

# CORRESPONDENCE

## Mother-to-child HCV transmission

Sir—The report by D M Gibb and colleagues (Sept 9, p 904)<sup>1</sup> adds information about vertical transmission of hepatitis C virus (HCV), and suggests that elective caesarean delivery will reduce mother-to-child transmission of the virus. We raise some points for discussion.

Gibb and colleagues report a history of drug use (78%) or blood transfusion in most of the women, whereas in an unselected population of individuals infected with HCV, the source of infection is generally difficult to identify.<sup>2</sup> An important selection bias might, therefore, strongly affect their results since the sociodemographic, immune, nutritional, and obstetric variables of injecting drug users are substantially different from those of non-drug using women, beyond the eventual co-infection with HIV-1. We think that more details on how women were classified as undergoing elective or emergency caesarean section, and the gestational age at birth in vaginal and caesarean deliveries should be provided. The population studied is also at increased risk of premature labour which might itself, influence the probability of transmission of bloodborne infections.<sup>3</sup> We had to exclude a high proportion of the 15 427 mother-child pairs we enrolled for a meta-analysis on the effect of caesarean section on vertical transmission of HIV-1,<sup>4</sup> since we could not precisely assess the exact mode of delivery.

Our third concern is that only 144 women, of the 441 studies, were tested for HCV RNA. 54% were positive, thus being potential transmitters of HCV to their children. We would like to know the rates of vertical transmission, according to method of delivery, in the women who could actually pass on the infection.

Finally, we think that the use of evidence for preventable peripartum transmission in the title of the paper could erroneously induce obstetricians to offer women with positive HCV status elective caesarean section. The efficacy of elective abdominal delivery to reduce HCV transmission remains to be proven; a review suggests highly variable transmission rates among different studies.<sup>5</sup> Once confirmed, elective

caesarean section should however be restricted only to mothers with positive HCV viraemia.

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- 1 Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000; **356**: 904–07.
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- 5 Thomas SL, Newell ML, Peckham CS, Ades AE, Hall AJ. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia of human immunodeficiency virus infection. *Int J Epidemiol* 1998; **27**: 108–17.

Sir—D M Gibb and colleagues<sup>1</sup> suggest that all pregnant women could be offered antenatal testing for HCV infection, since an elective caesarean section delivery might lessen vertical transmission risk. Given the consequent public-health implications, we assessed the strength of the evidence.

Data were collected partly prospectively and partly retrospectively over several years in centres in the UK. Definitive diagnosis of infection in children born to HCV-infected mothers was not possible in many cases because of limited duration and frequency of follow-up. Gibb and colleagues therefore used statistical inference, following methods developed for HIV-1 infection. Patterns of viraemia among HCV-exposed babies differ, however, from those among HIV-exposed babies.<sup>2</sup>

In their multivariate analysis, they allow for maternal HIV-1 co-infection, breastfeeding, and method of delivery, but not HCV viraemia; HIV-1 co-infected women were at increased transmission risk. The investigators do

not investigate interaction between maternal HIV-1 status and method of delivery. In an analysis of European data of 1474 HCV-infected women, of whom 503 were HIV-1 co-infected, interaction between method of delivery and HIV-1 co-infection was substantial.<sup>3</sup> In a stratified analysis, caesarean-section delivery was associated with reduced HCV vertical transmission only in HIV-1 co-infected women (caesarean section *vs* vaginal delivery, odds ratio 0.36,  $p=0.01$ ). Among women with HCV infection only, method of delivery (1.17,  $p=0.66$ ) or breastfeeding (1.07,  $p=0.83$ ), had no significant effect.

The timing of HCV vertical transmission is unclear. Mother-to-child transmission during delivery is biologically plausible for HIV-1, and elective caesarean section is recommended for HIV-1 infected women, since it decreases the risk of vertical transmission of HIV by more than 50%. For elective caesarean section to have similar effect in HCV infection, delivery would have to be a high-risk period for transmission.

Elective caesarean section delivery is defined as being done before rupture of membranes and before the onset of labour. Labour is thought to facilitate transmission of bloodborne agents, partly because uterine contractions could induce placental breaks, allowing infected maternal blood to be passed to the fetus. With defects in the trophoblastic surface being transient and occurring throughout gestation, the level of maternal viraemia is important.<sup>4</sup> A further putative mechanism for the transmission of HIV-1 during labour is through infected placental cells, which might be a source of infection. To date, there is no evidence that HCV infects the fetal compartment or the placenta, apart from one report of HCV contamination of the amniotic fluid after amniocentesis.<sup>5</sup> The proportional increase in the rate of HIV-1 vertical transmission with increasing maternal viral load is in agreement with the above routes of transmission. Although HCV viral load is probably associated with vertical transmission, the relation is less clear than for HIV-1, and a cut-off value below which transmission does not occur has not been identified.

Given these concerns about Gibb and colleagues' methods, lack of evidence of biological plausibility, and the potential large public-health implications, elective caesarean section delivery should not yet be offered to women with only HCV infection, and routine antenatal testing should not be started.

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- 1 Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000; **356**: 904–07.
- 2 European Paediatric HCV Network. Persistence rate and progression of vertically acquired hepatitis C infection. *J Infect Dis* 2000; **181**: 419–24.
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- 4 Burton GJ, O'Shea S, Rostron T, et al. Physical breaks in the placental trophoblastic surface: significance in vertical transmission of HIV. *AIDS* 1996; **10**: 1294–96.
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Sir—D M Gibb and colleagues<sup>1</sup> report that the sensitivity of HCV RNA was low soon after delivery and the transmission rate after delivery by elective caesarean section was lower. They suggest that HCV transmission occurs mainly around the time of delivery. The co-infection with HIV-1 and the presence of HCV RNA by PCR in women are suggested risk factors for HCV transmission.<sup>2</sup> High HCV viral load might be associated with immunosuppression caused by HIV-1.

Although Gibb and colleagues suspect perinatal transmission as a route of mother-to-child HCV infection, there was not enough evidence of direct cause to support their speculation. If transplacental transmission had occurred, serum IgC and IgM antibodies to HCV and HCV RNA on PCR should be detected from cord-blood samples.

80–90% of the population in Japan is seropositive to cytomegalovirus by age 20 years.<sup>3</sup> The characteristics of latency and reactivation of this disorder are shared with other members of the herpesvirus family. Generally, cytomegalovirus infections are effectively controlled by the immune system without the ultimate clearance of the

virus. Acquired systemic reactivation of the virus is also a major complication in patients with immunosuppression associated with HIV-1 infection. Perinatal cytomegalovirus infection associated with reactivation during pregnancy is acquired by transplacental transmission or by ascending infection from an infected cervix across intact membranes. We have been occasionally consulted for cases with mother-to-child transmission of HCV associated with cytomegalovirus infection in Japan (unpublished data).

A Kovacs and colleagues<sup>4</sup> did a prospective, multicentre study of cytomegalovirus infection and HIV-1 disease progression. They conclude that HIV-1-infected infants who acquire cytomegalovirus infection in the first 18 months of life have significantly higher rates of disease progression and central-nervous system-disease than those infected with HIV-1 alone. Perinatal cytomegalovirus infection might be a risk factor for perinatal HCV transmission and disease progression.

If HCV-infected mothers have positive results for HCV RNA on PCR towards the end of pregnancy, the possibility that secretions containing blood from birth canal were introduced into the baby is likely, even in the presence of transplacental maternal antibody. Prophylaxis for pregnant women and their babies with HCV infection seems to be absolutely necessary. Although Gibb and colleagues suggest a prospective effect of elective caesarean section for the intrapartum transmission of HCV, other trials, such as use of immunoglobulin to HCV for neonates, should be also considered.

Since some vertically HCV-infected infants might initially have negative results on PCR, as in HIV-1 infection,<sup>5</sup> refined new diagnostic assays are necessary for neonatal screening. Diagnoses of HCV infection should be applied for virological markers to assess the condition of pregnant women. Entirely new approaches to prevention and treatment of perinatal HCV infections are also necessary, including antiviral interventions and the development of a vaccine strategy.

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- 1 Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000; **356**: 904–07.
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transmission to infants born to mothers with and without HCV viremia or human immunodeficiency virus infection. *Int J Epidemiol* 1998; **28**: 108–17.

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- 5 Dunn DT, Brandt SD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS* 1995; **9**: F7–11.

Sir—D M Gibb and colleagues<sup>1</sup> provide an accurate estimate of the severity of PCR for HCV RNA in the neonatal period. Since a false-negative result could mean low or absent levels of viraemia, babies who acquire the infection intrapartum or immediately postpartum (ie, through breastfeeding) would account for the high number of false negatives at age 1 month. We would like to know whether the investigators found vaginal delivery or breastfeeding to be an important maternal risk factor in this subgroup of children who later seroconverted.

The low vertical transmission rate of HIV-1 in this study compared with other published data<sup>2</sup> prompts the question as to whether these mothers were taking antiretroviral medication. If they were, the drugs might have affected HCV transmission in the HIV-1-positive subgroup.

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- 1 Gibb DM, Goodall RL, Dunn DT, et al. Mother to child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000; **346**: 904–07.
- 2 Duong T, Ades AE, Gibb DM, Tookey PA, Masters J. Vertical transmission rates for HIV in the British Isles: estimates based on surveillance data. *BMJ* 1999; **319**: 1227–29.

Sir—D M Gibb and colleagues<sup>1</sup> conclude that elective caesarean delivery can lower the rate of vertical transmission of a bloodborne virus without effective vaccination. Although their findings confirmed our previous observation,<sup>2</sup> they did not address the possible mechanisms involved in the reduction of vertical transmission of HCV by this route.

The placental barrier in pregnancy can preclude direct communication between maternal and fetal circulations. Disruption of this barrier occurs after

uterine contractions, with threatened abortion, preterm labour, or, before, during, or after birth, allowing flow of maternal blood into the fetal circulation. We have noted that transplacental leakage of HBeAg-positive maternal blood is the most likely route of intrauterine infection with hepatitis B virus,<sup>3</sup> and might be applicable to other bloodborne viruses, including HCV hepatitis G virus, and HIV-1.

In addition to viral virulence, the efficacy of transmission of bloodborne viruses depends on viral load in the inoculum and transmission route, probably for in-utero and birth-canal infections. The viral load in the inoculum includes the amount of leakage and the maternal viral titre, and the transmission route includes transplacental leakage of maternal blood and breastfeeding.

Elective caesarean delivery has the least microtransfusion from mother to fetus,<sup>4</sup> as seen by the low cord placental alkaline phosphatase and HBsAg. In addition, high-titred maternal viraemia and method of delivery are the major determinants in causing vertical transmission of bloodborne viruses such as HCV and hepatitis G virus,<sup>2,5</sup> and elective caesarean delivery can avoid transmission of such viruses, as reported by Gibb and colleagues.

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#### Authors' reply

Sir—We agree totally that the evidence from our study is not sufficient to warrant routine caesarean section for HCV-infected pregnant women or setting-up antenatal testing programmes

for HCV infection. We expressed this view clearly in the article, as well as advocating the need for larger, confirmatory studies.

Augusto Semprini and colleagues suggest that caesarean section will probably benefit only mothers who have HCV RNA viraemia. Although in broad agreement, we believe that separation of infected individuals into viraemic or non-viraemic might be oversimplistic (we saw several women with discordant PCR results during pregnancy), and that the risk of transmission probably varies continuously with viral load. Similarly, Simona Fiore and colleagues interpret their data as showing that the protective effect of caesarean section delivery is limited to HIV-1-co-infected women, although they do not report whether this interaction is significant nor offer any theoretical justification for their hypothesis. They are largely dismissive that substantial HCV transmission occurs peripartum; how do they explain their association between method of delivery and HCV transmission in HIV-1-infected women?

Fiore and colleagues also raise some concerns about our method. There was no indication that transmission risk was higher in the retrospective phase of the study than in the prospective phase. We believe that the statistical model we used has wide applicability for vertical transmission of infections and that it was first applied in HIV-1 infection is irrelevant. Moreover, the patterns of HCV viraemia we saw were not strikingly different to those for HIV-1 viraemia; in particular, intermittent viraemia in presumed infected children, apart from very early negative tests, was rarely seen. The high frequency of this phenomenon in the European Paediatric HCV Network study cited by Fiore and colleagues might be related to the older ages of these children or historically less sensitive PCR tests.

Our sample size was too small to stratify by the outcome of early PCR tests, although we agree that such analyses would be worthwhile in larger studies. We do not have details of antiretroviral therapy (ART) received by HIV-1 co-infected women, although most would have received monotherapy rather than combination antiretroviral therapy at the time of the study. Highly active antiretroviral therapy could theoretically reduce HCV transmission, although its effect is probably indirect, through improvement in immunological status, rather than directly through lowering HCV viraemia. This effect needs to be investigated. Prematurity was not related to the risk of HCV transmission (5.0% at or

before 36 weeks' gestation *vs* 6.3% thereafter) which excluded a confounding effect of this factor. Although we ascertained method of delivery from obstetric notes, elective and emergency caesarean section delivery are generally clearly distinguishable. Also, duration of rupture of membranes was recorded for most women in the Dublin cohort.

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## Cystatin for estimation of glomerular filtration rate

Sir—In their Nov 11 commentary, Japp Deinum and Frans Derkx<sup>1</sup> discuss the use of plasma creatinine in the assessment of glomerular filtration rate (GFR). They state that creatinine assays are sensitive to interference by all kinds of substances. This effect is true for methods based on the Jaffe reaction (picric-acid method). However, even with this reaction, the interference has been kept to a minimum in many methods adapted to newly automated instruments. Furthermore, enzymatic assays of creatinine are much less prone to such interferences.

Deinum and Derkx also state that serum creatinine is influenced by muscle mass, a frequently seen statement in text books. However, the contribution of muscle mass to variation in serum creatinine is small.<sup>2,3</sup> In a study of 664 individuals (age 19.0–70.3 years) with a fat-free mass (lean body mass) of 23.0–53.7 kg, the contribution of lean body mass to serum creatinine was only 2.9%.<sup>3</sup> The differences in creatinine between individuals may be genetically determined and there is some evidence supporting this (D Hunter, R Swaminathan, T Spector, et al, unpublished observations).<sup>4</sup>

Muscle mass (lean muscle mass) might be an important contributor to variation in serum creatinine at extremes, such as in emaciated patients or body-builders with high fat-free mass. In most people, muscle mass contributes little to the variation in serum creatinine concentration.

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## Voluntary counselling and testing for HIV-1

Sir—Michael Sweat and colleagues (July 8, p 113)<sup>1</sup> make an important contribution to the understanding of the role of voluntary counselling and testing (VCT) in Africa.

We believe that many people will use variables from this study to estimate costs and effectiveness in other regions when relevant local parameters are not available. Many of Sweat's efficacy parameters are attributed to the accompanying paper by the Voluntary HIV-1 Counseling and Testing Efficacy Study Group (July 8, p 103)<sup>2</sup> but we cannot find them there. We would like to know how the investigators derived their estimates because some costs and benefits seem high compared with those from previous studies.

Sweat and colleagues suggest that condom use per act after VCT increased to 83–88% (shown in their table 1). We can find no information on per-act condom use in the accompanying paper, but at 12 months, 196 men reported intercourse with a main partner and 125 (64%) reported unprotected intercourse (a decrease from 79% at baseline). Another study found much less condom use per year after testing and counselling intervention.<sup>3</sup>

The estimated rates of HIV transmission (0.0189 in Kenya and 0.0172 in Tanzania) suggest that 64% of the uninfected partners of infected people would acquire infection after 54 sex acts (the average number of sex-acts per year). The Rakai study reported transmission among discordant couples to be 12% per year and genital-ulcer disease increased this transmission to 13.7% per year.<sup>4</sup> It looks like Sweat and

colleagues have misplaced a decimal point in their per-act infectivity estimates; they assumed a per-act infectivity of 0.01 and 0.02 based on a reference that reported a per-act infectivity of 0.001 and 0.002.

The estimate of ten cases prevented for every 100 people counselled (table 3) suggests that the incidence without intervention must be more than 10%. If so, we would expect the prevalence in the health information (control) group to increase by 5.8% (to 25.8%) during the 7 months before their first test. This change seems unlikely given the lack of difference in HIV-1 prevalence between the VCT group at baseline and the health information group measured at 7 months (table).

Labour costs per client seem high and were almost 50% of the total costs (Kenya US\$26.65, and Tanzania \$28.93). The income per person in Kenya (\$350) and Tanzania (\$220; www.worldbank.org/data.countrydata.html accessed on Jan 8, 2001) suggest a lower labour cost. A study from Zambia (income per person \$330) reported a total cost of \$8 per person after counselling.<sup>5</sup> Information on the average hourly wage and time taken for counselling and testing would be helpful for comparisons with past and future studies.

We believe that VCT is an important HIV-1 prevention intervention. Antiretroviral therapy, control of sexually transmitted diseases, and prevention of perinatal transmission are also important. Cost-benefit analyses can help efficiently allocate scarce prevention resources. These analyses always use assumptions and estimates based on the best available data. Future analyses can build on the foundation set by Sweat and colleagues, but, without details on the derivation of their estimates we cannot assess the strength of this foundation.

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- 1 Sweat M, Gregorich S, Sangima G, et al. Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. *Lancet* 2000; **356**: 113–21.
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gonorrhoea rates. *JAMA* 1992; **268**: 3338–43.

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- 5 McKenna SL, Muyinda GK, Roth D, et al. Rapid HIV testing and counseling for voluntary testing centers in Africa. *AIDS* 1997; **11** (suppl 1): 5103–10.

### Authors' reply

Sir—Beena Varghese and colleagues raise concerns over the specification of model parameters referenced in our analysis, citing “many” references we made to the main outcomes paper that they cannot find, leading to a lack of detail in the presentation of our assumptions. However, our cost-effectiveness paper refers only once to the main outcomes paper, for a review of the design of the larger study.

Varghese and colleagues also raise doubts over the veracity of the findings because other studies of the behavioural impact of HIV-1 VCT yielded different outcomes. We urge caution in interpreting comparisons to the studies they cite, especially since the studies were done in different countries, were targeted to childbearing women, used different measures of condom use, and were done 7–8 years ago. The people who participated in our study independently sought out VCT and were probably more ready to make behavioural changes than the childbearing women in W L Heyward and colleagues' 1993 study in Zaire (now the Democratic Republic of Congo) and S Allen and colleagues' 1992 study in Rwanda. Moreover, comparisons made by Varghese between our report on the efficacy of VCT, and that on the cost-effectiveness of VCT are not parallel, since the main paper includes data from Trinidad, and the cost-effectiveness paper is limited to the African sites.

For the infectivity parameter, in our original analysis we adjusted the parameter for HIV-1 transmission probability per sex act based on the high rate of sexually transmitted infection, and included a sensitivity analysis to account for variation in this parameter. We have previously reported on an expanded sensitivity analysis of the transmission probability parameter.<sup>1</sup> That analysis showed that even with the lower per-contact HIV-1 transmission probability, as suggested by Varghese and colleagues, VCT was shown to still be cost-effective by international standards. The impact on the cost-per disability-adjusted life year saved from using this upper bound value for the per-act probability of HIV-1

Country	VCT at baseline	Health information at 7 months
<b>Kenya</b>		
Total number tested	716	571
Number positive	146 (20.4%)	100 (17.5%)
<b>Tanzania</b>		
Total number tested	664	439
Number positive	132 (20%)	88 (20%)

### HIV-1 prevalence at baseline in VCT group and at 7 months in health information group

transmission was not substantial since the average contact rate per sex partner is so high. Also, we did not design our study to assess trends in HIV-1 incidence. Thus, the post-hoc analysis presented by Varghese and colleagues should be interpreted with caution. Their rough estimate of expected HIV-1 incidence of 10% does not account for HIV-1 transmission to the sexual partners of HIV-1-infected study participants, but only HIV-1-uninfected people receiving VCT. Our study was not powered for such an analysis, the time frame is only 7 months, and those in the health information group did not receive baseline HIV-1 tests.

Finally, Varghese and colleagues raise concerns over the labour cost estimates for VCT. We cannot do a full exposition of our highly detailed cost analysis here, but we can provide some additional detail to address their concerns. Labour estimates included costs for the director, secretary, financial manager, receptionist, counsellors, laboratory technician, security officers, custodial staff, and phlebotomists. The annual salary range, including fringe benefits, across all staff ranged from about US\$12 000 for the centre directors to around \$1500 for cleaners and security officers. Salaries for counsellors averaged around \$2900. Clients came for at least one pretest and one post-test visit, but frequently returned for more than one post-test session. Some clients also attended more than one counselling session before testing. Counselling sessions took about 30 min but were much longer for many clients. Counsellor labour costs also include times that the counsellors were not with clients, and there are various other staff needed to provide quality VCT. Varghese and colleagues' comparisons of labour costs in our study to per person income in Kenya and Tanzania seriously distorts the actual labour costs of implementing an intervention such as VCT. Tanzania and Kenya are largely rural agrarian societies, and urban labour costs for trained workers are substantially higher than what would be reflected by a national per person income average. It should be noted that if labour costs were lower, VCT would be an even more cost-effective intervention. Lower labour costs might be realised through an economy of scale with a larger programme, but an additional study would be needed to draw such a conclusion.

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- 1 Sweat M, Coates T. Reducing HIV-1 in Kenya and Tanzania. *Lancet* 2000; **356**: 1602–03.

Sir—The failure to provide voluntary counselling, testing,<sup>1</sup> and antiretroviral drugs<sup>2</sup> for AIDS patients in sub-Saharan Africa confirms human beings' cruelty to each other in a particularly repugnant way. Especially since the luxury world, intent on destroying itself physically and morally with excess production and consumption, is quite deliberately trying to ignore enormous suffering.

If we have not the motivation to do the best, the very least we can do is to provide speedily palliative care for those who need it. Excellent examples of this can be seen at Hospice Uganda and Mobile Hospice Mbarara. Treatment of a patient and family costs £5 per week.

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- 1 Sweat M, Gregorich S, Sangiwa G, et al. Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. *Lancet* 2000; **356**: 113–21.
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## Diagnosis of meningococcal septicaemia

Sir—In their Sept 16 commentary<sup>1</sup> Marcel van Deuren and Petter Brandtzaeg report that in children who have meningococcal septicaemia, spots do not blanch when glass is pressed against the skin (the glass test), which alerts parents to seek medical attention.

This diagnostic rash is haemorrhagic. In Argentina, our experience with children in the emergency department suggests that most patients generally present with skin manifestations, including purpura, petechial, and ecchymotic lesions. However, macular, papular, non-specific urticarial morbilliform, and pustular and bullous lesions are sometimes detected.<sup>2,3</sup> Difficulties occur because these are non-haemorrhagic rashes, sometimes similar to measles, that can be overlooked and lead to treatment delays. But the absence of haemorrhagic lesions should not deter the professional from suspecting this potentially fatal infection.<sup>4</sup> van Deuren and Brandtzaeg state that parents should be instructed to inspect their febrile child and use the glass test if spots are present. Although this recommendation is ideal, in most

Latin-American countries this method is impractical because of many complex socioeconomic and cultural reasons. I believe that parents should not be given the task of diagnosing rash in a febrile child. This test is the responsibility of the physician.

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- 1 van Deuren M, Brandtzaeg P. Parents' and GPs' key role in diagnosis of meningococcal septicaemia. *Lancet* 2000; **356**: 954–55.
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Sir—We agree with Marcel van Deuren and Petter Brandtzaeg<sup>1</sup> that parents and family physicians have a key role in the management of meningococcal septicaemia. However, we believe that adolescents must also be educated to recognise the signs and symptoms of this disease in their peers. They need to know that, in the early stages, symptoms of meningococcal disease are similar to those of flu or a hangover. They must feel empowered to ask for, and if necessary demand, urgent medical attention if they are concerned about themselves or their peers. Adolescents should know how to carry out the glass test.

The results of a survey<sup>2</sup> show that adolescents' knowledge is patchy about signs and symptoms of meningococcal disease. To try and improve knowledge we have collaborated with parents of a teenager who died from meningococcal septicaemia, to produce a short educational video, targeted at young people age 14 years or older. We hope it will be shown in many schools, and it is available on the University of Bath website ([www.bath.ac.uk/Students/meningitis](http://www.bath.ac.uk/Students/meningitis) accessed on Jan 8, 2001). Copies of the video can be obtained free of charge from Fiona Finlay or Rosemary Jones.

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- 1 van Deuren M, Brandtzaeg P. Parents' and GPs' key role in diagnosis of meningococcal septicaemia. *Lancet* 2000; **356**: 954–55.
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## Diuretic response to water loading

Sir—P Norsk and colleagues (Nov 4, p 1577)<sup>1</sup> describe an attenuated diuretic response to water loading in space. This effect could not be replicated during the 6° head-down bed-rest procedure, widely thought to simulate the physiological effects of weightlessness. They speculate on the mechanisms mediating the effects of zero gravity on body water regulation, and suggest that the effects observed might result from activation of antidiuretic mechanisms through weightlessness-induced transfer of fluid from the intravascular to interstitial compartment or through a reduced osmomediated suppression of vasopressin secretion in space. Observations of similar alterations in the regulation of body fluid compartments after birth suggest alternative explanations.

The fetus exists in a state of relative extravascular volume expansion.<sup>2</sup> In utero, the fetal heart functions against a low-resistance vascular circuit in which, additionally, the force of gravity is to some extent opposed by the circumferential hydrostatic force of amniotic fluid and myometrial contractility. After the transition from the fluid intrauterine environment to the gaseous postnatal environment, human extracellular fluid decreases in the interstitial compartment, which leads to early postnatal weight loss.<sup>3</sup> In neonates the loss of extracellular fluid seems to be primarily a natriuresis and a consequence of increased atrial natriuretic-peptide secretion as left atrial tension rises after delivery.<sup>4</sup>

The observations of Norsk and colleagues might be explained by reduced sodium excretory capacity in space, arising directly from the effects of zero gravity on myocardial function. Assessment of serum osmolality and urinary sodium excretion would help to confirm or refute this suggestion. If it were confirmed, whole-body immersion would be a more appropriate simulation in which to study the effects of weightlessness on human physiology than the 6° head-down tilt.

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## Care for stroke patients

Sir—Lalit Kalra and colleagues (Sept 9, p 894)<sup>1</sup> conclude that patients with moderately severe acute stroke should be admitted to a stroke unit, and that outcomes of care on general wards coordinated by a stroke team are worse than those in dedicated units. This message is of importance, since many hospitals still resist setting up stroke units. Some points, however, need clarification and the differences between strategies might not be as large as suggested.

First, Kalra and colleagues report treatment effects as odds ratios (in table 2), but the numbers presented are risk ratios. Second, the 69% reduction in the odds of death at 1 year (stroke unit 9% vs general ward 23%, odds ratio 0.31 [95% CI 0.16–0.63]) is substantial. Such large treatment effects are rarely encountered in medicine, and in trials with small sample sizes, might be due to chance, despite apparent significance.

Extreme results can occur when trials are stopped early after an interim analysis. This trial seems to have completed enrolment as planned, but the sample size calculations are incorrect. To identify the size of effect seen in the Stroke Unit Trialists Collaboration<sup>2</sup> (odds ratio 0.7) with a power of 90% at a 5% significance level would require at least 740 patients in each treatment group, not 135 as stated in the paper. Since the data on which the sample size calculations were based were not published until 2 years after the trial started, we wondered what assumptions Kalra and colleagues had made before starting their trial to arrive at their sample size.

Assignment might not have been truly random. If small blocks sizes were used (eg, six patients), the people enrolling patients might have guessed some treatment assignments in advance, and thus selected patients for inclusion to each group. Although the

comparisons of, and adjustment for, baseline variables, seem reassuring, such tests are insensitive to detect difficulties in randomisation.

Major differences in the medical care (eg, antibiotics) in the stroke unit and general wards could have affected mortality. We wondered whether there was any indication in this hospital that such differences existed. In a previous publication from the hospital, the 2-week case fatality for unselected acute stroke patients admitted to the general wards was 21%.<sup>3</sup> Patients who survived this period were randomly allocated to a stroke rehabilitation unit (in-hospital mortality nine [7%] of 124) or general ward (15 [12%] of 121). The cumulative in-hospital mortality was, therefore, 28% and 33%, respectively. Neither rate represents an unusually low or high hospital mortality rate in the UK.<sup>4</sup> In two previous randomised trials in this hospital, in-hospital mortality also differed (pooled odds ratio 0.38 [0.20–0.71]) between the stroke rehabilitation unit and general wards, but these data were confounded by a two-fold difference in the length of stay.<sup>5</sup> This flaw in the methods is avoided in the current study.

Before the results of this report can be applied; it would be useful to know more about the calculation of sample size, the method and security of randomisation, and of the medical care provided.

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- 1 Kalra L, Evans A, Perez I, Knapp M, Donaldson N, Swift CG. Alternative strategies for stroke care: a prospective randomised controlled trial. *Lancet* 2000; **356**: 894–99.
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Sir—Lalit Kalra and colleagues' report<sup>1</sup> has added substantially to the debate about stroke care. The outcome for patients assigned domiciliary stroke care is especially relevant, given the present emphasis on the development of intermediate care schemes.

The study was designed to include a

community group and exclude patients with severe stroke. The community team was specialist and multidisciplinary, and yet a third of the patients assigned community care were admitted to the hospital stroke unit within 2 weeks. Once admitted, these patients stayed longer in hospital than patients in the two hospital groups. Outcome for the community group was not otherwise reported because of the intention-to-treat analysis.

At present, we probably do not know what happens to stroke patients not admitted to hospital in most districts. G Hankey and C Warlow<sup>2</sup> suggest that up to 45% of acute stroke patients are not admitted in the UK, compared with 20% in Australia and Europe. In the catchment area of our hospital, a conservative calculation of stroke incidence suggests a minimum of 480 incident strokes per year; the maximum number admitted in the past 5 years is 263. Those patients who are not admitted are not receiving co-ordinated stroke care as presently defined.

The implications for hospital stroke services are substantial. All acute hospitals that receive stroke patients clearly should have a stroke unit. The National Clinical Guidelines for Stroke suggest that patients with acute stroke should be admitted to hospital unless certain strict criteria can be met by community services.<sup>3</sup> In districts such as ours, the number of stroke patients admitted to hospital could rise by up to 46% unless community stroke services are developed to the necessary standard. In a district with a population of 200 000, this rise could mean an additional 120 acute stroke patients admitted each year.

The National Health Service Executive target of lowering the rate of increase in emergency admissions in people older than 75 years<sup>4</sup> does not inspire confidence given that Kalra and colleagues' study population has a median age of 75 years and older. In our own Stroke Service, the average age of acute stroke patients is 76 years, and 42% are 80 years or older. The median length of stay is 23 days overall and 29 days for those older than 80.

Intermediate care schemes are seen by many as the answer to difficulties in the acute services, by preventing inappropriate admission and facilitating early discharge. This paper and expert guidelines suggest that most stroke patients require stroke-unit treatment in hospital at the onset of illness, and are, therefore, not appropriately managed in intermediate care.

Admission to hospital is appropriate for stroke patients, whatever their age.

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- 1 Kalra L, Evans A, Perez I, Knapp M, Donaldson N, Swift CG. Alternative strategies for stroke care: a prospective randomised controlled trial. *Lancet* 2000; **356**: 894–99.
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- 3 National Clinical Guidelines for Stroke. London: Royal College of Physicians, March 2000.
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#### Authors' reply

Sir—We agree with Martin Dennis and Peter Sandercock that large treatment effects are rarely encountered in medicine. One reason, often overlooked in trials of treatment policy is the trend towards undertaking large multicentre trials that include dissimilar settings in different geographic areas with variable population characteristics. Despite defined inclusion criteria, selection of participants is likely to be heterogeneous, since control for the whole range of variables that may affect outcome is not possible.<sup>1</sup> Moreover the delivery of interventions will probably differ between centres, which may result in a wide range of treatment effects for the whole study.<sup>1–3</sup> Treatment effects as large as 66–80% have been seen previously in other clinical studies.<sup>3,4</sup>

The results of the systematic review of stroke-unit care<sup>3</sup> have been available to collaborators since 1994. Dennis and Sandercock's power calculation is valid for a conventional fixed-sample design, but recruitment of such numbers in a tightly controlled single-centre study is not feasible. We addressed the question of power with the sequential analysis framework.<sup>5</sup> The distribution of sample size for a triangular sequential design set to detect an odds ratio of 0.7 with 90% power and 5% significance has an expected value of 429 per group and a 90th percentile of 685 per group. Sequential tests generally allow the same level of power for a given treatment effect as in large trials, and when analyses can be done is not limited. The first analysis should, however, be done when at least 20% of the maximum sample has accumulated since this provides enough information for covariate adjustment. The 138

patients quoted corresponded to 20% of the 90th percentile of the sample size for this sequential design. In addition, a subanalysis to adjust for bias introduced by early stopping yielded results similar to those of the conventional analyses; the (sequentially adjusted) median unbiased estimator for the odds ratio of Stroke Unit *vs* Stroke Team was 0.38 (95% CI 0.2–0.7). These details were omitted from the original paper for reasons of simplicity and brevity.

Randomisation could be affected by the small blocks (six to eight patients) used in many phase II and III studies, especially when treatment cannot be truly masked (eg trials on thrombolysis). However we randomised in blocks of 30 in an office remote from treatment areas. Staff enrolling patients could not have guessed assignment for the vast majority. The summaries in table 2 are relative risks not odds ratios, which was an oversight on our part.

We suspect that differences in mortality represent major differences in the acute medical care of stroke patients in different settings. We are in the process of analysing prospectively collected data on the processes of care and complications. Understanding of these processes is fundamental to implementing change in clinical practice. As Chris Durkin and Dennis Briley point out, the implications for the health services are great and will require a substantial investment in hospital stroke services to improve stroke care.

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- 1 International Stroke Trial Collaborative Group. The International Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997; **349**: 1569–81.
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## The idea and the experiment

Sir—In his provocative piece, John Martin (Sept 9, p 984)<sup>1</sup> uses as a strong argument for his hypothesis the example of Jenner and vaccination. He views Jenner's vaccination of a neighbour's child as the most obvious manifestation of the idea outweighing the experiment.

Martin implies that Jenner had simply applied his notion directly and so produced medicine's greatest advance. But this was not the case. If Martin reads Jenner's unpublished report, which was made widely available in a verbatim publication to commemorate the bicentenary of Jenner's death,<sup>2</sup> he will discover that Jenner was experimenting.

Jenner had seen the protective effect of natural cowpox infection in twelve people. For the thirteenth, "The more accurately to observe the progress of the infection, I selected a healthy Boy about eight years old for the purpose of inoculation for the Cow-Pox". Jenner inserted the cowpox on May 14, 1796, and observed the evolution of the lesion. "On the 1st of July following, this Boy was inoculated-with Matter immediately taken from a smallpox Pustule." Several punctures and incisions were made but no disease followed. The boy, who was James Phipps, was variolated with smallpox many times to prove his freedom from smallpox.

Jenner had followed the lessons of his former teacher and colleague, John Hunter, who, in their correspondence on the habits of hedgehogs, had written "but why think, why not try the Expt."<sup>3</sup> (sic).<sup>3</sup>

Ideas remain ephemeral until the experiment establishes their existence.

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- 1 Martin J. The idea is more important than the experiment. *Lancet* 2000; **356**: 934–37.
- 2 Edward Jenner. Born May 17th, 1749- died Jan 26th, 1823. *Lancet* 1923; **1**: 137–42.
- 3 Royal College of Surgeons. Letters from the past: from John Hunter to Edward Jenner. London: Dorrisston, 1976.

Sir—Whoever believes that "the expression of fantasy in abstract painting and music is superior to those in science", as John Martin does<sup>1</sup> should think again.

The leaps in abstract thinking by an Einstein, Planck, Bohr, or Feynman<sup>2</sup> represent an intellectual activity few are capable of, since it requires an

intimate knowledge of higher mathematics and physics that not many can muster. Besides, the flights of their imagination were unique and you wonder, would someone else ever have come up with the same solutions?

The major breakthroughs in science, especially in modern science, are no less than any artistic innovations by a Debussy, Stravinsky, or Schoenberg, or paintings by Manet, Cezanne, Picasso, or David Smith. In fact, modern art has benefited from more science, as Picasso and Braque were the first to admit, rather than the other way around. For the lesser contributions Ortega y Gasset noted that experimental science has progressed thanks mainly to the work of men who are astoundingly mediocre and even less than mediocre.<sup>3</sup>

Art is generally subjectively oriented, whereas science is mostly motivated by a desire to understand the world, even if the two disciplines make use of the same intuitive thinking. And, just as we would do as well without certain paintings (as an art and antiques dealer for the past 15 years I have become convinced that many are over-rated) and presumably many poems, novels, or musical compositions as well, in second-rank science someone else eventually will be there to make the same discoveries that keep rekindling the priority issue.

Contemporary physics or cosmology speak mostly to a small intellectual elite, but art is far more democratic in its appeal and its audience is commonly less discerning or discriminating. The rewards of both flights of fancy is in the beauty of the solutions they offer. As one tubercular doctor and poet once put it: A thing of beauty is a joy forever . . . ! (Don't you wonder what Beethoven might have done with Endymion?)

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- 1 Martin J. The idea is more important than the experiment. *Lancet* 2000; **356**: 934–37.
- 2 Kleppner D, Jackiw R. One hundred years of quantum physics. *Science* 2000; **289**: 893–98.
- 3 Ortega Y Gasse J. The rebellion of the masses. Norton, 1932.

### Author's reply

Sir—Peter Warren maintains that when Jenner vaccinated and later challenged a healthy boy with cow pox, he was experimenting. I maintain he was not experimenting but was applying his idea, directly as a therapeutic. The origin of the difference between the two viewpoints

probably lies not in an historical analysis of Jenner's actions but in the definition of the nature of experimentation.

Jenner had observed horse handlers transfer a pox infection to cows when they helped with the milking. Milkers infected with pustules from the cows were protected against smallpox. He conceived the idea that vaccination with cowpox would protect against smallpox. I believe that an essential part of the nature of experimentation is that the result is uncertain, otherwise the experiment would not be performed. This is in contrast to the development of, for example, a therapeutic, for which the result is predictable. Jenner vaccinated the boy with cowpox and later inoculated him with smallpox. If this process had been an experiment, Jenner would have been exposing the child to the possibility of death from smallpox. I believe he acted as though he was undertaking a demonstration of the correctness of his idea. John Hunter did indeed say to Jenner ". . . try the Expt", but he was referring to studies on the digestion and hibernation of hedgehogs; studies the outcome of which was unsure and, therefore, experimentation was needed.

I did not argue against the absolute necessity for rigorous experimentation in medical science. I underlined the importance of the idea in creating the right experiment and the direction of the experimentation.

Henry Gans says I should think again if I believe "the expression of fantasy in abstract painting and music is superior to its expression in science", but I actually said "If fantasy is a play of ideas, then I find the expression of fantasy in abstract painting superior to science for two reasons". First, art is superior because it is a tool of self-analysis—of the artist or of the observer. Knowledge of self is qualitatively more important (to the human being) than science, since the role of science is simply the measurement of nature in a way that nature can be predicted. Furthermore the work of the artist is unique, whereas many scientists would be capable of making any important discovery. We probably inappropriately honour the one that gets there first. If the artist's work is of value, then his or her honour is probably appropriate, since without that particular artist the work would never have existed.

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## Conjoined twins

Sir—In your Sept 16 editorial,<sup>1</sup> you rightly say that the Children Act was not drafted with the situation of the conjoined twins, Jodie and Mary, in mind. Those charged with drafting the Act could not have foreseen such circumstances, but the underlying philosophy of the Children Act applies in all cases.

The Act was designed to ensure the welfare of the child based on the belief that most children are best looked after within the family, with both parents playing a full part and without resort to legal proceedings.<sup>2</sup> In the case of Jodie and Mary, the parents acted with utmost sincerity with the best wishes of their children at heart. The judges made it clear in their statement that the doctors involved in the care of the twins could have acted on the parents' wishes without blame (www.court.service.gov.uk accessed on Jan 8, 2001) without invoking the power of the Children Act.

Since the Act specifically prohibits a court from making an order unless it considers that doing so would be better for a child than making no order at all,<sup>2</sup> the order to allow the separation, which resulted in the death of the weaker sister, Mary, is in serious error. To say that a disabled child's welfare is best served by her death is ethically unsound. All human life is precious and cannot be weighed up in a utilitarian way alone. Does this decision herald the re-emergence of the sociopolitical views strongly endorsed in the mid 20th Century in Germany?

The worrying and inadequately explained feature of the dilemma surrounding these little girls is that their case went to court in the first place. The Children Act was not deficient, but there was a failure to apply the spirit of the Act. The compassionate, ethical, and moral choice the parents made in the best interests of their babies satisfied all its requirements. The parents discharged their duty admirably; their decision was not criticised in any way by the court. That a legitimate parental decision to allow their babies to live and die, still conjoined, in peace was not adhered to is disturbing.

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1 Separation of conjoined twins. *Lancet* 2000; **356**: 953.

2 The Children Act 1989 guidance and regulations, vol 1: court orders. London: HM Stationery Office, 1991.

## Research in complex emergencies

Sir—Issues raised in your July 8 news item<sup>1</sup> are pertinent to the process of medical research in the international setting. We did a clinical antimalarial drug efficacy study in East Timor. We followed a series of uncomplicated falciparum malaria infections treated with chloroquine for 28 days to assess treatment failure. Our experience as an international medical aid organisation in the study draws attention to the importance of operational research in emergency or post-emergency circumstances, and tensions between scientific research and sensitivity to the needs of communities involved.

Our study showed high rates of treatment failure with chloroquine, which suggests that practice potentially puts lives at risk. Although the immediate post-emergency setting is not ideal for research, the study was urgently required to provide evidence on which to base clinical decision making. Chloroquine is still used as first line therapy for uncomplicated malaria (usually diagnosed clinically), despite reported widespread resistance elsewhere in the East Timor region and WHO recommendations to the contrary. Our study draws attention to the importance, indeed obligation, of the international emergency health sector to obtain data to improve the work of the sector that minimises avoidable morbidity and mortality.

Although there was an urgent need for results from our study, we thought of the future effect of our work. We aimed to collaborate with East Timorese health professionals at every stage of the research process to ensure skills transfer. Herein lies the first tension. Where access to highly trained health professionals is limited, which aim becomes the priority—rigorous data collection or capacity building? We made data collection the priority when possible so that validity of the study was not eroded, whilst ensuring as much autonomy as possible to the Timorese health workers working with us. Nevertheless, to ensure ongoing benefit after the departure of our international agency, the tension between short term achievement of research goals and the long term transfer of skills remains.

This first tension is underpinned by a second and much greater tension, between our desire to minimise avoidable morbidity and mortality, and our desire to support self determination. Our study was set in a traumatised community, with makeshift shelter,

destroyed infrastructure, under employment, and an uncertain future. Health workers were required to work in settings and at skill levels never before demanded of them. Many senior health workers were occupied primarily with the establishment of a new health system. Our prioritisation of anti-malarial drug efficacy studies did not necessarily fit with local priorities (ie, establishing a new national health system, or addressing the interests of health workers uncertain of their future employment). In the attempt to prioritise aims set by the international sector, we risked the impairment of local efforts at priority setting. Locally generated priority setting is an important part of self-determination. We achieved our aims in this setting, in which widespread use of possibly inappropriate antimalarials was potentially dangerous, whilst seeking support for the study from the overworked senior Timorese health professionals. Nevertheless, a research programme such as ours must incorporate sensitivity to local needs, a genuine determination to work in support of local communities, and an ongoing process to monitor programme implementation so that undermining self-determination is avoided.

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1 Morris K. Malaria-control partnerships key to combat disaster deaths. *Lancet* 2000; **356**: 144.

## Informed consent is flawed

Sir—More fundamental problems might be associated with the consenting process than Aslak Syse addresses (Oct 14, p 1347).<sup>1</sup> Many patients who would be legally competent do not have the intellectual training to make a reasoned judgment.

We did a small survey of patients attending a transient ischaemic attack and minor stroke clinic to investigate the determinants of potential decisions for use of tissue plasminogen activator for acute cerebral ischaemic events. Patients were given the information available from the National Institute of Neurological Disorders' trial<sup>2</sup> in a simplified form. The decision is fundamentally a statistical one about better outcome for disability being balanced by the risk of symptomatic haemorrhage. We

asked some simple statistical questions. 39% of patients did not know that a reduction of 25% was one in four; 44% did not know that a reduction of 25% was a reduction of a quarter; and 43% did not know that a reduction of 25% was equivalent to a reduction of 25 in 100. A substantial minority of people in this population, therefore, could not process simple statistical information.

If the consenting process is about informing patients so they can make balanced and reasoned decisions, and the logic behind those decisions is statistical, many cannot give informed consent. The consenting process should be more one of a personal interaction, in which a relationship of trust is established between the patient and doctor. Body language might, therefore, be more important than statistical considerations.

Informed consent is the bulwark of ethical conduct in clinical practice and research. It is the best we have, but it is flawed.

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- 1 Syse A. Norway: valid (as opposed to informed) consent. *Lancet* 2000; **356**: 1347–48.
- 2 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. *N Engl J Med* 1995; **333**: 1581–87.

## Research agenda in less-developed countries

Sir—Besides the “highjacking of clinical and research agendas” Richard Horton described in his Sept 23 commentary,<sup>1</sup> organisations in more-developed countries have attracted the largest funding for research, and have generally determined what research is ethical and what studies meet the health needs of poorer countries.<sup>2</sup> These workers find it easier to publish their research in leading medical journals and affect which papers by less-resourced scientists are published. The irony of these inequalities is that, at the end of the study, the local scientists are the ones who have to work with health authorities to develop relevant policies and interventions.

Western scientists remain suspicious of the quality of work of local scientists or workers, which undermines capacity-building in collaborative research. One institution imported its

own microscopists for basic microscopy on helminths in Ghana. Scientific interests in more-developed countries and those of the recipient poor countries might not always coincide, as when in the choice between studies on macroepidemiology and molecular epidemiology of infectious diseases.

Several large-scale trials of public health importance of infectious diseases have been done in Africa, mostly in collaboration with scientists from more-developed countries. The findings of such studies have been published in leading journals, but it is doubtful that these findings are known or have influenced clinical and public-health practices in the study countries. At the other extreme, policy makers have sometimes been overzealous to hastily implement findings obtained under controlled trial settings nationwide, as has been the case with bednets and community-based health planning and services in Ghana.<sup>3,4</sup>

In many poor countries, a lot of good relevant health research has been done. The documentation is, however, widely scattered across the country and, in some cases, is only available outside the country. This dissemination of data makes it difficult for researchers, policy makers, and other interested individuals to be readily aware of, access, or use the relevant findings to design interventions. As a priority, a central health research body should build and maintain updated databases on health-related research in each country.

My concerns are that not enough research is being done in less-developed countries (clinicians blame heavy workload), and the collaboration between the universities and health ministries is weak. Published studies in local medical journals are limited largely to those from the teaching hospitals and might not reflect health issues in other parts of the country. Few studies are interventional, which hinders the practice of evidence-based medicine.<sup>5</sup>

After the International Conference on Health Research for Development in Thailand, I expect scientists from poorer countries are better-placed to develop strategies and research-led policies and implement them to improve health behaviour and practices, and, ultimately, the health and quality of life for all people. Organisations from more-developed countries can help by funding research, promoting access to health information, and removing biases against publishing any articles from less-developed countries. The

universities, professional health associations, and health ministries in less-developed countries should play their roles in increasing health research.

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- 1 Horton R. Development aid: manna or myth? *Lancet* 2000; **356**: 1044–45.
- 2 Angell M. Investigators' responsibilities for human subjects in developing countries. *N Engl J Med* 2000; **342**: 967–69.
- 3 Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **343**: 7–12.
- 4 Binka F, Nazzari A, Phillips JF. The Navrongo Community Health and Family Planning Project: Studies in Family Planning. *Stud Fam Plan* 1995; **26**: 121–39.
- 5 Isaacs D, Fitzgerald D. Seven alternatives to evidence-based medicine. *BMJ* 1999; **319**: 1618

## Accuracy of references in theses

Sir—When I started working as an external examiner for MD and PhD theses about 40 years ago, I was given advice by Noel MacLagan. “At an early stage check a dozen random references for accuracy, preferably against the original articles, not Index Medicus—this was before the days of the internet when references could be transferred to the publication without being seen by the author. If you detect a mistake, check another dozen. You will find that a candidate who has consistent errors in the references will almost always have unacceptable errors in the thesis”.

Does this argument also apply to articles?<sup>1</sup> I found this advice reliable, and candidates whom I referred to correct errors in their thesis were told also to check all their references before resubmitting.

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- 1 Siefers R, Holt S. Accuracy of references in five leading medical journals. *Lancet* 2000; **356**: 1445.

## DEPARTMENT OF ERROR

*Treatment of acute otitis media with an antiadhesive oligosaccharide: a randomised, double-blind, placebo-controlled trial*—In this Article by P Ukkonen and colleagues (Oct 21, p 1398), the title should be: “Prevention of acute otitis media with an antiadhesive oligosaccharide: a randomised, double-blind, placebo-controlled trial”.