

# CORRESPONDENCE

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## Broad-spectrum antibiotics in ORACLE

Sir—Unlike workers in previous clinical trials of antibiotics for preterm and prelabour fetal membrane rupture, S L Kenyon and colleagues, in their study of broad-spectrum antibiotics for preterm and prelabour rupture of fetal membranes (March 31, p 979),<sup>1</sup> and that of antibiotics for spontaneous preterm labour (March 31, p 989)<sup>2</sup> do not have delay until delivery as the primary outcome. They chose an innovative approach that emphasises neonatal disorders. We commend them for this.

Unfortunately, their main outcome was a composite variable that included any of the following phenomena: death before discharge, oxygen supplementation at 36 weeks after conception, and major cerebral abnormality on cranial ultrasonography (not otherwise defined). Are they equivalent? Fortunately, Kenyon and colleagues did separate analyses to look at each of these components.

We wonder about the inferences they draw from their inability to show that erythromycin and co-amoxiclav, alone or in combination, reduced the frequency of the primary composite outcome among infants born to women who presented with spontaneous preterm labour with intact membranes. Kenyon and colleagues conclude that their results suggest that the part played by subclinical infection in the cause of spontaneous preterm labour has been overestimated. Because they do not report assessments of amniotic fluid or placenta microbiology, or indicators of an inflammatory response, it seems inappropriate to draw this inference.

Did they take into account that infectious or inflammatory phenomena that arise days to weeks before delivery can potentially lead to spontaneous preterm labour with intact membranes? Did they look into whether such phenomena might contribute to only some of the neonatal morbidities they assessed, but not all, or that such phenomena contribute to the onset of these morbidities long before the antibiotics are administered?

\*Alan Leviton, Elizabeth N Allred, Olaf Dammann, Karl Kuban, Camilla R Martin

\*Neuroepidemiology Unit, Children's Hospital and Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA; New England Medical Center and Tufts University School of Medicine, Boston; and Beth Israel Deaconess Medical Center and Harvard Medical School, Boston

- 1 Kenyon SL, Taylor DJ, Tarnow-Mordi W, for the ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001; **357**: 979–88.
- 2 Kenyon SL, Taylor DJ, Tarnow-Mordi W, and the ORACLE Collaborative Group. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. *Lancet* 2001; **357**: 989–94.

Sir—S L Kenyon and colleagues,<sup>1</sup> use a two-by-two factorial design for their study, but analyse the data as a four-group trial (ie, placebo, erythromycin alone, co-amoxiclav alone, and erythromycin plus co-amoxiclav).

They report as a significant finding ( $p=0.08$ ) that the erythromycin-alone group had fewer composite primary outcomes than the placebo group. Apart from not reaching the traditional level of significance, the justification for assessing erythromycin only in patients not receiving co-amoxiclav depends on there being an interaction between erythromycin and co-amoxiclav. In a logistic regression, the  $p$  value for the test of no interaction is 0.13. Therefore, two hypotheses, at  $p=0.13$  and  $p=0.08$ , must be rejected to show evidence in favour of erythromycin for a patient not taking co-amoxiclav.

This evidence is very weak, and I believe the results do not justify the recommendation of the use of erythromycin. If the hypothesis of no interaction is not rejected, the assessment of erythromycin comes from comparing the group of patients receiving no erythromycin (placebo and co-amoxiclav alone) with the those receiving erythromycin (erythromycin alone and erythromycin plus co-amoxiclav together). The  $p$  value for no treatment effect in this assessment of erythromycin is 0.32.

The evidence in favour of erythromycin is further strained by comparing erythromycin alone with placebo among singletons. An interaction needs to exist between erythromycin and whether or not the pregnancy was singleton. By use of a logistic regression, the  $p$  value for the test of no interaction is 0.11.

Andrew R Willan

Department of Clinical Epidemiology and Biostatistics, McMaster University, Centre for Evaluation of Medicines, St Joseph's Hospital, Level P1, Hamilton, Ontario L8N 1G6, Canada (e-mail: [willana@mcmaster.ca](mailto:willana@mcmaster.ca))

- 1 Kenyon SL, DJ Taylor, Tarnow-Mordi W, for the ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001; **457**: 979–88.

Sir—S L Kenyon and colleagues<sup>1</sup> report a four-fold risk for necrotising enterocolitis in babies born to women who had preterm prelabour rupture of membranes and received co-amoxiclav. A 2.5-fold risk of necrotising enterocolitis is noted in women treated with co-amoxiclav alone or in combination with erythromycin compared with those whose treatment scheme did not contain co-amoxiclav. However, no such effect is noted in their second report,<sup>2</sup> in which co-amoxiclav was given to women with spontaneous preterm labour with intact membranes.

Necrotising enterocolitis is the most common gastrointestinal emergency in neonates. The incidence is 0.3–2.4 cases per 1000 livebirths.<sup>3</sup> However, the pathophysiology is not clearly understood and current understanding is based on epidemiological studies. Prematurity and infection, whether systemic or localised to the intestinal tract, seem to be the most consistent risk factors associated with the development of necrotising enterocolitis.<sup>4,5</sup>

The baseline characteristics of patients in Kenyon and colleagues' two trials were similar, prematurity being the common denominator. However, the prevalence of neonatal positive blood culture, which is an indication for neonatal infection, was

	pPROM trial <sup>1</sup> (n/total)	SPL-IM trial <sup>2</sup> (n/total)	p
<b>Necrotising enterocolitis</b>			
All	61/4809 (1.3%)	30/6241 (0.5%)	<0.0001
Co-amoxiclav only	24/1205 (2.0%)	9/1534 (0.6%)	0.001
Any co-amoxiclav	44/2394 (1.8%)	20/3085 (0.6%)	0.0001
<b>Positive blood cultures</b>			
Overall	333/4809 (6.9%)	127/6241 (2.0%)	<0.0001
Co-amoxiclav only	82/1205 (6.8%)	28/1534 (1.8%)	<0.0001
Any co-amoxiclav	165/2394 (6.9%)	62/3085 (2.0%)	<0.0001

pPROM=preterm prelabour rupture of membranes; SPL-IM=spontaneous preterm labour with intact membranes.

#### Neonatal infection and proven necrotising enterocolitis in co-amoxiclav-treated neonates

significantly higher in the preterm babies born to women with ruptured membranes than in those born to women with intact membranes. Additionally, necrotising enterocolitis was more prevalent in preterm babies born to women with ruptured membranes than in those born to women with intact membranes. A higher rate of neonatal infection and proven necrotising enterocolitis was also present in the subgroups of babies in the trial of women with ruptured membranes treated by co-amoxiclav compared with those in that of women with intact membranes (table).

The higher rate of necrotising enterocolitis in the ruptured-membrane trial than in the intact-membrane trial points to the well proven association between neonatal infections and consequent necrotising enterocolitis. Since patients' characteristics and treatment schemes were similar in the two trials, including treatment with co-amoxiclav, and data were not corrected for neonatal infection, Kenyon and colleagues' conclusion about a causal relation between the treatment and necrotising enterocolitis seems questionable at least.

Shimon Ginath, Gustavo Malinger, Oscar Sadan, \*Marek Glezerman

\*Department of Obstetrics and Gynaecology, Edith Wolfson Medical Centre, PO Box 5, Holon 58100, Israel; and Sackler Medical School, Tel Aviv University, Tel Aviv (e-mail: mglezerman@bezeqint.net)

- 1 Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001; **357**: 979–88.
- 2 Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. *Lancet* 2001; **357**: 989–94.
- 3 Stoll BJ. Epidemiology of necrotizing enterocolitis. *Clin Perinatol* 1994; **21**: 205–18.
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- 5 Neu J. Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. *Paediatr Clin North Am* 1996; **43**: 409–32.

Sir—S L Kenyon and colleagues<sup>1</sup> note a significant excess of cases of necrotising enterocolitis in babies born to mothers receiving co-amoxiclav. They cite the selection of *Clostridium difficile* by co-amoxiclav to explain this observation, but do not substantiate this claim.

Few reports associate co-amoxiclav with *C difficile* infection, which is perhaps surprising given the broad spectrum of activity and widespread use of this antimicrobial combination agent and its availability in oral formulations.<sup>2</sup> Indeed, a league table of the nine most common antibiotics reported to the Medicines Control Agency as being associated with *C difficile* infection did not include co-amoxiclav, yet did cite amoxicillin.<sup>3</sup> Meta-analysis of studies of antibiotics associated with *C difficile* infection is of limited usefulness because of large CI, which reflect the wide variation in observed risk of individual antibiotics secondary to the many cofactors in this disorder.

Broad-spectrum, especially anti-anaerobic agents should be those most associated with *C difficile* infection because of their propensity to inhibit the anaerobic component of the gut flora—ie, to impair colonisation resistance. However, in the only prospective comparative study of antimicrobial-induced *C difficile* infection, the relative risk of diarrhoea after empirical treatment with cefotaxime was more than seven-fold that seen after piperacillin-tazobactam therapy,<sup>4</sup> and yet the latter antibiotic is active against most commensal gut flora. In-vivo antimicrobial activity, and, therefore, probable risk of *C difficile* infection, can be strikingly affected by factors such as drug penetration into the large gut lumen, specific and non-specific antibiotic binding, and gut pH and redox potential.

Various infectious agents and toxins have been implicated in the development of necrotising enterocolitis, but no one agent has been consistently associated with the disease. *C difficile* toxin has been

detected with equal frequency in necrotising enterocolitis cases and symptom-free controls.<sup>5</sup> When compared with healthy full-term neonates, premature infants have delayed gastrointestinal colonisation and develop a less complex flora, comprised mainly of *Enterobacter* spp and enterococci, with few anaerobes.

Overgrowth of enteric gram-negative organisms has been associated with the disorder in several studies, and this abnormal colonisation is thought to contribute to an excessive inflammatory response in the immature intestine.<sup>5</sup> Co-amoxiclav probably causes a greater reduction in maternal gastrointestinal *Enterobacter* spp than does erythromycin and, thus, would be judged less likely to be associated with necrotising enterocolitis. The greater impact of co-amoxiclav on other commensal gut flora might, however, permit overgrowth with resistant gram-negative organisms such as *Enterobacter* spp, *Citrobacter* spp, and *Pseudomonas* spp, which possess chromosomal P-lactamases. Exposure of premature infants to these bacteria in the absence of protective gram-positive and anaerobic flora might lead to gastrointestinal colonisation patterns that predispose to development of necrotising enterocolitis.

\*Mark Wilcox, Christine Hoy

Department of Microbiology, University of Leeds and Leeds Teaching Hospitals Trust, General Infirmary at Leeds, and St James's University Hospital, Leeds LS1 3EX, UK (e-mail: markwi@pathology.leeds.ac.uk)

- 1 Kenyon SL, Taylor DJ, Tarnow-Mordi W, for the ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001; **357**: 979–88.
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- 4 Settle CD, Wilcox MH, Fawley WN, Corrado OJ, Hawkey PM. Prospective study of the risk of *Clostridium difficile* diarrhoea in elderly patients following treatment with cefotaxime or piperacillin-tazobactam. *Aliment Pharmacol Ther* 1998; **12**: 1217–23.
- 5 Hoy CM. The role of infection in necrotising enterocolitis. *Rev Med Microbiol* 2001; **12**: 121–29.

#### Authors' reply

Sir—Analysis in singletons had always been planned on the basis of biological plausibility and was undertaken by the data monitoring

Treatment group	All cases (n [%])	p	Singletons (n [%])	p
Erythromycin vs placebo	168 (14.1) vs 212 (17.3)	0.03	141 (12.7) vs 190 (16.5)	0.001
Any erythromycin vs no erythromycin	345 (14.5) vs 400 (16.5)	0.06	295 (13.3) vs 351 (15.3)	0.05
Co-amoxiclav vs placebo	188 (15.6) vs 212 (17.3)	0.32	161 (14.1) vs 190 (16.5)	0.11
Any co-amoxiclav vs no co-amoxiclav	365 (15.2) vs 380 (15.7)	0.68	315 (14.1) vs 331 (14.6)	0.58
Erythromycin plus co-amoxiclav vs placebo	177 (14.9) vs 212 (17.3)	0.11	154 (13.8) vs 190 (16.5)	0.08

**Effect of broad-spectrum antibiotics for preterm prelabour rupture of membranes on composite primary outcome**

committee on each of the four occasions it met. Intrauterine infection plays a more important part in singleton than in multiple pregnancy,<sup>1</sup> and the time from membrane-rupture to delivery is shorter in multiple pregnancy (80.2 vs 62.1% delivered in 7 days in the placebo group). That the beneficial effects seen with erythromycin in the 2260 singletons were diluted by the 155 multiple pregnancies is, therefore, plausible.

Our protocol specified that co-amoxiclav and erythromycin would be tested singularly and in combination. Opinions differ as to whether adjustments should be made for multiple comparisons.<sup>2</sup>

External referees of the trial design debated which index of chronic lung disease should be used—ie, oxygen dependence at 36 weeks' post-conceptual age or at older than 28 days. They argued that, in the context of the ORACLE trials, the use of oxygen dependence at 36 weeks' would erroneously include babies who had received oxygen only briefly, such as those delivered at 34 or 35 weeks' gestation, and who would not have chronic lung disease. In published work and expert UK neonatal opinion there was no consensus and, therefore, we continued to use oxygen dependence at 36 weeks' post-conceptual age, as specified in the trial protocol. If the oxygen dependence at older than 28 days had been used, the results of the trial would have been as in the table.

In response to Alan Leviton and colleagues, the ORACLE II trial had more than 90% power to exclude a treatment effect of antibiotic therapy of 30%—ie, from 10% in the placebo group to 7% in the antibiotic group, if 10% of the women presenting in spontaneous preterm labour with intact membranes had intrauterine infection. The absence of significant differences (apart from one) or trends towards a treatment effect of antibiotic therapy on neonatal outcomes suggests that substantially fewer than 10% of such women had intrauterine infection. Evidence of benefit from antenatal antibiotics to women with

previous preterm birth suggests that there are infectious or inflammatory phenomena in a subgroup of women that still require investigation. We encourage laboratory and clinical scientists investigating the role of infectious or inflammatory phenomena in the genesis of preterm birth to classify their studies as those of spontaneous preterm labour with intact membranes or preterm prelabour rupture of the fetal membrane. Such classification will help to clarify the role of these phenomena, not only in the genesis of preterm birth but also their role in neonatal and childhood morbidity.

Shimon Ginath and colleagues suggest that we report no association between co-amoxiclav and necrotising enterocolitis in spontaneous preterm labour with intact membranes. We do report a doubled, but non-significant, risk of necrotising enterocolitis. The weaker association probably reflects the later gestational age at birth than of infants born with membrane rupture (266 vs 236 days). Ginath and colleagues also suggest that the finding between co-amoxiclav and necrotising enterocolitis is related to infection in the neonate and not to treatment with co-amoxiclav. If this relation were true, we might have seen a higher rate of necrotising enterocolitis in the placebo group. We did not.

We value the interpretations of Mark Wilcox and Christine Hoy of the biologically plausible association between co-amoxiclav and neonatal necrotising enterocolitis, and look forward to reading Hoy's review when it is published.

D J Taylor, \*Sara Kenyon,  
W Tarnow-Mordi

Department of Obstetrics and Gynaecology,  
Robert Kilpatrick Building, Leicester Royal  
Infirmary, PO Box 65, Leicester LE2 7LX, UK

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## Poliovirus immunisation in the Democratic Republic of the Congo

Sir—L Roberts (May 5, p 1421)<sup>1</sup> takes a narrow short-term view in his assessment of the polio-virus immunisation campaigns done in the Democratic Republic of the Congo (DR Congo). He compares the single poliovirus death recorded in his survey with hundreds of measles deaths, conjecturing how many more lives could have been saved if the same funds had been applied to primary health care, a general relief effort for victims of the war, or both.

Poliovirus campaigns were done as part of the global eradication initiative, which is closing in on its goal and must rapidly succeed in every remaining endemic country, including those at war. The campaigns were done in DR Congo despite the war and at great risk to national and international staff. The lives of many children could have been saved if the international community had mobilised a general relief effort in DR Congo. The political will and funds to do so were, unfortunately, not forthcoming. If, as Roberts suggests, polio had sat out the war, the situation would not be substantially different.

G MacQueen and colleagues<sup>2</sup> present a contrasting view of poliovirus eradication in their May 12 commentary on health and peace. They point out that poliovirus immunisation campaigns have been used as a stimulus for truces in many war zones. These so-called days of tranquillity have been an important step in resolving conflicts.<sup>3</sup>

With use of that model, WHO and UNICEF requested the assistance of the United Nations in organisation of the truces for poliovirus immunisation in DR Congo in 1999. Secretary General Annan responded by making polio eradication a specific item on the agenda of the peace talks. The urgency of carrying out the campaigns before the rainy season helped to bring those talks to a successful conclusion. The continuing poliovirus campaign was used as a lever to negotiate troop pullbacks from Kisangani when fighting erupted there.

By serving as an essential component of the peace process, the poliovirus campaigns achieved much more than immunisation of DR Congo's children against one disease. They have brought forward the time when the International Rescue Committee, WHO, UNICEF, and many other organisations can renew

the process of building a sustainable primary-health-care system in the wake of this tragic conflict. The poliovirus campaigns in DR Congo also are bringing the entire world closer to freedom from this crippling disease.

Harry F Hull

Minnesota Department of Health,  
717 Delaware SE, Minneapolis, MN 55414,  
USA

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## Multiple vaccination

Sir—Richard Jeffrys (5 May, p 1451)<sup>1</sup> raises a valid point about the issue of multiple vaccines being administered simultaneously or at short intervals. There is another related issue.

When writing out paediatric prescriptions for products other than vaccines, we take into account such things as weight. However, in the case of vaccines, no account is taken of these factors. The dose of BCG vaccine, for example, for children younger than 3 months is 0.05 mL. As soon as children reach age 3 months, the dose is doubled to 0.1 mL. Prematurity does not affect the dose.

Over the past 40 years, the immunisation schedules have been repeatedly changed. There was a time when, in realisation that younger babies do not obtain the full benefit from the triple antigen (diphtheria pertussis, tetanus), the first dose was given at age 4 months. Later, to protect the herd (never mind the individual child), the schedule was revised, lowering the age for starting the course.

Parents should be clearly told that what is good for the population as a whole is not necessarily good for the individual child. Some parents might, if the choice were given, choose the risk of mumps or rubella to that of autoimmune disorders for their offspring. We must also ask the question of how carefully the health service collects the statistics for adverse reactions to vaccines. If such statistics are indeed properly collected, comparison of the data for the different practices and those for England, Scotland, Wales, and Northern Ireland should be possible. The Yellow Card, I suspect, is

seldom used for vaccine-related adverse events.

J K Anand

68 Ledbury Road, Peterborough PE3 9PJ, UK

- 1 Jefferys R. T cells and vaccination. *Lancet* 2001; 357: 1451.

## Maternal mortality in East Timor

Sir—In her report on the state of the health-care system in East Timor (March 17, p 873)<sup>1</sup> Kelly Morris makes no mention of the state of health of mothers in that country, which is a substantial omission.

According to WHO, maternal mortality for East Timor is around 830 per 100 000 livebirths—one of the highest rates in Asia—mainly caused by haemorrhage, infection, pregnancy-induced hypertension, obstructed labour, severe anaemia, malaria, the lack of trained care givers, and access to antenatal care and emergency transport.

Present maternal health services are poor. Births are generally delivered at home by traditional birth attendants. There are 23 East Timorese doctors for a population of 500 000, none of whom are trained in obstetrics. The general hospital in Dili has the only obstetric unit, which provides level 1 obstetric services, and has 15 trained midwives; the country's one obstetrician left at the end of June. In Baucau, the second largest town, some obstetric services are provided by Médecins Sans Frontières in the government hospital, but facilities and equipment are limited.

The oversight in Morris's review is illustrative of the lack of attention given to maternal health care by governments, the media, and especially by our specialist colleges. In the past 50 years, technology has led to falling maternal death rates.

The Safe Motherhood Initiative was launched at the first international safe motherhood conference in Nairobi, 1987, to combat maternal mortality. Unfortunately, the response has been inadequate, despite the call being issued many times since. Reasons for failure have been given as missed opportunities, muddled thinking, mistaken priorities, the reduction in development assistance by the world's richest countries, and promotion by governments and international health organisations of reproductive health (abortion and contraception). Billions of dollars have been spent on birth-control programmes but only a

small fraction on emergency obstetric care.

Last year marked the 50th anniversary of the UN Charter of Rights, among which is the right to proper medical care. However, maternal mortality does not have the same political clout as, for example, AIDS or landmine injuries. The tragedy is that the solutions to this suffering have been known for decades and cost very little. Mothers are being neglected because there is neither the will nor the compassion to do what is necessary.

I am involved in MaterCare International, a newly formed group of obstetricians, that is attempting to organise an emergency service for East Timor. We need all the help we can get.

R L Walley

Discipline of Obstetrics and Gynaecology,  
Memorial University of Newfoundland,  
Health Sciences Centre, St John's,  
Newfoundland A1B 3V6, Canada

- 1 Morris K. Growing pains of East Timor: health of an infant nation. *Lancet* 2001; 357: 873–77.

## Adverse effects of nevirapine

Sir—Paul Benn and colleagues' report (March 3, p 687)<sup>1</sup> of serious adverse effects associated with nevirapine use in health-care workers (HCWs) and people receiving HIV-1 postexposure prophylaxis after sexual exposure, as well as other reports of serious nevirapine toxic effects among HCWs<sup>2</sup> justify the recommendation that nevirapine should not be used in this way.

Although adverse events during postexposure prophylaxis are common,<sup>3</sup> most are not severe. Life-threatening toxic effects, however, outweigh potential benefit when the incidence of HIV-1 transmission after an occupational exposure is only 0.3%. The importance of avoiding toxic effects during prophylaxis is strengthened by our observation that many health-care workers receive this type of treatment unnecessarily,<sup>4</sup> generally because the exposure was not great enough or the source patient was not infected or at risk. Overtreatment is more common than undertreatment. Because guidelines cannot address the unique characteristics of individual exposures, expert consultation can complement guidelines in assessment of exposure risk to find out whether postexposure prophylaxis is necessary and in recommending an optimum regimen.

The US National Clinicians' Post-Exposure Prophylaxis Hotline has received more than 19 000 calls. We recommend nevirapine for post-exposure prophylaxis only under extraordinary circumstances, when all of the following criteria are met: HCWs have had high-risk exposure; the source patient is HIV-1 infected and has high-level resistance (or suspected resistance) to most nucleoside reverse-transcriptase inhibitors and protease inhibitors; the alternative non-nucleoside reverse transcriptase inhibitor, efavirenz, cannot be used because of previous sensitivity or concern about related side-effects in the central nervous system or other toxic effects; and there is no pre-existing liver disease or concurrent use of hepatotoxic medications. If these criteria are met, the risks and benefits of nevirapine postexposure prophylaxis should be explained to HCWs and informed consent obtained. The HCW should be monitored carefully for toxic effects; nevirapine should be stopped if adverse events develop or are suspected.<sup>5</sup>

\*Ronald H Goldschmidt, David Bangsberg  
National Clinicians' Post-Exposure Prophylaxis Hotline (PEpline), San Francisco General Hospital, University of California San Francisco, 1001 Potrero Avenue, San Francisco, CA 94110, USA  
(e-mail: rongold@itsa.ucsf.edu)

- 1 Benn PD, Mercey DE, Brink N, Scott G, Williams IG. Prophylaxis with a nevirapine-containing triple regimen after exposure to HIV-1. *Lancet* 2001; **357**: 687–88.
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- 5 National HIV/AIDS clinicians' consultation center. www.ucsf.edu/hivcntr (accessed Aug 6, 2001).

Sir—Paul Benn and colleagues<sup>1</sup> report use of a triple-combination post-exposure prophylaxis regimen of stavudine, lamivudine, and nevirapine. Of 57 individuals, 16 did not attend follow-up and five had drug-induced hepatitis. These findings raise concerns about the safety of such a regimen in the general population.

Prophylaxis is recommended after occupational and sexual exposure to

HIV-1, although minimum evidence lends support to this recommendation.<sup>2</sup> Among the drugs available for the treatment of HIV-1 infection, zidovudine is the only agent that prevents HIV-1 transmission.<sup>3</sup> Therefore, zidovudine should be included in the regimen for postexposure prophylaxis. In fact, UK guidelines suggest a 4-week course of zidovudine, lamivudine, and indinavir, to start soon after exposure.<sup>4</sup>

Nevirapine has never been included in recommended regimens for post-exposure prophylaxis despite some evidence of prophylactic efficacy.<sup>5</sup> The US Food and Drug Administration has since reported that they have been notified of 22 cases of serious adverse events related to nevirapine used in this way between March, 1997, and September, 2000. One individual was a female health-care worker who had a hypersensitivity reaction that resulted in liver failure, requiring a liver transplant 35 days after starting prophylaxis with nevirapine, zidovudine, and lamivudine.

In light of the increased reports of severe hypersensitivity reactions to nevirapine, we suggest that this drug should not be used in first-line postexposure prophylaxis until the incidence and full spectrum of nevirapine toxic effects are clear. This caution is especially important if the risk of HIV-1 seroconversion after a needlestick injury is equal to or less than the risk of the life-threatening complication.

\*S Das, P S Allan, A A H Wade

Coventry Sexual Health Services, Department of Genito-Urinary Medicine, Coventry and Warwickshire Hospital Site, Coventry CV1 4FH, UK

- 1 Benn PD, Mercey DE, Brink N, Scott G, Williams IG. Prophylaxis with a nevirapine-containing triple regimen after exposure to HIV-1. *Lancet* 2001; **357**: 687–88.
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#### Authors' reply

Sir—We agree with Ronald Goldschmidt and David Bangsberg, and S Das and colleagues that nevirapine should not be routinely used in postexposure prophylaxis regimens after occupational or non-occupational exposure to HIV-1. The risk of severe toxicity outweighs potential benefit and for this reason we have now withdrawn the recommendation to use nevirapine from our local guidelines on post-exposure-prophylaxis regimens.

We endorse Goldschmidt and Bangsberg's comment that prescription of prophylaxis according to guidelines should always be complemented by expert consultation in assessing the HIV-1-exposure risk and, importantly, to provide psychological support. The need to start a post-exposure prophylaxis regimen in as short a time as possible after possible exposure is probably a strong factor in the decision to start prophylaxis and might, as Goldschmidt and Bangsberg comment, lead to overtreatment.

Whether zidovudine should always be included in the postexposure prophylaxis regimen, as Das and colleagues question, is debatable. A high incidence of transmitted primary resistance to zidovudine and other nucleoside analogues is reported for patients newly infected with HIV-1 infection in North America<sup>1</sup> and Europe. No regimen or drug is effective in preventing transmission of HIV-1 after occupational or sexual exposure to the infection. In animals, the nucleotide analogue, tenofovir, is protective in macaques after vaginal exposure to human-derived retrovirus if given within 36 h of exposure.<sup>2</sup> The characteristics of tenofovir in terms of its resistance and toxic-effect profile suggest that further studies to assess its possible role in postexposure prophylaxis regimens will be useful.

I G Williams, \*P D Benn

\*Department of Genitourinary Medicine, Camden and Islington CHS Trust, London WC1E 6AU, UK; and Department of Sexually Transmitted Diseases, Royal Free and University College Medical School, London

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## Nappies and transmission of *Giardia lamblia* between children

Sir—Ekramul Hoque and colleagues (March 31, p 1017)<sup>1</sup> report that exposure to nappies is an important risk factor for spread of *Giardia* spp to adults in the community. We agree that exposure to nappies represents an important risk factor for acquiring giardia infection but point out that exposure to nappies is also important for the spread of *Giardia* spp between children.

The health risks of paddling pools have been described.<sup>2</sup> We have managed the largest recorded outbreak of *Giardia lamblia* in the UK. At the same time we became aware of a form of water play in which children who were not toilet trained sit together in paddling pools, frequently while wearing nappies. A telephone survey of 17 local nurseries showed that this practice was allowed in ten of 16 for which data were available. Of these ten nurseries, six regularly allowed children to wear nappies while sitting together in the water. Only one of the nurseries reported the use of waterproof nappies.

The outbreak centred on one nursery catering for children age 3 months to 5 years. All household contacts of microbiologically positive cases were screened. 56 individuals had confirmed *Giardia lamblia* infection, 37 children, three child-care workers, and 16 parents. 17 individuals had symptoms and 39 were identified by screening. The epidemiology of the cases suggested person-to-person faecal oral spread rather than spread from a point source.

We did a retrospective case-control study to find out whether sitting in paddling pools was a risk factor for illness in the outbreak. Paddling was associated with a significant risk of microbiologically confirmed *Giardia lamblia* infection. We informed all UK environmental health departments of this common practice and the risk associated with it.

\*Eithne Linnane, Richard Roberts,  
Nick Looker

\*Public Health Medicine, Bro Taf Health Authority, Temple of Peace and Health, Cardiff CF10 3NW, UK; North Wales Health Authority, Mold; and Public Health Laboratory Service, Rhyl

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## Early detection of malignant change in breast cells

Sir—Ella Evron and colleagues (April 28, p 1335)<sup>1</sup> report on the detection of breast cancer cells in ductal lavage fluid by methylation-specific PCR (MSP). The ability to detect malignant change by MSP, even before the appearance of mammographic changes, provides a potential breakthrough in the early diagnosis of breast cancer.

One alteration that might contribute to early detection of malignant cells in ductal lavage fluid is a loss of cell-to-cell adhesion. By use of MSP, we have found methylation of the E-cadherin promoter in 84% of breast tumours, whereas it was absent in normal breast tissue.<sup>2</sup> Moreover, methylation of this gene has been reported in as many as 30% of patients with ductal carcinoma in situ (DCIS).<sup>3</sup> A clinical correlation of such an event is provided by the patchy expression of this gene in invasive breast tumours,<sup>4</sup> as well as the loss of E-cadherin expression observed in patients with DCIS.<sup>5</sup> Further evidence of early loss of cell-to-cell adhesion is provided by the presence of micrometastatic deposits in early breast cancer.

These data suggest that methylation is an early event in the evolution of breast cancer and its importance lies in the possibility of reversal by use of demethylating agents. These agents are being assessed, although toxic effects so far limit large-scale clinical applications.

Until further developments come about, the presence of methylation in certain genes within a tumour might be useful to identify more aggressive subtypes of cells. Such patterns of methylation in breast tumours may finally provide vital information for the individualisation of treatment.

\*V H Deshmane, I S Fentiman, I R Hart

\*12 Heliopolis, S Bhagat Singh Road, Mumbai 400 005, India; Breast Unit, Guy's Hospital, London, UK; and Richard Dimbleby Department of Cancer Research/ICRF Laboratory, St Thomas' Hospital, London, UK (e-mail: deshmanevinay@hotmail.com)

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## Serum cholesterol and haemorrhagic stroke

Sir—Il Suh and colleagues (March 24, p 922)<sup>1</sup> report the follow-up of a large cohort of 114 793 men over 6 years. They conclude that low total serum cholesterol is not an independent risk factor for intracerebral or sub-arachnoid haemorrhagic stroke in Korean men.

Despite the importance of these data, we believe the investigators have overlooked the characteristics of the cohort population, such as socio-economic status, type of occupation, and age. To show how these factors might have confounded the interpretation, we have some Korean population data to add.<sup>2,3</sup>

In Korea, three insurance schemes have been established: one for company-based industrial workers in certain companies, since 1977; one for all government employees and private school teachers, since 1979 (this is the group studied by Suh and colleagues); and one for all remaining people, since 1987. Of these three populations, government employees and private school teachers are thought to have the most stable socioeconomic status. They are virtually assured life-long employment with stable income, and are mostly non-manual workers. This population are less frequently admitted to hospital than the other two populations, and have less severe disease. All insured workers are required to have their general health assessed every 2 years, and in 1990 and 1992, 95% and 94% of insured workers, respectively, had assessments. Compared with an average of 48.4% all Korean men in 1992,<sup>3</sup> this proportion is high.

Moreover, the mean age of Suh and colleagues' population is 45.4 years (SD 6.7), which excludes most people who are at risk of haemorrhagic stroke; the association between low total serum cholesterol and intracerebral haemorrhage was evident only in the older age-group in a previous study.<sup>4</sup>

In summary, the cohort population of Suh and colleagues' study might not

be representative of all middle-aged Korean men, and, therefore, special care is required in interpreting the result.

\*Jongbae Park, Adrian White,

Hyunwoong Shin, Anthony Hemsley

\*Department of Complementary Medicine, University of Exeter, Exeter EX2 4NT, UK; Department of Medicine for the Elderly, Royal Devon and Exeter Hospital, Exeter, UK; and Korea Institute for Health and Social Affairs, Medical Insurance Research Team, Seoul, Korea  
(e-mail: J.B.Park@ex.ac.uk)

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Sir—The notion of Il Suh and colleagues<sup>1</sup> that low blood cholesterol is positively related with blood-vessel rupture and haemorrhagic stroke is tenuous. First, cholesterol is readily synthesised from precursors that are widely available. Second, most inland African and Asian populations have low blood cholesterol and yet the incidence of haemorrhagic stroke in these populations is not high.

There is an alternative explanation for the higher incidence of haemorrhagic stroke in societies such as the Koreans, which have low intake of land-animal products and high intake of marine foods.

We postulate that low concentrations of arachidonic acid (AA) in the endothelium is causatively related with haemorrhagic stroke. AA is a vital structural component of vascular endothelium and has a pivotal role in signal transduction, and receptor and enzyme activities. Moreover, its metabolites are involved in cell-cell communication and regulation of vascular tone.

Populations that consume low amounts of animal products have reduced membrane AA. The low AA level is further compromised by high intake of eicosapentaenoic acid (EPA), which replaces membrane AA in a dose-dependent way.<sup>2</sup> EPA, a nutrient primarily found in fish and seaweeds, has antiproliferative actions that may jeopardise vascular repair. Epidemiological data<sup>3</sup> show that the increased consumption of animal

Variables	KMIC (n=25 291)	1998 NHENS (n=290)
Age	51.9 (1.4)	52.0 (1.4)
Systolic blood pressure (mm Hg)	127.1 (16.9)	130.1 (19.1)
Diastolic blood pressure (mm Hg)	82.1 (11.3)	83.4 (11.7)
Total serum cholesterol (mg/dL)	198.5 (35.9)	193.9 (35.2)
Body-mass index	23.7 (2.6)	23.5 (2.7)
Cigarette smoking (%)		
Non-smoker	20.7	17.8
Ex-smoker	21.7	22.1
Current smoker	57.6	60.1

Data are mean (SD) except for smoking.

#### Characteristics of participants aged 50–54 years in Korea Medical Insurance Corporation (KMIC) trial and Nationwide Health Examination and Nutrition Survey (NHENS), 1998

products and  $\omega$ 6-rich vegetable oils in Okinawa, Japan, since 1945, correlate inversely with the incidence of apoplexy. We have reported a complete neurological recovery of a patient with haemorrhagic stroke treated with AA for 2 years.<sup>4</sup>

Our unpublished data reveal that Korean neonates at birth have lower concentrations of AA than UK neonates. This finding is interesting, since very low concentrations of AA in preterm babies have been implicated in the pathogenesis of the major vascular complications of prematurity. The high incidence of haemorrhagic stroke in communities with compromised AA might, therefore, have a prenatal origin.

Dietary cholesterol and AA come from the same food sources, mainly meat products, and are closely linked biologically. Consequently, cholesterol might have been acting as a surrogate for AA in studies in which an inverse association between cholesterol and haemorrhagic stroke has been shown. Haemorrhagic stroke is more likely to be caused by a deficiency of  $\omega$ 6 fatty acids, which cannot be synthesised de novo, rather than cholesterol, which can be easily synthesised.

\*Ivan Golffetto, Yoeju Min, Yiqun Wang, Kebreab Ghebremeskel, Michael A Crawford

Institute of Brain Chemistry and Human Nutrition, University of North London, London N7 8DB, UK

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#### Authors' reply

Sir—Jongbae Park and colleagues express concern about the possibility that our study population differs from the general Korean population for socioeconomic status, occupation, and age. The Korean Medical Insurance Corporation's clients include professionals and office workers as well as manual labourers, including custodians, railroad employees, and other service workers. Hence, the population comprises a wide spectrum of working-age men in Korea. We do not intend to make conclusions about individuals above the age range of our cohort.

To assess the generalisability of our results, we compared characteristics of our participants with corresponding data from the 1998 Nationwide Health Examination and Nutrition Survey (unpublished data). That survey is a small random sample drawn from the whole Korean population. We compared data for participants who were aged 50–54 years in 1998. The populations were similar for important health indices, such as blood pressure, total cholesterol, body-mass index, and smoking status. Although medical expenses seem to differ by type of insurance, as Park and colleagues note, reasons for this difference are totally unclear and might reflect non-medical factors or medical disorders that have little or no bearing on the relation between serum cholesterol and haemorrhagic stroke.

Our data show that serum cholesterol is unrelated to the risk of haemorrhagic stroke in Korean middle-aged men.

\*Il Suh, Sun Ha Jee, Chung Mo Nam, Hyeon Chang Kim, Lawrence J Appel

\*Department of Preventive Medicine and Public Health, Yonsei University College of Medicine, Seoul 120-752, Korea; Department of Epidemiology and Health Promotion, Graduate School of Health Science and Management, Yonsei University, Seoul; and Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD, USA

## Thyrotropin as first-line thyroid test

Sir—Wardle and colleagues' report (March 31, p 1013)<sup>1</sup> on the pitfalls of the use of thyrotropin (TSH) concentration as a first-line thyroid-function test covers an old issue that has been discussed in many national or international consensus on thyroid-function tests.

We think the researchers draw inexact conclusions from their study. First, they confound screening (the application of a test to detect a potential disease in a person who has no known signs or symptoms of that disorder<sup>2</sup>) and diagnosis. One thyrotropin assay may miss some patients with hypopituitarism in the general population but, as Wardle and colleagues stress, this disease is rare, far more rare than primary hyperthyroidism or hypothyroidism.

Although no definite consensus exists on the subject, screening for thyroid dysfunction in the general population is recommended in the USA in postmenopausal women<sup>2</sup> or in all adults older than 35 years,<sup>3</sup> but is not recommended in the UK.<sup>4</sup> However, screening for hypopituitarism, which would need assays other than thyrotropin and free thyroxine measurements, even if the incidence calculated by Wardle and colleagues were true, would not be reasonable. In their study most patients had signs compatible with hypopituitarism: asthenia, lethargy, weight loss, and so on. For most, electrolyte and glucose measurement was also required; hyponatraemia or hypoglycaemia, for example, could evoke hypopituitarism.

We think that the results do not reflect a pitfall of first-line thyrotropin measurement, but a misunderstanding of the meaning of a normal thyrotropin result by some clinicians. In this view, it is unclear whether the finding of a decreased free thyroxine concentration with normal thyrotropin value would have been correctly interpreted. The distinction between severe non-thyroidal illness, in which free tri-iodothyronine and free thyroxine, and sometimes thyrotropin, can be decreased may be very difficult in some cases, and only evolution allows a correct diagnosis.<sup>5</sup>

Given this information, how many non-thyroidal illnesses would be incorrectly diagnosed as hypopituitarism with the strategy proposed? The paper reminds us only that thyroid function tests, as every

test, must be interpreted in view of the patient's complaint.

\*Bernard Goichot, Anne-Elisabeth Perrin  
Service de Médecine Interne et Nutrition,  
Hôpitaux Universitaires, 67098 Strasbourg,  
France

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### Authors' reply

Sir—Bernard Goichot and Anne-Elisabeth Perrin have unfortunately fallen into the old trap of viewing our comments as a recommendation for screening. This is not the case.

We are recommending that when a request is made for a thyroid-function test that the pituitary-thyroid axis should be assessed. The signs and symptoms that we noted in the 17 patients in our study were not specific for hypopituitarism, and could be explained by many differential diagnoses. No tested patient was hypoglycaemic, and only three were hyponatraemic (sodium concentration in patient 2 was 134 mmol/L, in patient 10 was 126 mmol/L, and in patient 15 124 mmol/L).

The absence of specific symptoms is probably a reflection of the age of the patients and reminds us that many patients do not have specific complaints when thyroid-function tests are requested. Similar difficulties were encountered in the series of Waise and Belchetz,<sup>1</sup> who identified six cases of unsuspected central hypothyroidism by the use of appropriate front-line thyroid-function tests.

The statistics of our paper were peer reviewed and the CI values give us confidence in our quoted results. Clayton and Wass<sup>2</sup> have estimated an incidence of 20–30 cases per million population every year. It would be important for other investigators to confirm our findings in their populations.

We described two patients in our

series who had non-thyroidal illness who underwent some further tests for hypopituitarism. In our original submitted report, we suggested that estimation of tri-iodothyroxine, which is generally low in non-thyroidal illness and normal in hypopituitarism, would help in the differential diagnosis. We were asked to remove our comments on non-thyroidal illness after peer review. Although any laboratory result must be interpreted in light of the clinical findings, our data emphasise the major usefulness of intelligent application and interpretation of a combination of tests by clinical biochemists, especially in the presence of vague or non-specific symptoms.

Christine R Squire, \*William D Fraser  
Department of Clinical Chemistry, 4th Floor  
Duncan Building, Royal Liverpool University  
Hospital, Liverpool L69 3GA, UK

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## Precital signs on electroencephalography

Sir—David Fish writes in his Jan 20 commentary about the anticipation of epileptic seizures from standard electroencephalographic recordings.

The finding of precital signs in the electroencephalogram of epileptic patients<sup>1,2</sup> confirms the 1946 experimental findings of the late Grey Walter, the pre-eminent cofounder of the school of UK electroencephalography. By use of much cruder equipment, Walter was convinced that the spike and wave complex found in absence (petit mal epilepsy in Grey Walter's day) was a particular configuration of components present in the precital electroencephalogram.<sup>3,4</sup>

John C Shaw

Ivydene Cottage, Ivydene Crescent, Chidham,  
West Sussex PO18 8TR, UK

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## Selective cyclo-oxygenase inhibitors

Sir—We were disappointed to see Paul Emery and colleagues (March 10, p 809)<sup>1</sup> promoting selective cyclo-oxygenase inhibitors over other non-steroidal anti-inflammatory drugs (NSAIDs) on the basis of a relative risk reduction in admission rates for ulcer complications. They quote a reduction of 57%, a value derived from two major trials.<sup>2,3</sup>

In the CLASS study<sup>2</sup> the annualised incidence of upper-gastrointestinal ulcer complications in celecoxib-treated patients was 0.76% compared with 1.45% for patients taking NSAIDs. This difference was not significant and represents an absolute risk reduction of 0.69% or a number needed to treat of 145 patients treated for 1 year to avoid one upper-gastrointestinal ulcer complication. Emery and colleagues do not mention that in the group of patients taking concomitant low-dose aspirin, the beneficial effect of celecoxib was nullified.

In the VIGOR study,<sup>3</sup> the annualised incidence of complicated confirmed upper-gastrointestinal events in rofecoxib-treated patients was 0.6% compared with 1.4% for patients taking naproxen. This difference was significant, and represents an absolute risk reduction of 0.8% or a number needed to treat of 125 patients treated for 1 year to avoid one complicated upper-gastrointestinal event. If all confirmed upper-gastrointestinal events (including gastric or duodenal ulcer) are taken into account, the respective annualised incidence rates are 2.5% and 4.5%, an absolute risk reduction of 2.5% and a relative risk reduction of 50%. Emery and colleagues again, however, do not warn us that in this study there was a higher rate of cardiovascular events for rofecoxib than for naproxen, which suggests that naproxen has a coronary protective effect whereas rofecoxib does not.

The way in which data are presented can alter decisions about medical treatments and risk.<sup>4</sup> The risk of NSAID-related gastrointestinal bleeding or death can vary greatly dependent on the age of the patient.<sup>5</sup> We suggest that any wish for wider use of COX-2 inhibitors should be tempered by an acknowledgment that patients at low risk of NSAID-induced gastrointestinal complications might benefit little, if at all, from these more expensive agents.

\*Michael Wilcock, Ian MacKenzie

Cornwall and Isles of Scilly Health Authority,  
John Keay House, St Austell, Cornwall  
PL25 4NQ, UK

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### Authors' reply

Sir—We find it strange for Michael Wilcox and Ian Mackenzie to be disappointed by our recommendation of coxibs over non-selective NSAIDs on the basis of a substantial reduction in the risk of ulcer complications—strange but perhaps very British!

They are correct to point out that low-dose aspirin causes ulcer complications (whether patients are on coxibs or not) but careless to use the word nullified for an effect in the CLASS study that was based on such small numbers and which led to vastly wide CI. From other, more reliable data, we know that aspirin causes ulcer complications and that this risk can be reduced by restricting the dose for vascular prophylaxis to 75 mg daily (most patients in CLASS were on 325 mg daily) and usage to patients with established vascular disease.<sup>1</sup> For most of the adult population, coxibs have advantages in gastrointestinal safety.

Moreover, those needing aspirin may be better on a coxib than an NSAID,<sup>2</sup> even though some at high risk will require protection against aspirin with a proton-pump inhibitor. We discount the suggestion that naproxen rather than aspirin should be used for cardiovascular protection as dangerously unproven.

The least correct (unreferenced) assertion they make is that patients at low risk of NSAID-induced gastrointestinal complicated events may benefit little, if at all, from coxibs. In fact, in CLASS, the reduction in risk was greater for patients without than with risk factors (1.3 vs 0.3 events per

100 patient-years, US Food and Drugs Administration hearings Feb 7, 2001), and in the VIGOR study the relative benefits were reversed but fairly similar (reduction 1.7 vs 2.5 events per 100 patient-years without and with risk factors).

Critically, in patients with no risk factors, the absolute residual rates (0.2 and 0.3 events per 100 patient-years) were so low as to support a contention that hazards of NSAIDs had been eliminated, whereas in patients with risk factors, residual rates remained much higher (1.9 and 2.6 events per 100 patient-years in CLASS and VIGOR, respectively). That finding underscores the need in these patients to deal additionally with non-drug risk factors. Thus overall, coxibs probably offer more benefit in patients without than with the non-drug risk factors that render them high risk.

Wilcock and McKenzie refer to coxibs as more expensive agents, but new drugs generally are only more expensive than those they (should) replace because pricing arrangements are for introduction at maximum cost with no inflation-proofing increases thereafter. To give more weight to drug cost than the more than 10 000 admissions to hospital and 1000 deaths caused by NSAIDs would require a non-medical perspective that could potentially be challenged under the European convention on human rights. The cost issue is amenable to political solution, with sufficient will. Prescribers should concern themselves with safety and effectiveness and discard their current perverse obsession with cost (which generally measures affordability rather than value).

Good prescribing is normally cheap prescribing, when all costs are properly accounted for, but cheap prescribing is rarely good prescribing.

\*C J Hawkey, P Emery, A Moore

\*Division of Gastroenterology, University Hospital Nottingham, Queens's Medical Centre, Nottingham NG7 2UH, UK; Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds; and Department of Anaesthetics, Churchill Hospital, Oxford (e-mail: Cj.Hawkey@nottingham.ac.uk)

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## Choosing our own reviewers

Sir—An increasing number of medical journals has developed the habit of requesting that investigators submitting reports should also provide a list of potential reviewers, complete with addresses and fax numbers.

I suppose the reason behind this practice is that editors are finding it more and more difficult to keep abreast of the continuous cultural and technological changes taking place in their own specialties and to be fully updated in the various related subfields of knowledge. Thus, not only do the editors increasingly need the assistance of good reviewers, but they also need help in identifying the experts in a certain topic. Reasonable as it may be, the request for a list of potential referees for my reports always makes me nervous, to say the least. In fact, most of my potential reviewers fall into two distinct categories: friends and competitors.

To suggest a friend as a potential referee can be risky, since they sometimes reveal their true nature, proving the phrase “with friends like these you don’t need enemies”. Other times, to avoid showing favour to the investigator, the friendly reviewer feels obliged to show more severity than normal, thus endangering a report’s acceptance.

Our research competitors are easily identified. They never criticise our work, neither in reports nor in lectures, they simply fail to recognise its very existence. Even if published in peer-reviewed journals that such researchers peruse regularly, they mysteriously find our reports invisible and do not include them in their reference lists. To suggest the name of a competitor as a potential reviewer is, therefore, to offer him or her an opportunity to hamper, delay, or prevent entirely the publication of our data.

Therefore, we frequently end up searching through MEDLINE for names of workers whom we hardly know, but who, having already published a few reports on our own topic, could combine competence and neutrality. By such behaviour, we do little better than any member of editorial staff would in selecting the reviewers’ names. Clearly, there is something wrong with the system.

Mario Guslandi

Gastroenterology Unit, S Raffaele University Hospital, 20132 Milan, Italy  
(e-mail: guslandi.mario@hsr.it)

## National Health Service fails prisoners

Sir—Rachael Davies is right to highlight deficiencies in UK prison health care in her April 21 news item,<sup>1</sup> not only because difficulties with the recruitment and retention of medical staff are legion.

In psychiatry, attempts to quantify the nature and extent of disorders in prison settings<sup>2</sup> have generally made dismal reading. The Office of National Statistics’ 1998 document *Psychiatric Morbidity Among Prisoners*<sup>3</sup> did little to dispel anxiety when it reported on the prevalence of functional psychotic illness among sentenced men (7%), men on remand (10%), and women prisoners (40%). These numbers soar above comparable figures for community samples, and fuel was added to the fire by the finding that the prevalence of personality disorder among prisoners was a staggering 78%.

The Butler report,<sup>4</sup> in 1974, provided a kick start for the development of regional secure units in England and Wales, in recognition of the need to develop services for patients, frequently prisoners, who could not be cared for in open psychiatric wards, but who did not require the conditions of security afforded by special hospitals. After the report, piecemeal development of medium secure services took place throughout England and Wales in an attempt to address the issue. Despite this change, difficulties have persisted. Research confirms that services are currently not provided equally in different geographical areas.<sup>5</sup> Regions with lower demand and more resources provide a wider range of services than do others, whereas some are dependent on regularly admitting National Health Service patients to the private sector (at substantial cost) for assessment and treatment.

The Chief Inspector for Prisons for England, Sir David Ramsbottom, should be supported in his call for concerted and determined action, and the government announcement of extra money to solve the issue should be welcomed by all those who are interested in the treatment of the mentally ill. However, this issue will not simply disappear overnight. It requires commitment on the part of government in an area likely to win few votes, and a long-term strategy that may be lacking among politicians who stand for re-election every 4 or 5 years. It would be remiss of us not to remind them of this problem as often as it takes, for without substantial change the unseen misery of those who suffer from mental illnesses

and yet are detained in Her Majesty’s Prisons will continue. We should not forget about them.

Andrew Forrester

Camlet Lodge RSU, Chase Farm Hospital Site, Enfield EN2 8JL, UK  
(e-mail: andrewforrester@ukgateway.net)

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## Help with tobacco control

Sir—In your May 12 editorial<sup>1</sup> you claim that tobacco control needs help. I am happy to report that help is indeed on the way. It is coming from China, the largest cigarette consumer in the world.<sup>2</sup> Chinese lawyers are taking on big tobacco companies in an unprecedented lawsuit.<sup>3,4</sup>

A group of ten lawyers around China is gathering evidence against foreign and domestic cigarette makers, hoping one day to win a legal battle against companies they believe unduly target young people.<sup>4</sup> China’s production and consumption of cigarettes have ranked first in the world;<sup>2</sup> one of every three cigarettes manufactured in the world is consumed in China. Three of every five Chinese smokers begin smoking at age 15–20 years.<sup>2</sup> At least 50 million of the children now living in China will be killed by smoking.<sup>2</sup> Adults smoke; children follow.

The news that Chinese lawyers are taking on the big tobacco companies is indeed a breath of fresh air. What is more, a lawsuit against “Big Tobacco” would be against an entire industry, one that symbolises the state itself.<sup>4</sup>

Tsung O Chen

George Washington University Medical Center, Washington, DC 20037, USA

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## Nicotine patches in Japan

Sir—The smoking rate among Japanese men is the highest in more-developed countries.<sup>1</sup> Almost 2 years have passed since nicotine patches came on the market in May, 1999, as prescription medicines. Nicotine-replacement therapy (NRT), such as nicotine gum, patches, inhalers, and nasal sprays, is the only pharmacotherapy currently shown to be effective as an aid to smoking cessation.<sup>2</sup>

After the Japanese market was opened, Novartis Pharma KK, the only pharmaceutical company selling nicotine patches in Japan, reported that in fiscal 1999 the company gained ¥1 billion from sales of patches. In fiscal 2000, the patch sales were 1.5 times higher than the previous year. Thus, the use of nicotine patches has prevailed rapidly in Japan even though the patches are not covered by health insurance. This rise may indicate that the needs of smokers for nicotine replacement therapy have increased, that more smokers are learning about and using the patches, or both.

The Ministry of Health and Welfare for the first time recognised antismoking measures as an important public health theme in Healthy Japan 21, Japan's national plan for health established in 2000. This recognition is despite the plan's concrete goal—reduction of the smoking rate to half the current level by the year 2010—being rejected during the final review of the original Healthy Japan 21 proposal. Each prefecture and municipality has started to implement the goals of Healthy Japan 21 at the local level, which has created a good opportunity to establish more effective local strategies than have existed before. At last, population-based tobacco control has begun in Japan.

However, Novartis also reported that only 14% of physicians who prescribe nicotine patches provide smoking-cessation counselling to patients. This neglect might be caused by time constraints, a perceived lack of skills for physicians to be effective in this role, frustration because of low success rates, or misconceptions that smoking cessation is not an important professional responsibility.<sup>3</sup> In the case of Japan, we must also take into account an important factor—the high smoking rate among physicians.

The Japan Medical Association surveyed 4500 physicians randomly selected from its 15 000 members. 3771 physicians responded. 27% male physicians and 7% female physicians smoked. Only 44% of male physicians and 47% of female physicians agreed that physicians should not smoke.

We suggest that it is time for health-care professionals to recognise and change their own attitudes about smoking and tobacco control in Japan. It goes without saying that population-based strategies as well as individual-based strategies are indispensable to promote a permanent reduction in smoking and tobacco-related disease. Health-care professionals are the closest providers of tobacco control for most people in Japan. These professionals should realise that they now play a more important part than ever before in controlling tobacco within their own communities.

Kimiko Ueda

Harvard School of Public Health,  
677 Huntington Avenue, Boston, MA 02115,  
USA

(e-mail: kueda@xb4.so-net.ne.jp)

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## Use of Shewhart's technique

Sir—A R Henderson (May 12, p 1528)<sup>1</sup> and Tim Wilson and colleagues (May 12, p 1529)<sup>2</sup> highlight the importance of previous work in the use of Shewhart's technique, in response to our report.<sup>3</sup> We unequivocally acknowledge the work of others in this area (especially workers they mention) and feel there is a need for a systematic survey of the application of Shewhart's approach to health care. We are undertaking such a survey, to see who did what, and to learn more about the shortcomings of control charts in health care.

We see the work of Shewhart (and Deming<sup>4</sup>) not so much as a means of refining widget production<sup>2</sup> but primarily as a means of delivering clinical governance, and we attempted to relate the two.

We agree with Wilson and colleagues that processes need to be changed when there is only common-cause variation. We tried, perhaps insufficiently, to emphasise this in our report. Under the headings "common-cause and special-cause variation" and variation "cannot be eliminated", we underscore the need for action on the system to reduce common-cause variation. This message is repeated in case study 4: neonatal deaths for which only common-cause variation was seen.

Wilson and colleagues allege that we had to find the right epoch groupings before we found the right results for Bristol Royal Infirmary. This is

incorrect. The epochs were originally devised by Spiegelhalter and colleagues (reference 9 in our report) as part of their statistical evidence to the Bristol Inquiry. We aimed not to find the right results for Bristol, rather to guide action to improve paediatric cardiac surgery for all centres by acting on signals indicating special-cause variation.

We agree with Wilson and colleagues that statistics alone could not detect a murderer such as Dr Harold Shipman. Shewhart's approach enables us to identify when we should act to find and eliminate special-cause variation.

Henderson makes the point that additional rules have been shown to improve the sensitivity of Shewhart control charts. We did not emphasise this. However, we note that Shewhart himself was aware of the need for additional rules,<sup>5</sup> and that our case studies show there is much mileage in the use of Shewhart's primary rule for detecting special causes.

\*Mohammed A Mohammed, K K Cheng,  
Andrew Rouse, Tom Marshall

Department of Public Health and Epidemiology,  
University of Birmingham, Edgbaston,  
Birmingham B15 2TT, UK  
(e-mail: m.a.mohammed@bham.ac.uk)

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## DEPARTMENT OF ERROR

Lifeline Andrew H Kaye—In this Lifeline (July 7, p 82), the first line should begin: "Andrew H Kaye is James Stewart Professor of Surgery...".

Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial—In this Article by the GUSTO V Investigators (June 16, p 1905), there were some mistakes in the Study Group section. Under "Germany" (p 1911), the investigator at Klinikum der Ruprechts-Karl-Universität, Heidelberg, should have been J Ruedf. Under "UK" (p 1912), the investigators at Wycombe General Hospital, Bucks, should have been J Wiltshire, C P Clifford, J Scurrel, W Hendry; those at Friarage Hospital, North Yorks, should have been U Somasundram, J Johnson; those at the Royal Infirmary of Edinburgh should have been A D Flapan, M O'Donnell, L Flint; and those at Oldchurch Hospital, Romford, Essex, should have been J D Stephens, H Kadr. Under "Third Party Contractor" (p 1914), C Boyd, E James, M Adam, and W Sutherland are at the Canadian Vigour Centre, and C Thomas and S Dolan are at the Flinders Coordinating Center.