

CORRESPONDENCE

Prevention of vertical HIV-1 transmission

Sir—As obstetricians, we do not believe that the evidence presented in the European collaborative clinical trial on elective caesarean section versus vaginal delivery in the prevention of vertical HIV-1 transmission (March 27, p 1035)¹ is sufficiently strong to justify a policy of elective caesarean section in women who are HIV-1 positive. We suggest that it is more appropriate to randomly allocate patients elective caesarean section or elective induction of labour at term rather than spontaneous labour. Elective induction facilitates the optimum administration of anti-retroviral therapy in labour. In the trial, 70% of the caesarean section group (n=188) received antiretroviral therapy during pregnancy compared with only 58% in the vaginal delivery group (n=220).

The results of the trial may be no longer applicable given the important advances in the management of HIV-1 infection,² such as combination antiretroviral therapy and the development of reliable assays to quantify viral load. In the 89 study patients assigned vaginal delivery who received zidovudine during pregnancy, only three (3%) babies were subsequently HIV-1 positive. We also have no details, for example, on drug therapy, patient compliance, viral loading, labour course, or infant feeding in these three cases.

In HIV-1-positive women who comply with single or combination antiretroviral therapy, and who have low viral loads, induction of short labour may avoid vertical transmission and caesarean section. Although transmission may take place after vaginal delivery, the trial confirms that transmission may also occur after elective caesarean section.

In view of the established serious short-term and long-term implications of caesarean section for the mother, we believe that women who are HIV-1 positive should receive individual obstetric care and that a policy of routine elective caesarean delivery cannot be justified on the evidence.

*Juliet Skinner, Michael J Turner

Coombe Women's Hospital, Dublin 8, Republic of Ireland

- 1 The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999; **353**: 1035–39.
- 2 Temesgen Z, Wright AJ. Recent advances in the management of human immunodeficiency virus infection. *Mayo Clin Proc* 1997; **72**: 854–59.

Authors' reply

Sir—Juliet Skinner and Michael Turner suggest that a more appropriate study design would have been to randomly assign women to elective caesarean section or induction of labour at term, to facilitate medical treatment of mother and baby. In our opinion this point is irrelevant. In our series a large proportion of women did not receive antiretroviral therapy during pregnancy because most of them entered the trial before the publication and diffusion in clinical practice of the results of US-French trial¹ on zidovudine prophylaxis to reduce vertical transmission.

Skinner and Turner suggest that caesarean section is not a useful intervention, because therapeutic prophylaxis would have prevented most cases of vertical transmission. However, among women who received zidovudine in pregnancy in our trial, three (3%) infants of 92 women who delivered vaginally and three (2%) of 144 who delivered by caesarean section were HIV-1 infected. This difference cannot be evaluated statistically. Given the current low rate of vertical transmission, further analysis of mode of delivery is not feasible, but recent results from the European Collaborative Study confirm that elective caesarean section, prophylactic zidovudine, and gestational age are independently associated with vertical transmission.²

While awaiting further confirmation of the efficacy of zidovudine or combination therapy in preventing vertical transmission, caesarean section should be regarded as an option to prevent HIV-1 infection of the infant. There are few data on the effect of elective procedures on maternal health and we did not confirm previous suggestions of a high rate of complications.³

We have shown that elective caesarean section reduces the risk of mother-to-child transmission of HIV infection. On the basis of available information, any clinical decision is left, as always, to the physician and the woman.

*Fabio Parazzini on behalf of the

European Mode of Delivery Collaboration

Istituto di Ricerche Farmacologiche Mario Negri, 20157 Milan, Italy

- 1 Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994; **331**: 1173–80.
- 2 The European Collaborative Study. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS* 1999 (in press).
- 3 Semprini AE, Castagna C, Ravizza M, et al. The incidence of complication after caesarean section in 156 HIV-positive women. *AIDS* 1995; **9**: 913–17.

Sir—The European Mode of Delivery Collaboration¹ found a striking reduction in infant infection with use of elective caesarean section, analysed by intention to treat and actual mode of delivery. They also suggested that planned caesarean section before labour or ruptured membranes should become part of routine care for HIV-positive pregnant women. We find no fault with their methods. However, this study suffers the same fate as many other well-designed therapeutic trials in HIV-1 disease: advances in HIV monitoring and antiretroviral treatment have outpaced the development and conduct of these trials, thereby limiting the generalisability of their results. The investigators do not adequately address the limitations of this study.

First, HIV-1 RNA load is an important predictor of maternal-fetal HIV-1 transmission² and relevant to the issue of exposure to infected blood and genital secretions. The main rationale of caesarean-section is to bypass such exposure. This study does not report (perhaps they were not available) or even mention HIV-1 RNA load as a significant variable and possible confounder in the analysis.

Second, the dramatic reduction in HIV-1-related morbidity and mortality associated with use of combination antiretroviral therapies has resulted in

their use becoming standard of care in the treatment of both pregnant and non-pregnant adults infected with HIV.³ There is no evidence of substantial use of antiretroviral therapy other than zidovudine monotherapy during pregnancy in this study. Highly active antiretroviral therapy, generally involving three agents, results in greater and more sustained reductions of viral load when compared with any one agent alone. Whether the use of more optimum antiretroviral therapy will further reduce HIV-1 transmission over zidovudine alone remains to be seen, but that possibility should not be totally discounted and should have been addressed.

Third, there is little doubt that caesarean section, whether elective or emergent, is associated with greater costs and higher likelihood of complications than is vaginal delivery. This study also found a substantial increase in postoperative febrile morbidity in women undergoing caesarean section delivery, although frequency of complications was low. Schuitemaker and co-workers,⁴ in a nationwide study on cause of maternal death, reported a 3.5 times increase in maternal deaths in the Netherlands that was directly attributed to caesarean section, compared with vaginal delivery. Whether HIV status per se or as a surrogate for other risk factors will further increase risk with caesarean section remains unclear. This study, with routine use of prophylactic antibiotics and women largely without much immune compromise, cannot help to answer this question. Nevertheless, this issue has serious implications for practice in the USA and western Europe, but more specifically in less-developed countries, where availability of antibiotics and blood products is limited. In correspondence from a prospective cohort study in Rwanda, three of 20 HIV-positive women undergoing caesarean section died within 72 h from postoperative complications compared with none of ten HIV-negative women. No maternal deaths were seen as a direct result of vaginal delivery.⁵

It is the role of responsible investigators to clearly and effectively call attention to the limitations of their findings and to urge caution in the application of new and potentially unnecessary or dangerous interventions.

*Jean R Anderson, Gina Hanna,
Edith Gurewitsch

Department of Gynecology and Obstetrics,
Johns Hopkins School of Medicine, Baltimore,
MD 21287, USA

- 1 The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999; **353**: 1035–39.
- 2 Coutopoulos-Ioannidis DG, Ioannidis JP. Maternal cell-free viremia in the natural history of perinatal HIV-1 transmission: a meta-analysis. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **18**: 126–35.
- 3 DHHS Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for use of antiretroviral agents in HIV-infected adults and adolescents. *MMWR Morb Mortal Wkly Rep* 1998; **47** (RR3): 38–78.
- 4 Schuitemaker N, van Roosmalen J, Dekker G, et al. Maternal mortality after caesarean section in the Netherlands. *Acta Obstet Gynecol Scand* 1996; **75**: 332–34.
- 5 Bulterys M, Chao A, Dushimimana A, Saah A. Fatal complications after Caesarian section in HIV-infected women. *AIDS* 1996; **10**: 923–24.

Commentator's reply

Sir—Implicit in the recommendation that caesarean section be considered part of a package to be offered to an HIV-1-positive woman, is the caveat that the decision should be individual as for any other obstetric intervention. Any extra hazard to abdominal delivery will naturally also apply to operation for some other indication (eg, breech presentation). Extra hazards will include absence of blood and antibiotics, and there may likewise be no safe alternative to breastfeeding, which would also negate the offer. I cannot quarrel with the view that the cost and benefit of all HIV interventions need to be balanced on an individual basis.

C N Hudson

Department of Obstetrics and Gynaecology,
St Bartholomew's Hospital, London EC1A 7BE, UK

Sir—L M Mofenson¹ and C N Hudson² question the efficacy of prenatal zidovudine use and elective caesarean section, respectively, during the natural course of pregnancy and childbirth.

South Africa's health minister has refused to sponsor the former strategy for prevention of HIV infection and AIDS on the basis of cost in a nation whose health budget is severely limited.³ In South Africa, elective caesarean sections solely for preventing HIV infection would seem impractical, especially in the absence of prenatal zidovudine programmes.

About 25% of infants born to HIV-1-positive women develop AIDS, but usually thrive until polarised secondary germinal centres develop in their intestinal Peyer's patches at about 6 months of age. About three-quarters of infants born to HIV-1-positive women continue to live and develop normally without AIDS.

Unfortunately, 95–100% of offspring can expect to become orphans within 5–10 years.

Use of zidovudine near term and elective caesarean section seem to be lowering the incidence of HIV-1 infection and AIDS. However, the cost is considerable and there are potential long-term side-effects from use of nucleoside analogues, post-operative morbidity, prematurity, and infantile nutrition. Reasonable alternatives include better sex education; recommendations for the routine use of barrier contraceptives;⁴ and use of HIV-negative wet nurses.

Jack W Shields

1950 Las Tunas Road, Santa Barbara,
CA 93103, USA

- 1 Mofenson LM. Short-course zidovudine for prevention of perinatal infection. *Lancet* 1999; **353**: 766–67.
- 2 Hudson CN. Elective caesarean section for prevention of vertical transmission of HIV-1 infection. *Lancet* 1999; **353**: 1030–31.
- 3 Baleta A. South African government faces furious zidovudine debate. *Lancet* 1999; **353**: 908.
- 4 Shields JW. A national basis for safe sexual conduct in preventing the spread of AIDS. *Lymphology* 1993; **26**: 1–3.

Making and covering of surgical footprints

Sir—In her May 1 commentary on surgical adhesions Lena Holmdahl¹ fails to emphasise the positive contribution of adhesions in the prevention of spread of infection or leakage of fluids. For example, if a T-tube is put in the common bile duct after exploration, the surgeon relies on adhesions to form round it so there is no bile leak in the peritoneal cavity when the tube is removed. Some years ago, attempts to produce a T-tube that did not produce adhesions were nearly disastrous. Adhesions are very important in the prevention of any spread of small leaks around anastomoses.

Perhaps we should distinguish between the initial adhesion formation, which may be very beneficial, and reformation after further surgery (open or laparoscopic) to divide them. Obviously, in the second situation, the adhesions do not have any benefit because no anastomosis or infection is involved, and methods to prevent them are justified.

A G Johnson

Division of Surgical and Anaesthetic Sciences,
Department of Surgery, Royal Hallamshire
Hospital, Sheffield S10 2JF, UK

- 1 Holmdahl L. Making and covering of surgical footprints. *Lancet* 1999; **353**: 1456–57.

Hereditary angio-oedema in children

Sir—Attacks of hereditary angio-oedema (HAE), a genetically determined deficiency of C1 esterase inhibitor, are manifested during early childhood in two-thirds of patients. Most common symptoms are repeated angio-oedema of extremities and face (80%), followed by upper-airway obstruction and dysphagia (50%) and recurrent colicky abdominal pain (40%). Although prophylactic administration of androgens or antifibrinolytic agents is useful in reducing the frequency or severity of attacks in adult patients, little is known about the long-term management of HAE in children.

Most of the published work that addresses this issue states that: "antifibrinolytics and androgens are not recommended in children and pregnant women because of the known serious side-effects". In further support of this statement, Konrad Bork and colleagues (March 27, p 1066)¹ describe the first reported cases of hepatocellular adenomas in patients with HAE on long-term prophylaxis with danazol, an attenuated androgen. Use of danazol in children with HAE causes concern,² particularly since other treatment options are available. A role for replacement therapy with C1 inhibitor concentrate in children with HAE has been suggested,³ and an uncontrolled trial of C1 inhibitor concentrate (Immuno AG, Vienna, Austria) in children was reported in 1989.⁴ Acute attacks of HAE in six children were treated with one dose of 500 units of C1 inhibitor concentrate on 30 administrations. Progression of facial and laryngeal was aborted 30–60 min after the infusion and gradually disappeared over the next 24–36 h. In only two separate occasions, the dose had to be repeated after 60 min because laryngeal oedema continued to progress. Concentrations of C1 inhibitor and C4, when measured 12 h and 24 h after the infusion in two patients showed an expected increase. No side-effects were observed. None of the patients required endotracheal intubation or tracheotomy, and only one commenced on long-term prophylaxis with antifibrinolytics because the frequency of life-threatening attacks of laryngeal oedema increased to more than one per month. Kunschak and colleagues' results of a randomised, controlled, double-blind trial of C1 inhibitor concentrate confirm (1 inhibitor concentration as a safe, effective treatment for acute attacks of HAE).⁵ The psychological relief of both the patients and their

parents by the possibility of home treatment at the earliest sign of an attack involving upper airway is further advantage of replacement therapy with C1 inhibitor concentrate.

Mario Abinun

Department of Paediatrics, Newcastle General Hospital, Newcastle Hospitals NHS Trust, Newcastle upon Tyne NE4 6BE, UK (e-mail: Mario.Abinun@ncl.ac.uk)

- 1 Bork K, Pitton M, Harten P, Koch P. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet* 1999; **353**: 1066–67.
- 2 Barakat AJ, Castaldo AJ. Hereditary angioedema: danazol therapy in a 5 year old child. *AJDC* 1993; **147**: 931–32.
- 3 Waytes TA, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med* 1996; **334**: 1630–34.
- 4 Abinun M, Mikuska M. Hereditary angioedema in children: treatment with C1 inhibitor concentrate. 7th International Congress of Immunology. Berlin: Gustav Fischer Verlag, 1989: 144A (abstr).
- 5 Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion* 1998; **38**: 540–49.

Multiple sclerosis trials

Sir—Peter Rudge (March 27, p 1033)¹ raises important issues about therapeutic trials in multiple sclerosis (MS). The point is well taken that 2–3-year trials may not be appropriate for a chronic disease that has a mean duration of 30 years or more. However, duration of clinical trials is always a trade-off between wishful thinking and feasibility. High quality clinical trials are already very costly in MS. As long as these studies are almost exclusively funded by industry, efficacy will only be shown for more expensive compounds because no-one invests in an expensive good study for a cheap drug. Rudge's conclusion that "trials should not be prematurely terminated when a favourable effect is found" may be counterproductive. Fortunately, the marginally beneficial effect in the first part of the sulphasalazine trial did not fulfil the criteria now accepted for early termination because it was only found in one outcome measure and the p value was not lower than 0.023.² The adequate conclusion is that decisions should be taken on the basis of robust statistical criteria that take into account the difficulty of multiple comparisons.

Stopping rules that aim to protect patients participating in trials from unnecessary exposure to a harmful treatment or placebo if a treatment has been proven effective are

indispensable in therapeutic trials. The European study on interferon beta-1b in secondary progressive MS was terminated prematurely because of predefined robust statistical criteria. At the time of termination there was no hint of a declining efficacy of interferon beta-1b over time, either with regard to the primary outcome (time to confirmed progression)³ or by comparing active lesion counts in monthly magnetic resonance imaging during the first 6 months and during months 18–24.⁴ Besides ethical and financial difficulties, long-term extensions of parallel controlled studies may be difficult to interpret because of high and selective loss to follow-up, but also because the outcome measures designed for 2-year or 3-year studies may not be suitable for long-term observations. The claim that "better long-term studies are available for azathioprine" is not substituted. Although azathioprine has now been in use for over 30 years in MS, controlled long-term evidence is still lacking.

The table provided may be misleading because it does not take into account the methodological differences between studies. For example, the claim that with intravenous immunoglobulin the proportion progressing was significantly higher in the control group than in those on treatment is not based on sustained progression, but on one single assessment at endpoint,⁵ which in a relapsing-remitting population always includes a high proportion with reversible, relapse-related worsening. If unconfirmed progression was counted, both the Copolymer 1 and the interferon beta-1b relapsing-remitting studies would have yielded significant drug effects. The unusually high difference in relapse rates in favour of immunoglobulin may well be related to methodological bias, such as incomplete masking.

L Kappos

Neurologisch-Neurochirurgische Poliklinik, Kantonsspital Basel, CH-4031 Basel, Switzerland (e-mail: lkappos@uhbs.ch)

- 1 Rudge P. Are clinical trials of therapeutic agents for MS long enough? *Lancet* 1999; **353**: 1033–34.
- 2 Noseworthy JH, O'Brien P, Erickson BJ, et al. The Mayo Clinic-Canadian cooperative trial of sulfasalazine in active multiple sclerosis. *Neurology* 1998; **51**: 1342–52.
- 3 European Study Group on Interferon beta-1b Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998; **352**: 1491–97.

- 4 Miller DH, Molyneux PD, Barker GJ, et al. Effect of interferon β -1b on MRI outcomes in secondary progressive multiple sclerosis: results of a European multicentre, randomised, double-blind, placebo-controlled trial. *Ann Neurol* 1999 (in press).
- 5 Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B. Austrian Immunoglobulin in Multiple Sclerosis Study Group. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997; **349**: 589-93.

Author's reply

Sir—L Kappos' main comment relates to the financial feasibility of long-term trials of therapy in multiple sclerosis. His other points relate to matters of detail about individual trials.

He rightly points out that the short-term studies of interferon therapy show a small beneficial effect on the course of MS. However, we do not know the long-term effect of interferons in MS. In this era of evidence-based medicine, to extend indications beyond those shown to be beneficial in clinical trials is not valid. If that proves expensive, and it does, the cost of the trials will be included in the ultimate cost of the product. This higher drug cost will alter the cost-benefit analysis of the product and be a factor in determining whether the agent is prescribed. There are also ethical considerations here; without evidence of long-term effects it is wise to be cautious.

Kappos' additional adverse criticisms of my commentary relate to individual agents. The table is taken from published data and is not misleading. It is true that confirmed progression was not used in the analysis of the intravenous IgG study, and therefore the effect on progression could have been due to temporary impairment related to a recent relapse.¹ However, it is equally true that in all interferon trials the primary endpoint was the time taken to reach a specified decline in function (the first differential), not the proportion of patients attaining that decline at a predetermined interval (as in the intravenous IgG trial). Clearly the latter is the more convincing endpoint to attain, and of the published data on interferons only one of the trials attains this criterion.² Similarly, that trial was the only one that analysed progression in patients without relapses to ensure that any saving was independent of disability accruing as a result of incomplete recovery from relapse. Obviously, if there is a relapse rate reduction, progression will also decline because there will be fewer relapses that do not fully recover.

Kappos has misunderstood the statement about azathioprine. Azathioprine has better data in two senses. First, there are several double-blind controlled trials of this agent.³ Second, the largest azathioprine trial followed up half the patients for 4 years,⁴ whereas most other trials followed up the original cohort for 2 years and only one did so for 3 years.

P Rudge

National Hospital for Neurology and Neurosurgery, London WC1N 3BG, UK

- 1 Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997; **349**: 589-93.
- 2 European Study Group on Interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998; **352**: 1491-97.
- 3 Yudkin PL, Ellison GW, Ghezzi A, et al. Overview of azathioprine treatment in multiple sclerosis. *Lancet* 1991; **338**: 1051-55.
- 4 British and Dutch Multiple Sclerosis Azathioprine Trial Group. Double-masked trial of azathioprine in multiple sclerosis. *Lancet* 1988; *ii*: 179-83.

Keep antihypertensive drugs away from very old people

Sir—François Gueyffier and colleagues' (March 6, p 793)¹ meta-analysis of antihypertensive drug therapy in very old people shows an increased total mortality, which is at the border of significance ($p=0.05$). The investigators, however, in their conclusion see no suggestion of an age threshold above which hypertension should not be treated. This interpretation is strange if not dangerous for many elderly and frail patients.

Very elderly participants in these trials can walk and are probably in good health (not reported). A large proportion of people over 80 years, especially those in contact with the medical profession, will be quite frail and will thus be prone to side-effects from any medication. The health of some of those included in the studies may deteriorate, thereby producing higher mortality during antihypertensive treatment.

The indication for the treatment of hypertension in the very elderly should still be regarded as an open question and must be highly individualised. A healthy octogenarian might benefit, a patient with hypertensive heart failure will benefit, and a frail patient might be harmed. The instrument of geriatric assessment should be included in

future biomedical trials with elderly patients.

*Peter Oster, Günter Schlierf

Geriatrisches Zentrum Bethanien, D-69126 Heidelberg, Germany

- 1 Gueyffier F, Bulpitt C, Boissel J-P, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet* 1999; **353**: 793-96.

Thyroid function in hyperemesis gravidarum

Sir—M Hillbom and colleagues (May 8, p 1584)¹ describe a case of hyperemesis gravidarum complicated by Wernicke's encephalopathy, and emphasise the importance of thiamine supplementation in this disorder. However, they do not refer to their patient's thyroid status.

The association of hyperemesis gravidarum and thyrotoxicosis has been well described,²⁻⁴ and vomiting might be important as a cardinal symptom of thyrotoxicosis.⁴ The use of antithyroid medication in biochemical thyrotoxicosis associated with hyperemesis gravidarum has proved effective in symptom control and can be discontinued after resolution of symptoms.² This treatment provides an extra therapeutic option in the control of vomiting because conventional antiemetic drugs are often ineffective, with unproven safety profile in pregnancy. High-dose corticosteroid therapy⁵ has been advocated, although the outcome of randomised placebo-controlled trials are still awaited.

Thyroid function should always be assessed in patients with hyperemesis gravidarum. Appropriate therapy for biochemical thyrotoxicosis could lead to rapid control of vomiting, which, if long-lasting, could lead to nutritional deficit and fetal death, as seen in the reported case.

N N Chan

EURODIAB, University College London, London WC1E 6BT, UK

- 1 Hillbom M, Pyhtinen J, Pylvänen V, Sotaniemi K. Pregnant, vomiting, and coma. *Lancet* 1999; **353**: 1584.
- 2 Chong W, Johnston C. Unsuspected thyrotoxicosis and hyperemesis gravidarum in Asian woman. *Postgrad Med J* 1997; **73**: 234-36.
- 3 Kennedy RL, Darne J, Davies R, Price A. Thyrotoxicosis and hyperemesis gravidarum associated with a serum activity which stimulates human thyroid cells in vitro. *Clin Endocrinol* 1992; **36**: 83-89.
- 4 Rosenthal FD, Jones C, Lewis SI. Thyrotoxic vomiting. *BMJ* 1976; *ii*: 209.
- 5 Taylor R. Successful management of hyperemesis gravidarum using steroid therapy. *QJM* 1996; **89**: 103-07.

Tuberculosis in prisons

Sir—In their report on tuberculosis treatment in prisons, Rudi Coninx and colleagues (March 20, p 969)¹ highlight the low rates of treatment success (54%) obtained in a situation where resistance to antituberculosis drugs is high, despite use of the directly observed (short-course) treatment strategy (DOTS). This finding leads the researchers to question the strategy, particularly the first-line regimens.

What is surprising in their results is the low efficacy of treatment in individuals with susceptible bacilli. Results of drug susceptibility testing before treatment are available for only 101 (28%) of the 357 participants who completed treatment in prison. Of the 101 patients, 37 were failures (sputum-positive at the end of treatment), of whom three were not resistant and seven were resistant to a single drug before treatment. The treatment failure rate in Coninx's study is 12% in susceptible patients and 28% in mono-resistant patients (table).

These results conflict with those reported by Mitchison and Nunn² in a review of clinical trials that aimed to analyse the effect of primary resistance on treatment results. They showed that if the strain was susceptible to all antituberculosis drugs or mono-resistant to isoniazid or streptomycin, the failure rate of treatment regimens that contain rifampicin for 6 months was less than 1% (table).

Coninx and colleagues argue that the three failures with strains initially sensitive to all drugs may have been reinfected during treatment by a multiresistant strain.³ The same would need to be true for the seven mono-resistant individuals. Even in a situation where the prevalence of HIV-1 is high, which does not appear to be the case here, this hypothesis does not seem reasonable.

If the first-line regimens were truly so ineffective with susceptible or mono-resistant strains, any antituberculosis treatment strategy would be vain. The third-line regimens, which

are much less effective and more toxic, can in no way represent an alternative.

These results question the data presented by Coninx and colleagues. Their report is more an analysis of routine data within a programme than a prospective study; there may have been bias in the recruitment of patients or errors in recording results. Furthermore, the prison context creates behaviour patterns that are unusual. As indicated by the researchers, patients with tuberculosis are better off than the other prisoners, if only from the point of view of diet. As a result, it is not in their interests to be cured. Although they are theoretically under DOTS, do prisoners really swallow the drugs? Do the sputum samples at the end of treatment belong to the right patients? Whatever the reasons for these failures, changing the first-line regimen itself will not provide better results. If the results for susceptible and mono-resistant strains are doubtful, what could one say of the others?

The difficulty posed by cases of multidrug-resistant tuberculosis in ex-USSR prisons is serious. This issue requires particular attention, starting with a better understanding of what causes these multiresistant cases. The question is an important one, and it is not groundless criticism of DOTS, which has proved successful elsewhere,^{4,5} that will help find a solution to the problem.

Arnaud Trébuq

International Union against Tuberculosis and Lung Disease, 75006 Paris, France (e-mail: atrebuq@compuserve.com)

- 1 Coninx R, Mathieu C, Debacker M, et al. First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculosis* in prisons. *Lancet* 1999; **353**: 969–73.
- 2 Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986; **133**: 423–30.
- 3 Small PM, Schafer RW, Hopewell PC, et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. *N Engl J Med* 1993; **328**: 1137–44.
- 4 Netto EM, Dye C, Raviglione MC. Progress in global tuberculosis control 1995–1996, with emphasis on 22 high-incidence countries. *Int J Tuberc Lung Dis* 1996; **3**: 310–20.
- 5 WHO. Global tuberculosis control, WHO Report 1999: communicable diseases. Geneva: WHO, 1999: WHO/CDS/TB/99.259.

Authors' reply

Sir—Arnaud Trébuq asserts that the ten patients who had pansensitive or mono-resistant strains and in whom treatment failed was the result of a selection bias or errors in our recording

of data. Although we accept that errors in data can never be entirely excluded, we do not believe that this is the most likely explanation for our findings. Furthermore, Trébuq has misunderstood our central conclusion, which was not that DOTS should be abandoned, but that debate should take place about the selection of drugs used in DOTS programmes in settings where drug resistance is common.

There are various reasons why we believe errors in data recording do not substantially affect our results. Only two individuals entered the data analysed, and both were study investigators. Intake of medicines and collection of sputum samples were supervised closely. Other programmes that operate in similar settings have reported similar results and drawn similar conclusions.¹ Laboratory results were routinely cross-checked with two European reference laboratories, and showed a high degree of concordance as we stated. We also acknowledged in our report a selection bias that probably resulted in over-representation of patients infected with highly resistant strains.

We believe other factors may account for the non-response of these ten cases. The first is that in our study there were only ten such cases among a population of 50 versus the combined populations of over 3500 in the report by Mitchison and Nunn,² with which Trébuq believes our results can be compared. We question whether the most likely explanation for our outcomes would be important differences in the distribution of other predictors of treatment failure between our study population and those populations reviewed by Mitchison and Nunn. Our modelling indicates that factors other than initial resistance profile are important predictors of treatment failure. Cavitory disease, oedema on admission, and a body-mass index of less than 16 kg/m² on admission were all strongly and independently associated with treatment failure in our model including resistance profile data.

Seven of the ten cases had cavitory disease, four had oedema on admission, and four had a body-mass index below 16 kg/m² on admission. All ten cases had at least one of these risk factors. The distribution of these risk factors among our study population may differ substantially from the populations represented in the studies reviewed.

Trébuq misunderstands what we stated about exogenous reinfection. We did not assert that this was the, or even a possible, mechanism to explain

	Drug resistant		
	None	1	≥2
Coninx et al¹			
Number of cases	25	25	51
Number of failures	3	7	27
% of failures	12%	28%*	53%
Mitchison and Nunn²			
Number of cases	3177	334	NA
Number of failures	2	3	NA
% of failures	0.01%	0.90%	NA

NA=not applicable. *One patient was mono-resistant to rifampicin on recruitment to study.

Treatment failures by pattern of drug resistance

treatment failure. We suggested that individuals who acquired three additional resistances during treatment may have become exogenously reinfected.

We agree with Trébuq that the problem of resistant tuberculosis in ex-USSR prisons is serious. We also believe that only critical examination of outcomes in such settings will allow one to draw conclusions about the effectiveness of the currently recommended strategy, rather than to continue advocating for standardised treatment schemes limited to first-line drugs, irrespective of evidence of their shortcomings. To raise questions about this feature of DOTS is far from groundless and we are pleased to see that WHO is working on a revised strategy for such circumstances.³

*R Coninx, R de Haller, D R Meddings
International Committee of the Red Cross,
CH-1202 Geneva, Switzerland
(e-mail: rconinx@icrc.org)

- 1 Kimerling ME, Kluge H, Vezhina N, et al. Inadequacy of the current WHO re-treatment regimen in a central Siberian prison: treatment failure and MDR-TB. *Int J Tuberc Lung Dis* 1999; **3**: 451–53.
- 2 Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986; **133**: 423–30.
- 3 Spinaci S. Treatment failure and MDR-TB. *Int J Tuberc Lung Dis* 1999; **3**: 365.

Preoperative fasting

Sir—Stress and anxiety are not synonyms. I do not use the word stress in my commentary.¹ How can I be “wrong” for “say[ing] that stress does not delay gastric emptying”, as Jean-Pierre Tournadre and colleagues claim (May 8, p 1624).² Furthermore, unlike what these correspondents write, I do not “question [strict] rules of preoperative fasting”.² Others have already done so. I suggest that preoperative fasting recommended by anaesthetists’ associations (eg, in Canada, USA, UK, and Scandinavia)³ should be more widely adopted. Not “for gastrointestinal motility” as Tournadre claims I wrote, but merely “to reduce . . . thirst, headache, irritation, discomfort”.

Milk is not a clear liquid, consequently Maes’ study⁴ is not at odds with my reminder to shorten abstinence from clear liquids. Also, current guidelines, I stated, apply “provided gastric emptying is not delayed by drugs, trauma, or disease”, a point Tournadre reiterates when he mentions “stress, . . . pain, premedication” and diseases or

conditions that “affect their oesophageal, gastric, or pyloric function”.

Tournadre and colleagues also reiterate my assertion that the effect of reduced fasting times on postoperative nausea and vomiting “is not certain”; I used the word “perhaps” in my conclusion precisely for this reason.

Finally, intravenous hydration, however profuse, does not quench thirst—ie, it does not “procure the same benefit” as drinking. Tournadre and co-workers not only confirm my point “that opinions on preoperative fasting have fluctuated”, but also they show that they still do and that deep seated, ill-founded habits in medicine are hard to lose.

Bruno Simini
Ospedale, 55100 Lucca, Italy

- 1 Simini B. Preoperative fasting. *Lancet* 1999; **353**: 862.
- 2 Tournadre JP, Chambrier C, Boulétreau P, Chassard D. Preoperative fasting. *Lancet* 1999; **353**: 1624.
- 3 Eriksson LI, Sandin R. Fasting guidelines in different countries. *Acta Anaesthesiol Scand* 1996; **40**: 971–74.
- 4 Maes BD, Ghoos YF, Geypens BJ, Hiele MI, Rutgeerts PJ. Relation between gastric emptying rate and energy intake in children compared with adults. *Gut* 1995; **36**: 183–88.

Blood pressure measurements in genetic linkage studies

Sir—Zilla Wong and colleagues (April 10, p 1222)¹ report an interesting genetic linkage between chromosome 16p12 and systolic blood pressure. However, despite lower mean diastolic blood pressure differences in identical-by-descent allele-sharing siblings versus non-allele-sharing siblings ($M^* = -16$), this difference did not reach significance. A similar finding of linkage with systolic blood pressure, but not diastolic blood pressure, was previously noted on chromosome 8p22.² Although physiological reasons for such findings were suggested by Wong, the findings could also be explained statistically.

Korotkoff’s phases are routinely used in clinical practice to measure blood pressures. However, compared with Korotkoff I for systolic blood pressure, diastolic blood pressure measured manually by Korotkoff V are less precise. Although the clinical significance of this approach is generally negligible, it leads readily to decreased statistical power in quantitative linkage analysis since the variance for within sibling-pair differences is increased. This problem is further confounded by practical difficulties in obtaining an adequate

number of families,³ and the lower total population variance in diastolic compared with that of systolic blood pressure. Therefore, multiple and unbiased blood-pressure readings, such as ambulatory blood pressure monitoring, would be useful in this field of research settings.

William Y S Wang

Hypertension Gene Laboratory, Department of Physiology and Institute for Biomedical Research (F13), University of Sydney, NSW 2006, Australia
(e-mail: wwang@physiol.usyd.edu.au)

- 1 Wong ZYH, Stebbing M, Ellis JA, Lamantia A, Harrap SB. Genetic linkage of β and γ subunits of epithelial sodium channel to systolic blood pressure. *Lancet* 1999; **353**: 1222–25.
- 2 Wu DA, Bu X, Warden CH, et al. Quantitative trait locus mapping of human blood pressure to a genetic region at or near the lipoprotein lipase gene locus on chromosome 8p22. *J Clin Invest* 1996; **97**: 2111–18.
- 3 Colhoun H. Confirmation needed for genes for hypertension. *Lancet* 1999; **353**: 1200–01.

Authors’ reply

Sir—Dr William Wang suggests that practical difficulties in blood-pressure measurement might increase variance of differences in blood pressure between sibling pairs used in genetic linkage analyses. He proposes that greater variance of sibling-pair diastolic pressure differences compared with systolic pressure differences might explain the absence of linkage between chromosome 16p12 and diastolic pressure in our report. However, the variance of sibling-pair differences in diastolic blood pressure (74.0 mm Hg) was less than that for systolic pressure (116.6 mm Hg). Therefore, reduced statistical power as a result of increased variance does not explain the absence of linkage with diastolic pressure. Furthermore, the average difference in diastolic pressure for siblings identical-by-descent at both alleles of the *D16S403* locus on chromosome 16p12 was only 1.1 mm Hg less (not significant) than sibling pairs who were non-identical at both *D16S403* alleles. This contrasts with the corresponding difference of 6.9 mm Hg ($p=0.001$) for systolic pressure.

Independence of systolic and diastolic blood pressure has been recognised from epidemiological and physiological perspectives.^{1,2} There seems no reason to presume otherwise for genetic influences on blood pressure. Our recent genome-wide scan revealed seven loci linked to blood pressure (unpublished observations). This analysis favoured separate genetic control of systolic and diastolic pressures as four loci were linked to

systolic pressure alone, two were linked to diastolic pressure alone, and one locus was linked to both systolic and diastolic pressure.

Zilla Y H Wong, Margaret Stebbing,
Justine A Ellis, Angela Lamantia,
*Stephen B Harrap

Department of Physiology, University of
Melbourne, Parkville, Victoria 3052, Australia

- 1 Franklin SS, Gustin W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; **96**: 308–15.
- 2 Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med* 1993; **153**: 598–615.

Two-step swallowing provocation test for elderly patients

Sir—In response to Shinji Teramoto and colleagues' report (April 10, p 1243),¹ we question whether it is appropriate to test swallowing in an elderly patient in a supine position, which is not the normal position for eating or swallowing and therefore could not be assumed to mirror that condition. Postural drainage of fluid would, for example, be totally different in the two situations.

The investigators offer no rationale for an assessment of swallowing that introduces fluid transnasally. Surely they are not proposing that this result is indicative of performance on normal swallowing?

That the investigators already knew which of the patients had pneumonia and which were controls might have influenced their "observation of the characteristic laryngeal movements". Observing laryngeal movement is neither a definitive test of triggering of the swallow reflex nor an accurate way to assess oropharyngeal swallowing efficiency.

Two further points are that silent aspiration, by its definition could not be reliably tested by this method and use of 0.4 mL fluid initially is an amount so small as to dissipate into the pharyngeal mucosa, particularly if introduced into the "supratharynx" (we presume they mean the top of the oropharynx?), which again renders this method unreliable.

We have concerns that the "quick fix" two-step swallowing provocation test that the researchers propose for dealing with the limited availability of good services for swallowing assessments should be seen for its unreliability and not adopted as practice in an endeavour to cut costs

or detract from the lack of a quality dysphagia service.

We spend many hours teaching undergraduate speech pathologists accurate methods for assessment of dysphagia, both clinically (bedside evaluation) and through the use and interpretation of videofluoroscopy. There are many more reliable ways to assess aspiration than the one Teramoto and colleagues propose.

*Amanda Scott, Alison Perry

Dysphagia Studies, School of Human
Communication Sciences, Faculty of Health
Sciences, La Trobe University, Bundoora,
Victoria, Australia 3083

- 1 Teramoto S, Matsuse T, Fukuchi Y, Ouchi Y. Simple two-step swallowing provocation test for elderly patients with aspiration pneumonia. *Lancet* 1999; **353**: 1243.

Authors' reply

Sir—We appreciated the criticism by Amanda Scott and Alison Perry about our report of the simple two-step swallowing provocation test (STS-SPT) for detection of swallowing disorder in elderly patients with predisposition to aspiration pneumonia.

Although silent aspiration and swallowing disorder are linked to the risk of aspiration pneumonia in patients with stroke, they do not always cause aspiration pneumonia. One of the key difficulties in research on aspiration pneumonia is the misunderstanding of the relation between the rate of silent aspiration and the rate of aspiration pneumonia.¹ In healthy people, silent aspiration can occasionally occur while asleep,² but aspiration pneumonia is rare. Cough reflexes rather than swallowing reflex or mucociliary clearance are important for the prevention of aspiration pneumonia in elderly patients.¹ The depression of all airway reflexes by sedatives or cerebrovascular disease increase the risk of aspiration pneumonia.

The individual severity of swallowing disorder, but not the rate of silent aspiration, may affect the susceptibility to aspiration pneumonia in elderly people. That is why the detection of silent aspiration may not be suitable to assess the risk of developing aspiration pneumonia.

We believe some videofluoroscopic results are too sensitive to predict the risk of aspiration pneumonia. In our experience, more than half of the patients with abnormal swallowing function on videofluoroscopic examination did not exhibit aspiration pneumonia for at least 1 year. However, the patients showed abnormal response to second-step

SPT with 20 mL water is highly susceptible to aspiration pneumonia. Thus, STS-SPT may be not a perfect method for the detection of silent aspiration, but may be suitable to differentiate those patients with a predisposition to clinically significant aspiration in relation to aspiration pneumonia from those at low risk of aspiration pneumonia. Because fully physiological assessment of normal swallowing function may not be relevant to clinically significant aspiration, definitive observation of swallowing may be important to determine the type of dysphagia, but not to predict the risk of aspiration pneumonia. STS-SPT does not, therefore, have to be done on patients in an upright position. Furthermore, the fundamental method of STS-SPT has been established by several other studies.^{3–5} A bolus injection of 0.4 mL distilled water at the supratharynx through a small nasal catheter can always elicit swallowing in healthy individuals.^{4,5} Finally, we have to do further work to elucidate the predictive value of STS-SPT for aspiration pneumonia, since our study was not a prospective study. Nonetheless, we believe the STS-SPT is a particularly effective test for the detection of swallowing disorder in elderly patients with predisposition to aspiration pneumonia in clinical settings.

*Shinji Teramoto, Takeshi Matsuse,
Yasuyoshi Ouchi

Department of Geriatric Medicine, Tokyo
University Hospital, 7-3-1 Hongo Bunkyo-ku,
Tokyo, 113-8655 Japan
(e-mail: shinjit-ky@umin.ac.jp)

- 1 Teramoto S, Ouchi Y. ACE inhibitors and prevention of aspiration pneumonia in elderly hypertensives. *Lancet* 1999; **353**: 843.
- 2 Gleeson K, Eggle DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. *Chest* 1997; **111**: 1266–72.
- 3 Kobayashi H, Nakagawa T, Sekizawa K, Arai H, Sasaki H. Levodopa and swallowing reflex. *Lancet* 1996; **348**: 1320–21.
- 4 Teramoto S, Sudo E, Matsuse T, et al. Impaired swallowing reflex in patients with obstructive sleep apnea syndrome. *Chest* (in press).
- 5 Nishino T, Takizawa K, Yokokawa N, Hiragao K. Depression of the swallowing reflex during sedation and/or relative analgesia produced by inhalation of 50% nitrous oxide in oxygen. *Anesthesiology* 1987; **67**: 995.

Adverse effects of being a "healthy carrier"

Sir—We enjoyed Philip Mortimer's account (April 17, p 1354)¹ of the spread of typhoid from Mr N the milker to over 200 people in

Folkestone earlier this century. We have seen a patient who acquired enteric fever in another seaside town but, although she carried the organism for over 50 years, she does not seem to have transmitted infection to others. In her case, however, the long-term sequelae mean that she cannot be classified as a healthy carrier.

In August, 1998, a 72-year-old woman was admitted for investigation of increasing right loin pain, urinary frequency, night sweats, and weight loss. She had a long history of recurrent urinary tract infections and had a staghorn calculus in her right, non-functioning kidney. Imaging showed a mass in the upper pole of the right kidney suggestive of tumour. Her urine grew a coliform, but her fever did not respond to appropriate antimicrobials and her condition deteriorated, and so a radical nephrectomy was performed. Histopathological examination revealed that the renal tissue was almost completely replaced by a squamous-cell carcinoma, with a prominent inflammatory response surrounding a large staghorn calculus. Despite adjuvant radiotherapy, 3 months later she developed evidence of extensive retroperitoneal recurrence and she died at home a month later.

Preliminary investigations identified the coliform from her urine as a *Salmonella* sp, but it came as a surprise when the Laboratory of Enteric Pathogens (LEP), Colindale, identified the organism as *Salmonella paratyphi* B, since we had no recent local cases of paratyphoid fever and she had not left the southwest peninsula for many years. On further questioning, however, she revealed that she had acquired paratyphoid fever during an outbreak in Woolacombe, North Devon, in 1946. This outbreak was extensively investigated and traced to the wife of an ice-cream seller, who was herself a healthy carrier.² Review of our laboratory records showed that our patient had had several urine cultures carried out between 1995 and 1998, most of which yielded mixed bacterial growth of questionable significance. On only one occasion, in 1997, had a *Salmonella* sp been isolated, although on this occasion LEP had been unable to identify it to species level. However, records at LEP showed that she had grown *S paratyphi* B in stools in 1967.

We are not sure whether documented carriage of enteric fever salmonellae for 52 years is a record. However, in this lady's case it probably led ultimately to her death. Although we cannot prove the

sequence of events, we suspect that the presence of the organism in her urinary tract may have contributed to the formation of the staghorn calculus, and that the resulting chronic inflammation led ultimately to the development of a squamous-cell carcinoma. In this sense, she was certainly not a "healthy carrier". Fortunately, as far as we are aware, she did not give rise to a single secondary case during these 52 years.

We thank J C Hammonds for permission to report this case, M Barlow and K Cliffe for providing epidemiological information, and T Riordan and L Ward for providing background to the Woolacombe outbreak.

*Esther McLarty, *D A B Dance*

Department of Urology, and *Plymouth Public Health Laboratory, Derriford Hospital, Plymouth PL6 8DH, UK

- 1 Mortimer PP. Mr N the milker, and Dr Koch's concept of the healthy carrier. *Lancet* 1999; **353**: 1354-56.
- 2 Moore B. The detection of paratyphoid carriers in towns by the means of sewage examination. Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service, vol 6. London: PHLS, 1948: 241-48.

Vascular endothelial growth factor platelet counts and renal cancer

Sir—Kenneth O'Byrne and colleagues (May 1, p 1494)¹ report the poor outlook of patients with renal cancer and raised serum concentrations of vascular endothelial growth factor (VEGF-SL). They found a positive correlation of VEGF-SL and the platelet count in peripheral blood and concluded that VEGF-SL reflects VEGF released from platelets during blood clotting and circulating free VEGF. Their normal range for VEGF-SL was 62-707 pg/mL VEGF.

To keep the substantial range in values to a minimum the concentration of immunoreactive VEGF in serum can be adjusted to the platelet count. We measured the VEGF concentrations in serum and in corresponding plasma samples in 16 patients with cancer who were undergoing adjuvant chemotherapy with a commercially available ELISA. We also found (May 1, p 1529)² a strong correlation between peripheral blood platelet counts and serum concentration of VEGF, which allowed the prediction of platelet derived VEGF in serum. We calculated the amount of VEGF released from 10⁶ platelets (VEGF^{PLT}): the normal value was 1.74 pg (95% CI 1.36-2.11 pg, 56 samples) in patients with no measurable VEGF in plasma

samples—ie, in whom virtually no free immunoreactive VEGF was circulating in the blood. If in-vivo platelet destruction occurred (platelet transfusions, patients with sepsis) VEGF in plasma was increased (mean 56 pg/mL [range 26-237]). In those patients, VEGF^{PLT} was 2.79 pg (2.27-3.30, 68 samples, p=0.0003). In a woman with breast cancer VEGF^{PLT} was normal when she was in remission, but increased by three-fold at the time of relapse.*

Thus, raised VEGF^{PLT} values may indicate the release of VEGF from platelets in vivo or from other sources, probably from tumour cells. It would be useful to reanalyse the data reported by O'Byrne and colleagues by comparing VEGF^{PLT} and the course of the disease in their patients.

*Data available from the authors, on request.

**Eberhard Gunsilius, Andreas L Petzer, Guenther Gastl*

Division of Haematology and Oncology, University Hospital, 6020 Innsbruck, Austria (e-mail: eberhard.gunsilius@uibk.ac.at)

- 1 O'Byrne KJ, Dobbs N, Propper D, Smith K, Harris AL. Vascular endothelial growth factor platelet counts, and prognosis in renal cancer. *Lancet* 1999; **353**: 1494-95.
- 2 Gunsilius E, Petzer AL, Gastl G. Space flight and growth factors. *Lancet* 1999; **353**: 1529.

Unethical promotion of lactose-free formula

Sir—In its promotional leaflets for its lactose-free formula Similac LF, Abbott Laboratories says that "SIMILAC LF, the new approach for the treatment of babies with: symptoms of lactose intolerance, babies experience diarrhoea 1-3 times in their first year of life and develop lactose intolerance", and "unexplained fussiness, requiring special treatment until the symptoms stop". WHO has since 1981 imposed restrictions on the promotion of artificial milk formulae. And the International Code of marketing of Breast-milk Substitutes states (article 7.2) that, "information provided by manufacturers and distributors to health professionals regarding products within the scope of this code should be restricted to scientific and factual matters". Nonetheless, Abbott has made unjustified claims, without scientific grounds, that mislead physicians.

First, it should not label its product a "new approach" for lactose intolerance because the only treatment for this condition is a lactose-free

diet. How Similac is a new approach is incomprehensible. Second, symptomatic treatment is advised only for conditions in which an immediate diagnosis cannot be made and the cause is unknown, and to relieve acute signs and symptoms (eg, antipyretics for fever and analgesics for pain). Moreover, symptoms can be very similar in different conditions, and appropriate treatment should be started only after a correct diagnosis. Lactose intolerance is readily diagnosed by simple laboratory tests.^{1,2} Thus, established lactose intolerance, not symptoms only, is the indication for the use of lactose-free formulae. Additionally, each infantile episode of diarrhoea does not lead to lactose intolerance; this condition is in fact rare and only very occasionally requires treatment.³ Third, to include "unexplained fussiness" in the indications for use of a lactose-free formula, without reference to published work, is unethical. Fussiness is a vague term meaning excessive crying or irritability, which happens for many reasons in babies. How can we prescribe a lactose-free formula to an irritable baby without proper investigation to establish the cause of its irritability?

I have approached this company several times—in Riyadh and Greece (Middle-East office), and the USA (head office)—but I have received no official reply to my questions with respect to Similac LF.

Khalid Iqbal Tahir

Neonatal Intensive Care Unit, Maternity and Children Hospital, Madina Al-Munawara, Saudi Arabia

- 1 Laboratory manifestations, carbohydrates malabsorption. In: Behrman RE, ed. Nelson textbook of pediatrics, 14th edn. Philadelphia: WB Saunders, 1992: 973.
- 2 Lactose intolerance: dialogue on diarrhoea. London: AHRTAG Issue 37, 1990.
- 3 Lactose intolerance: readings on diarrhoea. Geneva: WHO/PRITECH, 1986.

Emotional involvement in physician-assisted suicide

Sir—In his essay P Reagan¹ describes how he aided and abetted the killing of his patient. We have a duty to be sceptical and to rigorously question the stated facts and motivations.

Reagan is clearly recruited by the family as a compliant physician who would do their will when their regular doctors refused to co-operate. He is captivated by the elderly patient for whom he develops an immediate

attraction. Despite her frailty and the carcinomatosis that leaves her in a wheelchair on continuous oxygen, she has a "delightful twinkle". Later he describes his conflict over her deliberate death and his reluctance to back out, not so much for ethical reasons but in case the family felt he was stringing them along and be insulted.

Emotional overinvolvement and blackmail continue. His patient said that he had brought joy to her life and he admitted that a deep emotional bond had formed that "enabled me to see how intensely she wanted to die". Surely a doctor should retain some professional distance to avoid this very trap.

The financial arrangements should also be examined. Did he accept a fee for his services? What, if any, were the advantages to the family of an earlier death of their relative? Was there any conflict with other un-named relatives over the will?

Histories often tell us more by what is left out than what is described. There is no hint in this well crafted but romantic essay of the darker motives that drive human behaviour. There is no hint of anger, resentments, jealousies, conflicts, or regrets. Reagan has betrayed the fundamental principle of a physician and has connived at the deliberate killing of an ill old woman who was his patient and who should have expected better.

George Dodds

49 Chalton Road, Bridge of Allan FK9 4EF, UK

- 1 Reagan P. Helen. *Lancet* 1999; 353: 1265–67.

Author's reply

Sir—George Dodds questions the financial circumstances of my interaction with Helen and her family. She had two clinic visits with me, and then three house calls. I billed the usual fee for the clinic visits and did not charge for the house calls. I do not have a rationale for doing this.

I have a continuing relationship with both of Helen's children, and have met and talked with their spouses and three grandchildren, one of whom has become my patient. Several of her family members wished she would have delayed her death until after the birthday that came on the following day, or an upcoming wedding, but she was insistent. I have not become aware of any financial issues that were modified by the timing of Helen's death, nor of any family members who were advantaged by it.

Dodds very properly comments on my level of emotional involvement. It surprised me too. I am grateful to my co-workers, the consultants, the hospice carers, my spouse, and to the Oregon Law itself, for keeping me on track.

Peter Reagan

2406 NE 19th Ave, Portland, OR 97212, USA

Research-agenda setting in developing countries

Sir—Michael Eddleston (April 3, p 1190)¹ mentions that the World Bank has announced a programme to strengthen research in developing countries in which the World Bank envisages long-term financial support to ensure high-quality outputs.

Eddleston is worried that the relationship between researchers from developed and less-developed countries is unequal. The joint Ghanaian-Dutch programme of health research for development was designed to prevent this unequal relationship. Agenda setting by Ghanaian partners is the basis for this programme and the challenges are to develop strategies to involve researchers from more developed countries in a meaningful way. Just saying that the research agenda has to be based on Ghanaian needs is not enough to reverse the existing relationship between researchers from more and less developed countries.

This year, the Ghanaian-Dutch programme will work towards a workshop in which the actual research plans for the years to come will be mapped out. As has become usual in agenda setting, different stakeholders will be involved in this process. The first step is to critically review existing research, and focus on access, equity, efficiency, linkages, and health financing. For each of these themes, we will look at a critical review of research results, methodology (conceptual frameworks, methods, and indicators) of the studies, and recommendations for improved health-care delivery resulting from the studies. Dutch researchers active in the same fields will then put the review into an international perspective, which should relate the Ghanaian findings to results of relevant research conducted in other countries. Apart from the input from researchers, we need input from the many end users: members of communities; policy makers at national, regional, and district levels; and health workers in Ghana.

Later this year, regional representatives and regional district health-care staff will share their ideas and discuss their perceptions of the priorities for research on health and health-care difficulties in Ghana and discuss mechanisms for priority agenda setting on a continuous basis, with support from a Dutch research institute that is experienced in participatory research. The community consultation will pay attention to sex, class, and ethnic differences in health care. Dutch researchers will be involved from the start, and their contribution may increase in the future.

After the agenda-setting workshop, a call for proposals and intentions will be distributed in Ghana. Dutch researchers will be involved in the resulting research and will play a part in capacity building. A research training workshop on how to review health-reform processes will also be organised. Preparation of an agenda for a 3-day workshop, and inputs of conceptual frameworks for reviews, tools, and indicators to be used will be done by a working group on health reform, which will include researchers from more developed countries.

In the Ghanaian-Dutch programme, researchers from developed countries need to have patience, because development of a research infrastructure and centres for research excellence takes time. There is a logical order of things that have to happen before the actual research can take place.

*I Wolffers, S Adjei

*Section Health Care and Culture, Medical Faculty, Vrije Universiteit, 1081 BT Amsterdam, Netherlands; and Health Research Unit, Ministry of Health, Accra, Ghana

- 1 Eddleston M. Encouraging high-quality clinical research in the tropics. *Lancet* 1999; 353: 1190.

Effects of NATO's bombing in the Balkans

Sir—The NATO bombings of Yugoslavia have damaged many clinical and hospital centres and caused new health problems. The maternity hospital in Belgrade, and the biggest hospital in the Balkans (Military Medical Academy Hospital), the orthopaedic hospital of Banjica, the hospitals in Cuprija and Aleksinac, and the medical centres in Pristina and in many other towns, have all been damaged. When the hospital of Dragisa Misovic in Belgrade was bombed, on May 19, three people were killed and the operating theatres destroyed.

The destruction of bridges ruptures the water mains and has left many communities and institutions without water. The destruction of all the three bridges in Novi Sad left the largest Yugoslav centre for the treatment of cardiovascular diseases without water.

Although NATO's leaders have claimed that these incidents were accidents, they have also admitted that they were an inevitable result of their bombing strategy. Therefore NATO leaders acted in open violation of the Protocol Additional to the Geneva Conventions of 12 August 1949, and the Protection of Victims of International Armed Conflicts (Protocol I), 8 June 1977.

Will Podmore

44 Clavering Road, Wanstead, London E12 5EX, UK

Evidence-based information

Sir—One of the beneficial results of the UK National Health Service (NHS) breast screening programme over its 10-year life has been a reduction in presentation of late-stage breast cancers. Women have not only become more aware of their breasts but they have become more responsible in finding and presenting these cases. The unexpected detrimental effect of the NHS breast screening programme has been to diagnose a previously hidden and undiagnosed group of cancers which includes a fifth of the total cohort of women diagnosed by this programme. These ductal carcinomas in situ are mostly impalpable and symptomless: in three quarters of cases they are not a threat to the woman's life. Their management is contentious and difficult. The evidence from the women (about 1000) who have been recruited to the UK ductal carcinoma-in-situ trial in the past 10 years will probably be inconclusive and of little help in determining management, as reported at the Cambridge International Screening Conference in April.

The UK General Medical Council guidelines¹ recognise the need for responsible citizens to have adequate information to give consent for screening and define what this should include. So, too, do those angry women whose bodies and lives, and the lives of their families, have been damaged by this zealous trawling to find breast cancer early. More and more women are being damaged by a programme that has not told them on invitation what it is able to achieve in mortality reduction. Instead, it continues to frighten them with incidence figures in

terms that are misunderstood even by many in the profession, rather than by giving the numbers needed to screen to save one life.²

Does the General Medical Council's recommendation and the clamour of damaged women give sufficient reason for the NHS breast screening programme to provide good quality information without further need for research³ or delay, so that responsible women can be treated with dignity, and thus be allowed to make up their own minds? The provision of information and methods of presenting facts and figures is ethically important.⁴

Hazel Thornton

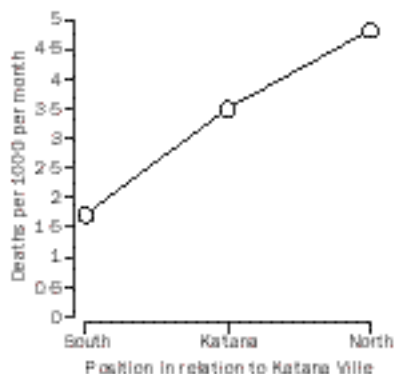
31 Regent Street, Rowhedge, Colchester, Essex CO5 7EA, UK

- 1 General Medical Council. Seeking patients' consent: the ethical considerations. Protecting patients, guiding doctors (paras 33 and 34). London: General Medical Council, 1998.
- 2 The screening muddle. *Lancet* 1998; 351: 459.
- 3 Webster P, Austoker J. Informed consent for screening programmes: information requirements of participants and the impact of such information on uptake and psychological health. *Oxford Health Services Research Unit Newsletter*, January, 1999.
- 4 Tversky A, Kahneman D. The framing of decisions and the psychology of choice. *Science* 1981; 211: 453–58.

Mortality in the Democratic Republic of the Congo

Sir—The Katana Health Zone is an area with 281 000 inhabitants in the South Kivu Province, Democratic Republic of the Congo. This area is controlled by the rebel government which is fighting against the Kinshasa-based government of Laurent-Désiré Kabila. In Katana, the rebel forces are now simultaneously battling a counter-insurgency group called the Mayi-Mayi. Little humanitarian assistance has reached this area since August, 1998, both because of insecurity and the unwillingness of western nations to recognise the rebel government.

The International Rescue Committee conducted a spatially-based mortality cluster-survey in Katana in February, 1999. At a random starting point, the five closest homes were interviewed about deaths of household members during 1998 and the first 7 weeks of 1999. From that starting point, additional sampling points were identified by the Global Positioning System at increments of 1 km, to the east and west across the health zone—a distance which varied between 3 and 8 km. The process of interviewing east-west transects was repeated at



Mortality in Katana, January, 1998 to February, 1999

intervals every 3.5 km to the north until an area of 24.5 km from north to south had been visited. 32 clusters of five households each were visited. Presently, and for the past several months, the southern portion of the survey area has been fairly stable and under rebel-government control. The northernmost portions have been much less stable and have endured periodic fighting between the Mayi-Mayi and rebel-government forces or their allies. The town of Katana is in the centre of the survey area and has had a moderate level of instability.

Reported mortality among the families of the 1051 household members included in the survey was 3.8 per 1000 per month, with rates higher in 1999 (6.0 per 1000 per month) than in 1998 (3.5 per 1000 per month). The expected or baseline mortality in this area is about 1.5 per 1000 per month. Malaria was the most frequently reported cause of death (18 of 54), followed by measles (six of 54). Only one death was attributed to violence.

Analysis of the data revealed that mortality varied according to geographical position (figure). People living in the northern insecure areas experienced three times the mortality of neighbours who live, on average, 15 km to the south in stable areas. A χ^2 test for trend shows that the association between latitude category and mortality was significant ($p < 0.01$).

The survey results are a good example of how a static line of conflict has created a health crisis simply by cutting off access to a population. With the exception of measles deaths (none of which occurred in the southern third of the study area), the people in the north and south of Katana are experiencing the same diseases and the same causes of death, there are simply more people dying in the war-torn north. Human rights and humanitarian relief organisations have made great strides in setting standards of service and basic rights, which should be guaranteed. Humanitarian corridors have been advocated as a solution to the

type of crisis now seen in Katana, though they are rarely created and usually ineffective. Is easy access to markets, to medical supplies, to stress-free environs a basic human right? If so, who should be its guarantor?

*Les Roberts, Michael Despines

*International Rescue Committee, Central and East Africa Regional Program, New York, NY 10168, USA; and International Rescue Committee, Democratic Republic of the Congo, Bukavu, Congo

Research funding

Sir—Paul Dieppe and colleagues (May 8, p 1626)¹ are right to emphasise how the pharmaceutical industry can influence research agenda and distort published evidence. What goes for arthritis also goes for acute stroke.

In 1954–94, we showed a substantial increase in the proportion of trials in acute stroke that were sponsored by industry, although it was often difficult to assess the exact nature of their involvement (Dorman P, Counsell C, Sandercock S, unpublished data). Although industry-driven trials will undoubtedly benefit mankind and lead to the licensing of new and effective treatments, they do have an opportunity cost. Clinicians who work on such trials have correspondingly less time available to work on, and perhaps also fewer patients are eligible for inclusion in, non-commercial trials. For researchers it is all too tempting to accept large sums of money by joining, or even appearing to run, heavily sponsored trials; but if the company demands complete control over the selection of sites, the protocol, data collection, analysis, and even the publications, the research design will inevitably meet industry and not public health priorities.

Several organisations support randomised trials of interventions for stroke that have no commercial potential. The UK Medical Research Council, the UK National Health Service Health Technology Assessment programme, and the Stroke Association (but not the Wellcome Trust) support trials of surgery, interventional radiology, non-commercial drugs, and feeding regimens in stroke, but they are given only a fraction of the resources required to test all the promising interventions that need evaluating.

The other major issues about such trials are the potential for conflict of interest and publication bias. In stroke, there is evidence that pharmaceutical industry involvement increases the delay in publication of negative studies.² We find it surprising that governmental departments of health

tolerate this situation if they are truly signed up to evidence-based medicine and cost-effective interventions. Journals should insist that trialists declare exactly who did what and how closely any sponsor was involved. Furthermore, someone should be making sure that trials with disappointing results see the light of day. Ethics committees should insist on absolute transparency of the amount of involvement by commercial sponsors in trials submitted for their approval, and declare that approval will be granted only if the results are published, irrespective of the final result. Multicentre research ethics committees could be directed to establish a mechanism for ensuring these requirements for multicentre trials in the UK at the very least.

Charles Warlow, *Peter Sandercock, Martin Dennis, Joanna Wardlaw

Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK

- 1 Dieppe P, Chard J, Tallon D, Egger M. Funding clinical research. *Lancet* 1999; **353**: 1626.
- 2 Liebeskind DS, Kidwell CS, Saver JJ. Empiric evidence of publication bias affecting acute stroke clinical trials. *Stroke* 1999; **30**: 268.

Centenarian scientists

Sir—The feature by Marilyn Larkin (March 27, p 1074)¹ on the centenarians attracted my attention. As one would expect, due to the reality of the explosion in the number of centenarians in the 20th century, the number of notable scientists and inventors who have become centenarians also show a noticeable increase. I can name only one eminent 19th century scientist who was a centenarian; the renowned French lipid chemist Michele Chevreul, who lived up to the age of 103 and died in 1889. Now, 110 years later, I can count five well known scientists and inventors who lived to celebrate their 100th birthday; namely, physical chemist Joel Hildebrand, sleep physiologist Nathaniel Kleitman, immunologist Michael Heidelberger, sex therapist Harry Benjamin, and aviation pioneer Thomas Sopwith.

Sachi Sri Kantha

5-16-305 Tsukimicho, Fukuroi City, Japan 437-0126

- 1 Larkin M. Centenarians point the way to healthy ageing. *Lancet* 1999; **353**: 1074.

DEPARTMENT OF ERROR

USFDA advisory panel urges ban on UK blood—In this news story by Alicia Ault (June 12, p 2050), the first sentence should end “between 1980 and 1996”.