CORRESPONDENCE

UK Government and WHO

Sir—Your Commentary (Sept 28, p 960),

gave a misleading impression of

UK policy towards the World Health Organization (WHO). This was based

on your misunderstanding of the

purpose of the Institutional Strategy Paper (ISP)1 issued by the Department for International Development (DFID) and the way this fits into broader UK

objectives. We would like the opportunity to present the full picture.

The UK Government is committed to supporting WHO in fulfilling its role and mandate across the full range of its

agreed strategic priorities and functions. These include normative functions, technical and policy support, and the pursuit of proper implementation of standards, and this is fully recognised in the ISP.

The Department of Health takes the overall lead for UK relations with WHO, adopting a joined-up approach across Government, working particularly closely with the Foreign and Commonwealth Office (FCO) and Department for International Development (DFID). The Chief Medical Officer, Sir Liam Donaldson, is currently a member of the WHO Executive Board, and pursues the UK’s objectives in that forum.

WHO, in its role as the world’s leading technical agency on health, has an essential role to play in setting norms and standards at a global level, and helping its member states to tackle the major burdens of disease, whatever their cause, and to strengthen their health capacities and infrastructures. Fighting the cause and spread of disease remains a major challenge, despite some notable successes WHO has had over the years.

As the world’s leading health agency, WHO has a major contribution to make in promoting health development and poverty reduction. It is thus a key agency with which the UK, through DFID, seeks to engage in support of our objectives in this area.

The UK is actively engaged with WHO across a range of issues. We strongly support efforts to produce an effective Framework Convention on Tobacco Control, and will be active in the fifth round of negotiations starting next week. We continue to work with WHO on health systems performance, risk, nutrition, mental health, access to medicines, and many other issues. The UK was a main sponsor of work now initiated to deal with the problem of quality in health systems, in particular interventions to reduce the number of adverse incidents which lead to preventable mortality and morbidity in very many countries round the world. We will continue to promote the effectiveness of WHO in these areas.

We also seek to work in partnership with governments and multilateral institutions that are committed to the Millennium Development Goals (MDGs), which represent a uniquely unifying opportunity to tackle global poverty and inequality. The MDGs have been signed up to by all nations and all UN agencies, including WHO. They include goals to reduce child mortality, improve maternal health and combat HIV/AIDS and other diseases. Progress on health outcomes is essential to achieve all the MDGs.

ISPs are prepared for the main multilateral institutions with which the UK, through DFID, works to pursue its development objectives. These have been clearly set out in two UK White Papers on International Development. The ISPs set out how we aim to contribute to achieving the objectives, in our work in partnership with each of the institutions concerned.

The WHO ISP therefore represents one aspect of the UK Government’s overall engagement with WHO. It focuses on DFID-led work in health and development and sets out how DFID will support the effective operation of WHO on this part of its remit. Consistent with our approach to broader UN reform, it focuses particularly on the responsiveness of WHO to Member States and to the needs of the poorest.

The DFID-WHO partnership objectives set out in the ISP reflect this focus and have been agreed with WHO. At no point does the ISP attack WHO’s mandate. The ISP recognises the WHO corporate strategy—which rightly emphasises a broad approach to health outlined above—as the framework for WHO business.

In discussion with its member states, WHO should continue to set priorities for its programme budget. It cannot do everything. We wholeheartedly agree with Richard Horton2 that WHO’s mission should not be manipulated by governments that exert powerful budgetary control, leading to competition between WHO programmes. With this in mind, the UK Government provides extra-budgetary funds to WHO in a way that will not distort internal priority setting nor undermine the direction, constitution, and management coherence of WHO. This is contrary to the impression given in your article.

The UK Government endorses the approach, as expressed by Horton, to health as complete wellbeing and as a “key to peace and security”. We believe that WHO is well positioned as a global health institution that can make a significant difference to the health and wellbeing of the world’s population, contributing to poverty reduction. Our job, as a major donor nation, is to ensure that WHO continues to fulfil its mandate as effectively and efficiently as possible, in accordance with agreed objectives, and is sensitive to the needs of Members States and their peoples—not least to the 1·2 billion living on less than US$1 per day.

Department for International Development, UK


2 Website of the Department for International Development (DFID), www.dfid.gov.uk.


2 Website of the Department for International Development (DFID), www.dfid.gov.uk.

AIDS in Africa

Sir—The Lancet’s important five-part series on AIDS and the essential role of prevention in sub-Saharan Africa (June 8, p 2011)1 endorses the view that almost all HIV in adults is heterosexually acquired. Since 1982–83, when AIDS cases not associated with male homosexuality or injecting drug use (IDU) were reported from Africa, experts have debated the importance of two HIV transmission channels suspected to differ from those noted in developed countries: heterosexual intercourse and unsterile health care.

We have observed, and taken part in,
this debate for more than 16 years. The extent to which each of these channels explains the HIV epidemic in Africa has yet to be resolved.

After nearly two decades of research, sexual variables only partly explain the high HIV prevalence in Africa. For example, a recent study in four African cities—two with high and two with low HIV prevalence—reported that a high rate of partner change, sex with prostitutes, concurrent sexual partnerships, large age difference between non-spousal partners, bacterial sexually transmitted diseases (STDs), dry sex, and lack of condom use were "NOT more common in the two high HIV prevalence cities". That "Differences in the spread of the epidemic can be accounted for by a complex interplay of sexual behaviour and biological factors ..." is an assumption in dire need of supportive evidence, especially evidence controlling for the confounding effects of parental exposures.

From the beginning, suspected cases of iatrogenic HIV in Africa have been consistently reported. Many studies show appreciable risk in African health-care settings—eg, hundreds of millions of unsafe injections every year, and transfusion of untested blood—and substantial proportions of HIV attributable to health-care exposures.

Ignoring such evidence, Anne Buve and colleagues dismiss iatrogenic transmission in one sentence: "blood transfusion, injections with infected needles, and scarification are thought to represent only a few infections." Interestingly, the only reference cited for that statement observes that "given the large number of injections administered by health-care providers and traditional healers in and out of the health-care setting in Africa, parenteral transmission could be contributing significantly to HIV infection".

From research to date, one cannot confidently ascribe the disturbingly high HIV rates reported among non-IDU and non-homosexual African adults to sexual transmission alone. Hence, one cannot have confidence that interventions proposed by Futures Group International, which address heterosexual transmission risks but ignore unsafe medical procedures, will stop generalised epidemics. Even worse, promotion of significant increases in parenteral exposures—eg, via treatment for STDs, phlebotomy for HIV, and other tests—without parallel initiatives to ensure that health care is safe may well violate the precept to "first do no harm." Our review of the evidence supports a policy of condoms, safer sex, and safe health care. Resources to combat the AIDS epidemic should include support for the health-care delivery system to ensure safe medical practices and clean equipment.

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Author’s reply

Sir—David Gisselquist and colleagues are right in pointing out that prevention of HIV transmission through unsafe injections and unsafe blood transfusions has been neglected in developing countries and I fully agree that more needs to be done to ensure that patients and health-care workers are not exposed to the risk of HIV infection in health care settings.

However, I disagree with Potterat and colleagues when they suggest that one cannot be confident that transmission through sexual intercourse is the main mode of transmission among adults in sub-Saharan Africa. Several studies have provided evidence that—an on a population basis—transmission through sexual intercourse is a more important route of transmission than unsafe injections and blood transfusions.

First, Hoelscher and colleagues estimated that only 0.4% of HIV infections in Mbye region, Tanzania, could be attributed to reuse of needles in public health facilities. In Mwanza region, also in Tanzania, it was estimated that health-care workers who had frequent needle-stick injuries had a yearly risk of HIV infection of 0.23%. Incidence of HIV infection in the general population in the same region was four times higher, at 1·9% over 2 years. Second, if nosocomial transmission were the major mode of HIV transmission in sub-Saharan Africa, one would expect that prevalence of HIV infection in children aged 5–12 years would be close to that in adults, because children of this age are likely to have been infected through vertical transmission but are equally (if not more) exposed to HIV transmission through injections and blood transfusions as adults. In Uganda, HIV prevalence among children aged 5–12 years was 0·4% and among adults 8·2%. Of the ten HIV-infected children identified, six were probably infected through their mother and one through sexual assault.

Lastly, Potterat and colleagues suggest that the findings of the multicentre study on factors determining the differential spread of HIV in four African cities may be confounded by nosocomial transmission of HIV. We do not have data for injections, but there are data for the rates of blood transfusions. For most countries in sub-Saharan Africa, including the four countries in which the study took place, the number of donations per 1000 population was less than five in 1995 and there does not seem to be any correlation between number of donations and prevalence of HIV infection.

In conclusion, there is compelling evidence that sexual transmission causes most HIV infections in adults in sub-Saharan Africa. Although clearly, more needs to be done to prevent the transmission of HIV infection in formal and informal health-care settings, such interventions are unlikely to have a major effect on the course of the HIV epidemics in sub-Saharan Africa.

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Sir—We would like to add a layer of complexity to, and maybe shed some light on, the看不见的infections between AIDs patients and other infectious diseases recently summarized by Corbett and colleagues (June 22, p 2177).1

Immunological results collected over time in the Gulu district of north Uganda, where prevalence of HIV infection ranges between 14% and 25%, show that lymphocytes from African HIV-infected individuals are abnormally activated. Thus, production of interferon γ and interleukin 10 by HIV-antigen-stimulated peripheral blood mononuclear cells of African HIV-infected individuals is higher than in European patients. Immune activation in the African setting is not limited to HIV-infected individuals; production of interferon γ and interleukin 10 is greatly augmented in HIV-uninfected individuals as well. This abnormal activation is associated with environmental conditions, including parasitic infections, poor hygienic conditions, and dietary limitations, since the immune response resembles a Th1-dominant pattern in Africans who move to Western countries.2

Susceptibility to HIV infection is thought to be higher, and disease progression faster, in African individuals than in European individuals. How could the peculiar cytokine profile seen in the African setting affect susceptibility to infection and the rate of progression to AIDS?3

In vitro, interferon γ and interleukin 10 increase expression of chemokine receptor 5 (CCCR5)—one of the main coreceptors for HIV on the surface of immune cells. Data show that CCCR5 is indeed upregulated in vivo in African individuals.4 The potential importance of this observation is underlined by results indicating that HIV infection in Africa is mostly supported by R5 viruses—i.e., the viral strain that uses CCCR5 as its coreceptor.5 Thus, immune activation would provoke upregulation of CCCR5 on target cells, and this would result in an evolutionary pressure on the viral quasispecies, leading to the preferential selection of R5 HIV strains. The net result is prevalence of R5 virus within a biological scenario (upregulation of CCCR5) that facilitates infection of target cells. Because CCCR5-expressing cells are concentrated in the female genital tract,6 and HIV infection in Africa is mainly heterosexually transmitted, the immune scenario detected in Africa could also be at least partly responsible for a facilitated heterosexual transmission of HIV infection.

This hypothesis is strengthened by preliminary data gathered in the Marashtra-mumbai region of India. In fact, despite the observation that R5 viruses are prevalent in this region,7 cells of HIV-infected and HIV-uninfected Marashtra-mumbai individuals mostly express the chemokine receptor CXCRC4 (unpublished data). CXCRC4 upregulation is seen in the presence of an immune profile that overlaps the one seen in African individuals, but that is also distinguished by abnormally increased secretion of interleukin 4, the cytokine that induces CXCRC4. In this scenario, characterized by the discordance between the predominant HIV strain and the prevalent viral coreceptor, progression of HIV infection is slower and similar to the one seen in Western countries.

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Sir—Paul J Weidie and colleagues (June 29, p 2261)1 present a comprehensive review of the advances in HIV treatment and “vaccine development in the developing world”. Missing, however, from the article is any mention of what the local people think. To exclude totally the views of prospective recipients of an HIV vaccine is to guarantee failure of the scheme.

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For personal use. Only reproduce with permission from The Lancet Publishing Group.
Sir—In his Viewpoint (June 6, p 78),¹ Justin O Parkhurst argues that false claims have been made about the magnitude of the drop in HIV prevalence in Uganda, about declines in incidence, and about the role of government in achieving reductions in incidence, levels. We believe that Parkhurst is poorly informed on all of these points.

First, HIV prevalence data for pregnant women show considerable variability across sites within Uganda and over time; however, there is clear evidence for a substantial drop in all sites of the Ugandan surveillance system. From 1993 to 2000, 12 antenatal sites in large and small cities in different geographical regions of Uganda had HIV prevalence data for at least 4 years, and showed varying HIV prevalence levels in 1993. HIV prevalence dropped by 50% or more in five sites, by 40–50% in four sites, and by 24–36% in the remaining three sites.²

Second, countries are advised to use prevalence in younger age-groups as a proxy for incidence, since members of this population begin encountering the risk of HIV infection for the first time as they become sexually active. In Uganda, there is consistent evidence of declines in HIV prevalence for the younger age-groups. For example, prevalence in 15–24-year-olds dropped by more than 60% between 1993 and 2000 at Kampala’s major testing centre.³

HIV prevalence among 15–19-year-old pregnant women attending antenatal clinics in urban and rural areas showed the same trend. In the Gulu district, for example, prevalence dropped from 21.5% in 1993 to 7.1% in 2000.⁴ Because cohort studies that can measure incidence directly are costly and have their own biases, few incidence cohort studies have been done. However, the results of a 10-year community-based cohort study in the Masaka district in Uganda were published recently, and showed a 37% reduction in HIV incidence at the population level between 1990–94 and 1995–99.⁵

An analysis of nationally representative behavioural data from Demographic and Health Surveys showed several beneficial behavioural trends. Between 1989 and 2000, the median age at first sex increased by 1–2 years for girls and 1.7 years for boys. Abstinence among women increased from 8% in 1989 to 13% in 2000. Condom use at last sex with a non-regular partner increased from 20% to 39% for women and from 5% to 25% for men between 1995 and 2000. Although the decline in HIV incidence cannot be exclusively attributed to one or more of these changes in behaviour or to specific interventions, these changes in sexual behaviour no doubt contributed to the decline in rates of HIV infection.

Finally, what does Parkhurst mean by “the decontextualised universal recommendations of international bodies such as UNAIDS or WHO”? UNAIDS has never claimed that “one intervention led to declines in prevalence”. It promotes the notion of a multisectoral response involving action by a broad alliance of all forces in society, fostered by government leadership—an approach that Uganda’s response typifies.

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**Author’s reply**

Sir—Peter Ghys and colleagues argue that there has been a decline in HIV-1 prevalence across all Ugandan surveillance sites. Yet the article they are responding to argued that no other African nation has seen such a decline.⁶ The authors ignore previous work by UNAIDS explaining that declines in HIV-1 prevalence may be exaggerated by surveillance of pregnant women. Younger women are more likely to become pregnant and contract HIV-1 in the early years of the epidemic (leading to a higher than nationally representative peak), but fertility of HIV-positive women declines over time (leading to a lower than representative fall).⁷

Second, they argue that declines in prevalence in younger age-groups act as a proxy for incidence, and that declining incidence has been measured in Masaka District as described by Mbuliête and colleagues. These were acknowledged in the original paper. The point made was that claims of incidence decline predated the availability of this evidence.

Finally the authors argue that UNAIDS promotes a multisectoral response to HIV. This is true, yet in making global recommendations, international organisations often must generalise. Uganda’s dynamic response has been shaped within a very specific historical and social context, as I have discussed elsewhere.⁸ So far, much of this context has been overlooked, particularly when oversimplified views of evidence and causality have been casually accepted.

Although I appreciate the concerns of Ghys and colleagues, I believe they missed the point of the original paper. It was not intended as a denial of Ugandan success (which was repeatedly acknowledged), but instead a comment on the interpretation of evidence as illustrated by the case of HIV-1. The way Ghys and colleagues have argued against this can provide further examples of the point of the article. In their letter, they mention “12 antenatal sites in large and small cities” and discuss the relative percentage drops in HIV-1 since 1993, but do not mention antenatal clinic data biases.

Data are often selectively presented in strategic ways to make a point—in this case to emphasise how Uganda was successful. Yet we need to be acutely aware of how data are being presented. Why discuss 12 sites in large and small cities starting at 1993? And why present the data as relative drops in prevalence from peak values? Questions such as these must be asked if we are to better understand how evidence is used.

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Sympathetic pain again?

Sir—R Baron and colleagues’ study (May 11, p 1655)1 is seriously flawed. Analgesia, within 24 h, to non-randomised, uncontrolled, unblinded sympathetic blocks cannot tell sympathetically maintained pain (SMP) from sympathetically independent pain in the context of complex regional pain syndromes.

Complex physiological events may confound the interpretation of diagnostic blocks and there are many limitations that weaken the theoretical basis for neural blockade as a diagnostic or prognostic tool.1–3 A positive test does not imply per se that the patient has the disease being investigated. To assess sensitivity and specificity, test results must be matched against other objective disease indicators that are lacking in SMP.

Test results depend on the disease prior probability; in fact, most patients with complex regional pain syndromes (around 90%) are believed not to have SMP. The definition of SMP is circular, so it implies a perfectly sensitive test, even if a test without false-positive or false-negative results is unrealistic in pain patients. Even with overoptimistic estimates of SMP prevalence, test specificity and sensitivity may show that the posterior probability for a patient with a positive sympathetic block to have SMP is still less than 49%.2,4 Even with allowance for SMP existence, the actual number of SMP patients in the SMP group remains unknown.

It is not stated whether the groups with SMP and sympathetically independent pain differed significantly for basal spontaneous pain and areas of basal hyperalgesia, nor whether patients were treated for their pain. Under experimental conditions, differences in spontaneous pain are reported in 100% of cases, in mechanical hyperalgesia in 84–6% of cases (dynamic SMP=71–4%; sympathetically independent pain=100%; punctate: 85–7%, and 83–3%), in heat-pain threshold in 76–9% of cases (85–7% and 66–6%). Missing data are not accounted for.

“Controlled” study is skewed. Controls used to assess effects of cooling and warming on heat-pain threshold are healthy volunteers. They differ from patients for sex (p=0.026) and age (p=0.005). Moreover, Baron and colleagues have not monitored heart rate, blood pressure, and body core temperature in patients because these variables did not change in controls. A simple direct measurement would have shown stability in these patients too. Therefore, central interference on pain transmission cannot be excluded.

Baron and colleagues state that complex regional pain syndromes can be relieved by sympathetic block, but their uncontrolled study does not show this effect. Since all participants experienced relief, the results point to a relevant placebo effect. In 1997, two critical reviews concluded that data from controlled randomised trials do not show that sympathetic blocks are more effective than placebo for relieving complex regional pain syndromes4,4 and no further clinical randomised controlled study has refuted this conclusion.

While the mismatch between the laboratory and the clinic continues,1 the clinic must not be ignored.

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4 Bonicalzi V, Canavero S. Controlled randomized trials failed to demonstrate that sympathetic blocks (SB) are more effective than placebo for relieving complex regional pain syndromes (CRPS). Pain 1999; 79: 317–19.

Authors’ reply

Sir—Vincenzo Bonicalzi and Sergio Canavero stress the existing mismatch between the solid animal experimental evidence that argues for the SMP concept on the one hand and the lack of evidence from clinical studies on the other.

In fact, we designed our study exactly to address this unsolved question. This is the first attempt to convert the animal experimental situation—eg, selective stimulation of sympathetic neurons and recording from nociceptive afferents—to the clinical setting as closely as possible. We used a novel technique to alter the level of sympathetic discharge selectively and to quantitatively assess its effect on pain experience in awake humans.

Such applied physiological studies that closely mimic the experimental conditions are extremely complex, laborious, and time-consuming for patients and researchers. For obvious reasons, perfect control of all confounding factors is not possible. However, we tried to find an acceptable compromise to allow for as many as possible. Some of these, such as body core temperature, were only obtained in the group of healthy volunteers to focus the patient’s attention on the sensory testing that measured the primary endpoints of the study.

Our most important, new, and unique finding is that, under experimental conditions, physiological discharge in sympathetic neurons can ease pain in some patients with complex regional pain syndromes and not in others. During the entire study the patients were unaware of the possible outcome. These results correlated well with the results of diagnostic sympathetic ganglion block that were carefully controlled for complete abolition of sympathetic neural activity (eg, skin temperature rise, Horner’s syndrome, no sympathetic vasoconstrictor reflexes, replication of result). Although this correlation strongly favours existence of SMP in a subgroup of patients with complex regional pain syndromes, the main barrier to proving the SMP concept is that all available sympathetic procedures are problematic, and even the most stringent protocol does not rule out placebo responses. For ethical reasons, however, at our and many other institutions, sympathetic chain injections are impossible to do without an active drug.

Sympatholytic procedures in clinical practice are at present the best approach to deal with the current definition of SMP, although a certain circularity is implied.1–3 Indeed, more careful adherence to diagnostic criteria and selection of patients as well as well-controlled trials of sympatholysis are needed to finally settle the issue.

However, we did not intend to address the therapeutic efficacy of sympathetic blocks. Uncontrolled studies in hundreds of patients done by experienced clinicians show a beneficial effect of sympatholytic procedures for patients with complex regional pain syndromes. Further, a controlled study on sympathetic blocks involving a small number of patients showed positive results.

Studies of physiological and pathophysiological events in awake patients inherently lack 100% control. However, this is the only way to investigate the clinically relevant pain-generating mechanisms that operate in our patients. We believe that this type of research will narrow the gap between laboratory and clinic tremendously.
peroperative transfusion in anaemic patients undergoing coronary artery bypass

Sir—D Zindrou and colleagues (May 18, p 1747) report on preoperative haemoglobin concentration and mortality after coronary artery bypass surgery (CABG). We have some comments on their findings.

They enrolled 2059 consecutive patients undergoing isolated CABG. We assume all patients underwent CABG under cardiopulmonary bypass. The mean number of grafts per patient is not given, although 96% of the patients received a graft from the internal mammary artery and, consequently, one graft to the anterior descending or right coronary arteries might have been done in some. If patients underwent off-pump CABG, the number should be noted because the postoperative course differs notably from that after on-pump surgery.1 If all patients underwent CABG under cardiopulmonary bypass, did any receive aprotinin? The number of treatments and the doses must be cited, since this drug can also modify patients’ outcomes.1 Zindrou and colleagues give no information about perioperative blood loss, blood-saving techniques, transfusion trigger, number of patients transfused in the non-anaemic group, number of units transfused per patient, or postoperative complications. This issue is important since there is a dose-dependent association between blood transfusion and the development of severe postoperative infection and death in patients undergoing cardiac surgery.2 For mortality, the crude data the investigators show in the figure are also confounded because discharged patients are not included. Despite this omission, the overall in-hospital mortality rate is slightly higher than that reported for a similar series of 2569 CABG patients, in whom transfusion trigger during cardiopulmonary bypass was a packed-cell volume of lower than 20%, and mortality was defined as death during hospital stay or within 30 days of surgery (3·37 to 2·79%).3

In Zindrou and colleagues’ study, patients with a haemoglobin concentration less than 100 g/L had the pump primed with blood. Administration of blood during cardiopulmonary bypass may begin a cascade of events that contributes to postoperative organ dysfunction and morbidity associated with complement activation. Since low packed-cell volume during cardiopulmonary bypass is well tolerated, blood transfusion should be delayed until the intervention is stopped, when the packed-cell volume may need to be higher, thus reducing morbidity.1 Finally, we agree that disease severity and comorbidity had the greatest effect on mortality in the anaemic group, which may have been aggravated by transfusion of stored blood, and the anaemia being just a consequence of some of the disorders, such as renal failure. Hence, whenever possible, preoperative pharmacological but not transfusional treatment of anaemia should be used.

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Authors’ reply
Sir—No patient in the study underwent off-pump CABG. The mean number of grafts per patient was 2·8 (SD 0·5). Only 44 (2%) patients received one graft. These data do not alter the overall results.

Perioperative blood loss was compensated for by autotransfusion. We have no systematic information on the amount of autotransfusion. We did report the preoperative transfusion trigger level. Perioperatively we gave transfusion if the packed-cell volume was lower than 20%. The recording of the number of transfusions given to patients with and without anaemia and complications among patients who actually received transfusions was beyond the scope of the study. However, 23 patients had reoperation because of postoperative bleeding, four of whom died. Aprotinin was given to about 20% of patients, mainly those at an increased risk of bleeding.1 The patients were not randomised for treatment with this drug and we did not attempt such subgroup analysis.

For the endpoint, we assumed that patients with low haemoglobin concentrations would stay in hospital longer and sustain more complications after major surgery than those with higher concentrations. We therefore thought it fair to report on in-hospital mortality. We included three deaths that occurred later than 30 days after surgery. We showed crude survival only up to 30 days in the figure for practical reasons.

Finally, we disagree with Muñoz and colleagues’ statement that there is a dose-dependent association between blood transfusion and development of severe postoperative infection and death. We do not think transfusions should be viewed in such an unambiguous way, at least in relation to death. Higher rates of perioperative bleeding complications will obviously lead to an increased rate of transfusions. However, transfusion per se is not necessarily a risk factor. The repeated operative trauma and raised risk of infection with repeated operations are probably more important for the outcome.

Furthermore, patients with anaemia are more likely to have blood transfusions while undergoing bypass surgery than patients with no anaemia, despite use of blood-saving techniques. We suggested that anaemia was a marker of disease severity or comorbidity, and we believe that this relation probably has a greater effect on outcome than does transfusion. We are not, however, advocating that
transfusions are harmless. We believe they may add to morbidity and possibly mortality after surgery. Yet, these considerations do not preclude the fact that transfusion can be an independent predictor of outcome after surgery, as Udey and colleagues noted. We simply believe that transfusions are merely the surrogate of a combination of operative difficulties, disease severity, and comorbidity.

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**Interferon beta-1a and beta-1b for treatment of multiple sclerosis**

Sir—In their thoroughly planned and well done study, Luca Durelli and colleagues (April 27, p 1453)1 compare every-other-day interferon beta-1b with weekly interferon beta-1a for treatment of relapsing-remitting multiple sclerosis. In the MRI groups, patients on interferon beta-1a seem to have more proton density lesions, enhancing lesions, and T1 hypointense lesions at baseline. I would like to know whether these imbalances were corrected for when calculating the significance of differences during the trial.

Durelli and colleagues state that no analysis of the results was done before the end of 2000. However, the 1-year results were presented in spring, 2001.2 Since the study was unblinded, I wonder what effect the early presentation had on the continuing assessment of patients, at least in the 2nd year of the study, for number of relapses and confirmed score on expanded disability status scale. I also do not understand how this 1-year analysis is compatible with the investigators’ statement that no interim analysis was planned and data were not monitored during the trial. Was there, therefore, no external quality control of the data provided by the participating centres, as is generally expected in studies done according to good clinical practice guidelines?3

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Sîr—Luca Durelli and colleagues’ INdependent COMparison of INterferon (INCOMIN) study1 is important, but a word of caution is necessary before every-other-day high-dose interferon beta-1b is generally accepted as more effective than weekly interferon beta-1a for treatment of multiple sclerosis.

They report a prospective randomised trial in which patients received once-weekly injections of 6 MIU interferon beta-1a or injections of 8 MIU interferon beta-1b every other day. The primary clinical outcome was the proportion of patients who remained free from relapses for the 24-month duration of the study. The primary MRI outcome measure was the proportion of patients free from new proton-density or T2 hyperintense lesions. The MRI outcome measures were assessed in a blinded analysis, but clinical outcomes were not.

The main reason for caution in accepting Durelli and colleagues’ results is that the findings are discrepant from those reported in the phase III clinical studies that established the efficacy of the interferons. Notably, the proportion of patients given interferon beta-1b who remained relapse free at 2 years was 51% in the INCOMIN study compared with 31% in the phase III study.2 The difference in yearly relapse rate between the two treatment groups in the INCOMIN study reflects a lower relapse rate in the interferon beta-1b group and a higher relapse rate in the interferon beta-1a rate than were reported in the respective phase III studies.3,4 The table shows these and other comparative data.

The phase III trials were prospective, randomised, double-blind, placebo-controlled trials. INCOMIN was not. Durelli and colleagues do acknowledge the potential limitation of the lack of blinding for the clinical outcome, but argue that this limitation is unlikely to account for the differences they note in favour of interferon beta-1b. Blinded analysis of outcome is particularly important for subjective measures and, to their credit, the INCOMIN investigators made every effort to objectify the measurement of relapses by requiring independent confirmation of relapse by one of the investigators. The potentially confounding effect of the lack of blinding is illustrated by the randomised controlled trial of cyclophosphamide in multiple sclerosis, in which a significant treatment effect of cyclophosphamide was noted by the treating (unblinded) neurologists but not by the assessing (blinded) neurologists.5

I cannot be certain that the results of the phase III clinical trials more accurately represent the treatment effects of the interferons in multiple sclerosis than do those of the INCOMIN study. Nevertheless, I believe that the discrepancies between studies and the limitations in the methods of the INCOMIN study should lead to caution.

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Author’s reply

Sir—I L Kappos notes that in the MRI analysis groups, interferon beta-1a patients have more proton density, enhancing, and T1 hypointense lesions at baseline. The two groups do not

<table>
<thead>
<tr>
<th>Interferon beta-1a</th>
<th>Interferon beta-1b</th>
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<tbody>
<tr>
<td></td>
<td>Phase III study</td>
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<tr>
<td>Proportion patients relapse-free</td>
<td>38%</td>
</tr>
<tr>
<td>Yearly relapse rate</td>
<td>0.61–0.67†</td>
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<tr>
<td>Proportion patients with &gt;1 point EDSS progression</td>
<td>21.9%–21.2%</td>
</tr>
</tbody>
</table>

EDSS=expanded disability status scale. †Data from patients who completed 104 weeks follow-up. T1 all patients in study with 2-year data estimated from Kaplan-Meier curves. "result from 3-year data since comparable 2-year data not available.

2-year outcome data from phase III and INCOMIN studies
differ significantly and were well matched for burden of disease, the MRI variable that best reflects disease history before starting the trial. The difference between the two treatments always favoured interferon beta-1b when patients were stratified according to baseline proton density or T2, or gadolinium-enhancing lesion number (table).

In consideration of Kappos’ point about the presentation of 1-year results, these were based on an analysis done at the beginning of 2001. Since more than 85% of patients were recruited between 1997 and 1998, almost all enrolled patients had completed the entire period of scheduled follow-up and almost all data had been entered into the database before completing records were sent to the coordinating centre at the end of each month. We do not believe this analysis affected the final assessment of results. No interim analysis was done, since the term generally refers to analyses done during recruitment of patients with the aim of halting recruitment if the primary endpoint has already been reached. The 1-year results came from a preliminary analysis done well after recruitment ended. All the data provided by the centres participating in the trial were checked by our statisticians according to good clinical practice guidelines.

Michael Benatar raises discrepancies between our results and those of phase III studies. The baseline clinical characteristics of INCOMIN differed from, and the definition of progression was more rigorous, than in those from, and the definition of progression established in INCOMIN probably fell within the range identified in previous controlled trials of interferon in multiple sclerosis. Rice and colleagues concluded that such trials were at best single-blind trials. The numbers of patients needed to treat (NNT) for different baseline risks of the main outcome were similar to those calculated in INCOMIN. Therefore, the NNTs probably fell within the range identified in previous controlled trials of interferon in multiple sclerosis.

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### Osteoporosis, risk of radiation-induced fracture, and quality of life

Sir—Panel 2 in the excellent review by J A Kanis (June 1, p 1929) represents a comprehensive list of factors that are directly or indirectly related to risk of osteoporotic fractures. Although Kanis includes factors such as smoking or alcohol consumption, we think that other external agents should also be taken into account to fully assess the risk of osteoporosis-related complications.

Ionsing irradiations used in cancer treatment interact with connective tissue, and may lead to delayed bone abnormalities that increase the risk of skeletal fractures in women whose malignant disease is treated with irradiation.

As Kanis points out, men at high risk of osteoporotic fractures include prostate-cancer patients after castration; but there are also elderly men with prostate cancer who have pelvic fractures after radiation therapy with no hypoandrogenism, which highlights a possible relation between age, previous radiation therapy, and risk of osteoporotic fracture.

On plain radiographs and bone scans, such fractures are similar to those caused by bone metastatic spread. Therefore, differential diagnosis is needed between benign fracture and bone metastasis with CT or MRI. If the possibility of osteoporotic fracture in a patient with cancer is not considered, then impairment in quality of life may be three-fold.

First, since radiological suspicion of malignant disease must be histologically confirmed, there is additional risk of irreversible necrosis after bone biopsy that could be prevented with an accurate differential diagnosis. Second, pathologists may misinterpret osteoporotic fractures as malignant disease when basing histological diagnosis in patients with a history of cancer, leading to interventions against a non-existent tumour. Finally, such invasive diagnostic procedure and misleading information about the possibility of metastatic disease imply unnecessary emotional stress for the patient and relatives, with potential consequences as irreparable as iatrogenic bone necrosis or oncological overtreatment.

Once we understand that quality of life in cancer patients is the key rationale to identify radiation therapy as a risk factor for osteoporotic fractures in both sexes, we will be able to design prevention strategies based on future studies to evaluate the potential risk of radiation-induced fractures and its interaction with other osteoporotic risk factors.

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Second-line treatment for chronic tuberculosis

Sir—Pedro G Suarez and colleagues (June 8, p 1980)1 tested a national programme to treat chronic tuberculosis patients who were previously observed treatment (DOT) with second-line drug for 18 months. Their findings give a definite message of hope for implementation of DOTS-plus in tuberculosis endemic countries with high prevalence of drug-resistant tuberculosis. The number of multidrug-resistant (MDR) tuberculosis patients is increasing since no definite programme is available to treat drug-resistant cases in many low-income and middle-income countries. A survey done in 35 countries has shown that MDR tuberculosis is the major constraint of tuberculosis control.2

We have assessed the clinical outcome of 40 MDR tuberculosis patients since December, 1998, with resistance to INH and rifampicin with or without resistance to ethambutol, pyrazinamide, or both. Investigation and treatment were mostly domiciliary. Everybody was prescribed second-line regimens according to WHO guidelines.3 Cure rate was only 40% (16 patients) despite all possible care. All patients were sputum negative for acid-fast bacilli at least for 18 months after sputum conversion. 13 patients defaulted and three died. Manageable drug toxic effects were noted in 26 patients, and in four, the drug had to be substituted. The high cost of drugs was the important deterring factor in adherence to treatment.

A new strategy is needed to bridge the gap between the present achievable and the desirable 85% cure rates for MDR tuberculosis cases and to shorten the average duration of infectiousness in patients. If we do not make every effort to contain MDR tuberculosis, we may eventually reach a point at which DOTS-plus will be of limited effectiveness.

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Targeting of children in filariasis mass drug administration

Sir—Balachandran Ravindran (June 1, p 1948) highlights important practical issues related to the execution of mass drug administration for control of lymphatic filariasis. He discusses the deworming role, macrofilaricidal effect on adult filarial worms, and lesser side-effects of albendazole. However, he does not focus on the usefulness of mass drug administration in children.

In studies of antigen detection, a third of children are frequently infected with lymphatic filariasis before age 5 years, and the need for targeting children in lymphatic filariasis elimination campaigns has been emphasised.4 About 27 million people, including children, are covered under mass drug administration in Tamil Nadu, India, and we studied a population of 321 000 to assess the efficacy of this treatment method on intestinal geohelminths in children.5

Our concurrent investigations on adult filarial worm antigenaemia prevalence and clearance are summarised.

Mass drug administration in March, 2001, with co-administration of albendazole and diethylcarbamazine produced significantly higher cure rates for any of three intestinal geohelminths, than did administration of diethylcarbamazine alone (74 vs 30%). A third more schoolchildren from the two-drug group perceived the benefit of expulsion of worms immediately after mass drug administration. Treatment adherence for drugs issued was low (53%) among children aged 2–5 years, presumably because their mothers feared side-effects, and antigenaemia prevalence changed by 22%, 1 year after mass drug administration (9% [n=354] to 7% [n=360]). In a separate group of nine villages, where the researchers have been working for the past 6 years, treatment adherence (90%) was higher for young children and youths (15–25 years) for the same mass drug administration. The antigenaemia prevalence decreased significantly by 63% in young children, but it declined by only 3% in youths. After three administrations between 1999 and 2002, antigenaemia clearance in 223 individuals followed up was significantly higher in children than in youths (18 [40%] of 45 vs 41 [23%] of 178, p=0.034).

Substantial reduction in antigenaemia prevalence with one mass drug administration, and significantly higher clearance of antigenaemia in young children and lower response in youths after three administrations is startling. However, the location of adult filarial worms and their numbers in human beings differ before and after puberty,6,7 and a substantial proportion of filarial worms in adult patients were not accessible to diethylcarbamazine and albendazole.8 One hypothesis suggests that a greater proportion of adult filarial worms in children might be accessible for killing by adulticidal mechanisms triggered by antifilarial drugs.9 The suspected survival of some filarial worms in adult patients despite active chemotherapy has been confirmed.10 The response in children is encouraging.

Targeting of children during mass drug administrations for rapid lymphatic filarial elimination by sensitisation of mothers is essential. The campaign for lymphatic filarial elimination should be fine-tuned to produce the best benefits.

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Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID follow-up study—In this Article by the LIPID Study Group (April 20, p 1379) reference 17 should have been: “MRC/BHF Heart Protection Study Collaborative Group. Randomised trial of cholesterol-lowering therapy and of antioxidant vitamins in 20 536 people at increased risk of coronary heart disease death. Circulation 2001; 104: 1B. http://circ.ahajournals.org/cgi/content/full/104/2/51B.”