

CORRESPONDENCE

Effect of zidovudine on perinatal HIV-1 transmission and maternal viral load

Sir—Nathan Shaffer and colleagues (March 6, p 773)¹ report that in a randomised placebo-controlled trial in Thailand, a short course of antenatal zidovudine administered from 36 weeks' gestation until delivery reduced perinatal HIV-1 transmission by 50%. The reduction in transmission and maternal viral load results observed in the Thai trial differed from those observed in an earlier US French trial, Pediatric AIDS Clinical Trials Group (PACTG) protocol 076, of a longer maternal and neonatal zidovudine regimen.^{2,3} We did additional analyses of data from PACTG 076 to gain further insight into these differences.

Shaffer and colleagues found that although short-course zidovudine reduced perinatal transmission by 50% overall (95% CI 15–71), presumed intrapartum transmission was reduced significantly (61% reduction [19–82]), but presumed in-utero transmission was not (29% reduction [–63 to 69]). In PACTG 076, the overall reduction in transmission was 68% (40–82).² On the basis of cases for which presumed timing of transmission could be classified,⁴ the reductions in presumed transmission in utero and intrapartum were significant and of similar magnitude (table). The conclusions did not change when the unclassifiable transmissions were assumed to be all in utero in one treatment group and all intrapartum in the other (data not shown).

Shaffer and colleagues also reported a larger net reduction in plasma HIV-1 RNA load from entry to delivery, compared with PACTG 076 (0.56 log₁₀

vs 0.24 log₁₀ copies/mL). Of the explanations they proposed, we could address only one with data: their conjecture that in PACTG 076 there may have been a larger reduction in viral load in the first few weeks of treatment, followed by a rebound before delivery. We had insufficient data to estimate the RNA reduction after 4 weeks of zidovudine treatment to allow a direct comparison, but we found no clear evidence of a larger early decrease in RNA on the basis of an analysis of median change in plasma HIV RNA loads according to quartile of treatment duration (net median RNA reduction 0.16, 0.41, 0.20, and 0.24 log₁₀ copies/mL with <7.3, 7.3–11.3, 11.4–16.9 and ≥17 weeks of treatment, respectively).

Finally, the two studies differed in the estimated proportion of zidovudine treatment effect explained (PTE) by maternal plasma HIV-1 RNA load at delivery, which was 80% (36–336) in the Thai study and 11% (–0.5 to 32) in PACTG 076. We had insufficient data to calculate PTE according to treatment duration. However, it is difficult to draw reliable conclusions from such PTE analyses about the relative importance of viral load reduction versus fetal prophylaxis, because of the lack of a measure of fetal prophylaxis and the wide CIs, which can extend beyond 0% or 100%.⁵ A meta-analysis of the Thai, PACTG 076, and other zidovudine trials might yield further insight. Nevertheless, the table suggests that the full PACTG 076 zidovudine regimen should continue to be recommended for prophylaxis of

perinatal HIV-1 transmission in countries that can implement it.

This work was supported by the Statistical and Data Management Center of the Pediatric AIDS Clinical Trials Group, under National Institute of Allergy and Infectious Diseases cooperative agreement no U01 AI41110.

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Sir—Reports on progress in prevention of vertical HIV-1 transmission, such as that by Nathan Shaffer and colleagues,¹ include discussion of the ethical principle that trial participants should be assured of the highest standard of care practically available in the host country, a point that is also made in the consensus statement of the Perinatal HIV Intervention Research in Developing Countries Workshop Participants (March 6, p 832).² In Bangkok, Médecins Sans Frontières (MSF) provides home care to people with HIV/AIDS whose basic needs have not been met by the health-care system,

	Number infected	Total	Transmission risk (95% CI)	p*	Efficacy (95% CI)
In utero†					
Zidovudine	4	192	2% (1–5)	0.005	75% (27–92)
Placebo	16	190	8% (5–13)		
Intrapartum‡					
Zidovudine	6	188	3% (1–7)	<0.001	75% (39–90)
Placebo	22	174	13% (8–18)		

Efficacy = 1 – risk ratio in zidovudine versus placebo group.

*Pearson χ^2 test. †In-utero transmission risk is number of infants infected in utero divided by total number of infants.

‡Intrapartum transmission risk is number of infants infected intrapartum divided by sum of all uninfected infants plus number of infants infected intrapartum (infants infected in utero excluded because no longer at risk).

Zidovudine efficacy by presumed timing of perinatal HIV-1 transmission in PACTG 076

including those specialist hospitals that are participating in clinical trials of treatments for HIV/AIDS.

I report the case of a study participant in the Bangkok perinatal HIV-1 transmission trial. She had symptomatic HIV-1 infection (oral candidosis, pruritic papular dermatitis, and cervical lymphadenopathy) when she was enrolled in the study at 36 weeks' gestation in November, 1997. It was not until 7 months after enrolment that she was prescribed trimethoprim-sulphamethoxazole as prophylaxis for *Pneumocystis carinii* pneumonia by the study physicians and referred for medical care of her symptomatic HIV-1 infection.

She consulted the study physicians 10 weeks later with fever and weight loss, but was not investigated nor offered treatment. She turned to MSF's AIDS programme for support. *P. carinii* pneumonia was diagnosed and treated. She improved with treatment, but later died of another AIDS-related illness. Her child has symptomatic HIV-1 infection and is being treated with dual therapy (zidovudine and didanosine) in the paediatric department of the study hospital.

This case gives a picture of the range of investigation and treatment available for patients with HIV/AIDS in public hospitals in Thailand. Prophylaxis of *P. carinii* pneumonia with trimethoprim-sulphamethoxazole in cases of symptomatic HIV-1 infection is the policy of the Ministry of Public Health³ but is not consistently prescribed. Many patients are not told about treatment options, even though antiretroviral drugs are available. Of patients who attend specialist HIV/AIDS departments, about 5% take dual therapy and 1% take triple therapy. Most patients need to pay the full cost, which few can afford, but children commonly receive free treatment. The well publicised gap exists not only between developed and developing nations, but also between different departments of the same hospital in Thailand. The task of defining an appropriate standard of care for trial participants is therefore difficult,² but surely includes access to basic care services as a guaranteed minimum.

Some argue that investigators from the developed world have a responsibility for creating ethical structures in developing countries:⁴ these could include support groups for people with HIV/AIDS in trial hospitals, which could then provide advocacy for study participants. Such groups are already active in some Bangkok hospitals, but not in the hospitals collaborating in the Bangkok

perinatal HIV-1 transmission trial. I believe that international non-governmental organisations also have responsibility.

I thank Wimol Siriwasin of Rajvithi Hospital for providing a case summary before referral to MSF, and the trial sponsors for discussing the case.

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- 1 Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 in Bangkok, Thailand: a randomised controlled trial. *Lancet* 1999; **353**: 773-80.
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Authors' reply

Sir—The new PACTG 076 data provided by David Shapiro and colleagues highlight several key questions. What is the role of viral load reduction in the prevention of perinatal HIV-1 transmission? Does viral load reduction affect both in-utero transmission and intrapartum transmission? And does neonatal prophylaxis provide a different, overriding mechanism of protection? Our data indicate that the short-course Bangkok regimen primarily prevents intrapartum transmission, which accounts for about three quarters of transmission in the absence of breastfeeding.¹ The PACTG 076 data suggest that longer antenatal treatment also reduces in-utero transmission, and that infant treatment also helps reduce in-utero and intrapartum transmission. Why reduction in viral load was so low in the PACTG 076 trial is not clear; specimen processing, assay methods, adherence, or viral subtype may be factors.² We agree with Shapiro and colleagues that a meta-analysis of the Bangkok, PACTG 076, and other trials may help us to better understand how and when zidovudine protects against perinatal transmission.

In response to David Wilson, our study was designed to assess antenatal zidovudine for reducing perinatal HIV-1 transmission. In addition to covering all protocol costs, including infant formula, the study provided direct support for mothers and infants for non-study medications, admission to hospital, laboratory tests, and transportation. Medical care was

provided by coinvestigator obstetricians and paediatricians, who are responsible for providing care for HIV-1-infected pregnant women and their children at the study hospitals.

Because obstetricians do not treat serious HIV-1-related conditions and in the Thai system do not prescribe antiretroviral drugs for treatment, women with advanced disease are referred to the medical departments in the study hospitals or elsewhere. Study nurses and social workers help participants to obtain medical care and social support within this system.

To define and provide appropriate treatment for HIV-1 infection in a country such as Thailand, with limited resources and high HIV-1 prevalence, is a challenge. There is frequently a gap between treatment guidelines and practice. Resources to pay for treatment need to be pieced together from several sources, such as government and hospital funds, non-governmental organisations, research projects, charity, insurance, and personal funds. More resources per patient are available for HIV-1-infected children, because there are fewer infected children than adults, and the cost per treatment is less. In addition to financial limitations, hospital care and referral systems for people with HIV-1 infection are stretched by high demand. A 1995 World Bank and WHO review advised Thailand to focus its limited HIV drug resources on prevention of perinatal HIV-1 infection.³

We agree that advocacy groups should help patients, whether in clinical trials or not, should obtain the best care and social support they can, and we welcome their advocacy for increased resources to care for people with HIV-1. At our invitation, Médecins Sans Frontières staff who are planning to initiate short-course antenatal zidovudine at several district study hospitals, have visited our study hospitals, where we care for nearly 800 HIV-1-infected pregnant women each year and now provide short-course zidovudine routinely to reduce the risk of perinatal HIV-1 transmission.

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child HIV transmission, Bangkok, Thailand. *AIDS* 1999; **13**: 407-14.

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Sir—The findings of Nathan Shaffer and colleagues¹ confirm that short-course zidovudine can play a part in prevention of perinatal infection. Lynn Mofenson's accompanying commentary² provides a list of requirements to implement these regimens. Her list gives everything we have not been able to realise in many years of development cooperation, among others antenatal care to pregnant women. In many developing countries it has been impossible to reduce maternal mortality, to provide full immunisation coverage, to get rid of unnecessary infant mortality with only biomedical interventions. Will it be suddenly different in the case of the HIV-1 epidemic?

There are different views on the most effective way of dealing with the epidemic. The medical paradigm puts emphasis on the individual. Health is seen as a product, and progress in medical sciences is presented as a series of new technological products. The idea that individuals can influence their behaviour by making correct choices is linked to the idea that our society is organised through the principle of the market. By contrast, in the development paradigm, the emphasis is not on the individual and risk, but on society and vulnerability.³ Interventions based on the development paradigm target communities, put emphasis on solidarity and empowerment, and try to improve the conditions in which people have to survive.

Seidel⁴ makes a distinction in approaches of "control and exclusion" and those of "rights and empowerment". According to him, the medical discourse inhibits empowerment, participation, and solidarity, and as such belongs to the discourse of control and exclusion. The conflict between these two paradigms is reflected in the heated debate on the use of zidovudine for preventions of perinatal infection in South Africa. Pregnant women have to be tested routinely to identify those women to whose offspring zidovudine treatment will have any benefit. Women have to be educated to understand the effect of testing for their survival strategies. What is the most effective investment of

funds, human resources, and time to have a sustainable and long-term impact? This question is especially important because the medical paradigm leads to a very costly intervention, leaving little room for substantial funding of other preventive activities. This issue is interesting in view of the planned boycott of some US scientists of the 13th World AIDS Conference in Durban (South Africa) in the year 2000. They protested against the decision by South Africa's health minister, Nkosasana Zuma, to abandon a pilot programme to administer zidovudine to HIV-1-infected pregnant women. Some AIDS researchers from developing countries reacted to the boycott threat by calling this an arrogant attitude. In the market-oriented individualist culture in which consumers' choices are not fiction and in which therapies are available, basing of AIDS policies on the medical paradigm does not seem strange.

In developing countries, the development paradigms is vital. There is a need to bring together stakeholders who represent these different perspectives to look for sustainable interventions and not blackmail societies to adopt biomedical approaches that are effective under favourable conditions. That is what I miss in the consensus statement⁵ that has a writing group of 11 with one representative from a developing country, reporting about a workshop of 40 participants with only seven from developing countries. To me this looks like an unacceptable under-representation of those from developing countries.

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Sir—Since the publication last July of the UNAIDS, UNICEF, and WHO policy statement (<http://www.unaids.org/unaids/document/mother%2Dto%2Dchild/infant.html>, accessed on April 12, 1999) on HIV and infant feeding, the International Child Health Group of the Royal College of Paediatrics and Child Health has been unhappy about this endorsement of artificial feeding. The policy statement shows signs of strain in its construction of consensus, but finally decrees it to be important "that women be empowered to make fully informed decisions about infant feeding", and then that with "nutritionally adequate breast-milk substitutes that are safely prepared and fed to them, they [infants of mothers living with HIV] are at less risk of illness and death if they are not breast-fed". As a global policy, this consensus has more potential for daily harm than good, because despite the post-industrialisation force for empowerment of women and freedom of choice, it is in countries where deprivation is greatest and therefore bottlefeeding most dangerous that a woman is more likely to make a disastrous choice on the basis of false information. Surely it would be better, with the prevailing and foreseeable poverty in most of the world, to promote exclusive breastfeeding for 4-6 months. We should also be attempting to reduce mother-to-child transmission by increasing the use of short-course zidovudine in any setting in which this is realistic, while working on the many factors that contribute to HIV infection and that prevent social and economic development. With further reports of the effectiveness of advances on the medical prevention of vertical transmission to breastfed babies in regions of poverty,¹⁻³ UNAIDS, UNICEF, and WHO should urgently revise their policy statement (which does not mention perinatal antiviral therapy) and declare their uncompromising affirmation of breastfeeding for all, in the interests of the women and children in most of the world.

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Debate on Di Bella therapy

Sir—In their report on the Di Bella alternative therapy for cancer, Rodolfo Passalacqua and colleagues (April 17, p 1310)¹ contend that media coverage of alternative therapies may provide false hopes. Inferences are made that such coverage could lead to three things: depression and anxiety of the patient, distrust of oncologists, and abandonment of traditional treatments.

In Canada there was a widely publicised case involving Tyrell, a 13-year-old boy with osteosarcoma. A court order was issued on March 19, 1999, for further chemotherapy with or without leg amputation, against the wishes of Tyrell and his parents. He immediately sought alternative therapy outside Canada. Apparently, within 24 h, the alternative medicine practitioners had Tyrell up and walking and completely off pain medication. While it is still early, Tyrell's future seems a little more promising than the terminal death sentence given just a short while ago. Unlike the suggestions of Passalacqua and colleagues, when faced with alternative therapies Tyrell was no longer depressed or anxious. However, the family must now face the legal problems that await them back in Canada with respect to the court order for chemotherapy and amputation.

An interesting feature of this case is that the choice for alternative therapy did not prevent Tyrell from receiving traditional therapy initially. However, given the lack of transparency and choice of treatment options, especially when children are involved, among the traditional oncology community, I think Passalacqua and colleagues are correct that there is a distrust of oncologists. However, this distrust has little to do with media coverage and more to do with the lack of evidence-based available treatment options.

A new cancer concept, anticellular senescence,^{2,3} seems to provide a better explanation and working hypothesis of what cancer is and thus how to treat it.* This alternative view on the nature of cancer might offer more hope for a cure than the currently accepted view,

which wrongly assumes cancer has something to do directly with high proliferation rates.³

The false hope of which Passalacqua and colleagues speak seems a more appropriate description for the traditional approaches to cancer therapy, since they are based largely on unfounded premises, such as increased proliferation rates. Furthermore, there are hundreds of published randomised clinical trials that indicate that radiation and chemotherapy do not provide much if any of a survival advantage, even in the best case scenarios, although notable exceptions exist (testicular cancer, retinoblastoma, non-Hodgkin lymphoma). For the traditional cytotoxic approach to cancer, it is no longer a question of false hope, but one of malignant malpractice.

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- 1 Passalacqua R, Campione F, Caminiti C, et al. Patients' opinions, feelings, and attitudes after a campaign to promote the Di Bella therapy. *Lancet* 1999; **353**: 1310-14.
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Sir—Rodolfo Passalacqua and co-workers¹ nicely show that a media campaign to promote so-called miraculous anticancer therapy greatly influenced both the opinions and attitudes of cancer patients. However, they did not investigate whether the negative results of the subsequent phase II study in Italy on the Di Bella therapy² changed such opinions and attitudes.

In March, 1998, when the mass media campaign was at its peak, and later on in September, 1998, when the negative results of the Di Bella therapy were made public and the Di Bella therapy was officially declared ineffective, 100 patients with cancer who were receiving conventional anticancer therapies at the inpatient section of the Division of Medical Oncology A of the National Cancer Institute Aviano were surveyed on the Di Bella therapy through a nine-item questionnaire. The main question was: "Would you choose to be treated with the Di Bella therapy?". In March, 1998, 70% of the patients said they would choose Di Bella therapy, whereas in September, only 30% would choose the therapy. Another

important question was "After the negative results of the Di Bella therapy are you more confident with the traditional oncological anticancer therapies available today?"—in September, 80% replied yes.

Our study shows that the prompt response, although controversial,³ from the Italian scientific community with a formal prospective phase II study² was able to substantially change the opinions and attitudes of cancer patients with respect to the unconventional Di Bella therapy proposed by the Italian media as a miraculous anticancer therapy.

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Stroke from traumatic arterial dissection

Sir—Adel Malek and colleagues (April 17, p 1324)¹ report the case of a strangled wife, in whom high bilateral carotid dissection occurred after attempted strangulation by her spouse.

The Canadian Stroke Consortium is doing a prospective survey of extracranial arterial dissection. Such analysis allows a more detailed current history with respect to trauma. We have serious reservations that spontaneous dissection ever occurs, and so far have been able to document direct trauma in 21 of 27 cases of ischaemic stroke, all verified by angiography (22 vertebral and five carotid). Of 22 vertebral artery dissections, 19 were traumatic, whereas in carotid dissections only two were traumatic. In 15 cases, stroke occurred within 48 h after therapeutic manipulation of the neck, causing vertebral dissection at C1 level, and in the remaining five vertebral cases there were other causes, such as severe accidental forced hyperextension of the neck. The strangled wife showed bilateral carotid dissection, and eight of our cases (six vertebral and two carotid) also had bilateral dissections, suggesting an inherent weakness of the arterial wall seen in skin biopsy samples of patients with dissection in whom collagen abnormalities were shown.²

*Panel of the new cancer concept available on The Lancet's website (<http://www.thelancet.com>).

Although we doubt that domestic violence causing stroke from extracranial arterial dissection is as common as Malek and colleagues imply, we do believe that obtaining a careful history for previous trauma, especially neck manipulation, may explain otherwise cryptogenic strokes, especially in the young.

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- 1 Malek AM, Higashida RT, Phatouros CC, Halbach VV. A strangled wife. *Lancet* 1999; **353**: 1324.
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Sir—A M Malek and colleagues¹ report a young woman with bilateral internal carotid stenosis after manual strangulation. This case reminds us of a 40-year-old woman who was admitted to our department for isolated left internal jugular vein thrombosis. No risk factor for thrombosis was found, including the use of oestrogen, ovarian hyperstimulation, or antiphospholipid antibody syndrome. Antithrombin, protein C, protein S, and activated protein C resistance were within the normal range. When questioned about possible direct trauma to her neck, she reported that her husband had tried to strangle her 3 weeks before. Evolution was uncomplicated after 3 months of oral anticoagulant.

Internal jugular vein thrombosis, an unusual site of venous thrombosis, has been described mainly in patients with ovarian hyperstimulation syndrome,² after trauma or cervical traction.^{3,4} Both carotid artery dissection and unexplained isolated thrombosis of jugular vein must raise the question of strangulation and domestic violence.

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- 1 Malek AM, Higashida RT, Phatouros CC, Halbach VV. A strangled wife. *Lancet* 1999; **353**: 1324.
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Tuberculosis chemoprophylaxis for infants and teenagers

Sir—P R Donald (March 20, p 1001)¹ recommends preventive therapy for tuberculosis for infected infants and infected HIV-exposed teenagers, in high tuberculosis prevalence countries. Incidence of active tuberculosis among tuberculosis-infected infants (<1 year) was estimated to be nine in 100 in South Africa, and Donald uses these data to support his plea for chemoprophylaxis against the disease in this population. Although not explicitly stated, such high rates must have been estimated for a population not BCG immunised.

BCG vaccination of newborn babies and infants reduces the risk of tuberculosis by over 50% on average.² In 1996, BCG coverage at 1 year was 64% in sub-Saharan Africa, 91% in South East Asia, and 95% in South Africa.³ What then is the relevance of recommending tuberculosis preventive therapy for infants in high tuberculosis incidence countries where BCG coverage is high?

In a population of BCG-immunised, tuberculosis-infected infants in South Africa or any other country with similar tuberculosis incidence, the number to treat with tuberculosis chemoprophylaxis to prevent one case would in theory be no less than 22 (with 100 infected, nine cases, and 50% BCG protection). This estimate assumes that infected infants can be adequately targeted. Unfortunately the test used to diagnose tuberculosis infection (tuberculin skin test) is notoriously difficult to interpret after BCG vaccination; moreover, the test is often not available in less-developed countries. An alternative would be to systematically give chemoprophylaxis to all infants at high risk of infection (close contacts of smear-positive tuberculosis cases), but the number to treat would be even less favourable. M Donald also advocates preventive therapy for tuberculosis-infected pregnant teenagers and close contacts of smear-positive tuberculosis cases, in settings where HIV incidence is high. These groups, it is argued, are, or soon will be, sexually active, and therefore at risk of HIV infection; and the risk of developing active tuberculosis increases dramatically among people dually infected with tuberculosis and HIV. First, HIV-uninfected people cannot be seen as a priority for preventive therapy compared with HIV-infected people. Second, a short course of preventive therapy offers some protection against tuberculosis in people with tuberculosis

and HIV infection, at least in the short term, but long-term benefits remain to be shown⁴ because a short course of preventive therapy cannot prevent tuberculosis reinfection. Several workers have reported that recent transmission accounts for a substantial number of tuberculosis cases in adults, for instance more than 50% in a cohort of HIV-1-infected female sex workers in Kenya.⁵ Should teenagers be given preventive therapy for the rest of their sexually active life?

Tuberculosis control programmes in countries with high tuberculosis incidence are struggling to achieve acceptable cure rates and detection rates, and very few countries have met these priorities. Implementing preventive therapy runs the risk of diverting resources from efforts to attain these priorities. Where these priorities have been met, preventive therapy should first focus on groups in which it is mostly likely to be cost effective (HIV-infected people) and not on BCG-immunised infants or HIV-uninfected teenagers.

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Author's reply

Sir—M-L Lambert's comments about my proposals for protecting children against tuberculosis are appreciated. With respect to young children and infants exposed to sputum smear-positive tuberculosis, the possible protective effect of BCG may be overwhelmed by "excessive and indiscriminate exposure to . . . disease".¹ Many children born in communities with a high incidence of tuberculosis will be born in homes, or return to homes in which a case of sputum smear-positive tuberculosis may be present immediately after birth, before BCG can be expected to have any effect. Even if BCG has a 50% protective efficacy, a large number of infants are still unnecessarily exposed

to serious forms of tuberculosis, such as miliary tuberculosis and tuberculous meningitis, because of the very high incidence of disease after infection at this age. Many of these children are easily identifiable as contacts of sputum smear-positive adults. These adults must themselves be treated and it would surely cause a small increase in workload if the infected contact were to receive prophylaxis at the same time as the adult index case.

Working among communities with a very high rate of tuberculosis and HIV-infection I am only too well aware of the consequences of diverting resources from the main objective of identifying and treating adults with sputum smear-positive disease. However, we are not winning the battle and we need to be more adventurous in assessing all possible options. I do not suggest the immediate incorporation of various forms of preventive therapy in national programmes without first evaluating their value, but it might well be worth assessing the impact of high dose, fixed combination, multiple drug, short course, intermittent prophylaxis in certain situations. Since recent infection may account for a large number of cases of tuberculosis in adults, it would be interesting to know what the effect of high dose, short course, intermittent chemoprophylaxis might be if given to all close household contacts of an index case. This therapy could possibly prevent the development of sputum smear-positive tuberculosis in a certain number of individuals and so reduce the annual risk of infection, which must be the ultimate aim of all our tuberculosis control activities.

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- 1 Rosenthal SR, Loewinson E, Graham ML, et al. BCG vaccination in tuberculous households. *Am Rev Respir Dis* 1961; **84**: 690-704.

Promotion of exclusive breastfeeding

Sir—Ardythe Morrow and colleagues (April 10, p 1226)¹ report the findings of a randomised controlled trial of peer counselling to promote exclusive breastfeeding and make an important contribution to the discussions about effective methods to increase breastfeeding. However, we have three concerns about the generalisability of their findings. The first concern is that the small number of women who may not have been representative of the population as a whole.

Representativeness may have been further reduced by the randomisation process which was by community rather than individual.

Our second concern arises from two key definitions used by the investigators. Morrow and colleagues state that "exclusive breastfeeding was defined by WHO criteria". However, they also included mothers who introduced supplementary feeding and then returned to exclusive breastfeeding as exclusive breastfeeders. According to the WHO criteria,² exclusive breastfeeding means only breastmilk with no other foods or liquids (apart from vitamins or medicines) from birth. The mothers in this study should arguably have been classified as predominantly breastfeeders. The health outcome for a baby who has received any supplementary feeding before age 3 months differs significantly from that of a baby who has been exclusively breastfed.³ The term peer counselling in the context of infant feeding usually refers to a woman who has previously successfully breastfed her baby for a minimum period. Morrow and colleagues used specially trained field workers rather than peer counsellors in the conventional sense.

Finally, Morrow and colleagues' study should be viewed in its cultural context. In Mexico breastfeeding is highly valued and initiation rates are high. The extent to which the study's findings can be applied to a more developed country is questionable. We investigated breastfeeding in a part of Scotland where bottlefeeding is the norm and found that most mothers in socially disadvantaged urban estates do not wish to breastfeed and those who do may find success elusive in an unsupportive environment.⁴ Morrow and colleagues' assertion that "the finding of this study are relevant to many countries" is unlikely to hold true in our region which has one of the lowest rates of breastfeeding in Europe.²

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- 1 Morrow AL, Guerrero ML, Shults J, et al. Efficacy of home-based peer counselling to promote exclusive breastfeeding: a randomised controlled trial. *Lancet* 1999; **353**: 1226-31.
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intervention designed to increase the prevalence of breastfeeding in a socially disadvantaged urban area. *Prenat Neonat Med* 1996; **1** (suppl 1): 130.

Authors' reply

Sir—The study included nearly all the eligible mothers in San Pedro Martir, and thus was representative of our target population. Sample size and cluster randomisation do not affect the representativeness of our study population. We entirely agree with Rhona McInnes and David Stone that our study should be viewed in its cultural context. We showed the efficacy of timely and accessible counselling to increase exclusive breastfeeding among mothers who live in a culture that values breastfeeding. In cultures that do not value breastfeeding, we would not expect such a dramatic increase. Nevertheless, the need for social and informational support for mothers who want to breastfeed seems to be universal, which is implied by McInnes and Stone's comment that in Scotland the few who elect to breastfeed "find success elusive in an unsupportive environment". Thus, peer counselling is used worldwide for breastfeeding promotion and support. Among the low-income populations in the US Women, Infants and Children Program, in which breastfeeding rates historically have been low, peer counselling increased rates of breastfeeding.¹

Although we agree that breastfeeding peer counsellors are usually mothers who have successfully breastfed, Eng and colleagues² point out that peer counselling can take various forms. The peer counsellors in our study met accepted definitions: they were residents of the same community, their educational attainment was typical of the community, and they were not health professionals. Our counsellors were trained by La Leche League, which has trained lay counsellors worldwide. Indeed, research indicates that the success of peer counsellors is dependent on their training and the support they receive from health professionals.¹ As a result, WHO, UNICEF, and other organisations have developed training courses and materials to help to ensure that breastfeeding counsellors are adequately prepared.³

We applied the WHO criteria for exclusive breastfeeding (no other liquids or foods given), with two specified time orientations. As we noted in our report, exclusive breastfeeding for up to 3 months postpartum was maintained by 50% of mother-infant pairs in the group visited on six

occasions, by 38% in those visited on three occasions, and 12% in the control group. However, we also reported that an additional 17% and 12% of mother-infant pairs listed on six and three occasions, respectively, were exclusively breastfeeding at 3 months but did not maintain that status at each assessment. McInnes and Stone correctly note the bad news: some mothers who were exclusive breastfeeders at 3 months did not maintain that status for the entire recommended period and thus incurred increased risks for infant health. By contrast, we see the good news: that a substantial proportion of mothers who did not maintain exclusive breastfeeding for the entire recommended period returned to exclusive breastfeeding—an important observation for population behaviour change.

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Naturally acquired immunity to vivax malaria

Sir—Ernay Camargo and colleagues (April 24, p 1415)¹ report that symptom-free carriers of *Plasmodium vivax* were found among native Amazonians living in an endemic area of vivax malaria. They state that these findings reflect a certain degree of premunition in the population, similar to that described for falciparum malaria, and that this has not been reported previously.

In our study site on the western border of Thailand, vivax malaria is endemic, and symptomless carriage is not rare. In 1992, we followed two cohorts to describe the epidemiology of malaria in this area.² Malaria cases were diagnosed by a combination of active and passive detection. Thus, we were able to identify symptom-free carriers and to follow them.

The incidence of vivax malaria was 0.5 infections per person and per year

and the age-specific pattern showed a steady decrease with age, reflecting increasing premunition in the population. Moreover, individuals with patent *P vivax* parasitaemia were more likely to be symptomfree than those with *P falciparum* infections: 43% (81/137) vs 16% (15/92) ($p < 0.001$) in the cohort of schoolchildren, and 18% (35/190) vs 7% (9/130) ($p = 0.003$) in the cohort of participants of all ages. During active screenings, 59% (81/137) of schoolchildren and 48% (37/77) of all participants in whom *P vivax* was detected were symptomfree at the time of the screening and remained so 3 days later when they were called back and treated. By that time spontaneous clearance of the parasite had occurred in some individuals and the others had low parasite counts. These symptom-free *P vivax* carriers were treated and thus it was not known if they would have developed symptoms subsequently.

From 1995 to 1996, we conducted a drug trial to assess the efficacy of chloroquine for the treatment of vivax malaria.³ Each patient was followed for a minimum of 63 days. When a patient presented with *P vivax* on a blood smear, but without symptoms, he or she was not retreated and was followed weekly. 22 (15%) of the 143 patients with *P vivax* relapses or reinfections remained symptom-free for some weeks (one for 7 weeks) and eventually cleared parasites spontaneously. The geometric mean of parasite densities in symptom-free carriers was 384 (range 39-4600) parasites per μL .

Other workers have reported that in areas endemic for *P vivax*, morbidity is confined to early life, reflecting the rapid development of clinical immunity.^{4,5} Naturally acquired immunity to vivax malaria exists and its development seems more rapid than for falciparum malaria.

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Thrombosis in pregnancy

Sir—Ian Greer (April 10, p 1258)¹ is concerned mainly with the diagnosis and treatment of proximal deep venous thrombosis (DVT) by venous ultrasonography. The notion of not having to diagnose and treat isolated distal DVT during pregnancy is questionable, and this practice may be risky because it is mainly based on extrapolation from studies that have excluded pregnant women.^{2,3}

In day-to-day clinical practice in the UK, serial non-invasive venography to exclude propagation of any possible previous distal DVT usually means one further ultrasound 7 days after the initial one. Pregnancy (including puerperium) is an 11-month period of hypercoagulable state and is an independent major risk factor for venous thromboembolism. Evidence-based guidance on the number and frequency of serial venous ultrasonography in pregnant women with thrombosis symptoms but an initial negative result for DVT will be necessary for those clinicians who choose not to treat distal DVT in pregnancy. Otherwise, there is a risk of that same distal DVT or recurrent DVT during that same pregnancy could present in the form of pulmonary embolism between antenatal appointments. Others may wish to play safe and treat any venous thromboembolism during pregnancy.⁴

Kearon and colleagues⁵ review evidence-based recommendations for non-invasive diagnosis of DVT. They recommend that if venous ultrasonography of the proximal veins is normal and there is high clinical suspicion of isolated distal DVT in a pregnant woman, limited venography with abdominal shielding should be considered (grade B). It is important to know of the presence of distal DVT in symptomatic pregnant women if this information is going to influence future if not current management decisions. Because patients are increasingly encouraged to take part in decision making about management of their medical disorders, clinicians will need to fully convince themselves that the presence of isolated distal DVT at any stage in pregnancy will not affect management of current and future pregnancies or the decision to prescribe oestrogen contraception at the patient's request in future. These questions will

not be answered without prospective randomised clinical trials.

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Contamination of animal feed by multiresistant enterococci

Sir—Richard Schwalbe and colleagues (Feb 27, p 722)¹ report the isolation of vancomycin-resistant enterococci (VRE) from animal feed in the USA. In the USA and Sweden, where the glycopeptide antibiotic avoparcin is not registered for use in food animals, no glycopeptide-resistant *Enterococcus faecalis* or *E faecium* have been isolated from faecal samples of food animals, healthy people, or from meat products.² However, in European countries that allowed the continuous feeding of avoparcin to food animals to enhance growth, not only are exposed animals colonised with VRE but healthy human populations are also colonised.³

Moreover, VRE have also been isolated from meat, suggesting a dissemination from animals to people via the food chain.⁴ However, only the *VanA* gene cluster caused resistance in *E faecalis* and *E faecium*.²⁻⁴ Therefore, avoparcin seems to select only for *VanA* resistance type in these enterococci.

In more than 600 VRE isolates from faecal samples of healthy people, pigs, and poultry from the Netherlands, we did not detect any multiresistant enterococcus (minimum inhibitory concentration of vancomycin ≥ 10 mg/L, amoxicillin ≥ 25 mg/L, gentamicin ≥ 1000 mg/L). Amoxicillin resistance was not encountered and 31 isolates showed high level of gentamicin resistance but not in combination with vancomycin resistance. We believe that it is unlikely that the contamination

described by Schwalbe and colleagues is from animal origin, but most probably from human (or hospital) origin, because multiresistant VRE with *VanB* resistance type have only been isolated from hospital patients.

Their warning that these VRE might colonise food animals and reach people via the food chain is unlikely, because in this case the human population is the most likely reservoir of *VanB* VRE, from the use of glycopeptide antibiotics and cephalosporins in hospitals.⁵

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- 1 Schwalbe RS, McIntosh AC, Qaiyumi S, Johnson JA, Morris JG Jr. Isolation of vancomycin-resistant enterococci from animal feed in USA. *Lancet* 1999; **353**: 722.
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Authors' reply

Sir—We appreciate the comments made by Anthony van den Bogaard and Ellen Stobberingh. As they point out, avoparcin has not been used in livestock feed in the USA, and consequently there does not seem to have been the same pattern of transfer of vancomycin-resistance genes from animal to human populations in this country. In the absence of animal VRE isolates in the USA, we cannot comment on Bogaard and Stobberingh's hypothesis that avoparcin selects only for *vanA*.

In the mid-Atlantic region of the USA, VRE is unquestionably endemic in populations of patients. In periodic point-prevalence studies done in our university hospital since 1993,¹ we have found that 20-25% of a random sample of all hospitalised patients are colonised with VRE, with *vanA* and *vanB* phenotypes represented. In longitudinal studies, we also find that

colonisation tends to persist: whereas stool cultures may become negative for VRE after a patient leaves hospital, the same strain (as identified by molecular typing) can often be isolated from a patient's stool on subsequent admissions.² We have not isolated VRE from normal, healthy, previously unhospitalised adults. However, this result may merely indicate that VRE is present at concentrations that are not detectable on routine (selective) culture. In keeping with findings in Europe,³ positive cultures might be obtained if these people were placed on antibiotics before obtaining cultures.

The VRE strain that we isolated from chicken feed does indeed resemble the strains found in our patients, with multiple antibiotic resistances and a *vanB* genotype. The source for this isolate remains unknown. However, given the endemicity of VRE in hospitals, it is not implausible that it originated from human sources. Spread of antibiotic resistance generally requires both the availability of appropriate genetic material (ie, resistance genes) and antibiotic pressure. The finding of VRE in chicken feed suggests that the genetic material is available to animals. Administration of any of the antibiotics to which this organism is resistant may select for resistant strains, with the potential for subsequent transfer back into people.

What emerges from this is a sense of the increasing availability of antibiotic resistance genes in (and the inexorable linkages among) human, animal, and environmental reservoirs. In view of the key role of antibiotics in selection of resistant strains, more judicious use of antibiotics in clinical and agricultural settings is urgently needed. We need also to carefully model the dynamics of antibiotic resistance within the ecosystem as a whole, with a risk-assessment framework to develop appropriate interventions to limit further spread of resistance.

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- 1 Morris JG Jr, Shay DK, Hebden JN, et al. Enterococci resistant to multiple antimicrobial agents, including vancomycin: establishment of endemicity in a university medical center. *Ann Intern Med* 1995; **123**: 250-59.
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Drug development output: what proportion for tropical diseases?

Sir—Despite the ever-increasing demand for effective, safe, and affordable drugs, tropical diseases, by their nature and prevalence, are a low priority for private industry.¹

Of the 1223 new molecular entities sold worldwide during 1975-96, less than 1% were destined for tropical diseases. Only a few of these drugs are genuine products of research by pharmaceutical companies. Most of the drugs for tropical diseases are either incidental discoveries recovered from veterinary medicine or molecules discovered by governmental or academic institutions and only later acquired and sold by the pharmaceutical industry (eg, artemisinin derivatives from China, halofantrine and mefloquine from the US Walter Reed Institute of Research). Eflornithine, a new drug for sleeping sickness, was discontinued because it was unprofitable. Of the new antimalarial drugs, the development of atovaquone was endangered until its effectiveness in AIDS-related infections was discovered, and a similar danger exists for pentamidine in sleeping sickness.¹

What prevents drug companies from doing research and development (R&D) for tropical diseases? First, the cost to risk ratio of drug R&D compounded by the low purchasing power of the endemic countries. The average cost of bringing a new drug to the market is about US\$224 million.² As drug companies expand through repeat mergers, the target in terms of sales for a development candidate increases, and tropical diseases drop down the priority list. Donation programmes are commonly preferred (eg, albendazole) to dual-pricing for wealthy and indigent customers, a strategy that could jeopardise sales of expensive compounds marketed for non-parasitic indications. In return, companies get tax-waivers and low-cost publicity (eg, atovaquone). Second, the protection of proprietary rights and recovery of investments. With the long pay-back period, costs are frequently not recovered when a compound runs off-patent and generic products may be introduced. A sales decline of more than

50% is expected within the first few months of generic entry. Moreover, unfair competition and counterfeit products are not uncommon.³ Finally, the effect of regulatory requirements on the length and costs of the process, hence the ultimate market price of the product. Increasingly high standards favour the larger wealthy companies that have little interest in tropical diseases. Nevertheless, dossiers do not necessarily undergo the same level of review the world over, sometimes because of bare-bone health budgets, and sometimes because of a misconception of the regulatory process.

The net result is that fewer drugs adapted to the needs of the poor are in development. The immediate pipeline sounds rich: there are new drugs for malaria and leishmaniasis in clinical phases or nearing registration. But few developments are need-driven, some compounds are predictably expensive, and no further candidates for development are expected in the short-term.

This and previous analyses show the need for a broader debate on worldwide R&D and marketing strategies for tropical diseases. The present profit-driven system is unable to keep pace with current and evolving needs, and so far the public sector has been unable to provide the optimum environment for such activities (eg, orphan drug schemes).⁴ There is room for new approaches.⁵ Opportunities exist: basic academic research generates leads that are not exploited and candidates that are not developed. Increased representation of disease-endemic countries and of their market size are needed. The new climate of interaction between the public and private sectors could, we hope, break new ground.

We thank P Etienne Barral for his contribution to the pharmaceutical data study and L Baldry for reviewing the manuscript.

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Ciprofloxacin in typhoid fever

Sir—E J Threlfall and colleagues' report (May 8, p 1590)¹ of treatment failure with ciprofloxacin in typhoid fever could not have been more timely. This issue is a cause of great concern, especially in the Indian subcontinent.

The investigators rightly suggest that in cases of treatment failure with ciprofloxacin, minimum inhibitory concentrations to ciprofloxacin should be used instead of breakpoints of the National Committee for Clinical Laboratory Standards (NCCLS) or the British Society for Antimicrobial Chemotherapy. These breakpoints cannot detect the decreased sensitivity of *Salmonella typhi* to ciprofloxacin and hence may delay the administration of an alternative antibiotic to the patient.

The antibiotic sensitivity testing for the clinical isolates is done by the disc diffusion technique with Stokes method in our clinical bacteriology laboratory.² We studied the minimum inhibitory concentrations against ciprofloxacin by broth dilution method and NCCLS guidelines in *S typhi* isolates from patients with typhoid fever when the treating physicians recorded lack of clinical response to ciprofloxacin. These strains were reported as sensitive by the clinical microbiologist. We observed that in 1998, of 60 *S typhi* isolates, 20 had minimum inhibitory concentrations that ranged from 0.125 mg/L to 1.0 mg/L. These isolates had all been reported as sensitive with the disc diffusion technique. Between January and March, 1999, there were two isolates from patients with treatment failure that had a minimum inhibitory concentration to ciprofloxacin of 2 mg/L. One encouraging trend that we reported (April 10, p 1241)³ is the re-emergence of strains of *S typhi* resistant to chloramphenicol and amoxicillin in our region.

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Performance of doctors

Sir—We welcome Sir Donald Irvine's call for a new professionalism for doctors (April 3, p 1174),¹ but are concerned that he makes no mention of crucial issues regarding quality of care. There is a recruitment crisis in the UK that affects primary and secondary care in settings where patients already face inequitable access to services, and many overstretched doctors and other health professionals work in isolation. To make its efforts credible, the General Medical Council (GMC) should speak out more clearly about the need for resources to improve equity and quality. Without such efforts, health professionals in underserved areas may leave and not be replaced, which will result in an overall deterioration in the quantity and quality of care.

Irvine does not address rationing of care: balancing health-care needs against the ability of the health service and its professionals to meet these needs, and the conflicting expectations of the public, the government, the media, and professionals. Irvine states that we should be "putting patients first", but fails to define what this statement means. Does it mean that doctors should try and respond immediately to demanding and vocal patients? Or, at the other extreme, should they prioritise the needs of the sometimes less articulate patients who are chronically or terminally ill, and who rely on repeated contacts, patience, and continuity of care?

There is a need to rethink the wave of initiatives by different institutions, all dedicated to the improvement of clinical professionals. A sense of ownership by the professionals concerned is essential if quality of care is to be improved. Yet these professionals may soon feel overpowered by the competing demands of the primary care groups or trusts, the defence organisations, the colleges, the National Institute for Clinical Excellence, the Commission for Health Improvement, and the GMC itself. The current initiatives may even widen the gap between what is expected and what can be delivered and engender a politicised context, in which institutions squabble about the blame in every incident, and devote their attention more to their position on the moral high ground than to the realities of care.

We have seen that the public, given sufficient information and the opportunity to consider the issues, accepts that rationing is taking place and that it should be made explicit and

more equitable. The government is also tentatively joining the rationing debate, as shown by its position on prescribing sildenafil. We hope that the GMC will engage fully in the debate about rationing, equity, and the role of doctors to make its vision of a "new professionalism" a success.

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1 Irvine D. The performance of doctors: the new professionalism. *Lancet* 1999; **353**: 1174-77.

Fair trade for less developed countries?

Sir—John Yudkin (May 1, p 1519)¹ and Nick Hopkinson in the same issue (p 1530)² call for debt relief as a way to increase funds for health care in poor countries. Yet some controls are needed to ensure that the funds released are spent on health care or other socially beneficial projects, rather than to line the pockets of corrupt governments. Campaigning for appropriate debt relief is important, but there is something more direct, and potentially more effective, that health-care professionals can do as well.

We get our coffee and cotton cheaply from developing countries, as Yudkin remarks, so cheaply that, in most cases, the people who toil to produce it cannot even afford doctors' fees when they or their relatives fall ill. Yet there is now an alternative—fair trade companies ensure that the farmers who grow their beverages are protected by minimum health and safety standards, and are paid a fair wage, which enables them to access health care. For example, one group of Sri Lankan tea-plantation workers have used the premiums from fair trade to buy an ambulance (see <http://www.fairtrade.org.uk>; accessed June 4, 1999).³

Brands such as Cafe Direct and Clipper teas are available in most UK supermarkets, yet they have captured only about 2% of the UK market, because most consumers do not think or care about the health of the people who grow their goods. The NHS is probably the largest consumer of tea and coffee in the UK. If all our practices, clinics, and wards were to switch to fair trade beverages, at a small extra cost, the lives of countless impoverished people would improve, as would their access to health care.

It is easy to campaign for our government to do things, but are we prepared to make changes in our own spheres of influence to benefit these countries?

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Mental health of refugees from Kosovo

Sir—We read with interest Kaz de Jong and colleagues' report (May 8, p 1616)¹ of Médecins Sans Frontières programme for mental health care for refugees from Kosovo, which drew on the organisation's extensive experience in Bosnia. We would like to add to the important issues they raise.

There is a publication bias in medical journal articles that focus on the Balkan crisis. Authors have been predominantly international, whereas local people and agencies (who have played a major and continuing role in meeting the humanitarian needs of the displaced and needy) have been poorly represented. The reasons are complex. International agencies and individuals have various interests in maintaining visibility for their work, they may find it easier to adopt the dispassionate and factual stance required, and may be more familiar with writing for medical journals. By contrast, local writers do not see publication as a priority and may face an additional barrier of language or even access to medical journals. Thus, the story is sometimes only partly told.

The aid juggernaut in the Balkans has been massive and its wake has swamped and sidelined the local health system. During the height of the humanitarian response in Bosnia, over 180 organisations were known to be providing psychosocial support and counselling to at-risk clients.² The quality, cultural appropriateness, and sustainability of these programmes was, in our experience, variable. Liassing with such a vast number of agencies stretched local resources. As a result, local health staff who had to meet and brief this plethora of agencies, suffered from "mission fatigue".

In the prewar Balkan hospital-based and drugs-oriented system, psychiatric

care was focused largely on chronic and severe cases. The international mental-health response was more heavily weighted towards meeting the immense needs of traumatised people who had previously been well. The intractable issue of what to do with the region's densely populated psychiatric and psychogeriatric hospitals received little attention, yet these were some of the neediest victims of the war. The conflict presented an opportunity to review the whole approach to mental health, yet many of the international aid programmes, driven by short-term goals and limited mandates, ignored the existing system. An imbalance was created when local people, trained by and working for aid agencies, could earn a living wage counselling clients while psychiatrists and nurses got paid late and little if at all.

International attention and aid dollars are now focused on the emergency needs of Kosovo and it is difficult to obtain funding for psychosocial support programmes in Croatia or Bosnia, yet the mental-health needs still exist. Perhaps the most useful of the international programmes were those that acknowledged their own short lifespan and emphasised capacity building and strengthening of local services.

We can be confident of the outcomes of any set of actions only across a short time-frame. There are three outcome horizons in primary health care (and we argue that most emergency relief can be classified as this): outcomes for today (measurable health gains), outcomes for tomorrow (improved health care or health-promotion delivery), and outcomes for the day after tomorrow (enhanced institutional, professional, and community capacity).³

The footprint of the emergency aid phase is persistent. Local capacity building in the form of true partnerships with local people, joint planning, skill transfer, and long-term investment in the human capital of the region must be an integral part of the emergency response. International agencies should always plan for when they will no longer be around.

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- 1 de Jong K, Ford N, Kleber R. Mental health care for refugees from Kosovo: the experience of Médecins sans Frontières. *Lancet* 1999; **353**: 1616-17.
- 2 Agger I. Psychosocial support programmes in Bosnia and Croatia. London: European Community Humanitarian Organisation, 1993.

- 3 Legge D. The evaluation of health development: the next methodological frontier? *Aust N Z J Public Health* 1999; **23**: 117-18.

Auditory hallucinations and the bicameral mind

Sir—Jay Goldstein,¹ a foresighted thinker in the field of neurosomatic disorders, such as chronic fatigue syndrome, recently made me aware of an important book from 1976 by Julian Jaynes: *The origin of consciousness in the breakdown of the bicameral mind*.² According to Jaynes' daring hypothesis, man had no consciousness until 1000 BC. Before that time, language had developed slowly for a long period: commands from 40 000 BC, nouns from 25 000 BC, and names from 10 000 BC, at the time of the emergence of agriculture. Language, the speech areas, evolved in the left hemisphere (in right-handed) which, as Jaynes underlined, is a mystery since most human structures are bilateral and a neurological organisation necessary for language also exists in the right hemisphere, but with no observable function.

Jaynes proposes that the bicameral mind in man operated between 10 000 BC and 1000 BC. The left hemisphere was the site for speech, the right for hallucinations, which expressed voices and commands of gods and demons. The breakdown of the bicameral mind was according to Jaynes caused by "the weakening of the auditory by the advent of writing, the inherent fragility of hallucinating control, the unworkableness of gods in the chaos of historic upheaval, the positing of internal cause in the observation of differences in others . . . and a modicum of natural selection". Then consciousness and self-awareness evolved—and (hopefully) still does.

Jaynes founded his theory on psychohistorical analysis and on such neurobiological knowledge that was available around 1970. As a psychologist, an important part of Jaynes' theories were based on observations of schizophrenic patients. Neuroimaging techniques of today have illuminated and confirmed the importance of Jaynes' hypothesis. Belinda Lennox and colleagues (Feb 20, p 644)³ used spatial and temporal mapping of neural activity in a right-handed schizophrenic patient to show that his auditory hallucinations occurred in various parts of his right hemisphere, but not in his left which

"could explain why the activations are misinterpreted as alien". Similar findings were reported by Dierks and co-workers.⁴ Thus, Jaynes' bold hypothesis on schizophrenia has been revived. But, in a broader context, his theories might be important with regard to two questions. Can differences in the evolution and the transition of the unicameral to the bicameral mind to present man with consciousness explain the horrors of our civilisations? What will, as evolution inevitably proceeds, the fourth "camera" contain?

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- 1 Goldstein JA. *Betrayal by the brain*. New York: Haworth Medical Press, 1996.
- 2 Jaynes J. *The origin of consciousness in the breakdown of the bicameral mind*. Boston: Houghton Mifflin Company, 1976.
- 3 Lennox BR, Bert S, Park G, Jones PB, Morris PG. Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet* 1999; **353**: 644.
- 4 Dierks T, Linden DE, Jandl M, et al. Activation of Heschl's gyrus during auditory hallucinations. *Neuron* 1999; **22**: 615-21.

DEPARTMENT OF ERROR

Indications for cholesterol-lowering medication: comparison of risk-assessment methods—In this article by Prof P N Durrington and colleagues (Jan 23, p 279), the vertical axis in figure 1 was incorrect. The corrected figure is shown below.

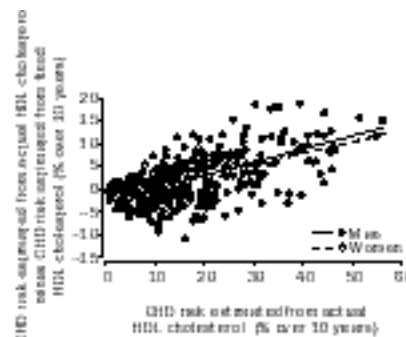


Figure 1: Regression analysis of difference in CHD risk (% over 10 years) between that calculated from actual HDL cholesterol concentration and that calculated from standard value for HDL cholesterol (1.15 mmol/L in men, 1.4 mmol/L in women) plotted against CHD risk calculated from measured HDL cholesterol

Men: SE=0.03, r=0.60, p<0.001. Women: SE=0.03, r=0.57, p<0.001.

Occupational asthma in Europe and other industrialised areas—In this article by M Kogevinas and others, and the European Community Respiratory Health Survey Study Group (May 22, p 1753), the *Fundacion Mapfre Medicina* should have been included as one of the granting agencies for the Spanish component of the international study.