

# CORRESPONDENCE

## Organ donation and permanent vegetative state

SIR—Raymond Hoffenberg and colleagues (Nov 1, p 1320)<sup>1</sup> discuss whether organs from patients in a permanent vegetative state (PVS) should be used for transplantation. They debate whether a patient's death might be accelerated by lethal drug injections, after the decision to withdraw nutrition and fluids has been made. A natural death after nutrition withdrawal would yield organs no longer in optimum condition. Although active killing is still illegal, the authors believe that there is no ethical difference between the omission of treatment and more active ending of life. If a patient, family, or both refuse life-sustaining interventions, the cause of death will be the underlying disease. The intention is here not to sustain life by means of senseless technical support. By contrast, by euthanasia, active killing is intended and the cause of death is the injection of a lethal drug.<sup>2</sup> The authors argue that if the legal definition of death were to be changed to include comprehensive irreversible loss of higher brain function such as PVS, it would be possible to stop a patient's heart by a lethal injection and remove organs for transplantation. To my mind, this demonstrates the difficulty with definitions of deliberate death which have emerged with high-technology medicine.

This argument is presented by a distinguished international group and was published in *The Lancet* without an editorial or commentary. As a German, I am sensitive here, recalling the euthanasia during the Nazi era. The Hippocratic oath reminds us "I will never give a lethal remedy" and the biblical commandment "Thou shalt not kill" is recognised by the Jewish and Christian religions. However, the imperative to do everything that is technically possible is a dominating feature today.

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1 Hoffenberg K, Lock M, Tilney N, et al.

Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997; **350**: 1320–21.

2 Annas GJ. The bell tolls for a constitutional right to physician assisted suicide. *N Engl J Med* 1997; **337**: 1098–103.

SIR—Although in his letter to the *Sunday Telegraph* of Nov 9, Raymond Hoffenberg attempted to deny that he and his colleagues were proposing that those in a permanent vegetative state (PVS) should be killed for their organs, any ordinary reading of their *Lancet* paper<sup>1</sup> would reach exactly that conclusion. The paper discusses some practical and moral problems and how these might be got around to satisfy the demand for organs. The authors have attempted to escape the accusation by arguing that it would be the Law Lords, by their decision in the Bland case, who would really be responsible and that the transplant surgeons would be simply making practical use of the opportunity.

The Bland decision was a bad one but, accepting that it has been made, I would point out that legality and morality are separate. The legal decision, which was based on an argument that tube feeding a patient is treatment and may therefore be discontinued, cannot exonerate those who then deliberately and actively kill a patient, however worthy the end in view. Furthermore, for all the arguments about the definition of and differentiation between persistent and permanent vegetative state (a temporal distinction only), these people are not dead, even in the way that those fulfilling the criteria of brain death are regarded as being. They are not separated off by some qualitative step from those very severely damaged by head injury and are not in a state much worse than the elderly with advanced dementia or children afflicted with severe brain injury at birth. To accept the transplant ethicists' proposal, therefore, would be to set out on a very dangerous path.

It is clear that, by calling for this debate, Hoffenberg and his colleagues, having reluctantly concluded that their

arguments would not at present be acceptable to the populace or the medical profession, wish gradually to win both around by persistent and persuasive presentation of their underlying proposal. It is not being alarmist to call to mind what happened in Germany in the 1930s and to fear for the moral state of the profession and, indeed, of the country as a whole, if their argument were to prevail. As a retired neurosurgeon with a reasonable acquaintance with the sort of patient being discussed I think there is nothing to discuss. The proposal is unthinkable.

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1 Hoffenberg K, Lock M, Tilney N, et al. Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997; **350**: 1320–21.

SIR—The announcement on television and radio by J Radcliffe-Richards on behalf of the International Forum for Transplant Ethics (preceding the group's *Lancet* paper<sup>1</sup>), suggesting that patients in permanent vegetative state (PVS), in whom a court had given consent to withdrawal of treatment, could be given a lethal injection to expedite death so that their organs can be removed for transplantation must be challenged. This group of doctors, lawyers, and ethicists holds no official position within the British Transplant Society or the International Transplantation Society and cannot represent the views of the transplant community as a whole. However, publication of their views, although stimulating debate, could have a detrimental effect on organ donation through adverse or even hostile public reaction. I and others dedicated to advancing the cause of organ transplantation wish to do so with the full support of the wider public and our colleagues in medicine.

The use of a lethal injection to terminate the life of an individual who is clearly alive although without cognitive brain function and in whom established brain death criteria are not fulfilled is to be deplored, however well meant. The proposal suggests

euthanasia and, even worse, smacks of the activities of totalitarian regimes. The transplant community must separate its objective of improving quality of life for patients with kidney failure and preventing premature death in patients with heart and liver failure from controversies such as euthanasia.

There is a fine line between withdrawal of treatment and general support for patients who have PVS and expediting their death. Raymond Hoffenberg and colleagues<sup>1</sup> claim that there is no moral distinction between the two measures since the outcome is the same. I disagree: the former is an act of omission whereas the latter is a premeditated action under the guise of a humanitarian act ("to reduce the misery imposed by a long drawn-out death on family, nursing staff, and others") but in reality in order to generate a few more organs for transplantation.

There is a perennial shortage of cadaveric organs for transplantation but the transplant community does not wish to be perceived as wanting to obtain organs at any price. The whole idea of mercy killing is highly contentious without the dimension of organ donation; it would bring transplantation into disrepute and should be condemned.

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- 1 Hoffenberg K, Lock M, Tilney N, et al. Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997; **350**: 1320–21.

**SIR**—Raymond Hoffenberg and colleagues<sup>1</sup> perpetuate misunderstanding of the way in which organs for transplantation are currently acquired from the so-called "brainstem dead" who are, they say, "deemed in law to be dead" even though their bodies are still perfused by their spontaneously beating hearts. Hoffenberg et al say that "When cardiopulmonary support is withdrawn, spontaneous function of the heart and lungs rapidly ceases, the circulation stops, and immediate organ retrieval is allowed". That is not the way of things.

Although kidneys and eyes may indeed be useful for transplant purposes when taken after the circulation finally ceases, hearts, lungs, and livers have to be removed while mechanical ventilation continues and the donor's body remains perfused with oxygenated blood pumped by a spontaneously beating heart. This highly relevant fact is not well enough known, even in medical circles. Those who have signed organ donor register

forms in the belief that they are assenting to removal of their organs after circulation has finally ceased—ie, when they are dead in the commonly understood sense—have made their generous offer on a false premise.

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- 1 Hoffenberg K, Lock M, Tilney N, et al. Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997; **350**: 1320–21.

**SIR**—The article by Raymond Hoffenberg and colleagues<sup>1</sup> shows how far we have crept towards euthanasia. The withdrawal of nutrition, as in the Bland case,<sup>2</sup> was, as the authors say, an act intended to end life. It was said at the time the patient had no best interests because he was unable to sense anything. Notwithstanding the doubt about sentience in patients with permanent vegetative state (PVS) and its misdiagnosis<sup>3</sup> we are now told that it is humane to kill such patients by lethal injection. The reality is that patients who cannot express their wishes are being killed without their consent and without evidence of any benefit to them. The intentional ending of life by lethal injection or by withdrawal of nutrition should remain anathema to all doctors. Otherwise patients will be unable to trust doctors with their lives.

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- 1 Hoffenberg K, Lock M, Tilney N, et al. Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997; **350**: 1320–21.
- 2 Airedale NHS trust v Bland. [1993] 1 All ER 821.
- 3 Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *BMJ* 1996; **313**: 13–16.

*Author's reply*

**SIR**—The criticisms of our article contain familiar arguments which were not unexpected. Several letters imply we glossed over the ethical difference between allowing patients to die by omitting treatment and active killing; in fact, we discussed this at some length. The judgment of the House of Lords confirmed the crucial importance of the legal distinction but was less certain about the moral position. Lord Mustill referred to "the morally and intellectually dubious distinction between acts and omissions" and said "the ethical status of the two courses of action is for all relevant purposes indistinguishable". The fact that we, and many ethicists, share his view does not necessarily

make it right. Nor does it make it wrong; as Karlheinz Engelhardt, T T King, and A Bakran appear to assume. They claim there is a moral distinction between omitting treatment and actively killing. Therefore, the former may be acceptable but the latter is not—no reasons, no debate, no place for divergent opinion. Is it unreasonable to propose further debate on a subject about which, whether our critics like it or not, there is no universal agreement?

King dislikes the House of Lords decision in the Bland case; so, no doubt, do others. The decision was bound to displease some people but one expects a more reasoned force of argument than a categorical statement that it is wrong. I was surprised to note his analogy between our paper and what happened in Germany. In a liberal society open discussion of issues like this should be encouraged, in direct contrast with pre-war Germany where it would have been impossible. Engelhardt's shock that *The Lancet* chose to publish our paper suggests that this debate could still not take place in that country.

Bakran wishes to dissociate the "transplant community" from the views we expressed. We did not claim to speak on behalf of this undefined group. Most of us are not connected with transplantation, and it is this multidisciplinary approach that allows us to venture objectively into an area of public and social interest which more closed professional societies might find it difficult to address.

David Evans, who for many years has criticised the death criteria, makes a point about the method of retrieval of organs in ventilated patients which does not alter the sense of what we were saying and we do not see why this knowledge should affect those who wish to be donors.

Finally, Adrian Treloar raises the issues of sentience in patients with PVS and the possibility of misdiagnosis. We are aware of Andrews' important work, but Andrews himself states that the fear of misdiagnosis should not constitute an argument against ending the life of a patient. We carefully confined our consideration to those patients in whom, regardless of the diagnosis, a decision had been taken to allow them to die. We discuss his point about possible sentience in our paper. He also raises the question of organs being taken without the patient's consent. The court would naturally take this into account in coming to a decision and would require the consent of nearest relatives and their affirmation

that the deceased would not have objected to this use of his organs.

May I conclude by referring to the final sentence of our group's paper?<sup>1</sup> We agreed that, for religious, cultural, and other traditional reasons, the proposal to use organs from patients in PVS would not be acceptable but we felt there were arguments that warranted debate. If this debate ever takes place we hope it will be thoughtful and rational and not based on gut reactions.

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- 1 Hoffenberg K, Lock M, Tilney N, et al. Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997; **350**: 1320–21.

## Contamination of doctors' and nurses' pens with nosocomial pathogens

SIR—Christian Datz and colleagues (Dec 20/27, p 1824)<sup>1</sup> report the isolation of several species of bacteria from doctors' pens. However, the organisms they isolated were a mixture of common skin commensals (propionibacteria, corynebacteria, micrococci, coagulase-negative staphylococci), bacteria that are rarely if ever involved in crossinfection (branhamellae, moraxellae, *Bacillus* spp, *Streptococcus viridans*) and two species of *Pseudomonas* of low pathogenicity unrelated to any outbreak of infection. They rightly point out that these results do not directly implicate pens as vehicles of crossinfection.

We have investigated contamination of doctors' and nurses' pens on five wards affected by methicillin-resistant *Staphylococcus aureus* (MRSA), one ward with a simultaneous outbreak of MRSA and vancomycin-resistant enterococci (VRE), and one ward with an outbreak of gentamicin-resistant and multidrug-resistant (MDR) *Klebsiella pneumoniae*. We cultured pens for 48 h in 100 mL nutrient broth at 37°C (sensitive enrichment culture method). Numerous skin and environmental bacteria and fungi were present but we looked only for our outbreak pathogens by subculturing the broths onto selective media: oxacillin-salt agar (7.5% NaCl, 5 mg/L oxacillin) for MRSA, plain MacConkey agar for enterococci, and MacConkey agar containing gentamicin 20 mg/L for MDR klebsiellas. Organisms were

presumptively identified by colonial appearance and then confirmed by standard methods of identification and antimicrobial susceptibility testing.

36 pens were tested from six wards affected by MRSA, and nine of them (25%) were contaminated by this pathogen. The antibiotic resistance patterns of the pen isolates were the same as that of the outbreak strain on the ward concerned. The contamination rate varied from zero on two wards (none of six and two pens, respectively) to 50% (four of eight) on one ward. Six pens were collected from the VRE ward and one (17%) was positive for VRE. None of the eight pens from the MDR klebsiella ward was contaminated by this pathogen.

All three of the pathogens investigated here are well known to be transmitted on staff hands, and MRSA and VRE survive well in the environment. Klebsiellas are less resistant to drying than gram-positive species, and it is not surprising that we were less successful in growing this organism from staff pens. Nevertheless, like Datz and colleagues, we grew several other gram-negative species from pens, and klebsiellas can survive quite well on surfaces.<sup>2,3</sup>

These results confirm Datz and colleagues' suspicion that staff pens can become contaminated with important nosocomial pathogens, but the results should still be interpreted with caution. It is well recognised that the hospital environment can become contaminated with pathogens from infected patients without necessarily being involved in the transmission of infection;<sup>4,5</sup> for this reason we do not encourage routine environmental or surveillance swabbing. The contamination of doctors' and nurses' pens with MRSA and VRE may merely be a reflection of staff hand contamination. Nevertheless, staff may unwittingly re-inoculate their hands with these organisms if they use their pens after handwashing, pathogens might be spread between staff if they share or remove pens from the nurses' station, as is common, and pens might be the route of transmission of infection between wards.

These results re-emphasise the importance of staff handwashing in the prevention of crossinfection, but we are not sure what to do about pens. Regular disinfection with alcohol might reduce contamination of pens, but would be difficult to implement. In high-risk areas such as intensive care units, special pens that are disinfected daily and disposed of after discharge might be kept by each patient's bed. Better still we are thinking of issuing

warning labels to stick on staff pens saying "Now please wash your hands".

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- 1 Datz C, Jungwirth A, Dusch H, Galcan G, Weiger T. What's on doctors' ball point pens? *Lancet* 1997; **350**: 1824.
- 2 Hart CA, Gibson MF, Buckles AM. Variation in skin and environmental survival of hospital gentamicin-resistant enterobacteria. *J Hyg* 1981; **87**: 277–85.
- 3 Cooke EM, Brayson JC, Edmonson AS, Hall D. An investigation into the incidence and source of klebsiella infections in hospital patients. *J Hyg* 1979; **82**: 473–80.
- 4 McGowan JE. Environmental factors in nosocomial infection—a selective focus. *Rev Infect Dis* 1981; **3**: 760–69.
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## *Trichomonas vaginalis* and amplification of HIV-1 transmission

SIR—D J Jackson and colleagues (Oct 11, p 1076)<sup>1</sup> justifiably suggest that *Trichomonas vaginalis* may have an important role in the amplification of HIV-1 transmission in developing countries. We would add that the impact of trichomonas on the dynamics of HIV-1 transmission may also be substantial in industrialised countries. We found high rates of trichomonas infection among women with HIV-1 at a public clinic in Los Angeles County, USA.<sup>2</sup> Trichomoniasis was the most common sexually transmitted disease (STD) in these women; the highest rates were among African-American women infected with HIV-1, 38% of whom were diagnosed with trichomoniasis. In multivariate analysis, African-American origin was independently associated with trichomonas infection. Although data are limited, studies indicate that trichomonas is one of the most common STDs in the USA, especially among African-American women in urban centres.<sup>3</sup> The high rate of HIV-1 in black communities in the USA may, in part, reflect the amplifying effect of trichomonas and other STDs on HIV-1 transmission.

The cumulative information suggests that trichomonas has an important role in increasing HIV-1 transmission. The biological rationale for this is compelling: the organism

typically elicits an aggressive local cellular immune response, with heavy infiltration of leucocytes, even in symptom-free patients. In addition, in about 50% of infected women, punctate haemorrhages can be observed on colposcopy. In an HIV-1-negative person, the pathology of white blood cells and lesions in the genital contact area can enlarge the portal of entry for HIV-1 by increasing the number of HIV-1 target cells available and viral access to the bloodstream. In an HIV-1-infected patient, the leucocyte infiltration and haemorrhages induced by trichomonas may expand the portal of exit and increase shedding of HIV-1 in the genital area.<sup>4</sup> Thus, trichomonas may amplify HIV-1 transmission by increasing susceptibility in an HIV-1-negative person and the infectiousness in an HIV-1-positive patient. Other aspects of the natural history of this organism, including its often symptomless nature and protracted carriage, may also contribute to increasing HIV-1 transmission. In addition, data from Africa show an association between trichomonas and HIV-1 infection in women, with estimated relative risks ranging from 1.8 to 3.0.<sup>5</sup>

Even if trichomonas amplifies HIV-1 transmission by a small degree, the amount of HIV-1 transmission attributable to this agent (attributable risk) and its impact on epidemic spread may be substantial because the infection is common. Most studies document high rates (13–47%) of trichomonas infection in young sexually active women in both industrialised and developing countries, and limited data suggest similarly high rates in men. For example, if trichomoniasis increases the risk of HIV-1 transmission by a modest 90% (relative risk 1.9) and the prevalence of trichomonas is 25% in a population, the amount of HIV-1 transmission attributable to trichomoniasis in this community would be nearly 20%. Aggressive screening and treatment for trichomonas infection in high-risk groups may reduce community transmission of HIV-1.

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- 1 Jackson DJ, Rakwar JP, Bwayo JJ, Kreiss JK, Moses S. Urethral *Trichomonas vaginalis* infection and HIV-1 transmission. *Lancet* 1997; **350**: 1076.
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Angeles County: implications for HIV prevention. *Am J Trop Med Hyg* (in press).

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- 5 Laga M, Manoka A, Kivuvu M, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS* 1993; **7**: 95–102.

## Causes of testicular cancer

SIR—I would like to focus on the concluding remark of Louise Parker's Sept 20 commentary: "Does testicular tumour increase the risk of testicular tumour?" I believe the answer is certainly yes, and would like to discuss papers that illustrate this point. However, because Parker's last sentence seems out of context with the rest of the paragraph it may be that the real question is whether testicular biopsy increases the risk of testicular tumour.

Osterlind and colleagues<sup>2</sup> reported that the cumulative incidence of bilateral germ-cell testicular cancer during a 25-year period was 5.2% in the Danish Cancer Registry. They also found that when synchronous bilateral tumours were excluded, the relative risk of a patient developing a contralateral tumour was 24.8 times higher than the chances of an age-matched member of the male population developing testicular cancer.

Colls and co-workers' New Zealand Study<sup>3</sup> showed similar findings. 16 examples of bilateral germ-cell testicular cancer were reported in 741 men during a 15-year period; five of these tumours were bilateral at presentation and 11 were meta-synchronous. The cumulative incidence of second testicular tumours was also 5.2%. When the investigators excluded the synchronous tumours, the relative risk of these patients developing a contralateral tumour was 27.5 times higher (95% CI 14–49) than the risk of the age-matched normal population developing germ-cell testicular cancer. Since biopsy of the contralateral testis in patients with a primary germ-cell testicular cancer has not been routinely practised in New Zealand, this feature cannot be commented upon. However, two of the patients in this series were shown to have carcinoma in situ in the contralateral testis, and subsequently

developed a second testicular cancer.<sup>3</sup>

There seems little doubt that a previous testicular germ-cell tumour is a very strong aetiological factor in the development of a subsequent testicular cancer. If previous testicular trauma (eg, orchiopexy) increases the relative risk by a factor of 7.5<sup>4</sup> it would seem very likely that the combination of these risk factors would set such patients up for the development of a second tumour. Indeed, Swerdlow and colleagues<sup>4</sup> report seems to emphasise this point by demonstrating the greatest risk in those who had a biopsy at the time of their orchiopexy. I too would welcome a case-control or cohort study to delineate this point.

B M Colls

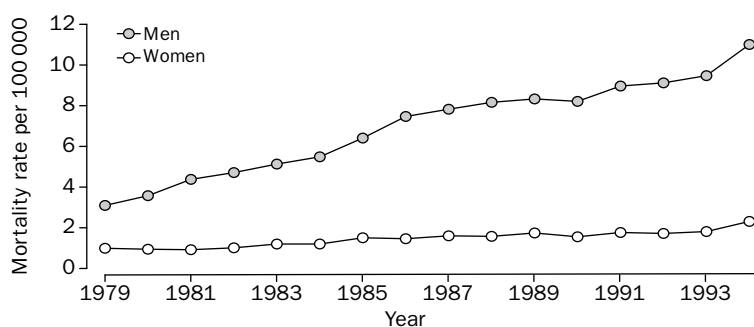
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- 1 Parker L. Causes of testicular cancer. *Lancet* 1997; **350**: 827–28.
- 2 Osterlind A, Berthelsen JG, Abilgaard N, et al. Risk of bilateral testicular germ cell cancer in Denmark: 1960–1984. *J Natl Cancer Inst* 1991; **83**: 1391–95.
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## Trends in primary liver cancer

SIR—Simon Taylor-Robinson and colleagues (Oct 18, p 1142)<sup>1</sup> report an increase in primary liver cancer in the UK in 1979–94, and suggest it could be caused by a hepatitis C virus (HCV) epidemic. A similar trend was observed in France (figure). Between 1979 and 1994, mortality from all causes of primary liver cancer (ICD9 155.0) increased four-fold for men (from 842 to 3545) and two-fold for women (from 326 to 790). Mortality rates were age-standardised according to the French population in 1979. Between 1979 and 1994, the age-standardised mortality rates per 100 000 people increased from 3.2 to 11.1 in men and from 1.2 to 2.5 in women.

There has been much improvement in the detection of liver cancer, but ultrasonography and measurement of serum  $\alpha$ -fetoprotein have been routinely used since 1980 and could not explain the increase in mortality observed between 1985 and 1994. Our recent work on natural history of HCV infection,<sup>2</sup> with a model of fibrosis progression,<sup>3</sup> showed that HCV



#### Age-standardised mortality rates per 100 000 of the French population for primary liver cancer (ICD9 155.0), 1979–94

Data from the French National Centre of Mortality Statistics, Institut National de la Santé Et de la Recherche Médicale, Service Commun 8.

infection could explain the rise in mortality from liver cancer.

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- 1 Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979–94. *Lancet* 1997; **350**: 1142–43.
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SIR—Similar reports to that by Simon Taylor-Robinson and colleagues<sup>1</sup> have been published in the context of the effect of oral-contraceptive use on mortality from liver cancer in the UK<sup>2</sup> and elsewhere.<sup>3</sup> The UK study by Mant and Vessey<sup>2</sup> examined the age-specific mortality of primary liver cancer (ICD8, 9 155.0) for England and Wales, between 1975 and 1992, in men and women aged 25–74 years, grouped in 10-year age bands. The authors excluded cholangiocarcinoma since case-control studies had not shown any relation to use of oral contraceptives. The rates of cancer were higher in men than in women across all age bands, as shown by Taylor-Robinson and colleagues. However, the increase over time was restricted to men aged 25–34 and 65–74 years and to women aged 55–64 years. Thus, factors that contribute to the observed increase may be operating selectively on certain age groups. Because Mant and Vessey's analysis<sup>2</sup> was restricted to England and Wales, it may be useful to repeat the age-specific analysis for Taylor-

Robinson's data, which cover the whole of the UK, to ascertain the age-groups that show the increase.

Another point is the trends in the consumption of aflatoxin (a hepatotoxin produced by certain strains of *Aspergillus flavus* predominantly found in contaminated cereals and peanuts) which is a potential risk factor for hepatocellular carcinoma.<sup>4</sup> Although population exposure to aflatoxins in Europe is low compared with high-risk areas,<sup>5</sup> changes in storing and distribution of farm produce over the years might have altered the population consumption of this potential hepatocarcinogen. To our knowledge, there are no available data on trends on aflatoxin consumption on a population basis in the UK. Indeed, an increase in exposure to aflatoxin could have partly contributed to the increase in primary liver cancer observed by Taylor-Robinson and colleagues.

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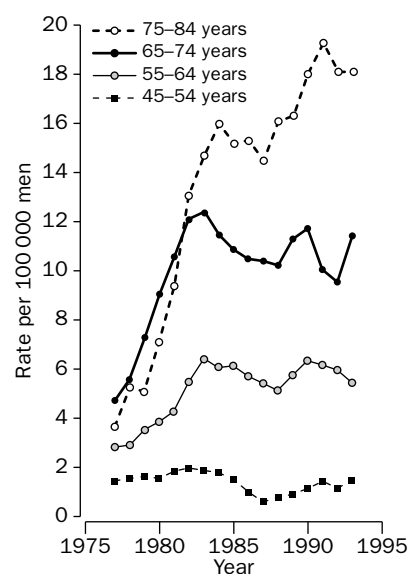
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SIR—Simon Taylor-Robinson and colleagues<sup>1</sup> focus on the increase in mortality from primary liver cancer, pointing out that it is difficult to ascertain whether or not there has been an increase in deaths due to hepatocellular carcinoma (HCC) in the UK and that in cases with a histological

diagnosis the recorded rates of HCC have remained static. They forecast an increase in the incidence of HCC secondary to cirrhosis in individuals who contracted hepatitis C virus (HCV) from intravenous-drug use in the late 1960s and early 1970s.

The West of Scotland Cancer Registry has recorded histology and measured incidence for many years, and its incidence data are both complete and valid. The figure shows age-specific incidence rates for HCC (ICD9 155.0; ICD0 8170) in men between 1975 and 1995. There was a dramatic increase in the incidence of HCC in men, particularly among those aged 75–84 years between 1975 and 1985. In the mid-1980s the rates stabilised. There has not been an increase in incidence among men younger than 55 years. By contrast, incidence of HCC among women has increased only slightly, although from a similar baseline in the mid 1970s.

We believe that the place to look for clues to this steep rise in older men in the west of Scotland is Japan, where there has been a similar epidemic. Since 1970, the incidence of HCC has increased by about three-fold and, as is typical for low incidence countries, the rate is higher in Japanese men.<sup>2</sup> This sex difference in the developed world is not surprising because many of the primary and secondary risk factors for HCC—eg, hepatitis B, alcoholism, haemochromatosis, homosexual intercourse, haemophilia, and intravenous-drug use—are more common in men than in women. Nevertheless, Japanese case-control studies have shown that 80% of men with newly diagnosed HCC tested positive for hepatitis C and that substantial numbers of new HCC



Incidence of hepatocellular carcinoma among men in west of Scotland, 1975–95

patients have undergone major surgery requiring large transfusions from the 1940s to the 1960s, including nephrectomy and lobectomy for tuberculosis.<sup>2</sup> Older studies revealed that 20–40% of non-A, non-B hepatitis-associated HCC patients received a blood transfusion many years previously.<sup>2</sup>

Haydon and colleagues<sup>3,4</sup> study of HCV-associated HCC cases diagnosed between 1985 and 1994 in the east of Scotland showed that a blood transfusion was the risk factor in 62% of cases. Only one of 24 patients with HCV-associated HCC had a history of intravenous-drug use, suggesting that the cohort referred to by Taylor-Robinson and colleagues has yet to develop HCC.

Could a similar scenario to that seen in Japan have caused the increase in HCC in the West of Scotland? If a latency of 30 years<sup>2</sup> is applied to our increasing incidence between 1975 and 1985, the period of exposure becomes the 1940s and 1950s. Given the high rates of tuberculosis in the west of Scotland<sup>5</sup> at this time, we suggest that the rise in HCC might reflect iatrogenic transmission of HCV via blood transfusion as a result of the propensity after World War II for aggressive surgical management of this bacterial infection, which was common among the poorly nourished population.<sup>5</sup> This is just one hypothesis, and it is possible that other infectious or non-infectious factors could have been responsible for the observed increase in HCC. A case-control study is clearly indicated.

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## Primary biliary cirrhosis

SIR—In his Oct 11 commentary, Nicholas LaRusso<sup>1</sup> questions the value of methotrexate in the treatment of primary biliary cirrhosis (PBC).<sup>2</sup> We followed these five patients for 7–14 years. All had well documented PBC (mean duration of disease before treatment 3.2 years [range 1–7]) and received methotrexate for 6–7 years without side-effects. All blood tests became normal and the patients became symptom free. Liver biopsies, assessed under masked conditions by two pathologists, showed a decrease in histological stage from 2.5 to less than 1.0. This improvement meets the current definition of effective therapy.<sup>3</sup> This is encouraging in a disease that is widely believed to be untreatable and ultimately fatal unless liver transplantation is done. We included 14 additional patients for completeness although they were not followed for similarly long periods of time. The mean follow-up of “about 4 years” to which LaRusso alludes is that of all patients.

On the basis of the encouraging results of our observational study, I believe that future prospective trials should also include intermediate endpoints of success rather than only endpoints of failure—ie, death or liver transplantation. Appropriate endpoints should include normalisation of liver-function tests, remission of symptoms, and improvement in liver histology. Our preliminary data suggest that the judicious sequential use of ursodeoxycholic acid, colchicine, and methotrexate in combination in PBC is effective in most patients with PBC,<sup>4</sup> and that prospective studies which use these agents in combination may hasten the time that the average patient with PBC receives appropriate therapy. Methotrexate has been used safely to treat hundreds of thousands of patients with rheumatoid arthritis, and unwarranted fear of its toxicity should not preclude its use in future prospective trials of PBC.

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## Calcium antagonists and cardiovascular events in patients with hypertension and diabetes

SIR—Stimulated by Robert Byington and colleagues' (Oct 11, p 1075)<sup>1</sup> suggestion that adverse effects of calcium antagonists may be amplified in diabetic patients, we reanalysed a case-control study of the effect of drug treatment on cardiovascular events in hypertensive patients.<sup>2</sup>

The 387 participants (189 cases) in our study included 34 individuals (19 cases) with a history of diabetes. Diabetics and non-diabetics differed significantly only in entry fasting blood glucose (176 vs 102 mg%,  $p < 0.0001$ ) and pretreatment diastolic blood pressure (90 vs 95 mm Hg,  $p = 0.012$ ). The odds ratio for a cardiovascular event in patients taking any calcium antagonist compared with those taking other drugs was 6.85 (95% CI 1.50–31.34) in the diabetic group, which was 5 times the odds ratio of 1.35 (0.88–2.07) in the non-diabetic group (table). A similar comparison of diuretic use versus other drugs, and  $\beta$ -blocker use versus other drugs revealed no difference in the pattern of cardiovascular events between diabetics and non-diabetics.

This unique and remarkable clustering of adverse cardiovascular outcomes related to use of calcium antagonists in diabetic hypertensive patients lends support to, but does not prove, the biologically plausible hypothesis that diabetic patients have increased susceptibility to the adverse effects of calcium antagonists. However, in view of these data and results from randomised clinical trials,<sup>3,4</sup> prudence dictates that, pending definitive evidence, calcium antagonists be reserved for those hypertensive

Drug	Diabetics		Non-diabetics	
	Cases (n=19)	Controls (n=15)	Cases (n=170)	Controls (n=174)
Any calcium antagonist*	12 (6)	3 (0)	79 (17)	68 (4)
All other drugs	7	12	91	106

\*Numbers in parentheses are patients taking short-acting calcium antagonists.

**Cardiovascular events by diabetic status and drug use**

patients in whom other therapies are ineffective or unacceptable.

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## Discrepant analysis and screening for *Chlamydia trachomatis*

SIR—Jørgen Hilden, in his Sept 27 commentary<sup>1</sup> celebrates a criticism based on statistics, but does not discuss the actual results obtained, the biological issues that are involved, nor the magnitude of the purported errors. Hadgu's "sober quantitative arguments" have included a calculation that shows (incorrectly) that culture is more sensitive than the DNA amplification test, and a calculation of specificity that requires specimens containing both chlamydial genes and antigens be classified as false positive.<sup>2–4</sup>

Clearly, the absence of an accurate gold standard is a difficulty for those evaluating newer diagnostic tests. Culture sensitivity for *Chlamydia trachomatis* is highly variable, being dependent on swab adequacy, cold chain maintenance, tissue culture efficiency and other factors. When the first non-culture tests (antigen detection tests such as enzyme immunoassay (EIA) and direct fluorescent antibody (DFA) were compared with culture, a substantial proportion of specimens that tested positive for antigen were culture negative. To have simply accepted that group of discrepant results as false-positives would doom us to accept culture as 100% sensitive and never recognise a better test.

With the antigen detection methods, two distinct targets were the chlamydial major outer membrane protein (DFA) and the lipopolysaccharide (EIA). An algorithm was generated that accepted

as true positive any specimen that was culture positive, as well as specimens that were culture negative but positive in the two different antigen tests. False positive results were antigen positives that were culture negative and did not confirm by the second antigen test. The argument that all specimens should have been tested by all tests is rendered moot by this algorithm, since any specimen that was culture negative and EIA negative could not be identified as a true positive by the DFA test. Without being positive in two tests, it would be considered a false positive DFA result.

When DNA amplification procedures were introduced it became clear that they were far more sensitive than any other method. They could detect 10<sup>1</sup> organisms, whereas antigen-detection methods had a threshold of greater than 10<sup>4</sup>. Thus, further testing of discrepant specimens had to be undertaken with other more sensitive DNA amplification procedures. The simultaneous use of several amplification tests in evaluations has demonstrated the superior sensitivity of the nucleic acid amplification tests, as compared with earlier generations of non-culture diagnostic tests, or with culture itself.

Classifying culture negative, nucleic-acid-amplification positive results as false-positives because the confirmatory test was not applied to all negative specimens is wrong. It incorrectly estimates the specificity of nucleic acid amplification because most of these specimens can be shown to contain chlamydiae, and it incorrectly inflates the sensitivity of the comparison test (culture) that failed to detect the organism.

Hilden's comments provide no solution as to what researchers should do when attempting to evaluate a test that is demonstrably better than the existing gold standard. He is concerned that "exaggerated statistics lead to poor tests ousting better ones from the market", whereas in reality the failure to appropriately categorise discrepant results generated by the new tests exaggerates the performance of older and inferior tests and could delay acceptance of new and better tests.

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### Author's reply

SIR—In reply to Julius Schachter and colleagues, let me recall the simple fact that discrepant analysis allows the new test under evaluation to influence what data are collected to reach a best possible classification of each case: this goes against clinicometric logic, and bias may result. There is no reason to be anything but grateful to Hadgu for pointing out this fact, even if it imposes a burden on researchers in that they must either demonstrate that the bias is negligible or re-orient their research so as to circumvent the snag—as Schachter's team emphasise that they did on particular occasions. (If Hadgu erred numerically, this does detract from his methodological messages.)

All parties agree "that the absence of an accurate gold standard is a difficulty for those who evaluate newer diagnostic tests", and to cling to an imperfect gold standard—chlamydia culture in this instance—would doom us never to recognise a better test.

Here my comments are said to "provide no solution as to what researchers should do when attempting to evaluate a test that is demonstrably better than the existing gold standard". True again, apart from the question-begging lurking in the phrase demonstrably better, to which I shall return. I did, however, mean to be constructive when warning that any attempt to overcome gold-standard imperfection is (wrong or) based on assumptions that cannot be checked on clinical data. Marking the limits of construction is itself constructive, is it not?

The assumptions could, of course, be supported by laboratory evidence, such as the finding that "DNA amplification procedures . . . could detect 10<sup>1</sup> organisms, whereas the antigen detection methods [and culture, I presume] had a threshold of greater than 10<sup>4</sup>". In that sense the DNA procedures are already demonstrably better than the existing gold standard. Taking this as a fact implies, however, that one has already decided that they are superior. The old gold standard has then lost its relevance, and one should openly discard it and navigate very carefully towards a clinical evaluation of the new tests, with a judicious combination of sampling and laboratory evidence.

That is the course to steer, rather

than patching something on to the research paradigm geared to error-free gold standards—viz, the usual true false-positive/negative sampling paradigm, as is done in discrepant analysis. At any rate, such a patched-up approach should be seen as a second-line device, which one is willing to give up when critics point to a fault in its foundation.

I would add that several people have indicated that my invited commentary was really too kind to discrepant analysis, *inter alia*, because I took pains to go through several reasons why the resulting bias might not, after all, matter so much.

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## Non-invasive diagnosis of *Pneumocystis carinii* pneumonia

SIR—Jannik Helweg-Larsen and colleagues (Nov 8, p 1363)<sup>1</sup> describe the advantages of an inhibitor-controlled PCR with a touch-down program for the non-invasive diagnosis of *Pneumocystis carinii* on oral washes: touch-down PCR detected *P carinii* DNA in all eight patients with *P carinii* pneumonia whereas standard PCR detected only four. Although initially promising, these results are slightly misleading. The standard PCR protocol is known to be a less sensitive method, and Southern-blot hybridisation of its amplified product is used to improve sensitivity.<sup>2</sup> However as a routine test, Southern-blot hybridisation is expensive, time-consuming, and requires the use of radioactive reagents. We have developed a hemi-nested PCR with the same external primers and an internal primer pAZ102-L2,<sup>2</sup> which is more sensitive than the standard PCR protocol. This test can also be completed within 1 working day and confirms the specificity of the product amplified during the single-step PCR.<sup>3</sup>

We have tested 153 invasive and non-invasive respiratory samples from 66 patients with HIV-1 AIDS and 87 patients with other forms of immunocompromise by the hemi-nested PCR; we also found this technique a useful adjunct to the diagnosis of PCP in patients with forms of immunocompromise other than HIV-1/AIDS. Among patients with HIV-1/AIDS, there was no advantage of the hemi-nested PCR over the standard method. In such patients there is a greater organism load,<sup>4</sup> and so infection can be detected by less invasive methods.

Thus, samples from patient group with HIV-1/AIDS is best tested by a non-invasive method such as oral washes. However, in patients with non-HIV-1/AIDS immunocompromise, non-invasive diagnosis of *P carinii* pneumonia can be quickly achieved with hemi-nested PCR.

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## Unethical promotion of rapid opiate detoxification under anaesthesia (RODA)

SIR—We wish to express our concern about the activity of the CITA organisation (Centro de Investigación y Tratamiento de las Adicciones) founded in Spain by Juan Legarda. CITA claims to have developed a unique and highly successful method of rapid opiate withdrawal detoxification under anaesthesia (RODA) followed by maintenance treatment with naltrexone, for which an international patent (PCT/ES94/100108) has been applied. On the basis of this claim, CITA has been trying to franchise the technique in several countries. They call their treatment Ultra-Rapid Opiate Detoxification (UROD) and have trademarked the term.

The basic RODA technique was developed and described as early as 1988 by Loimer et al,<sup>1</sup> and CITA did not use RODA until late in 1992.<sup>2</sup> Post-detoxification treatment with supervised naltrexone is a well established and effective (though underused) technique, first described in the early 1970s.

CITA publicity claims that treatment is “painless” and entirely safe, but although many patients recover rapidly, some have distressing withdrawal symptoms for several days or even weeks, after treatment—a fact conceded by CITA-International’s medical director. Although no deaths have taken place during anaesthesia, deaths have occurred in the immediate post-

anaesthetic period, including one in a former CITA clinic in London in October, 1996.

CITA’s manipulation of the media is especially deplorable since the hopes and fears of opioid addicts and their families are easily exploited. Typically, they offer “exclusive” interviews to journalists, who generally have no medical knowledge. Despite unvalidated claims for “70% success rates” at 6 months, the only published work indicates relapse rates of around 50% after a year. Recent publicity campaigns in Australia involving CITA and the Megama organisation, headed by former CITA director André Waismann have been criticised in the medical press.<sup>3</sup>

RODA is a useful technique, particularly for those with unusually severe withdrawal symptoms, striking detoxification phobia, or large opioid habits.<sup>4</sup> However, simpler rapid detoxification techniques that use oral sedatives and antiemetics may be adequate for many patients and are very much cheaper.<sup>5</sup> Since the various CITA clinics only offer a single treatment, the advice they give about methods of detoxification may not be truly impartial and in the best interests of the patient. The contract between Legarda’s parent company and the now-defunct British franchise contained an especially objectionable clause requiring CITA-UK to treat a minimum of 240 patients in 6 months or risk losing its franchise—presumably to a more aggressive franchise-holder.<sup>3</sup> Some CITA organisations also require their employees to sign non-disclosure agreements to protect their “trade secrets”. We and others regard such behaviour as unacceptable in an open, international, and fundamentally altruistic profession.

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## Benefits of post-mastectomy radiotherapy

SIR—John Yarnold's Nov 15 commentary<sup>1</sup> examines the role of radiotherapy in reducing breast-cancer mortality in the light of the evidence provided by the Canadian and Danish trials. These two randomised-controlled trials, with a long-term follow-up, showed that post-mastectomy radiotherapy significantly reduced the rate of locoregional recurrence, systemic recurrence, and mortality in premenopausal women with node-positive breast cancer.

We agree with Yarnold's comments that this systemic benefit has been shown in previous trials, but the results did not reach statistical significance because of fatal radiotherapy-related cardiac diseases which can now be avoided with the use of improved radiotherapy techniques.

Yarnold also assumes that radiotherapy mediates this systemic benefit by eliminating the residual locoregional disease, which is the source of future systemic dissemination. However, this assumption does not provide an adequate biological explanation for the effects of radiotherapy in reducing systemic recurrence and mortality from breast cancer. We believe that radiotherapy exerts these systemic effects by affecting the immune system, cytokines, and growth factors. There is increasing evidence that, in women who develop breast cancer, there is an immune promotion of oncogenesis. At least eight studies have shown that the immunoreactivity in patients with an increased risk of developing breast cancer is higher than in healthy cohorts. Robinson and colleagues<sup>2</sup> found that natural-killer-cell activity was higher in women treated for bilateral breast cancer than in women not treated, and decreased with adjuvant tamoxifen therapy. The number of CD4 cells and the CD4/CD8 ratio also decreased with tamoxifen treatment. Stewart and co-workers<sup>3</sup> reported a 25% reduction in breast-cancer incidence in women who were chronically immunosuppressed after organ transplantation.

Depletion of immunocytes probably promotes resistance to cancer growth and metastases. Radiotherapy is known to cause extended T-cell lymphopenia after radiation for breast-cancer treatment.<sup>3</sup> This consequence of radiotherapy may explain its systemic effects in reducing distant metastases and mortality. Certain cytokines and growth factors secreted by cells of the immune system, especially T-

lymphocytes, are emerging as important factors in the regulation of oestrogen synthesis in peripheral tissues and breast-cancer cells.<sup>5</sup> These cytokines and growth factors act to increase oestrogen synthesis by the stimulation of aromatase, oestrone sulphatase, and oestradiol dehydrogenase,<sup>5</sup> thus creating an oestrogenic environment that favours breast-cancer growth.

Radiotherapy is likely to decrease the production of these cytokines and growth factors, and so lead to decreased activities of oestrogen synthesising enzymes. This sequence of events may provide a biological explanation for the results from the Danish and Canadian trials.

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SIR—In his Nov 15 commentary,<sup>1</sup> John Yarnold highlights the long-term follow-up of two randomised trials<sup>2,3</sup> that report a significant 9% and 10% year-survival advantage, respectively, at 10 years with the addition of post-mastectomy locoregional radiotherapy to adjuvant treatment.

Such a clinically significant survival advantage is conferred, as Yarnold states, to premenopausal node-positive women in both trials. However, in the Danish trial,<sup>2</sup> women with other high risk factors (eg, tumours >5 cm, invasion of skin, pectoral fascia) also had improved survival. By contrast, the 1995 overview of randomised trials of radiotherapy<sup>4</sup> did not identify a survival advantage of this magnitude. In some of the trials included in the overview (eg, the Manchester Q trial<sup>5</sup>) the dosage would by current standards be deemed inadequate and less likely to sterilise microscopic disease.

Adequate radiation dosage is clearly important if the explanation of the

survival advantage shown in the Danish and Canadian trials is the sterilisation of locoregional disease which might otherwise have given rise to distant metastases. In the much larger Danish trial<sup>2</sup> the dosage and fractionation was delivered with an internationally accepted dose and fractionation schedule (50 Gy in 25 fractions over 5 weeks at megavoltage). There is a real danger that the overview process may underestimate important survival advantages from post-mastectomy radiotherapy that well conducted, randomised controlled trials have clearly identified.

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## Child labour

SIR—David Parker (Nov 8, p 1395)<sup>1</sup> provides us with a timely reminder of some of the effects of child labour, with the International Conference on Child Labour having just taken place in Oslo. However, he concentrates exclusively on children who work in industrial settings in developing countries and fails to mention that children routinely work in all countries. In some circumstances this work can actually be a valuable experience in the child's interests.

Although highly visible, most child labourers are in fact not employed in industry, and the high-profile and much maligned export industry probably accounts for less than 5% of all child labour.<sup>2</sup> Most children who work do so in domestic and rural settings, much of this goes on unrecognised, and research into the health and social effects of such labour is limited. Parker's focus could feed the myth that a total ban on all export goods produced by child labourers would make a positive contribution to

resolving this issue. Such bans have not been effective in the past, and many children have been forced as a result into even more harmful employment.

Of course children should not be involved in hazardous or exploitative employment, but child labour is a complex issue and needs to be opened up for much fuller discussion. The families of child labourers, and not least the children themselves, have an important contribution to make to this debate and, unlike recent events in Oslo where children were prevented from speaking, their participation should be encouraged.

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- 1 Parker D. Health effects of child labour. *Lancet* 1997; **350**: 1395-96.
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## Ethics of HIV trials

SIR—Your Nov 22 correspondents (p 1546)<sup>1</sup> who attack your Sept 27 editorial<sup>2</sup> (in which you support us in our efforts to redesign placebo-controlled trials of zidovudine to prevent perinatal HIV transmission so that all women receive active treatment),<sup>3</sup> question the applicability of the results of the original placebo-controlled trial to the developing world context. In that trial, ACTG 076, the perinatal HIV transmission rate in a non-breastfeeding population was reduced from 23% to 8% by a zidovudine regimen that included prepartum and intrapartum administration to the mother as well as to the newborn child.<sup>4</sup>

The Centers for Disease Control and Prevention (CDC), for example, claim that because of cost and logistical barriers, the 076 regimen, as Kevin De Cock and colleagues<sup>1</sup> say, "has not been implemented in developing countries". Yet, data from three developing or underdeveloped countries that have implemented regimens similar to ACTG 076 show perinatal transmission rates remarkably similar to that in ACTG 076 itself: Thailand 8% (Phanupak P, personal communication), Poland 8%, and Bahamas 12%. The CDC also states that the feasibility of oral zidovudine during labour "has not yet been studied". Ironically, it was a trial conducted by CDC researchers in Thailand (including two who signed the CDC letter to *The Lancet*) that demonstrated similar drug levels in women receiving oral or intravenous

zidovudine during labour.

R D Semba<sup>1</sup> claims that placebo-controlled trials are justified because many women in developing countries breastfeed. But breastfeeding is estimated to result in perinatal transmission in 14% of women, and the ACTG 076 regimen reduced transmission by 15% compared with placebo. Therefore, the only way the 076 regimen could be no better than placebo would be if every woman whose HIV transmission was prevented by 076 now passed on HIV by breastfeeding—an unlikely event. The real question for Semba is how he can justify not providing alternatives to breastfeeding to HIV-1-positive women in his studies.

Finally, P A Cooper<sup>1</sup> points out that women in developing countries may attend antenatal clinics only late in pregnancy. However, CDC recommended in 1994 that at least some American women presenting at greater than 34 weeks of gestation receive zidovudine and that it be offered to women who present in labour.<sup>5</sup> More fundamentally, data from the 076 study itself show that there was no univariate relation between duration of therapy (mean 17 *vs* 7 weeks) before delivery and effectiveness in reducing HIV

transmission compared with placebo.<sup>3</sup>

Rather than offering weak supposedly scientific rationale for these trials, these authors should accept that the game is up: one study, according to the *New York Times* (Oct 24, 1997), has recently eliminated its placebo group, and more are likely to follow.

A full reference list is available from the authors or *The Lancet*, on request.

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- 5 Centers for Disease Control and Prevention. Recommendations for the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. *MMWR* 1994; **43**: 8-12.

## DEPARTMENT OF ERROR

*Randomised comparison of combined step-down prednisolone, methotrexate, and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis*—In this article by Maarten Boers and colleagues (Aug 2, p 309), the dose of methotrexate given in figures 1 and 2 should be 7.5 mg/week, as stated in the text, not 7.5 mg/day.

*Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials*—In table 3 in this article by Klaus Linde and colleagues (Sept 20, p 834), the odds ratio (95% CI) for predefined main outcome should have read 2.27 (1.62, 3.18), and that for complex homoeopathy should have read 2.94 (2.12, 4.08). The diagram of the odds ratios is correct. In addition, in table 4, the odds ratio for Wiesenauer<sup>sm</sup> should have read 1.28 (0.64, 2.53). In the same table, the odds ratios for the pooled fixed effects and the pooled random effects models should both have read 1.87 (1.37, 2.56).

*Life, Death and Decisions*—We apologise to Hazel McHaffie and Peter Fowlie, the authors of this book, whose names were misspelt in our review (Sept 27, p 967); the publishers were Hochland and Hochland, Hale, Cheshire.

*Lothian Surgical Audit: a 15-year experience of improvement in surgical practice through regional computerised audit*—In this review by R J Aitken and colleagues (Sept 13, p 800), the solid points and open points in figure 1 were erroneously reversed. The correct figure is shown below.

