CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Transparency at the International Agency for Research on Cancer (IARC)

Sir—Your Jan 18 Editorial[1] repeats allegations directed at the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. These concerns are not supported by the facts.

Despite your assertions, the monographs programme does have effective and transparent means for handling potential conflicts of interest. The names and affiliations of all involved are published in each volume. Since 1998, all participants have been required to declare any conflicts of interest and, since 2001, to complete a detailed WHO declaration of interests form before the meeting. Whether there is a conflict of interest incompatible with participation is then decided. Participants are also required at the start of each meeting to declare openly any potential conflicts of interest; this disclosure can lead to exclusion from voting. Our procedures and standards are subject to regular review and are very similar to those adopted by *The Lancet* and other leading journals.[2,3]

The Editorial states that "expert advisers often have links with industry". In the past 20 meetings, among more than 450 participants, only seven have been employed directly by industry. Such an association is sometimes difficult to avoid, since toxicological studies are now predominantly done in industrial laboratories; nevertheless, to avoid any perception of bias, the programme has ceased to invite industry employees as working group participants. However, for transparency reasons, we do allow observers from industry, usually one to three among 20 to 25 invitees (a total of 23 in 20 meetings). Observers never chair the meetings or subgroups, and do not vote in the evaluations. The claim that a substantial group of independent experts might be unduly influenced by such a small minority is inherently improbable and an insult to the hundreds of bona fide scientists who participate in this important programme.

Re-evaluation of compounds takes place when new epidemiological or mechanistic data become available. Your Editorial reiterates claims that industry influence has led to a general downgrading of carcinogens to a lower risk category. This accusation is not borne out by the facts. Since 1996, more than 60 exposures have been re-evaluated; of these, 21 have been upgraded and 12 downgraded by the respective working groups; the categories of the others remain unchanged. The individuals and groups quoted in your Editorial object to any downgrading in principle; since they lack scientific arguments, they have resorted to unsupported allegations of industry influence.

We are not aware of any comparable evaluation programme which is more transparent. The evaluation method is spelled out clearly at the start of each meeting and printed in the preamble to every monograph volume. The list of all observers and their affiliations is printed in each monograph. You argue that the meetings should admit non-industry third parties. Such observers have attended on several occasions and will continue to do so, provided they have a relevant scientific background. I am also happy to invite you to any meeting of your choice.

The programme is funded by grants from US Government agencies (National Cancer Institute, Environmental Protection Agency, and National Institute of Environmental Health Sciences), the European Commission, and from the IARC budget. It receives no funding from industry. The process is monitored by publicly accountable representatives of these external funding bodies who attend the meetings regularly.

The monographs programme is a rigorous scientific evaluation, but we are fully aware of its unique effect on regulatory and public-health policies worldwide. Ever since its creation in 1972, it has been attacked, mainly by industry, which has occasionally referred to the evaluations as the "kiss of death" for their products. Today, IARC is criticised with equal fervour by consumer protection and environmental activist groups. My colleagues and I remain committed to the highest standards of scientific and ethical conduct and will not permit any special interest group to exert undue influence on the working groups. I have no doubt that my successor will have an equal commitment to the programme.

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1 Editorial. Transparency at IARC. *Lancet* 2003; **361:** 189.
2 James A, Horton R. *The Lancet*'s policy on conflicts of interest. *Lancet* 2003; **361:** 8–9.
3 Drazen JM, Curfman GD. Financial associations of authors. *N Engl J Med* 2002; **346:** 1901–02.

Sir—With respect to your Editorial about transparency at IARC,[1] the issue really is: experts in the the field versus experts outside the field. When experts in the field are chosen, some will come armed with their zealously-promoted and ferociously-defended versions of the "truth", making predictable what they will recommend at the end of the review process. Others come with open minds and a willingness to listen and even modify their views. Furthermore, when there is controversy about the issue being addressed, the working group of experts in the field is likely to be weighted to reflect the distribution of existing opinion. Thus, interpretation of, and support for, evidence might be similarly weighted. To disregard inconvenient evidence and disdain minority views is always tempting. These issues are probably generic to consensus panels.

Unfortunately, experts outside the field will be unfamiliar with the relevant "literature". However, agencies assembling expert panels might find it useful to consider experts outside the field to chair working groups and to specify the selection criteria applied for all participants.

The IARC procedure requiring invited experts to declare conflicts of interest at the beginning of meetings does not reassure. To believe that this procedural minuet will necessarily be followed by the exercise of even-handedness is naive.

Finally, all participants in an IARC working group should ideally be given the opportunity to review the editing that occurs in the interval between group adjournment and publication,

especially participants who contribute draft chapters.

The truth might be that we dream an impossible dream when we strive for objectivity—but IARC should keep trying, and transparency will always help.

I am co-principal investigator on the Canadian National Breast Screening Study; an invited participant on the 2002 IARC Working Group on Breast Screening, the 2002 Milan Global Summit on Mammography, and the 1997 US NIH Consensus Conference on Breast Cancer Screening; and an author on the 2002 Physical Examination Work Group on American Cancer Society Guidelines for Breast Cancer Screening.

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1 Editorial. Transparency at IARC. *Lancet* 2003; **361:** 189.

Comments on the common cold

Sir—Terho Heikkinen and Asko Järvinen's Seminar (Jan 4, p 51)[1] on the common cold seems to disregard natural, unpatentable remedies and favour prescription medications. Furthermore, Heikkinen seems to have financial conflicts of interest relating to support from the pharmaceutical industry.

Citing two Cochrane reviews,[2,3] Heikkinen and Järvinen correctly point out that vitamin C and extracts of the plant *Echinacea* are probably ineffective for the prevention of colds. However, these substances are used primarily to treat colds, not to prevent them. Heikkinen and Järvinen make no mention of vitamin C and *Echinacea* as potential treatments, even though R Douglas and colleagues[2] report that vitamin C seems to provide "modest benefit in reducing duration of cold symptoms", while "the majority of the available studies [of *Echinacea*] report positive results".

Heikkinen and Järvinen discuss influenza-specific antiviral drugs in some detail. The relevance of that discussion to the treatment of the common cold is not clear. Heikkinen has received financial support from the company that sells one of these antiviral drugs and has also been paid by various pharmaceutical companies for giving lectures on respiratory infections.

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1 Heikkinen T, Järvinen A. The common cold. *Lancet* 2003; **361:** 51–59.
2 Douglas RM, Chalker EB, Treacy B. Vitamin C for preventing and treating the common cold (Cochrane Review). *The Cochrane Library*, Issue 4. Oxford: Update Software, 2002.
3 Melchart D, Linde K, Fischer P, Kaesmayr J. Echinacea for preventing and treating the common cold (Cochrane Review). *The Cochrane Library*, Issue 4. Oxford: Update Software, 2002.

Authors' reply

Sir—Contrary to Alan Gaby's assertions, we are not opposed to any remedies for the common cold, whether made by nature or synthesised in high-technology facilities. What we are opposed to, however, is making favourable statements about treatments that have not been shown to be effective. In our Seminar, this principle also applies to medicines manufactured by pharmaceutical companies.

Anyone who reads the Cochrane reviews[1,2] with an open mind will notice that Gaby has selected quotations out of context. D Melchart and co-workers[1] concluded that there is not enough evidence to recommend *Echinacea* preparations for the treatment or prevention of common colds, because of methodological shortcomings in design, conduct, and reporting of the trials. In a high-quality study, B Barrett and colleagues[3] found that *Echinacea* had no effect on the duration or severity of colds. R Douglas and colleagues[2] called for further research on the role of vitamin C. The available evidence suggests that high doses of vitamin C may reduce the duration of a cold by less than 0·5 days. For comparison, many people believe that the reduction by 1–2 days in duration of influenza afforded by anti-influenza drugs is too small to be deemed clinically significant.

Since respiratory infections caused by influenza viruses are often indistinguishable from infections caused by other viruses, we chose not to disregard influenza in our Seminar. Influenza is the only respiratory infection against which specific antiviral treatments are available, so not mentioning these treatments would have been strange.

Does Gaby really think that speakers who give lectures at scientific meetings supported by pharmaceutical companies and who receive honoraria for their work will automatically turn into uncritical advocates of the products that the companies are trying to sell? Gaby's way of thinking undervalues not only the scientific integrity of such speakers and authors, but also the intellectual capacity of their audiences and readers. The current requirement by many medical journals for authors to disclose all potential conflicts of interest is to be welcomed. Full disclosure allows the reader to judge whether the authors' conclusions are biased or not. Such transparency has also made authors more circumspect about what they say, because any unwarranted statements could be used against them.

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1 Melchart D, Linde K, Fischer P, Kaesmayr J. Echinacea for preventing and treating the common cold (Cochrane Review). *The Cochrane Library*, Issue 1. Oxford: Update Software, 2003.
2 Douglas RM, Chalker EB, Treacy B. Vitamin C for preventing and treating the common cold (Cochrane Review). *The Cochrane Library*, Issue 1. Oxford: Update Software, 2003.
3 Barrett BP, Brown RL, Locken K, Maberry R, Bobula JA, D'Alessio D. Treatment of the common cold with unrefined echinacea: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002; **137:** 939–46.

Sir—We want to add eotaxin, a pivotal C-C chemokine, to Terho Heikkinen and Asko Järvinen's list of inflammatory mediators related to the pathogenesis of the common cold.[1] N Papadopoulos and co-workers[2] found that rhinovirus-infected bronchial epithelial cells could up-regulate mRNA and protein concentrations of eotaxin in vitro. These findings suggest that rhinovirus infection results in local airway inflammation, partly as a result of eosinophil recruitment and activation. H Haeberle and colleagues[3] showed that respiratory syncytial virus infection induces lung eotaxin, as well as other pro-inflammatory chemokines, in vivo.

Since these observations point to an association between viral infections of the common cold and increased local activation of eosinophils, eotaxin should be considered as a possible molecular target in future research into the common cold.

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1 Heikkinen T, Jarvinen A. The common cold. *Lancet* 2003; **361:** 51–59.
2 Papadopoulos NG, Papi A, Meyer J, et al. Rhinovirus infection up-regulates eotaxin and eotaxin-2 expression in bronchial epithelial cells. *Clin Exp Allergy* 2001; **31:** 1060–66.
3 Haeberle HA, Kuziel WA, Dieterich HJ, et al. Inducible expression of inflammatory chemokines in respiratory syncytial virus-infected mice: role of MIP-1 alpha in lung pathology. *J Virol* 2001; **75:** 878–90.

Sir—Terho Heikkinen and Asko Järvinen[1] make no mention of the effect of the common cold on patients receiving general anaesthesia for surgical procedures.

The common cold is a potential cause of morbidity and mortality in these patients, especially in children. Children with upper-respiratory-tract infection who receive a general anaesthetic are at increased risk of bronchospasm, laryngospasm, and hypoxaemia. Increased vagal tone can lead to bradydysrhythmia and asystole. R Fairgrieve and D Robinson[2] found that use of anaesthesia increased the risk of an adverse respiratory event in these patients by 2–7 times, and that this risk increased by 11-fold if the child's trachea was intubated. J Van der Walt[3] reported that the risk of such complications continues for 6 weeks after a viral respiratory tract infection.

Current guidelines in the UK recommend postponing surgery in patients aged younger than 1 year who have wheeze or need intubation. If the child is actively unwell, surgery should be postponed for 2 weeks. There is no need to postpone surgery in patients with only a mild upper-respiratory-tract infection with no asthma who do not need intubation, and who are undergoing a minor surgical procedure.

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1 Heikkinen T, Järvinen A. The common cold. *Lancet* 2003; **361:** 51–59.
2 Fairgrieve R, Robinson DN. Viral respiratory tract infections and anaesthesia in children. *CPD Anaesthesia* 2002; **4:** 12–14.
3 Van der Walt J. Anaesthesia for children with viral respiratory tract infections. *Paediatr Anaesth* 1995; **5:** 257–62.

Basic ideas of medicine

Sir—The apparently low proportion of patients near death who reported serious dignity concerns in the investigation by Harvey Max Chochinov and colleagues (Dec 21/28, p 2026)[1] neither shows whether dignity is or is not, nor whether dignity should or should not be, an important issue in the care of the dying. It rather suggests that Chochinov's patients received good care. As Agrawal and Emanuel point out,[2] the first step for improving end-of-life care is to specify the components of a good death. The second step is to assess these components empirically.

Specification of the components of a good death includes delineation of a notion of dignity, but also an idea of disease. This requirement cannot be done empirically because no basic idea can be defined empirically; it needs philosophical analysis. Even if no dying patient would perceive a loss of her or his dignity, it would still be a basic category in the treatment near death—and not merely there—because it is an integral constituent of the modern notion of a human being. It is, however, interesting to flesh out which experiences patients connect with dignity.[3]

The same holds true for the idea of disease. It is first necessary to delineate a coherent notion of disease[4] and then to empirically explore this idea. Medicine's primary task is to treat the disease of the patient even in the palliative situation.[5] To alleviate dying should be seen as part of proper treatment of the actual disease, not as an extra task. It is important to stress that palliative and terminal care are not distinct from the rest of medicine, but the same principles apply with respect to the basic ethical notions and the idea of disease itself. There is no need to create a special terminal medicine, but there is need to develop a wider and, at the same time, more coherent idea of disease on the basis of bioethical advances, with respect to the image of the patient as a self-determined individual, and on biomedical advances.

It is time to discharge an outdated idea of medicine and disease, which assumes that biology is the basis of proper treatment. A social scientific integrated notion emerges from philosophical analysis and is increasingly supported by empirical evidence. It is built on an understanding of the patient as a self-determined individual, whose life and quality of life are in jeopardy. Medical treatment is to respond to people with dignity, and help them out of and come to terms with disorders directly affecting their life and quality of life. It is increasingly necessary to reconsider the basic ideas of medicine to avoid incoherencies that might—among other errors—give rise to the mistaken impression that medicine is only able to ameliorate quality of life, but not quality of dying.

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1 Chochinov HM, Hack T, Hassard T, Kristjanson LJ, McClement S, Harlos M. Dignity in the terminally ill: a cross-sectional, cohort study. *Lancet* 2002; **360:** 2026–30.
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More on ISAT

Sir—The results of the International Subarachnoid Aneurysm Trial (ISAT; Oct 26, p 1267)[1] show that, for this particular subset of aneurysm patients cared for in these particular centres, those with ruptured aneurysms treated with coiling fared better at 1 year than those treated with clipping. The purpose of this letter is to indicate points that we believe warrant emphasis and clarification.

Most centres were located in Europe (particularly England) and Canada. Only two patients were entered into the study from a single centre in the USA. The results from ISAT might not be applicable to patients in the USA where practice patterns, particularly in reference to the degree of sub-specialisation of neurovascular surgeons in major centres, are different. We believe that a carefully planned and executed randomised trial in the USA would be of value.

We would be interested to know how many practitioners in ISAT did craniotomies for aneurysm clipping and how many did endovascular procedures for aneurysm coiling. The absolute risk reduction for coiling compared with clipping at 1 year of follow-up is only 6·9%. If the number of coiling cases per endovascular practitioner is significantly greater than the number of clipping cases per neurosurgical practitioner, better outcomes in the coiled patients could be completely explained by a difference in practitioner experience and expertise. The number of neurosurgical and endovascular practitioners in the study and the number of procedures each did should be published.

Physicians and surgeons involved in ISAT felt that one form of treatment was preferred in almost 80% of patients for whom records are available. Of 9559 patients with ruptured intracranial aneurysms assessed for eligibility, only 2143 were randomised. In those not randomised, more patients underwent clipping than coiling as treatment for their ruptured aneurysms. In other words, over the course of this trial, neurovascular teams in the

participating centres felt that surgery was the best option for most patients with ruptured aneurysms who were not randomised. Therefore, if an experienced vascular neurosurgeon recommends clipping as the best option for a patient, that patient should continue to be offered surgery as the treatment of choice. The results of ISAT do not apply to such patients, because they were not assessed in the randomised trial.

We await with interest the long-term follow-up data on these patients. It is crucial to determine whether or not coiling will be as effective as clipping in preventing rebleeding over each patient's lifetime. During the relatively short follow-up of the interim report, 2·6% of endovascular patients had a haemorrhage after treatment compared with 0·9% of surgical patients. In addition, 139 patients treated by coiling have required further treatment compared with 31 patients treated by clipping. Although rebleeding rates more than 1 year after treatment have been low in both groups, if a differential rate of rebleeding persists over time, the modest 6·9% absolute risk reduction with coiling at 1 year will disappear. As the authors note, these patients need to be followed up for many years before legitimate conclusions can be drawn about whether coiling or clipping is the safer treatment for patients with ruptured intracranial aneurysms.

The ISAT report is an important step in defining the roles of endovascular and microsurgical treatment of patients with ruptured intracranial aneurysms. However, to extrapolate the early results of this study to all patients with ruptured aneurysms would be a misinterpretation of the ISAT data and a serious disservice to our patients and our profession.

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1 International Subarachnoid Haemorrhage Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002; **360:** 1267–74.

Authors' reply

Sir—The ISAT study inevitably reflects predominantly European practice and patterns of care, and thus has most applicability to a European population. We agree that practice patterns differ between the USA and Europe. The major reason for this difference, we suspect, is that in Europe, more than 90% of patients are treated in regional neuroscience units, with both clipping and coiling available. In the USA, only 25% are managed in such centres.[1] This fact alone has major relevance to any potential US randomised trial of ruptured aneurysm treatment. If such a trial were to be done through only the major centres, the trial would produce results that were not applicable to 75% of the US population unless practice patterns changed substantially in the meantime.

In response to the issues of ascertainment and excluded patients, there were wide variations in the proportion of patients entered between centres (1–40%). As we stated in our earlier letter,[2] some centres that espoused a subspecialty interest in neurovascular surgery joined the trial, but randomised few patients; those surgeons chose not to offer coiling or entry into the trial because presumably they considered that equipoise did not exist for these patients. This exclusion means that their surgical outcomes have not been exposed to the rigorous methods of a randomised controlled trial. However, this was their choice, and is not a flaw in the trial.

Robert Harbaugh and colleagues are therefore correct that, during the period of trial recruitment, a surgeon's recommendation to undergo clipping was entirely reasonable. However, we believe that the deduction from the ascertainment data that, because a vascular neurosurgeon thinks clipping is the best option it should be offered as the primary treatment, is no longer valid. As soon as the unblinded data became available to investigators, and now to patients and the medical community, it clearly becomes applicable to patients with aneurysms similar to those enrolled in the trial—ie, good grade, small, anterior-circulation aneurysms suitable for both treatments.

Once recruitment into the trial had been halted and the investigators had access to these data, to say that this situation still pertains is incorrect. We believe that clinicians caring for patients have a duty to inform patients of the findings of this trial to guide patients or relatives in their decision about treatment. We addressed the issue of relative expertise in our last letter.[2]

We will work hard to provide the additional data that will come over time from the continued follow-up and analysis of the trial data. We emphasise that we have not suggested that the ISAT results be extrapolated to all patients who have had a rupture of an intracranial aneurysm, but we believe that they are applicable to the population within the trial.

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1 McNeil DG Jnr. Fixing aneurysms without surgery. *New York Times* Nov 12, 2002.
2 Molyneux A, Kerr R, on behalf of the ISAT collaborators and writing committee. The ISAT trial. *Lancet* 2003; **361:** 432.

Nestlé in Ethiopia

Sir—Your Jan 4 Commentary[1] concerned Nestlé negotiating for US$6 million compensation for a Nestlé-owned company that had been previously seized by the Ethiopian government and sold to private investors in 1998 for about US$9 million. The case was handled by a small subsidiary of Nestlé Germany in consultation with an outside-retained lawyer in Addis Ababa. Negotiations had been opened in 2001 by the Ethiopian government, which had asked the Multilateral Investment Guarantee Agency (MIGA) of the World Bank to help resolve the issue.

As announced on Dec 23 by Peter Brabeck-Letmathe, Chief Executive Officer of Nestlé SA, the company is not interested in taking money out of a country confronted with famine. Nestlé has therefore informed MIGA that it will accept the offer of US$1·5 million from the Ethiopian government and will immediately upon receipt return the settlement proceeds to efforts aimed at feeding the Ethiopian people.

Nestlé reiterates its commitment to doing the right thing for the people of Ethiopia, both in helping to deal with the famine crisis, and in helping to strengthen the government's reputation with foreign private investors.

Thus, a delegation of Nestlé senior executives was in Addis Ababa a short time ago, settling the issue with the Ethiopian government and discussing with non-governmental organisations how best to channel resources to famine relief.

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1 McNamee D. Nestlé's own goal. *Lancet* 2003; **361:** 12.

Shigella dysenteriae type 1 with reduced susceptibility to fluoroquinolones

Sir—Epidemic dysentery caused by multidrug-resistant *Shigella dysenteriae* type 1 has been a recurrent challenge in many parts of the developing world. This organism caused an extensive epidemic of shigellosis in eastern India in 1984.[1] The strains isolated were resistant to streptomycin, tetracycline, and chloramphenicol; moderately sensitive to ampicillin, kanamycin, neomycin, and co-trimoxazole; and sensitive to nalidixic acid, furazolidone, and gentamicin. During this epidemic, highly encouraging results of treatment with nalidixic acid were reported.[2] However, within a short period, widespread use of this drug resulted in the emergence of nalidixic-acid-resistant *S dysenteriae* type 1 strains.[3]

After a lapse of about 18 years, an outbreak of bacillary dysentery was reported in April, 2002, among the labourers of tea gardens in eastern India. Investigations revealed an overall attack rate of 25·6%, with 16 deaths. Cases started increasing suddenly in affected tea gardens from the first week of April, 2002, and continued until the day of investigation in the second week of May, 2002. Children younger than 5 years were affected most, with an attack rate of 32·5%. The case-fatality ratio due to bacillary dysentery was 0·9%, and the death rate due to shigellosis among those admitted to hospital was 6%. The prominent clinical features of fatal cases were anuria, haematuria, dyspnoea, convulsions, and encephalopathy.

We examined stool specimens, with or without blood or mucus, from 30 patients using standard microbiological techniques.[4] Ten samples yielded an *S dysenteriae* type 1 strain. These ten patients presented clinically with fever, abdominal pain, tenesmus, and vomiting as well as bloody or mucoid stools. None had features of dehydration.

All ten *S dysenteriae* type 1 strains were resistant to ampicillin, co-trimoxazole, nalidixic acid, and norfloxacin, with intermediate susceptibility to ciprofloxacin; all were sensitive to ofloxacin. This finding indicates that indiscriminate use of antimicrobial agents by the local community has probably led to the development of resistance to fluoroquinolone derivatives, which are the only drugs until recently that are effective orally in treating multidrug-resistant *S dysenteriae* type 1. Ofloxacin is relatively expensive, and its use for shigellosis in the affected tea gardens is not common. The rational use of effective drugs in the community requires improvement of logistical support and community compliance to avoid further resistance.

This drug-resistant Shiga bacillus is likely to spread further in the near future, and will pose tremendous challenges among clinicians treating shigellosis. There is an urgent need for alternative drugs to treat drug-resistant shigellosis.

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1 Pal SC. Epidemic bacillary dysentery in West Bengal. *Lancet* 1984; **1:** 1462.
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Need for a true placebo for vaginal microbicide efficacy trials

Sir—Researchers must pay close attention to the selection of comparison groups in vaginal microbicide trials, or the results will be difficult or impossible to interpret. A true placebo product should be clincally indistinguishable from the potential microbicide and should have no effect, positive or negative, on women's susceptibility to infection.

In Lut Van Damme and colleagues, study of the vaginal gel COL-1492 (Sept 28, p 971),[1] the rate of HIV-1 seroconversion was significantly higher among women using COL-1492 than those in the comparison group. Use of COL-1492 probably increased women's susceptibility to infection, as shown by the higher risk of infection among women who used the product more frequently. However, another contributing factor might have been that use of the comparison product, Replens, was protective. There is evidence to support this possibility, which was also noted by the study authors.

Both products contain carbopol and polycarbophil—negatively charged polymers that could have microbicidal properties. According to the manufacturer, "polycarbophil is a weak acid with a high buffering capacity. It maintains the vaginal pH in the physiological range, about 4·5, and thus helps protect against infection".[2] Replens was nearly as effective as COL-1492 in protecting mice from vaginal infection with herpes simplex virus type 2 infection,[3] and in a clinical trial, use of a polycarbophil gel had some activity against bacterial vaginosis[4]—a disorder that probably increases susceptibility to HIV-1 infection.

Each dose of COL-1492 contains 52·5 mg nonoxynol-9; Replens contains none. If that were the only difference between the two products, the trial might have been a fair assessment of nonoxynol-9. However, gram for gram, Replens has more than twice the acid-buffering capacity of COL-1492, and therefore contains substantially more carbopol or polycarbophil (personal communication, Thomas Moench, ReProtect). Negatively charged polymers are also the active ingredient in other potential microbicide products entering advanced clinical trials. The lower infection rate for women using Replens makes these other candidate products also seem more promising.

No established placebo product is known to have zero effect on women's susceptibility to HIV-1 infection. Accordingly, future microbicide efficacy studies will include, in addition to the active treatment group, a group of women who use a comparison gel that researchers hope will not affect susceptibility, and a comparison group who use no vaginal product.[5] All participants will be provided with male condoms. Inclusion of a "no-product" group is, however, not a panacea. That group cannot be made unaware of treatment assignment, and differences in risk behaviour and other biases are likely to be introduced as a result. Ideally, infection rates will be significantly lower in the group using the candidate microbicide than in the group of women using the placebo product and those using no product. If infection rates and risk behaviours are similar in the placebo and no-product groups, investigators might then have also identified a true vaginal placebo product.

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1 Van Damme L, Ramjee G, Alary M, et al, for the COL-1492 Study Group. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360:** 971–77.
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Authors' reply

Sir—We are aware of the possible protective effect of Replens. However, we would like to draw attention to our exploratory analyses which have shown that, with increased use of COL-1492, the incidence of lesions with an epithelial breach increases, as does HIV-1 incidence. Both increases are much more prominent with COL-1492 than with Replens. The increase in lesions with increased nonoxynol-9 use is consistent with previous findings.[1,2] Moreover, our data showed a two-fold increase in the risk of HIV-1 infection in women who had at least one episode of a lesion with a breach compared with women who did not have such an event.

We agree that inclusion of a no-treatment group in future effectiveness trials could be an option, but we should be aware of any possible bias as a consequence of an open-label study; many investigators are concerned that a no-treatment group might have an effect on recruitment. Once enrolled, the women in the no-treatment group might be less motivated to stay in the study or to adhere to the study requirements. This potential source of bias, and those mentioned by Peter Kilmarx and Lynn Paxton, cannot be assessed at the end of the trial. If the loss-to-follow-up differs between the study groups, result interpretation is even more difficult. Additionally, the sample size for such trials will typically be at least 50% larger than a standard two-group, placebo-controlled trial. These difficulties might make this type of study design altogether unfeasible.

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Use of weapons of mass destruction

Sir—*The Lancet* should be applauded for its concern about the people of Iraq should their country be attacked by the USA and the UK (Jan 11, p 95).[1] However, in its anticipation of "a war that may involve weapons of mass destruction on an unprecedented level", it became part of the propaganda machine that is moving the world ever closer to yet another imperialist war.[2] Use of the word "unprecedented" is especially inappropriate. It overlooks the use, by the USA, of nuclear weapons in Hiroshima and Nagasaki, their use of chemical weapons in South Vietnam, and their use of biological weapons in Korea and China. In most imperialist wars, truth is the first casualty. The war in Iraq will be no exception.

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Humanitarian effects of war on Iraq

Sir—The evident anguish of our colleagues at the London School of Hygiene and Tropical Medicine (Jan 25, p 345)[1] at the possibility of thousands of innocent casualties that could result from an attack on Iraq must resonate with the despair of many who similarly see war as an outdated, unacceptable instrument of political influence. What their plea fails to consider, however, is that when national or religious leaders play to a different set of rules—one in which human life is only considered in terms of promoting the political ambition of the leader or the advancement of religious influence—then the moral reasons advanced to accommodate them become meaningless.

Not only is the value of life perceived differently by people such as Saddam Hussein, but the accepted ground rules of social and political engagement also differ fundamentally.[2] Clearly, if the monies from Iraq's enormous natural oil resources had been directed into education, health, industry, and infrastructure development instead of an endless pursuit of futile and wasteful military hardware, she would have been a thriving superpower in the Middle East by now.

Failure to appreciate all this results in the kind of reasoning embodied in the letter, which is based on the assumption that Hussein is himself amenable to argument based on ethical and humanitarian consideration—an assumption that his military record and oppressive regime contradicts. No less important, however, is that in a part of the world where religion and state are inseparable, Hussein's tactics are viewed as an important testing of Western resolve to define the limits of political tolerance. Those who were vocal in their condemnation of Israel for bombing the Iraqi nuclear reactor in 1981[3] were using a similar yardstick to that of the letter's signatories—one that gave no thought as to what the atomic weapons to be produced would have been used for.

Given Hussein's performance since 1981, would the signatories of the letter care to suggest how things would look today if the view of the then critics had prevailed and Hussein been left to develop a nuclear arsenal?

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Preparedness of London hospitals for a chemical weapons attack

Sir—The UK National Audit Office has warned that many National Health Service (NHS) hospitals are ill prepared to cope in the event of a major terrorist attack.[1] The situation is particularly serious in London. Although better prepared than before Sept 11, 2001, the report found that a large-scale incident "would challenge the NHS in London".

Successful hospital treatment of mass casualties resulting from the deliberate release of chemical agents is dependent on several variables, including decontamination procedures, adequate staff training, access to antidotes, and access to intensive-care facilities.[2] We decided to find out whether medical staff knew of their hospital's policy concerning chemical weapon release, and their individual role in that policy.

	Aware of hospital policy	Aware of role in policy	Received training/ practised role	Knowledge of antidote	
				Sarin	Cyanide
Staff members					
Senior onsite AE personnel	4/5	4/5	2/5	3/5	4/5
Senior onsite anaesthetists	0/5	0/5	0/5	1/5	2/5
Senior onsite intensivists	0/5	0/5	0/5	1/5	1/5

AE=accident and emergency.

Staff contacted at five strategic London hospitals, and their responses

Key medical personnel at five hospitals in London were contacted by telephone on Dec 1, 2002. The hospitals were chosen for their strategic proximity in relation to possible terrorist targets in London. Those contacted were asked whether they were aware of the hospital's chemical weapons incident policy, whether they were aware (or had been told) of their role in that policy, whether they had received training (or had practised) their role, and whether they knew the correct antidotes to be given to patients exposed to either nerve agents (eg, sarin) or cyanide.

Every member of staff who was contacted agreed to answer our questions. Some personnel were aware that hospital policies concerning the management of mass casualties after a major chemical agent attack were available, but most were unaware of their individual role, and had received little, if any, training in self-protection or management of patients (table). Additional comments made by the respondents indicated a negatively fatalistic attitude towards such an event. However, it has been suggested that if health-care professionals are made aware of the symptoms, pathophysiology, and treatment of illnesses caused by the most likely chemical agents to be used, the efficacy of the medical response can be improved.[3] Several informative sources are available to hospitals and individual staff members who wish to learn more about the treatment of chemical weapon injuries.[3–5]

The National Audit Office reported that more than 80% of 20 hospitals in London described themselves as "prepared" or "well-prepared" in the event of a chemical incident. However, our audit suggests that this reported preparedness does not equate with actual preparedness. We recommend that hospitals nationwide, particularly those in London, ensure that staff urgently receive training and practice in self-protection measures and patient management principles in the event of a chemical weapons release.

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Pre-Medline evidence of stroke mortality trends

Sir—In their paper (Dec 7, p 1818), Lawlor and colleagues[1] discuss the different trends in mortality by stroke subtypes. They conclude that the closely related trends in cerebral infarct and coronary heart disease suggest a common cause, whereas the different trend of cerebral haemorrhage probably indicates a different cause. This conclusion represents knowledge that has been widely published in pre-Medline literature.

Atherosclerosis is located in the medium-sized and large arteries of the coronary and cerebral vascular system, which accounts for the similar trends in mortality. However, vessel disease leading to cerebral haemorrhage is quite different. It affects the small arteries and arterioles. The main cause of this kind of vascular disease is hypertension, which is only a very weak risk factor for atherosclerosis. This cerebral small-vessel disease can be combined with microaneurysms (Charcot-Bouchard).[2] Affected small vessels can become occluded—leading to lacunar stroke—or to rupture, leading to cerebral haemorrhage. High blood pressure provokes these events; lowering the pressure might prevent them. Differences in vascular pathology of atherosclerosis and hypertension, and differences in their pathogenesis, very simply explain the findings of the authors.

The investigators do not mention the importance of hypertension and its treatment. Up to 1950, there was little or no effective treatment for hypertension (diet, surgery, or emergency treatment). The breakthrough came in the 1950s, when drugs became available, which allowed effective long-term treatment. This development led to a striking change in the prognosis and endpoints of the disease. The malignant phase was reverted, heart failure—being so far the final event in about a third of cases—became rare, cerebral haemorrhages were reduced as was uraemia, and patients survived much longer. Myocardial infarction, however, did not diminish, and due to a reduction in other causes of death, even became more frequent in the pattern of endpoints of the disease.

The "natural history of hypertension" did change into the "history of treated hypertension", which might account for the increase in the ratio of cerebral infarct to cerebral haemorrhage since about 1960 (authors' figure 2), and also for the different trends of mortality from cerebral haemorrhage on the one hand and from cerebral infarct or myocardial infarction on the other.

Much of the evidence for this knowledge is contained in Sir George Pickering's masterpiece *High blood pressure*".[2]

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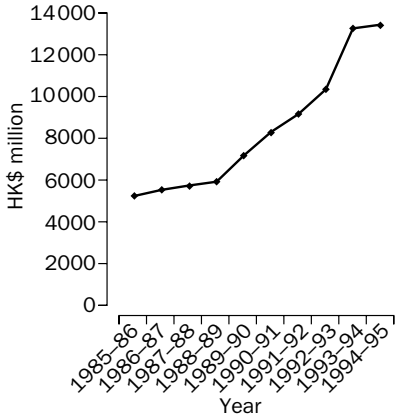
Relation between sulphur dioxide concentration and all-cause mortality

Sir—Anthony Johnson Hedley and colleagues investigated changes in mortality after legislation to reduce sulphur dioxide (SO_2) emissions was introduced in Hong Kong (Nov 23, p 1646).[1] They showed that SO_2 concentrations, but not other pollutants, fell after the intervention, and showed a reduction in mortality for all causes, especially in elderly people and for cardiorespiratory diseases.

Interventions to improve air quality are welcome, but we think that the reduction in seasonal deaths and the annual proportional change in mortality



Public-health expenditure in Hong Kong, 1985–95

might not be attributable to a fall in ambient SO_2 concentrations alone. As the authors noted, the mechanism by which use of low-sulphur fuels would result in immediate benefit is uncertain.

During this period, there was a fundamental restructuring of the health-care system in Hong Kong, with the introduction of the Hospital Authority and a concomitant increase in funding, from an annual budget of HK$3·09 billion in 1985 to $18·06 billion in 1995 (from UK£0·26 billion to £1·5 billion, by an exchange rate of HK$12 to UK£1).[2] The rise in consolidated public-health expenditure, adjusted for inflation (figure), is attributable to a sharp rise in government spending for the two organisations that provide public-health care in Hong Kong—the Department of Health and the Hospital Authority. Locally only a small fraction (10%) of inpatient care is provided by the private sector.[3] This rise in expenditure resulted in construction of new hospitals, purchase of up-to-date equipment, and more hospital beds and staff per capita.

Increased allocation of resources does not automatically translate into better health provision for residents,[4] but it does provide an alternative, scientifically plausible explanation for the fall in mortality in Hong Kong from 1985 to 1995.

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1 Hedley AJ, Wong CM, Thach TQ, Ma S, Lam TH, Anderson HR. Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet* 2002; **360:** 1646–52.

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Use of mobile phones in hospital: time to lift the ban?

Sir—Hospitals in the UK have had a ban on mobile phone (cell phone) use on their premises since the early 1990s. This ban was prompted by a warning issued by the UK Medical Devices Agency highlighting the possible risks of mobile phones inadvertently interfering with medical equipment. However, there are, we believe, at least three good reasons to review the current position.

First, almost 10 years after the ban's introduction, there remains an absence of evidence of any real risk to patients' safety. Although a few studies provide some support for the current policy,[1,2] most investigators have been more sceptical about the actual risk posed. In a 6-month survey of mobile phone interference in a hospital ward, Hietanen and colleagues[3] found no evidence of equipment failures. Irnich and Tobisch[4] tested medical devices used in intensive care units for electromagnetic interference from mobile phones, and concluded that "prohibition of mobile phones in hospitals is based not on real evidence, but on an intellectual and precautionary impression without knowledge of susceptibility of the devices". They further argue that "prohibition of mobile phones in patient wards is not justifiable in terms of patient safety".

Second, mobile phones have evolved greatly since the ban was introduced. Evidence suggests that Digital Global System Mobile (GSM) phones currently in use interfere less with medical devices than did their analogue predecessors.[3] In light of these technological developments, some groups have suggested that mobile phones may be used even in areas with many instruments, such as critical care units, provided that a separation of at least 1 m is maintained from medical devices.[5]

Third, the reality is that mobile phones are used in hospitals by patients, their relatives, and medical staff. At present, even when on hospital premises, many consultants prefer to be contacted by mobile phone. Some hospitals have issued specialist registrars with mobile phones so that they can be contacted directly by general practitioners. Furthermore, in our experience, mobile phones are frequently left on in operating theatres, where much potentially vulnerable equipment is in use.

Although mobile phones have not officially been integrated into hospital life, they have become an essential communication tool for modern society; figures from the UK Office of Telecommunications (Oftel) show that 80% of households own at least one. Thus, any ban is likely to prove difficult to enforce.

The absence of any real evidence of risk to patients' safety, coupled with advances in handheld technology, should cause hospital trusts and their advisory bodies to reappraise the current restriction against mobile phone use in hospitals.

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DEPARTMENT OF ERROR

Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. Lancet *2002;* ***360:*** *835–41*—In table 1 of this Article (Sept 14), the difference (95% CI) should be, "0·7 (–2·2 to 4·2)" for treatment failure and treatment success in all randomised patients; "1·3 (–2·2 to 4·8)" for treatment failure and treatment success in clinical pneumonia after exclusions; and "2·7 (–12·8 to 7·3)" for treatment failure and treatment success for pneumonia diagnosed by radiography.

Imamura H, Takayama T, Sugawara Y, et al. Pringle's manoeuvre in living donors. Lancet *2002;* ***360:*** *2049–50*—In the table of this Research letter (Dec 21/28), the p value for Peak ALT concentrations (IU/L) should be "0·0464".