom and civilisation, not a war of destruction as you suggest.

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- 1 Editorial. Iraq: harm reduction through health. *Lancet* 2002; **360**: 1031.
- 2 How Saddam 'staged' fake baby funerals. *The Observer*, June 23, 2002.
- 3 UN Medicine being sold on black market. *Telegraph*, Sept 24, 2000.

Sir—Your Editorial<sup>1</sup> made clear why a war whose goal is regime change is no solution to the health crisis facing Iraq.

In March, President George W Bush declared: "Inaction is not an option". Clearly, Saddam's regime is evil and clearly something needs to be done to help the Iraqi people who have suffered under it for so long. But "inaction", in the sense of military inaction, is an option and is the only constructive and ethical one.

As a general practitioner, may I suggest an analogy with medical practice. A serious, life-threatening disorder exists. There is a dramatic surgical intervention available as treatment. But this "cure" would produce high morbidity, the long-term results are unproven, and there is no evidence that it would prevent a recurrence. There is great pressure on the doctors to "do something". Surgery also offers opportunities for career advancement. The alternative approach is to support and build up the patient's immune system to enable him to fight the disease from within, and to develop a strong management team with other colleagues. This option is less dramatic and requires more patience, but promises a better outcome for the patient.

The latter is clearly the preferred treatment option unless, of course, career (empire) advancement is actually the aim, and the surgeon's fees for the intervention (oil) are valued more highly than the wellbeing of the patient.

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- 1 Editorial. Iraq: harm reduction through health. *Lancet* 2002; **360**: 1031.

Sir—There is much similarity between the suffering of Iraqi children<sup>1</sup> and the looming public health crisis among Palestinian Arabs.<sup>2</sup> It is strange, then, that although Saddam is rightly indicted for "a cycle of purges, extrajudicial executions, attempted genocide, and reckless war making", no charge is made against the Palestinian regime and its policy of terror and violence—the ultimate

cause of the suffering of Palestinian children.

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- 1 Editorial. Iraq: harm reduction through health. *Lancet* 2002; **360**: 1031.
- 2 Kapp C. WHO gives warning on failing Palestinian health. *Lancet* 2002; **360**: 1081.

## Alcohol-based hand gels and hand hygiene in hospitals

Sir—In their report, Axel Kramer and colleagues (April 27, p 1489)<sup>1</sup> describe a laboratory-based efficacy study in which they compared commercially available alcohol-based hand gels and rinses with the European reference alcohol hand-rub solution (60% 2-propanol [isopropanol]) according to methods specified by the European Norm (EN) 1500 testing standard for hygienic hand rubs.

The alcohol-based hand gels reduced bacterial counts on artificially contaminated hands of 15 volunteers by 2–4 Log<sub>10</sub>, which is significantly less than the reference alcohol solution. Therefore, the investigators classified the gels as not meeting the EN 1500 standard for alcohol-based hand rubs. Results for alcohol-based hand rinses were similar to those recorded for the reference alcohol solution.

Kramer and colleagues conclude that the replacement of currently used alcohol hand rinses by any tested gel would lead to increased risk of cross-infection. Additionally, they conclude that the hand gels are unsuitable for hand antisepsis in health care because their antimicrobial efficacy may be insufficient to prevent the spread of pathogens. Unfortunately, these conclusions are not supported by the data presented.

The level of reduction of bacterial counts on hands of health-care staff (eg, 90% [1 Log<sub>10</sub>], 99% [2 Log<sub>10</sub>], 99.9% [3 Log<sub>10</sub>], or 99.99% [4 Log<sub>10</sub>]) required to prevent cross-transmission of nosocomial pathogens is not known.<sup>2,3</sup> Therefore, the Committee on European

Standardisation's policy, which states that alcohol-based hand rubs with reduction factors significantly lower than the reference alcohol solution (average reduction factor of 4 Log<sub>10</sub>) do not meet the EN 1500 standard, is completely arbitrary.<sup>3</sup>

In the USA, the Food and Drugs Administration requires that effective hand-wash agents for health-care staff (including alcohol-based hand rinses and gels) must lower bacterial counts on hands by 2 Log<sub>10</sub> after one use, and 3 Log<sub>10</sub> after ten applications.<sup>4</sup> The reduction factors for alcohol-based hand gels are greater than those observed with brief hand washing with plain soap, and are similar to or exceed those noted for antimicrobial detergents used for hand washing in health-care facilities.<sup>1,3</sup>

Although microbiological efficacy is an important feature of hand hygiene products, acceptance and frequency of use of products by health-care staff are of equal, perhaps greater, importance. Use of a well-accepted alcohol-based hand gel will probably prevent cross-transmission more effectively than no hand washing, which is currently a common practice. In one study, promotion of frequent use of an alcohol-based hand gel significantly reduced the incidence of several nosocomial pathogens.<sup>5</sup>

Prospective, randomised controlled clinical trials that measure health-care-related infection rates as the primary outcome variable are needed to find out whether alcohol-based hand rinses and gels differ significantly in terms of their efficacy in reducing the incidence of health-care-related infections.

JMB is a consultant to a European manufacturer of soaps and alcohol-based hand rinses. ELL has previously received research funding from Procter and Gamble, 3M, Johnson and Johnson, and Steris, who manufacture soaps and alcohol-based hand hygiene products.

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- 1 Kramer A, Rudolph P, Kampf G, Pittet D. Limited efficacy of alcohol-based hand gels. *Lancet* 2002; **359**: 1489–90.
- 2 Larson EL, APIC Guidelines Committee. APIC guideline for handwashing and hand antisepsis in health care settings. *Am J Infect Control* 1995; **23**: 251–69.
- 3 Rotter M. Hand washing and hand disinfection. In: Mayhall CG, ed. *Hospital epidemiology and infection control*, 2nd edn. Philadelphia: Lippincott Williams and Wilkins, 1999: 1339–55.
- 4 Food and Drug Administration. Tentative final monograph for healthcare antiseptic drug products; proposed rule. *Fed Reg* 1994 **59**: 31441–52.

- 5 Gopal Rao G, Jeanes A, Osman M, Aylott C, Green J. Marketing hand hygiene in hospitals: a case study. *J Hosp Infect* 2002; **50**: 42–47.

Sir—Axel Kramer and colleagues<sup>1</sup> report that 30 s exposure to the liquid preparations reduced contamination by around 99·99% compared with 99·9%, for gels, and conclude that gels should not be used. We disagree with this interpretation.

Casewell and Phillips<sup>2</sup> enumerated *Klebsiella* spp found on nurses' hands after normal contact with colonised patients. The typical recovery was around 100–1000 organisms; the highest was 7000. All except two of the ten alcohol gels that Kramer and colleagues tested would, therefore, have eliminated the typical numbers.

What is important is that any preparation is used before and after close contact with any patient.<sup>3</sup> We believe that anything that makes such preparations more acceptable to users is at least as important as a ten-fold difference in efficacy on a standard test. Kramer and colleagues note that the main reason for use of gel formulations is to reduce skin irritation and dryness. User acceptability is vital to the overall effectiveness of any product. Bischoff and colleagues<sup>4</sup> have shown introduction of easily accessible dispensers containing an alcohol gel can significantly improve hand decontamination rates among health-care workers.

The standard used by Kramer and colleagues is an important method of testing hand rubs, but hand-rub use on wards will be more variable than under the test conditions. The investigators estimate that alcohol application times are more likely to be 8–15 s in daily practice, compared with the 30 s application of the standard test. Therefore, decontamination will be less from both types of preparation than in the study, with smaller differences between them.

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- 1 Kramer A, Rudolph P, Kampf G, Pittet D. Limited efficacy of alcohol based hand gels. *Lancet* 2002; **359**: 1489–90.
- 2 Casewell M, Phillips I. Hands as a route of transmission for *Klebsiella* sp. *BMJ* 1977; **2**: 1315–17.
- 3 Cookson B, Teare L, May D, et al. Draft hand hygiene standards. *J Hosp Infect* 2001; **49**: 153.
- 4 Bischoff WE, Reynolds TM, Sessler CN, Edmond MB, Wenzel RP. Handwashing compliance by healthcare workers, the impact of introducing an accessible alcohol based hand antiseptic. *Arch Intern Med* 2000; **160**: 1017–21.

Sir—In the midst of a continuing hand hygiene campaign at our hospital, concerns started to be raised about our selected product because of the findings of Axel Kramer and colleagues.<sup>1</sup>

Their conclusions are based solely on a finding of statistical significance. No data is referenced or presented that suggests that more than a 99·9% reduction in bacterial counts on health-care workers' hands increased pathogen transmission compared with a reduction of more than 99·99%. Nor do Kramer and colleagues address the potential magnitude of the effect on adherence associated with the increased drying effect of rinses, although they do suggest the use of a protective skin cream may help.

Careful readers can place the findings in context, but the translation that might reach many providers, such as through media accounts, is that the alcohol gels are not suitable for hospitals and can increase the risk of pathogen transmission.

I suggest an alternative conclusion that doesn't confuse statistical significance with clinical importance, and efficacy with effectiveness: whether the incremental difference in reduction of bacterial counts between alcohol gels and rinses translates into a real difference in risk for pathogen transmission is unclear, and awaits further study. The effect on hand hygiene adherence associated with the effect on skin health of gels versus rinses must be included in any assessment of the relative merits of these products.

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- 1 Kramer A, Rudolph P, Kampf G, Pittet D. Limited efficacy of alcohol-based hand gels. *Lancet* 2002; **359**: 1489–90.

Sir—The data of Axel Kramer and colleagues<sup>1</sup> confirm the information reported by Pietsch<sup>2</sup> and the results of rub products for the tests EN 1500. However, we think the findings may have a dangerous effect on infection control policies.

First, gels for rubbing are perhaps less efficient than rinses, but are more efficient than scrubs, about which data are probably not widely known.

Second, the introduction of rubs seems to efficiently reduce the rate of nosocomial infections,<sup>3</sup> but the most important effect is probably because of improved adherence to hand disinfection. Good adherence is possible only if the product is well tolerated.<sup>4</sup> In our experience, and in other reports,<sup>5</sup> gels are agreeable. Use of handrubbing

doubled when we changed rinses for gel rubs in care units. We did not change to gels for surgical hand disinfection but kept a hand rinse.

Third, Kramer and colleagues put the gel effect before the composition effect. However, the type and number of associated alcohols are perhaps more important than the carrier formulation.

In future gels, which are becoming increasingly fluid and easy to apply, may become as efficient as rinses and as well tolerated as old gels.

Another important issue is efficacy of hand rubs on viruses, which is awaiting European testing. Although, however, the efficacy of the product should be a criterion, if our target is the reduction of nosocomial infections, tolerance and acceptability by health-care workers are also important.

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- 1 Kramer A, Rudolph P, Dampf G, Pittet D. Limited efficacy of alcohol based hand gels. *Lancet* 2002; **359**: 1489–90.
- 2 Pietsch H. Hand antiseptics: rubs versus scrubs, alcoholic solutions versus alcoholic gels. *J Hosp Infect* 2001; **48** (suppl A): 533–36.
- 3 Pittet D, Boyce J. Hand hygiene and patient care: pursuing the Semmelweis legacy. *Lancet Infect Dis* 2001; **April**: 9–20.
- 4 Rotter ML. Arguments for alcoholic hand disinfection. *J Hosp Infect* 2001; **48** (suppl A): S4–8.
- 5 Boyce JM, Kelliher S, Vallande N. Skin irritation and dryness associated with two hand-hygiene regimens: soap and water hand washing versus hand antisepsis with an alcoholic hand gel. *Infect Control Hosp Epidemiol* 2000; **21**: 442–47.

#### Authors' reply

Sir—Alcohol-based hand rubs approved for use, whether gels or rinses, reduce bacterial counts on health-care workers' hands more than do antimicrobial soaps or detergents.<sup>1</sup> Rubs are fast-acting, and cause less skin irritation and dryness.

We fully agree with John Boyce and colleagues, Peter Hoffman and colleagues, and Dan Diekema that more clinical data are necessary to assess the effectiveness of hand gels. To clarify the issues under discussion, the ultimate goal of hand hygiene is to reduce cross-transmission and infection rates and two main features contribute—adherence to recommendations and agent efficacy.

We have shown previously that factors that determine adherence are multiple,<sup>1,2</sup> but one is health-care workers' acceptance of agents. The concern that rinses might be less accepted than gels is legitimate. Nevertheless, no data yet suggest that adherence is higher when using gels than when using rinses, although the impact on attitudes of an excessively market-driven, health-care industry is clear.<sup>3</sup> Moreover, in one study, fewer than half of health-care workers were satisfied with a newly introduced gel, and more than half found it uncomfortable to use, which threatened adherence (table).<sup>4</sup> To our knowledge, the only reported experience of successful and sustained hand hygiene promotion with a parallel drop in nosocomial infection used a rinse.<sup>5</sup>

We recognise that despite the availability of standard laboratory tests and, especially EN 1500, in no clinical trial has the extent to which hand microbial counts need to be reduced to decrease cross-transmission been established. Whether the difference in log reduction between rinses and gels is clinically important remains unknown. However, if we assume an identical degree of acceptance, the agent with greater efficacy should be favoured until more data from controlled clinical trials are available.

We believe our data raise concern that should stimulate researchers and manufacturers to invest in the development of agents with maximum antimicrobial efficacy, tolerance, and acceptance. Increase of the ethanol content of gels is one step towards improved efficacy. To end the controversy, we invite the scientific community to collaborate to decide international norms for the testing of hand rubs, especially in hospitals, and

ideally to assess the dynamics of hand contamination.<sup>5</sup>

In health-care institutions where hand washing with medicated soap is still used, we strongly recommend a change to use of alcohol-based hand rubs, whether rinses or gels, whichever produces the best adherence. In hospitals where adherence has improved and infection rates decreased because of rinse use,<sup>2</sup> we are tempted to say don't change a winning team.

Adherence to hand hygiene is a complex behavioural issue; successful promotion strategies should use multiple methods.<sup>1,2,4</sup> Efficacy, acceptability, and good skin tolerance of hand rubs are important but are only one brick in the wall of adherence.

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- 1 Pittet D, Boyce J. Hand hygiene and patient care: pursuing the Semmelweis legacy. *Lancet Infect Dis* 2001; **April**: 9–20.
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## Postmortem diagnosis of testicular cancer

Sir—H De Boer and colleagues (May 11, p 1666)<sup>1</sup> describe an adolescent who died 4 days after a car accident. Postmortem diagnosis revealed metastatic testicular cancer. In their accompanying May 11 Commentary, Jeremy Steel and R Timothy Oliver<sup>2</sup> discuss the perils of very late presentation of testicular cancer.

De Boer and colleagues and Steel and Oliver offer several explanations for late presentation. We have started a study on reasons for delay in testicular cancer. On the basis of reports on delay and disease-specific characteristics of testicular cancer, we developed a questionnaire to assess possible characteristics of patients' and doctors' delay.

25 testicular-cancer patients, median age 23 (range 16–43) years, have so far completed the

Item	Responses (n=62)		
	Agree	Neutral	Disagree
Overall, I was satisfied with the hand gel	45%	34%	21%
The gel helped to improve my hand hygiene adherence	42%	23%	35%
The gel was conveniently located	57%	29%	14%
The gel caused less skin irritation than did handwashing	42%	29%	29%
The gel caused a sticky, uncomfortable feeling	53%	24%	23%

Adapted with permission from reference 4.

#### Healthcare workers' satisfaction and perceptions towards a recently introduced hand gel

questionnaire. Median time between awareness of an unexplained symptom and seeking medical consultation was 35 (1–365) days. 12 patients knew of testicular cancer as a disease before diagnosis, but knowledge was not significantly correlated with delay. 21 patients mentioned a change in the testicle as a first symptom, three reported other symptoms (back pain, gynaecomasty) before they discovered a change in the testicle, and one never noted a change in his testicle.

Of the 24 patients who reported an abnormal testicle, only four thought of cancer as a possibility, ten had no explanation, and ten attributed their symptoms to another illness. Six patients expressed embarrassment about the abnormality in the testicle. Embarrassment was strongly related to patients' delay. All 24 patients consulted their family physicians about the abnormality in the testicle and ten were immediately referred for further examination. The remaining 14 patients were initially misdiagnosed, which led to delays of up to 112 days, although the median doctor delay was only 12 days.

The median delay for patients and doctors is limited, but the range is large. An unanticipated result was that interpretation of symptoms was an important determinant of delay, whereas patients' knowledge of testicular cancer seemed unimportant. The low prevalence of testicular cancer and vagueness of the symptoms augment the chances for misinterpretation. Delay in diagnosis of the disease may lead to more extensive disease, combined methods of treatment, and a reduction in disease-free survival.<sup>3</sup> Therefore, family physicians should always bear testicular cancer in mind when adolescents and young men present with inguinal or scrotal complaints.

We agree with Steele and Oliver, that continuous education is needed for patients as well as medical professionals to alert them to the fact that testicular abnormalities may constitute medical emergencies.

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1 de Boer HD, Haerens MH, van der Stappen SW, van Ingen G, Wobbes T. Testicular carcinoma: postmortem diagnosis after a car accident. *Lancet* 2002; **359**: 1666.

2 Steele JP, Oliver RT. Testicular cancer: perils of very late presentation. *Lancet* 2002; **359**: 1632–33.

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## Use of galantamine to treat vascular dementia

Sir—The masking of treatment assignment prevents bias at several stages of randomised controlled trials. Doubts on this pivotal trial feature are legitimate for Timo Erkinjuntti and colleagues' study (April 13, p 1283)<sup>1</sup> of galantamine in dementia.

In obtaining consent for randomisation, patients and caregivers are informed of potential adverse effects of the drug under study. As with all cholinesterase inhibitors, galantamine has notable cholinomimetic side-effects. The frequency of nausea (24%) and vomiting (13%) reported in the galantamine group was substantially higher than that in the placebo group (7% and 6%, respectively). Given the high frequency of gastrointestinal side-effects and the knowledge of its hidden meaning in physicians, patients, and caregivers, it is highly unlikely that the masking of treatment was maintained throughout the entire study period for all patients.

Erkinjuntti and colleagues do not address the issue of unintentional loss of blinding similar to other studies on cholinesterase inhibitors, blinding at the time of randomisation is simply stated as a matter of fact, but data are lacking that support its success rate and preservation throughout the study. The burden of proof for effective blinding, however, rests on the investigators. At the last visit, patients, caregivers, and physicians should be asked to guess what treatment was provided. If the number of correct responses does not exceed the level of chance, it is reasonable to assume that blinding was successfully maintained. If such hindsight on blinding is not provided, however, there is room to speculate that small effect sizes, such as noted by Erkinjuntti and colleagues, may be due to bias that is based on knowledge of treatment assignment in patients, caregivers, or physicians.

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1 Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002; **359**: 1283–90.

Sir—Timo Erkinjuntti and colleagues' report on galantamine<sup>1</sup> will fuel the debate over whether cholinesterase inhibitors are a rational treatment choice for patients with vascular dementia. Despite evidence from preclinical and postmortem studies that the pathological changes in vascular dementia seem to be associated with cholinergic deficits, some experts remain unconvinced.

Erkinjuntti and colleagues provide convincing evidence that the acetylcholinesterase-selective inhibitor galantamine is effective in patients who have Alzheimer's disease with cerebrovascular disease (mixed dementia). However, galantamine provided no significant benefit over placebo in patients with pure vascular dementia. The researchers suggest that this lack of effect was due to the study not being powered to detect significance in the pure vascular dementia subgroup, and because there was a slow placebo decline.<sup>1</sup> However, the results will inevitably be interpreted by some critics to suggest that the efficacy of galantamine in mixed dementia stemmed only from the drug's effects on the Alzheimer's features of the disorder.

We challenge such interpretations and express our support for the continued study of cholinesterase inhibitors in patients with vascular dementia. Existing data provide evidence that the cholinergic hypothesis is applicable, and that cholinesterase inhibitors may provide benefits in patients who have dementia with a vascular component.

We have published data from a small study in patients with frontosubcortical vascular dementia, showing that 3–6 mg rivastigmine daily—an acetylcholinesterase inhibitor and butyrylcholinesterase—improved executive function and behaviour for 12 months, compared with baseline and a control group receiving cardioaspirin.<sup>2</sup> These are the two domains that characterise frontosubcortical vascular dementia. These benefits were maintained over 22 months of treatment<sup>3</sup> and may reflect the drug's effects on the cholinergic system, and its particular activity in frontal areas of the brain.<sup>4</sup> Furthermore, Kumar and colleagues,<sup>5</sup> in a large randomised study, showed that rivastigmine provided even greater benefits in patients with Alzheimer's disease and vascular disease than in patients with pure Alzheimer's disease. Rivastigmine was well tolerated in both studies.<sup>2,3,5</sup>

We agree with Erkinjuntti and colleagues that there may be a cholinergic deficit in patients with

dementia with a cerebrovascular component in addition to that linked to the Alzheimer's feature in mixed dementia. This hypothesis is supported by data from preclinical and postmortem investigations, and by clinical studies of rivastigmine. Further assessments of cholinesterase inhibitors in patients with vascular dementia might result in an effective and well-tolerated treatment option for a group of patients for whom there is currently no recommended treatment.

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- 1 Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002; **359**: 1283–90.
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#### Author's reply

Sir—W A van Gool raises issues that extend beyond the investigation of acetylcholinesterase inhibitors as a class of drug for the treatment of dementia. Initial proof-of-concept trials are needed to provide support for longer-duration trials. However, ethical concerns about the use of the placebo in proven cases of disease limit the duration of these controlled trials.<sup>1</sup>

The early work from the US Food and Drug Administration in the late 1970s through to its draft guidelines in 1990 used the method of providing evidence for showing efficacy in Alzheimer's disease.<sup>2</sup> The resulting process streamlined the development of clinical investigation with a 6-month, randomised, parallel-group, placebo-controlled trial that uses accepted cognitive, global, and functional measures as primary outcomes. In addition, global ratings provide an index

of clinical importance of change that cannot be obtained from quantitative assessment measures such as mental-status assessments.

Significant clinical benefit has been noted in all outcome measures in previous clinical trials of galantamine in Alzheimer's disease.<sup>3–5</sup> We used the same accepted measures of change in cognition (Alzheimer's disease assessment scale, cognitive subscale [ADAS-cog]), function (disease assessment in dementia scale), behaviour (neuropsychiatric inventory), and overall global change (clinician interview-based impression of change, plus carer interview [CIBIC-plus]). The ADAS-cog, disease assessment in dementia scale, and neuropsychiatric inventory are recorded by supervising site investigator, but the CIBIC-plus must be done by an independent investigator unaware of treatment status.

Comprised of Likert scales, which assess disease severity and change, the CIBIC-plus allows written accounts that summarise semi-structured interviews independently assessing behaviour, cognition, and function. CIBIC-plus investigators were not required to address issues related to the rate of adverse events, nor enquire what the caregiver thought of the patient's progress. In studies with galantamine, the caregiver role in the CIBIC-plus enables investigators to validate answers provided by patients for which the investigator has no knowledge—eg, “I visited my daughter yesterday”. The CIBIC-plus ensures that treatment effect is independently rated and not subject to bias from patients, caregivers, or investigators.

In addition, in a post-hoc analysis of adverse events in the trial of galantamine in dementia with cerebrovascular disease, the rate of nausea and vomiting increased in both treatment groups at each visit. Furthermore, the rates and reasons for drop out were similar in the two treatment groups for the duration of the trial.

Even if, as van Gool suggests, investigators were to question the patients and caregivers at the end of the trial about guessing treatment assignments, they would have to assume that the guesses were right and related to the efficacy and safety profiles. Furthermore, a drug that has a significant treatment effect over baseline and placebo would be unfairly penalised in this measurement of bias.

We acknowledge van Gool's concern about bias in clinical trials of acetylcholinesterase inhibitors in dementia, we think that the use of a global scale, such as the CIBIC-plus, galantamine in dementia with

cerebrovascular disease ensures that masking of assignment is maintained.

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#### Citation of group-authored papers

Sir—We would like to draw attention to problems relating to the indexing and citation of group-authored papers. On July 10, 2002, we did several general searches of the Science Citation Index (SCI) to find all seven journal articles published in the name of the Early Breast Cancer Trialists' Collaborative Group. Each search consisted of the journal title (or truncated versions) and an entry in either the author field or the topic field (where the user can enter terms from the article title, keywords, or abstract).

Once all the records were found, we did additional cited reference searches to try to supplement the number of citations which SCI had attributed to each record. Each search included the year of publication in the cited year field, the journal title (or truncated versions) in the cited work field, and various different truncated names—including members of the writing committee or the first listed member of the collaborative group, from the acknowledgments at the end of the article—in the cited author field (eg, EAR\* OR EBC\* OR CLARK\* OR ABE\*).

We could not find any of the articles by entering Early Breast Cancer Trialists' Collaborative Group (or truncated versions of this name) in the author field of the general search

	Designated author in SCI record	Number of citations linked to SCI record	Additional number found by cited reference searches	Total number of citations found
<i>N Engl J Med</i> 1988; <b>319</b> : 1681–92	[Anon]	0	164	164
<i>Lancet</i> 1992; <b>339</b> : 1–15 (1st part)	[Anon]	0	799	799
<i>Lancet</i> 1992; <b>339</b> : 71–85 (2nd part)	Abe O...	0	656	656
<i>N Engl J Med</i> 1995; <b>333</b> : 1444–55	Abe O...	0	306	306
<i>Lancet</i> 1996; <b>348</b> : 1189–96	Clarke M...	1	114	115
<i>Lancet</i> 1998; <b>351</b> : 1451–67	Clarke M...	25	661	686
<i>Lancet</i> 1998; <b>352</b> : 930–42	Abe O...	3	314	317
<i>Lancet</i> 2000; <b>355</b> : 1757–70	[Anon]	0	74	74

#### Results of SCI searches (ISI Web of Science)

interface. All of the articles could be found by leaving the author field blank and searching for text from the article titles together with the journal title. For some of the articles, the author had been designated “[Anon]”. The others had either the first listed member of the writing committee or the first listed member of the collaborative group, from the acknowledgments, as first author. The maximum number of citations attributed to a single article that could be found in this way was only 25 (table). However, additional cited reference searches found many more citations. For example, the record for the most recent report on tamoxifen<sup>1</sup> had 25 citations directly linked to it, but we found nearly 700 additional citations. In total, we found 29 citations attributed to the seven articles (once we had found the relevant records using the “general” search), but a further 3088 citations when we did additional searches. Even this figure may be an underestimate. Previously, when we were able to search for cited references by cited year and cited work only (leaving the author field blank), we found many more additional citations to two of the articles (eg, in January, 2001, a total of 2784 citations were found for the 1st and 2nd parts of the 1992 publication). It was not possible to retrieve all of these this time, however, due to a change in the way results are displayed by the interface we use.

We would like to add our voice to the call for “indexing services [to] change their practices to include group authors in the author field”.<sup>2</sup> This would be one step along the way to more reliable citation counts. The ISI has recognised the problem,<sup>3</sup> but until their products change, it will remain difficult or impossible to find group-authored papers and anything more than a small proportion of the citations to them.

The authors are both members of the Early Breast Cancer Collaborative Group Secretariat.

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### Medical triage and legal protection in Japan

Sir—In their Letter, Takashi Yokota and colleagues (May 25, p 1949)<sup>1</sup> note that legal protection for people doing triage is an issue in Japan.

They stated that in the Kobe earthquake, limited medical supplies were used inefficiently because of insufficient triage training. They suggest that despite the lessons supposedly learned from this event, triage was poorly again done after the fireworks accident in Akashi. We agree with their opinion. However, we point out that these two tragedies are quite different in scale and the damage done to medical facilities and staff.<sup>2,3</sup>

When the Kobe earthquake hit in 1995, its magnitude was beyond all expectations, and the contingency plans for a large disaster proved to be totally inadequate. It should be remembered that medical staff were also quake victims.<sup>3</sup> Therefore, the issues are not only insufficient triage training but also catastrophic medical events and shortage of supplies.

The growing effect of disasters shows the need to further advance mitigation through well coordinated activities.<sup>4</sup> As Yokota and colleagues state, legal protection of medical triage would be an issue for that process.

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### Periconceptual parental smoking and sex ratio of offspring

Sir—Misao Fukuda and colleagues (April 20, p 1407)<sup>1</sup> provide evidence for an interesting link between periconceptual smoking and a decrease in the male-to-female ratio of offspring. However, their conclusions should be interpreted with caution because of potential confounders.

Alcohol, increased maternal age, presence of lupus antibodies, and high caffeine intake all increase the rate of miscarriage and are, therefore, confounders to the findings. The mechanism that decided sex ratio in the studied population could be early miscarriage, with a selective disadvantage for male fetuses. This risk could be subclinical in women who did not realise they were pregnant, or clinical since no data on miscarriages are shown. In addition, caffeine raises the risk of first-trimester miscarriage in non-smoking but not in smoking women.<sup>2</sup> Caffeine-induced clinical or subclinical miscarriages might primarily affect male fetuses. Therefore, even if caffeine intake was similar in smoking and non-smoking mothers it could still explain the lower male-to-female ratio.

Moreover, Fukuda and colleagues cite the National Birthday Trust British Perinatal Mortality Survey from 1958<sup>3</sup> to justify their conclusion that smoking reduces the sex ratio around the time of conception rather than imposing a selective disadvantage on male fetuses. I would not feel that this study is appropriate since smoking habits in the UK were very different at that time than at present. In 1958, many more men than women smoked and, more importantly, smoking was not restricted in public places. Consequently, even non-smoking women had a high environmental exposure to tobacco that could have masked differences in infant sex ratio between smokers and non-smokers.

Fukuda and colleagues' study supports this theory, since non-smoking mothers whose partners smoked fewer than 19 cigarettes per day (a source of

environmental exposure to tobacco smoke similar to that of non-smoking women in 1958) had a similar offspring male-to-female ratio to smoking mothers who smoked fewer than 19 cigarettes per day and whose partners also smoked fewer than 19 cigarettes per day. Yet when truly non-smoking women are assessed—ie, neither parent smoked and exposure to tobacco smoke was minimal because of restrictions on smoking in public places—the ratio differs.

Smoking may cause a decrease in the male-to-female ratio around the time of conception. However, to conclude this from the present data without control for potential confounders is premature.

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- 1 Fukuda M, Fukuda K, Shimizu T, Andersen CY, Byskov AG. Parental periconceptional smoking and male/female ratio of newborn infants. *Lancet* 2002; **359**: 1407–08.
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Sir—I have a possible explanation for Misao Fukuda and colleagues' findings on parental smoking and the sex ratio of offspring.<sup>1</sup>

Many data have been collected which support the hypothesis that mammalian (including human) parental hormone concentrations around the time of conception partly control the sexes of the resulting offspring. Low concentrations of testosterone and oestrogen are associated with the births of daughters.<sup>2</sup> The antioestrogenic effect of smoking in women is well established.<sup>3</sup> In men, it is suggested that gonadal hormones may act as confounders between some behavioural risk factors, including smoking, and some pathological disorders, including poor sperm quality.<sup>4</sup> Presumably this is the reason for the inconclusive results from cross-sectional studies on the relation between smoking and testosterone concentrations.

Longitudinal studies, however, suggest that smoking directly reduces testosterone concentrations in men.<sup>5</sup> Accordingly, I suggest that the data of Fukuda and colleagues are explained by the suppressive effect of smoking on oestrogen concentrations in women, and on testosterone concentrations in men.

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Sir—I believe Misao Fukuda and colleague's findings<sup>1</sup> are potentially misleading.

First, their sampling method may result in selection bias. They used convenience sampling from their clinics without reference to the population coverage or generalisability of the clinic attendees to the community at large.

Second, stratification of smoke exposure by the number of packs may mask important subtle associations. The researchers essentially separated their sample according to whether participants smoked less than one pack of cigarettes or one pack or more. Whether this was done out of necessity because of the questionnaire's structure or whether it was the result of post hoc collapsing of more detailed exposure variables should be clarified.

Third, no adjustment for potential confounders is apparent in the statistical analysis. Only crude odds ratios from their retrospective cohort were presented, which might have been prone to a wide range of confounding factors.

Our prospective, population-based birth cohort study of Hong Kong Chinese infants born in 47 Maternal and Child Health Centres in April and May of 1997 casts further doubt on their findings.<sup>2</sup> Our study covered 88% of all births in Hong Kong during the recruitment period. We

collected information on parental sociodemographics, smoking exposures in utero and postpartum, and obstetric history. We used logistic regression to assess the sex ratio in children born to fathers who reported smoking one to five, six to 15, and 16 or more cigarettes compared with those who did not smoke. Due to the very low maternal smoking prevalence in Hong Kong (4.6%), we restricted the analysis to 7734 offspring of non-smoking mothers.

The male-to-female sex ratio was higher for infants whose fathers smoked than for those who had non-smoking fathers (table). The sex ratio ranged from 1.161 to 1.278 for the different classifications of paternal smoking compared with 1.069 for non-smokers. The overall sex ratio of our study was 1.113 and is similar to Hong Kong's ratio of 1.088 in 1997.

Thus, we suggest that Fukuda and colleagues' findings may have been an artefact limited by study design. We propose that the potential link between tobacco smoke exposure and sex ratio remains open to further investigation.

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- 1 Fukuda M, Fukuda K, Shimizu T, Andersen CY, Byskov AG. Parental periconceptional smoking and male/female ratio of newborn infants. *Lancet* 2002; **359**: 1407–08.
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Authors' reply

Sir—Vassilios Vassiliou claims that our conclusions should be interpreted with caution because of the potential confounders alcohol consumption, increased maternal age, presence of lupus antibodies, and high caffeine intake. Alcohol consumption does not alter the offspring sex ratio in maternal non-drinkers or in maternal drinkers.<sup>1</sup> The maternal age was similar in the non-smoking mothers and mothers smoking 1–19 cigarettes per day (33.7 vs 33.4) or more than 20 (33.3). Most of our study population was fertile and the presence of lupus antibodies is unlikely to be important. For caffeine

	Male/female ratio (numbers of births)	Adjusted odds ratio*
<b>Paternal smoking (number of cigarettes)</b>		
Non-smoker	1.069 (2679/2506)	1.00
1–5	1.278 (704/551)	1.19 (1.05–1.37)†
6–15	1.161 (367/316)	1.11 (0.93–1.32)
≥16	1.126 (268/238)	1.07 (0.88–1.31)

\*Adjusted for mother's age and education level, maternal exposure to environmental smoke during pregnancy, father's age and education level, parity, and type of housing. †p<0.01.

**Sex ratio of liveborn infants of non-smoking mothers by paternal smoking**

intake, only a few cups of coffee per day are generally consumed in Japan.

These lifestyle confounders should also be assessed in light of a study by Tidswell<sup>2</sup> from 1912, in which the offspring male-to-female sex ratio was higher in non-smokers than that for paternal smokers. These old data correlate well with our present findings and suggest that smoking itself actually may affect the offspring sex ratio. We imagine that habits of alcohol and caffeine intake, and maternal age differ from those of 1912 and may provide information on confounders of potential importance for the offspring sex ratio.

William James suggests suppressive effects of smoking on concentrations of oestrogen in women and of testosterone in men. We have previously reported a trend towards more boys resulting from oocytes originating in the right ovary compared with oocytes from the left ovary in an infertile population.<sup>3</sup> Midluteal serum oestradiol was higher in right-sided ovulation than left-sided.<sup>4</sup> These observations may support the assumption of low oestrogen concentrations being associated with the births of daughters.

Gabriel Leung and colleagues query whether the sampling in our study is representative of the general Japanese population and that our suggestion of a link between parental periconceptional smoking and offspring sex ratio is potentially misleading. We cannot exclude a possible bias in the sampling method, but find it unlikely, since the number of participants is quite large. We asked each woman how many cigarettes she and her husband smoked per day. Initially, we analysed data according to the following groups: non-smokers, one to nine, 10–19, 20–39, and more than 40 cigarettes per day. The result of this analysis did not differ from the stratification used in the published data. We have adjusted for possible confounding by the other parent's smoking, which differed little from unadjusted ratios ( $p=0.96$ ) and suggests little confounding.

The complete lack of interaction between the smoking status of mothers and fathers can be interpreted literally, suggesting independent effects of maternal and paternal smoking. Leung and colleagues report no effect of paternal smoking on the offspring sex ratio. They show that smoking habits were monitored some time after pregnancy was achieved,<sup>5</sup> thereby resembling the 1958 National Birthday Trust British Perinatal Mortality Survey, in which there was no effect of maternal smoking during pregnancy.

Our data suggest a specific effect of smoking on the offspring sex ratio just around the time of conception.

We thank Don Emerson for sending the book by Tidswell.

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## Acarbose for type 2 diabetes prevention

Sir—Jean-Louis Chiasson and colleagues (June 15, p 2072)<sup>1</sup> report that after a mean follow-up of 3.3 years, patients with impaired glucose tolerance (IGT) receiving acarbose, an  $\alpha$ -glucosidase inhibitor, less frequently developed diabetes and more frequently showed a reversion to normal glucose tolerance than did patients assigned placebo. These conclusions could be used to delay development of type 2 diabetes in patients with IGT. One key question is, however, whether these positive results could be interpreted as a real prevention of the disease or only as a delay in its progression or simply a masking effect due to an acute metabolic effect of the drug.

The curves of the cumulative probability of remaining free of diabetes over time are almost parallel beyond year 1 in the acarbose and placebo groups, which may suggest that acarbose retards rather than really prevents type 2 diabetes. In the Diabetes Prevention Program (DPP),<sup>2</sup> after an average follow-up of 2.8 years, treatment with metformin reduced the rate of diabetes compared with placebo in people with IGT. Thus, the results of both pharmacological interventions were similar, although less impressive than those of lifestyle intervention.

In the DPP, however, the final oral

glucose tolerance test was done while the patients still were taking metformin with no wash-out period. Short-term administration of metformin for only 48 h is sufficient to improve glucose tolerance in patients with IGT;<sup>3</sup> therefore, a treatment effect rather than a true prevention of type 2 diabetes could not be excluded in the DPP.

Acarbose also exerts acute effects on glucose tolerance in people with and without diabetes.<sup>4</sup> However, at the end of Chiasson and colleagues' trial, and by contrast with DPP, all patients were given single-blind placebo for 3 months, after which all outcome measures were repeated. During this period, the rate of diabetes in patients who had not converted before was higher in the group originally assigned acarbose than that first randomised to placebo, so that the final difference in conversion to diabetes was reduced by more than a third compared with that noted under active treatment 3 months before. This observation suggests that a treatment effect of acarbose is present (as most probably is with metformin in the DPP), which could simply mask diabetes and disappear as soon as drug administration is stopped.

By contrast, preservation of B-cell function and protection from type 2 diabetes persisted 8 months after interruption of troglitazone in the recent TRIPOD trial,<sup>5</sup> a finding that suggests a long-lasting protection effect with thiazolidinediones. The question remains open whether the results of the STOP-NIDDM trial with acarbose, as for those of the DPP with metformin, correspond to preventing, delaying, or partly masking effects of type 2 diabetes.

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- 1 Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359**: 2072–77.
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	Intervention			
	Acarbose <sup>1</sup>	Lifestyle <sup>2</sup>	Lifestyle <sup>3</sup>	Metformin <sup>3</sup>
<b>Follow-up (years)</b>	3·3	2·0	3·0	3·0
<b>Risk of diabetes</b>				
Intervention group	32%	6%	14%	22%
Controls	42%	14%	29%	29%
<b>Relative risk reduction</b>	24%	57%	52%	31%
<b>Absolute risk reduction</b>	10%	8%	15%	7%
<b>Difference in change in blood glucose control</b>				
Fasting (mmol/L)	NR	0·3	0·3	0·3
2 h after glucose load (mmol/L)	NR	0·8	NR	NR
Glycosylated haemoglobin (%)	NR	NR	0·15	0·09

NR=not reported.

#### Mean relative and absolute risk reductions of diabetes and glucose control

Sir—To be able to interpret the possible clinical relevance of Jean-Louis Chiasson and colleagues' data,<sup>1</sup> changes in blood glucose and glycosylated haemoglobin values need to be reported. The impressive values for absolute and relative risk reductions might relate to only minimum and clinically unimportant changes in glycaemia.

This assumption is supported by two previous diabetes prevention studies in which data on blood glucose control are reported.<sup>2,3</sup> In one study, lifestyle changes reduced the risk of diabetes by 58% after 4 years.<sup>2</sup> After 2 years, 6% of the intervention group compared with 14% of the control group had developed diabetes. The mean changes of fasting glycaemia were  $-0.1$  mmol/L in the intervention group and  $0.2$  mmol/L in the control group; the changes of plasma glucose concentrations 2 h after an oral glucose challenge were  $-0.8$  mmol/L and  $0$  mmol/L.

In the second study, the 3-year rate of diabetes was reduced by 52% by lifestyle changes, and by 31% by metformin compared with placebo.<sup>3</sup> I have estimated the corresponding changes in glycaemia from figure 3 of that study (table). After 3 years, the mean fasting plasma glucose was about  $5.9$  mmol/L in the two intervention groups compared with  $6.2$  mmol/L in the placebo group, and glycosylated haemoglobin values were about 6.0% and 6.1%, respectively. Available evidence does not support any clinical relevance for these changes in blood glucose control.

In those two studies and that by Chiasson and colleagues, the primary endpoint was manifestation of diabetes. High-risk patients with impaired glucose tolerance already at the brink of diabetes manifestation were studied. In such patients minimum changes in blood glucose control of as little as  $0.3$  mmol/L might relate to impressive reductions in the primary endpoint.

Thus, I suggest that all diabetes prevention studies should also report blood glucose and glycosylated haemoglobin values, and investigators should comment on the difference between the potential relevance of a diagnosis of diabetes and the degree of blood glucose control.

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- 1 Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359**: 2072–77.
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#### Authors' reply

Sir—André Scheen's question is a valid one. In fact, the same question he raises for acarbose and metformin holds for lifestyle modification. All these interventions have one thing in common—they decrease insulin resistance.<sup>1–3</sup> If insulin resistance is a major player in the development of type 2 diabetes, any intervention that can improve insulin sensitivity would prevent or delay the early onset of the disease.

We do object, however, to the term masking, meaning to cover or conceal, which suggests that nothing changed underneath the mask. Acarbose does decrease insulin resistance in people with IGT.<sup>1</sup> This effect is obviously an indirect effect through competitive inhibition of  $\alpha$ -glucosidases, thus slowing carbohydrate absorption and

decreasing postprandial hyperglycaemia. As such, it can have no direct effect on the absorption of the monosaccharide glucose during the oral glucose tolerance test.<sup>4</sup>

We saw a decrease in the rate of diabetes and in the reversion to normal glucose tolerance. Those are strong endpoints that are truly occurring under the mask that Scheen proposes. As for metformin and lifestyle modification, it is also not unexpected that, if acarbose is discontinued, the beneficial protective effect of the intervention wears off with time. We believe that it is reasonable to say that, in general, all prevention studies, particularly for cardiovascular disease, are only delaying the outcome. Death is inescapable, but if we can delay it, we will settle for that.

We have much difficulty following the reasoning proposed by Ingrid Mühlhauser. We totally disagree that the objective of diabetes prevention study should be to decrease fasting plasma glucose or glycated haemoglobin, or even the 2 h plasma glucose after 75 g glucose. The objective is to prevent the progressive increase of fasting plasma glucose and more particularly the 2 h plasma glucose into the range in which diabetes-related complications occur.<sup>5</sup>

That objective was achieved in the Finnish Diabetes Prevention Study and the DPP, as she cites, as well as in the STOP-NIDDM Trial. Even more relevant would be the reduction in risk of cardiovascular events associated with IGT. That, however, remains to be shown.

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## Have we forgotten the victims of the Tiananmen tragedy?

Sir—On the night of June 3–4, 1989, the Chinese army entered the city of Beijing to end a series of student demonstrations. Live ammunition was used against unarmed civilians, and tanks rolled over the bodies of the victims, causing hundreds of deaths and thousands of injuries.<sup>1</sup> In the aftermath of the massacre, many student leaders and their supporters were arrested, imprisoned, and some subjected to torture. The Tiananmen massacre is an incident of gross human rights violations deliberately committed by a government.

Apart from physical injuries, media reports indicated that many survivors of the tragedy, family members of the dead, and participants of the demonstrations also suffered from symptoms of post-traumatic stress disorder, depression, and anxiety. The Chinese government has thus far denied all requests for a fair investigation of the tragedy and for compensation to the families. Survivors and families continue to live in injustice and this situation is likely to affect their health. In the 13 years since the atrocity, there have been barely any apparent efforts to assess the health consequences of the Tiananmen tragedy and to provide treatment and care for the victims. A preliminary search of Medline resulted in no entry that deals with this topic. The only exception to our knowledge is a report by David J Lam in 1990, which stated that the Hong Kong Psychological Society had offered a telephone counselling service to Hong Kong residents after the Tiananmen tragedy.<sup>2</sup>

The Chinese authorities ought to provide medical services for those who suffered from the Tiananmen tragedy, either physically or mentally, to grant permission, and offer assistance so that investigations into the health effects of the incident may take place. Such measures would be a step towards keeping Beijing's promise to improve human rights.

Beijing's current position on the tragedy makes it impossible for researchers in China to study this topic. Health-care professionals who reside outside China therefore have a special responsibility to become engaged. Such studies will not only benefit medical science, but also help alleviate the sufferings of the victims and promote human rights in China.

Despite the difficulties, certain types of research should be feasible. For

example, many participants of the 1989 demonstrations now live in the West and could be recruited for clinical assessment and treatment.

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- 1 Human Rights In China. [http://iso.hrichina.org:8151/iso/article\\_listing\\_s3.adp?category\\_id=30&subcategory\\_id=138](http://iso.hrichina.org:8151/iso/article_listing_s3.adp?category_id=30&subcategory_id=138) (accessed Oct 21, 2002).
- 2 Wu K. Posttraumatic stress disorder. Hong Kong: Mingpao Press, 2002: 16 (in Chinese).

## Screening for factor V Leiden mutation in pregnant women

Sir—In their analysis, Peter Clark and colleagues (June 1, p 1919)<sup>1</sup> report that universal screening for factor V Leiden in 967 pregnant women would have averted 2.5 maternal complications and 0.5 neonatal deaths had prophylaxis reduced complication rates by 50%. After assessment of the real cost of screening, they conclude that it had no potential cost-effectiveness. Nevertheless, neonatal death could be seen not merely as a pregnancy complication, but as a full life, with the potential to last for about 77 years.<sup>2</sup>

Provided that future life of neonates contributes to overall effectiveness of the screening and that heparin prophylaxis has a potential efficacy of 50%, only 25 women would need to be screened to save 1 year of life, which is a good yield for such an intervention.<sup>3</sup> Moreover, screening would cost around UK£1000 per year of life saved, which is a very attractive cost-effective ratio. Despite infertile couples being willing to pay several thousands of pounds for a take-home baby,<sup>4</sup> we still do not know how much society and the public health-care system are willing to pay for a new healthy life. However, clear-cut statements, such as that reported by Clark and colleagues, risk being embraced as recommendations against prenatal care and replacing regulatory guidelines.

Furthermore, Clark and colleagues analysed a scenario in which only women with a personal or family history of venous thromboembolism were screened. This screening strategy might have been anticipated to have a low yield, since family history of thromboembolism has a very low positive predictive value for the presence of factor V Leiden mutation.<sup>5</sup> By contrast, selective screening targeting women with a personal history of severe pregnancy

complications or pregnancy-related venous thromboembolism seems more attractive, since the expected value of perfect information on the factor V gene increases as prevalence reaches 20–40%. Consequently, the cost of selective screening would have fallen by roughly a quarter to a half, dependent on the specific history, thus being much more cost effective and less financially demanding than universal screening.

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- 1 Clark P, Twaddle S, Walker ID, Scott L, Greer I. Cost-effectiveness of screening for the factor V Leiden mutation in pregnant women. *Lancet* 2002; **359**: 1919–20.
- 2 Aedes AE, Sculpher MJ, Gibb DM, Gupta R, Ratcliffe J. Cost effectiveness analysis of antenatal HIV screening in United Kingdom. *BMJ* 1999; **319**: 1230–34.
- 3 Wright JC, Weinstein MC. Gains in life expectancy from medical interventions: standardizing data on outcomes. *N Engl J Med* 1998; **339**: 380–86.
- 4 Neumann PJ, Johannesson M. The willingness to pay for in vitro fertilization: a pilot study using contingent valuation. *Med Care* 1994; **32**: 686–99.
- 5 Schramm W, Heinemann LA, Spannagl M, Dick A, Assmann A. The Bavarian Thromboembolic Risk Cohort Study (BATER): study protocol, state of the investigation and first results. *Dtsch Med Wochenschr* 2000; **125**: 2–6.

## Alternatives to nucleic acid testing in the blood transfusion service

Sir—Peter Simmonds and colleagues, in their May 18 Commentary,<sup>1</sup> advance sound arguments for the need of a more rational discussion on the appropriateness of nucleic-acid testing (NAT) for hepatitis C virus (HCV) in the UK blood transfusion service. Concern has also been raised in other countries, such as France<sup>2</sup> and the USA,<sup>3</sup> about the cost-effectiveness and the low rate of NAT-only positive results. Unless a rational discussion occurs, the blood transfusion service could find itself imposed with the high costs of single-unit NAT testing, as well as viral inactivation when these procedures are licensed.

An alternative technology is available. The hepatitis C core antigen (murine monoclonal) ELISA screening test (Ortho-Clinical Diagnostics, Inc, Amersham, UK) is nearly as effective as NAT and detects the HCV antigen viral marker within only 2–3 days after NAT in individuals undergoing seroconversion. Around 90% of early-

phase samples that were NAT positive were also HCV Ag positive.<sup>4</sup> In practice, the degree of NAT sensitivity may be shorter or longer, dependent on the level of viraemia and the number of samples pooled for NAT screening. The HCV antigen test on individual donor samples is already used in several European countries, such as Spain, Italy, and Poland, and has been put forward by other authorities as possibly being a more appropriate alternative based on cost-effectiveness.

Since the HCV antigen screening test costs less than half that of NAT, uses no special technology, can be automated, avoids any pooling, and requires no special laboratory to reduce contamination, the HCV core antigen test should be included in the open discussion suggested by Simmonds and colleagues. Although this antigen-based approach may still not come into the cost-effective range for medical interventions cited by them, Franklin<sup>5</sup> has pointed out that governments adopt a different measure of the cost-effectiveness for blood screening than is used for other medical interventions. However, the use of a more cost-effective HCV antigen screening test that is 90% as effective as NAT, together with a sensitive HCV antibody test, seems a much more rational approach to blood screening.

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- 1 Simmonds P, Kurtz J, Tedder RS. The UK blood transfusion service: over a (patent) barrel? *Lancet* 2002; **359**: 1713–14.
- 2 Loubiers S, Rotily M, Durand-Zaleski M, Costagliola D. Including polymerase chain reaction in screening for hepatitis C virus RNA in blood donations is not cost-effective. *Vox Sang* 2001; **80**: 1999.
- 3 Busch MP, Dodd RY. NAT and blood safety: what is the paradigm? *Transfusion* 2000; **40**: 1157.
- 4 Couroucé AM, Le Marrec N, Bouchardeau F, et al. Efficiency of hepatitis C virus core antigen detection during the pre-seroconversion window. *Transfusion* 2000; **40**: 1198.
- 5 Franklin IM. Regarding including polymerase chain reactions in screening for hepatitis C. *Vox Sang* 2002; **82**: 50–51.

Sir—Peter Simmonds and colleagues<sup>1</sup> open a discussion on the legitimacy of the implementation of NAT of blood donations for HCV to improve the safety of blood and blood products.

In France, the risk, assessed just before the implementation of NAT, is estimated as one per 870 000 donations—ie, less than three (95% CI 1–8) potentially infected blood units

per year.<sup>2</sup> This estimate is supported since only one donor in the past 10 months (July, 2001, to May, 2002) has been positive on HCV NAT and negative for HCV antibody, identified from more than 2 million donations. Thus, as in the UK, the effect of NAT in terms of public health is not clear for HCV infection.

Simmonds and colleagues estimate that 25% of HCV-infected recipients could develop a clinical HCV infection over time. With the same calculation, we estimate that 4 years of NAT screening would prevent only one post-transfusion chronic hepatitis case in France. They suggest use of a less-expensive measure, such as HCV core antigen ELISA, the sensitivity of which is similar to that of NAT for detection of HCV infection,<sup>3,4</sup> as an alternative to NAT. However, NAT can be applied to more than one virus by multiplexed techniques. In France, health authorities implemented NAT for HCV and HIV in 2001, and the introduction of NAT for hepatitis B virus will probably be discussed soon.

Another argument by Simmonds for discarding HCV NAT testing is that treatment should be started early in blood recipients who become infected through a window donation. Indeed, a significant virus elimination rate is obtained if antiviral therapy is started within 100 days of HCV exposure. However, for transfusion-linked contaminations, previous recipients of blood components from newly diagnosed donors are recalled and tested for possible HCV transmission. In France, only about 50% of donors redonate within 6 months. Thus, early diagnosis may be compromised in 50% of cases. NAT screening in a transfusion laboratory makes feasible immediately large-scale blood screening for any hypothetical blood-borne emergent agent, especially if diagnosis of this agent is based only on molecular biology.

In France, NAT in transfusion seems an irreversible strategy because the French health authorities recommend adopting all reasonable measures increasing the safety of blood. Initially, NAT implementation permits reconsideration of the usefulness of markers implemented several years ago to reduce the residual risk of HCV infection such as alanine aminotransferase or antibody to HBc. Secondly, the impact of major serological markers (antibody to HCV and HIV, and HBsAg) will be compared with that of NAT in terms of diagnostic efficacy. Despite NAT's high sensitivity, serological markers could remain indispensable.

A third debate, in the future, will be the interest of NAT itself (and of any screening of infectious agents) if a procedure of inactivation of pathogens in blood components is implemented.

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- 1 Simmonds P, Kurtz J, Tedder RS. The UK blood transfusion service: over a (patent) barrel? *Lancet* 2002; **359**: 1713–14.
- 2 Pillonel J, Laperche S, Saura C, Desenclos J, Couroucé C. Trends in risk of transfusion-transmitted viral infections in France, 1992 to 2000. *Transfusion* (in press).
- 3 Widell A, Molnégren V, Piekma F, Calmann M, Peterson J, Lee SR. Detection of hepatitis C core antigen in serum or plasma as a marker of hepatitis C viraemia in the serological window-phase. *Transfus Med* 2002; **12**: 107–13.
- 4 Muerhoff AS, Jiang L, Shah DO, et al. Detection of HCV core antigen in human serum and plasma with an automated chemiluminescent immunoassay. *Transfusion* 2002; **42**: 349–56.

#### Authors' reply

Sir—Fundamentally, we agree that policies for blood-donor screening strategies may not be fully amenable to the cost-effectiveness calculations that are made for the assessment of medical interventions such as surgery or drug treatment. Indeed, we suggested that the perception of blood safety and confidence in blood transfusion by the general public is paramount, and this provides transfusion services with substantial justification for implementing the current range of serology tests, even if they fall outside the National Institute for Clinical Excellence's guidelines for cost-effectiveness. The costs, however, of HCV NAT and anticipated royalty payments are so out of line even with the existing implementation of transfusion safety measures that a broader discussion is warranted.

John Diment and Mark Calmann report that testing for HCV viral antigen by ELISA is an effective alternative screening strategy to HCV NAT, and is in widespread use to detect window donations for HIV-1. We agree that HCV antigen assays would be able to detect the most window donations missed by conventional serology screening. However, whether it would be more cost effective depends on the policy

pursued by Chiron in the exploitation of their HCV patent. If large numbers of transfusion services in Western Europe who use or are about to implement NAT screening switch away from NAT and use antigen screening, there would be a substantial loss of royalty revenue (US\$70–140 million per year will be payable for HCV NAT licences, based on the planned individual testing charges of €5–10 on at least 14 million donations). Chiron might, therefore, simply apply the same licensing fees to antigen ELISAs. The point is that HCV NAT on pooled donations is not intrinsically more expensive than ELISA screening; it is the threatened high royalty payments that distort current plans for implementation.

Syria Laperche and colleagues raise the issue of the acceptability of a policy by which a potentially pathogenic agent may be transfused under the pretext that an effective treatment is available. Although two wrongs do not make a right, transmission of pathogenic viruses is precisely what currently happens by (from many examples) transfusion of cytomegalovirus-positive donations to seronegative recipients, and of cellular components from donors infected with human herpes virus 8. At least for HCV, an effective, curative treatment for people infected by this route is available. As we noted, it is unrealistic to adopt all possible measures to improve the safety of blood, despite the ruling by Justice Burton.<sup>1</sup> Rational choices, including the possible implementation of other, much more cost-effective measures unrelated to virology screening, should be made.

Finally, there is the prospect for the effective inactivation of labile components (red cells and platelets) in addition to plasma-derived products within the next 5–10 years. Given the difficulty of discontinuing obsolete tests once they have been implemented (such as alanine aminotransferase), would it really be wise to encumber transfusion services with additional virology screening assays of minimum effectiveness at the precise moment when they become unnecessary?

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1 A & ORS v National Blood Authority & ORS. *All England Law Reports* 2001; 3: 289.

## Health-care inequalities in the UK

Sir—Richard Horton's comment that little has been done to increase the evidence base on health inequalities (July 20, p 186)<sup>1</sup> is inaccurate. For the past 2 years, the Health Development Agency has been building the evidence base on what works to reduce health inequalities. The systematic drawing together of all the published evidence to inform the commissioning of new research and the development of policy is a key element in the reduction of health inequalities.

To develop the evidence base, the Health Development Agency set up the Public Health Evidence Steering Group. This collaboration is chaired by the Department of Health and comprises leading players in evidence-based public health, including the Cochrane Collaboration and the National Health Service Centre for Reviews and Dissemination.

For some areas, there is a lot of evidence—this is clear from the Health Development Agency's new series of evidence briefings. A briefing on the prevention and reduction of alcohol misuse has already been published.<sup>2</sup> Others, including the prevention of sexually transmitted infections, drug use, and accidental injuries will be produced over the coming months. The amount of evidence available should not be underestimated; there is a wealth of case studies and small-scale evaluations providing information that we can gather, quality-assure, and summarise and this information will be the basis of the second editions of the evidence briefings.

Despite the fact that there is considerable evidence available, there are also gaps, particularly relating to cross-government interventions that might be required to tackle health inequalities effectively. Part of our role is to point out these gaps in the evidence to the research bodies and funders, which we are also doing. New research and projects can help fill the gaps in the existing evidence on what works to reduce health inequalities. The Government has invested in a range of programmes including Sure Start, the National Healthy School Standard, Health Action Zones, and Healthy Living Centres. Assessments from these programmes will provide new high quality evidence.

Building the evidence base for public health will help this area move into the same arena as clinical interventions. Public health faces the "Cochrane challenge"—ie, moving away from the hunch-based approach and creating a

more systematic method of developing future policy and practice. The Health Development Agency is assisting Government and practitioners to meet this challenge.

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- 1 Horton R. What the UK Government is (not) doing about health inequalities. *Lancet* 2002; 360: 186.
- 2 Health Development Agency website. www.hda-online.org.uk (accessed Sept 31, 2002).

## Hyper-hyphenosis?

Sir—Winston Churchill was prompted to reconsider his use of the hyphen when he came across the construction "hotheaded" in Macaulay.<sup>1</sup> Your front-page solecism "Peptic-ulcer disease" (Sept 21)<sup>2</sup> may, for different reasons, have the same effect on *Lancet* readers. Its use here corresponds to none of the six main uses of the hyphen described in *Fowler's Modern English Usage*.<sup>3</sup> I have written before on this subject,<sup>4</sup> and, detecting no change in subeditorial policy, am tempted to turn my attention to the semicolon.

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- 1 Jenkins R. Churchill. London: Macmillan, 2001: 450.
- 2 Chan FKL, Leung WK. Peptic-ulcer disease. *Lancet* 2002; 360: 891–94.
- 3 Burchfield RW, ed. *Fowler's modern English usage*, 3rd edn. Oxford: Clarendon Press, 1996.
- 4 Jones R. Hyphenosis. *Lancet* 1997; 349: 290.

## DEPARTMENT OF ERROR

*Vertical transmission of hepatitis B virus despite maternal lamivudine therapy*—In this Research letter by Syed Kazim and colleagues (April 27, p 1488), the scale on the X-axis of figure 1 should have been "0, 3, 6, 9, 12, 15, 18, . . ."

*Sodium-channel defects in benign familial neonatal-infantile seizures*—In this Research letter by Sarah Heron and colleagues (Sept 14, p 851), the first sentence of the last paragraph on the first page should have read "We identified no mutations in *KCNQ2* and *KCNQ3* in family A by SSCA."

*Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial*—In this Article by the ATAC Trialists' Group (June 22, p 2131), J Fodor's name was missed off the list of Principal and main co-investigators in ATAC trial (p 2138). He should have been cited under Hungary. Also, P Borrego should have read MR Borrego.