

CORRESPONDENCE

Vascular complications associated with use of HIV protease inhibitors

Sir—The potency and sustained efficacy of highly active antiretroviral therapy (HAART) including protease inhibitors have led to declining morbidity and mortality in patients with advanced HIV infection. However, Keith Henry and colleagues (May 2, p 1328)¹ and others² have shown lipodystrophy and vascular complications during treatment with protease inhibitors. We analysed lipid abnormalities in patients on protease inhibitors who developed hypercholesterolaemia with symptomatic coronary or peripheral atherosclerosis. We report vascular complications in two of these patients.

A 60-year-old HIV-infected man (CD4 T cell count 204/ μ L) was admitted with a first episode of angina pectoris. Increased serum concentrations of creatine kinase (173 U/L [normal <80 U/L]), troponin (0.88 μ g/L [<0.1 μ g/L]) and electrocardiography confirmed anterolateral myocardial infarction. He had a history of cigarette smoking, but had been receiving HAART, including the protease inhibitor saquinavir, for 9 months. Analysis of lipid indices showed increased total cholesterol (7.3 mmol/L [<5.3 mmol/L]) and increased LDL-cholesterol (5.2 mmol/L [<4.2 mmol/L]); both were normal before initiation of treatment. Serum concentrations of apolipoproteins (apo) lipoprotein [a], apo A-I, apoB, apoA-II, apoE) as well as fibrinogen, homocysteine, and antiphospholipid antibodies, were normal. ApoE genotype was normal (3/3). However,

oral glucose tolerance test (OGTT) was impaired, with raised serum glucose concentration of 11.3 mmol/L after 60 min and insulin of 209 mU/L after 120 min (figure).

A 58-year-old man with HIV infection for more than 12 years complained of pain in his right leg. His course was complicated by Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, and non-Hodgkin lymphoma. CD4 cell count was 228/ μ L and HIV RNA less than 400 copies per mL. He had been on protease inhibitors (indinavir finally) for 19 months. Angiography revealed a large embolic occlusion of the right femoral artery that was treated successfully by lysis and dilatation. Ultrasonography showed arteriosclerotic plaques in the carotid arteries. Single-photon-emission computed tomography of the myocardium indicated no signs of coronary atherosclerosis. He had hypercholesterolaemia (7.3 mmol/L), by contrast with normal cholesterol values (5.2 mmol/L) before starting HAART, hypertriglyceridaemia (3.1 mmol/L), raised LDL-cholesterol (4.6 mmol/L), very low-density lipoproteins (1.1 mmol/L), and greatly increased serum concentration of lipoprotein (a) (1.58 g/L), and reduced HDL-cholesterol (0.9 mmol/L [>1.0 mmol/L]). These abnormalities were in accord with increased serum apo B (1.53 g/L), but reduced apoA-I (1.09 g/L) and apoA-II (1.8 g/L). ApoE genotype was normal (3/3). OGTT and homocysteine were normal but fibrinogen was increased to 8.1 g/L (normal <3.5 g/L).

In both patients the development of lipid abnormalities and vascular events were closely associated with initiation of protease inhibitor therapy but not with signs of lipodystrophy. Characterisation of important risk factors for atherosclerosis and atherothrombosis [high Lp(a)] in dyslipoproteinaemia caused by HAART is needed to establish which patients are at risk on protease inhibitors. Our findings add evidence of vascular complications independent from abnormal fat accumulation.^{3,4}

HIV patients given protease inhibitors should be assessed.

This work was supported by the Bundesminister für Gesundheit (RKI 415-4476-09/10).

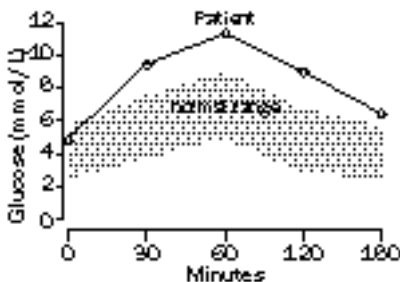
*Georg Behrens, Hartmut Schmidt, Dirk Meyer, Matthias Stoll, Reinhold E Schmidt

Divisions of *Clinical Immunology and Gastroenterology and Hepatology, Hannover Medical School, Hannover, D-30623 Germany

- 1 Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998; **351**: 1328.
- 2 Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998; **12**: F51-F58.
- 3 Miller MD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* 1998; **351**: 871-75.
- 4 Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. "Buffalo hump" in men with HIV infection. *Lancet* 1998; **351**: 867-70.

Sir—Keith Henry and colleagues¹ speculate about the potential for accelerated atherosclerosis in patients given protease inhibitors. We report three AIDS patients who developed coronary artery disease during such treatment.

A 33-year-old HIV-infected man was admitted because of inferoposterior wall myocardial infarction. He smoked 20 cigarettes daily. Ritonavir was started 14 months before admission. Cholesterol concentration increased from 4.88 mmol/L to 7.85 mmol/L 1 month later, and triglycerides from 1.63 mmol/L to 7.85 mmol/L. Ritonavir was changed to nelfinavir 1 month before admission because of plasma HIV RNA of 60 000 copies per mL. Concurrent drugs were stavudine and didanosine. On admission, cholesterol concentration was 5.70 mmol/L and triglycerides concentration was 2.94 mmol/L. Peak serum creatine kinase was 1330 U/L. Coronary arteriography showed a subtotal occlusion of the right coronary artery, and percutaneous transluminal coronary angioplasty (PTCA) was successful. 4 months later, the patient had a recurrent myocardial infarction.



Impaired oral glucose tolerance test

Increased serum glucose concentration after glucose ingestion was accompanied by delayed and excessive insulin and C-peptide serum concentrations (not shown).

Coronary arteriography showed reocclusion of the right coronary artery, and a second PTCA was done with coronary stenting.

A 32-year-old HIV-infected man was admitted because of anterolateral wall myocardial infarction. He had been treated for 18 months with indinavir, lamivudine, and stavudine. Plasma HIV RNA was 649 copies per mL 5 months before admission. He smoked 40 cigarettes daily. On admission, cholesterol and triglycerides were normal (4.45 mmol/L and 1.25 mmol/L, respectively). Peak serum creatine kinase was 290 U/L. Coronary arteriography showed a 90% stenosis of the left anterior descending artery, and PTCA with coronary stenting was successful.

A 54-year-old HIV-infected man presented with angina. He had *Pneumocystis carinii* pneumonia and cytomegalovirus retinitis at age 49. He had been treated for 21 months with lamivudine and zidovudine, and saquinavir was added 13 months before presentation. Initiation of protease inhibition was followed by a striking rise in cholesterol and triglycerides (from 6.48 mmol/L to 16.32 mmol/L and 6.56 mmol/L to 22.30 mmol/L 11 months before presentation, respectively), leading to treatment with fenofibrate. An exercise test induced chest pain with ischaemic ST-segment depression. The patient declined coronary arteriography. Acetabulol, transdermal glyceryl trinitrate patches, and aspirin were started. Angina resolved, and exercise test while on medication was negative.

A rise in lipid concentrations and peripheral lipodystrophy have been described with protease inhibitors.¹⁻⁵ Two of our three patients had severe hyperlipidaemia after starting these drugs, which could have led to accelerated atherosclerosis. However, our two young AIDS patients with myocardial infarction were heavy smokers, which could have favoured premature coronary artery disease. Current information on the side-effects of protease inhibitors is based on treatment of only a few thousand patients per drug, and other toxic effects may be recognised with longer and wider use.³ Premature coronary artery disease might be one of these effects, and clinicians should be aware of this danger.

*Bruno Gallet, Marc Pulik,
Philippe Genet, Pierre Chedin,
Michel Hiltgen

Departments of *Cardiology, Haematology and AIDS, and Endocrinology, Victor Dupouy Hospital, 95107 Argenteuil, France

- 1 Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998; **351**: 1328.
- 2 Sullivan AK, Nelson MR. Marked hyperlipidaemia on zidovudine therapy. *AIDS* 1997; **11**: 938-39.
- 3 Flexner C. Drug therapy: HIV-protease inhibitors. *N Engl J Med* 1998; **338**: 1281-92.
- 4 Mulligan K, Tai VW, Algren H, Chernoff DN, Lo JC, Schambelan M. Evidence of unique metabolic effects of protease inhibitors. In: Programs and abstracts of the 5th National Conference on Retroviruses and Opportunistic Infections: Chicago, Illinois, Feb 1-5, 1998 (abstr 414).
- 5 Hengel RL, Watts NB, Lennox JL. Benign symmetric lipomatosis associated with protease inhibitors. *Lancet* 1997; **350**: 1596.

Sir—Keith Henry and colleagues¹ report is important in the care of AIDS patients, since the decline in mortality is linked to the introduction of protease inhibitor. We report four severe vascular diseases in four HIV-infected patients (three on such drugs).

Coronary angiography showed a 90% left anterior descending coronary artery stenosis without thrombus in patient 1, a 90% stenosis of the left anterior descending coronary artery and a 70% stenosis of the left circumflex and obtuse marginal artery in case 3, and a 90% stenosis of the right coronary artery, and 70% stenosis of the left anterior descending and of left circumflex artery in case 4 (table). Magnetic resonance imaging showed two lacunar images related to anterior cerebral artery occlusion. Patients 1, 2, and 3 remain healthy 1 year, 7 months, and 1 year respectively, after development of vascular disease. Indinavir was not discontinued despite the vascular event because CD4 count continued to increase. Patient 4 died of AIDS 2 years after myocardial infarction.

Case no	1	2	3	4
Age (years)	36	40	47	36
CDC staging	C3	B3	B2	C3
CD4 count (/mmL)	190	210	290	30
Viral load (log ₁₀ /mL)	5.5	<2.3	4.6	5
Antiviral treatment at time of event	Indinavir, zidovudine, lamivudine	Indinavir, stavudine, lamivudine	Indinavir, stavudine, lamivudine	Zidovudine, lamivudine
Time on drugs	12 mo	16 mo	3 wk	10 mo
Vascular event	Anteroseptal myocardial infarction	Transient recurrent ischaemic attacks	Anteroseptal myocardial infarction	Inferior myocardial infarction
Treatment of vascular event	PTCA*, aspirin, diet, beta blockers	Aspirin, diet, beta blockers	PTCA, aspirin, diet, beta blockers	PTCA, stent, aspirin
Risk factors				
Cigarette smoking†	150	280	No	280
Genetic factors	No	No	Yes	No
BMI‡	24-26	21-35	21-68	21-35
Hypertension	Border line	No	No	No
Hyperglycaemia	No	No	No	No
Triglyceridaemia§	4-1	7-9	Normal	Normal
Cholesterolaemia¶	Normal	7-2	7-6	Normal
Insulinaemia	77	Normal	Normal	Normal
C peptide**	Normal	Normal	Normal	Normal

*PTCA=primary percutaneous transluminal coronary angioplasty; †cigarettes/wk; ‡body mass index (kg/m²); §normal 0.6-1.7 mmol/L; ¶normal 4-6.7 mmol/L; ||normal 2-15 µU/mL; **normal 1.4-4.9 ng/mL

Characteristics of four HIV-infected patients treated with or without protease inhibitors, with severe vascular disease

Severe vascular diseases can arise in young people with HIV infection given antiretroviral drugs. Protease inhibitors, which induce metabolic abnormalities (hypertriglyceridaemia, hypercholesterolaemia, and raised insulin and C peptide²) may accelerate atherosclerosis. In fact, we noted three vascular complications in 787 patient-years in our cohort of HIV-infected patients receiving a protease inhibitor. The onset of vascular complications raises an important dilemma about continuation of these drugs. In our patients, therapy was maintained in association with transient anticoagulation followed by antiplatelet agents and a diet with reduced cholesterol and saturated fat intake. Indeed, others have shown that as the number of cardiovascular risk factors increases so does the severity of symptomless coronary and aortic atherosclerosis.³ Cardiovascular risk factors (cigarette smoking, familial factors, hypertension, diabetes mellitus, and hyperlipidaemia) should be evaluated before starting protease inhibitors, especially when they are introduced at a very early stage of HIV infection.

*D Vittecoq, L Escaut, J J Monsuez

Service de Médecine Interne, Hôpital Paul Brousse, 94804 Villejuif, France

- 1 Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998; **351**: 1328.
- 2 Viraben R, Aquilina C. Indinavir associated lipodystrophy. *AIDS* 1998; **12**: F37-F39.
- 3 Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N Engl J Med* 1998; **338**: 1650-56.

Sir—Keith Henry and colleagues¹ suggest an association between the lipid abnormalities which occur during protease inhibitor therapy in HIV-1 infection and severe coronary artery disease. However, premature cardiac disease in the absence of identifiable confounders such as antiviral drugs, herpesvirus infection, HIV-linked hyperlipidaemia, and common risk factors for atherosclerosis is an important sequela of HIV-1 infection. This disorder is increasing in prevalence and should be considered more frequently in the evaluation of HIV-1 positive patients.

At the start of the AIDS pandemic, cardiac disease led to morbidity in under 6% of cases and was a primary cause of mortality in 1.1%.^{2,3} With increased scrutiny and better survival in HIV-1 disease, these numbers have risen substantially. Cardiac changes may evade detection on routine clinical examination, but echocardiography and necropsy studies reveal abnormalities in 40–50% of individuals with advanced HIV-1 infection.³ Between 1994 and 1996, cardiac disease was the primary cause of death in 9.1% of HIV-1-positive individuals.³

HIV-1-linked cardiac disorders have been recognised at all clinical and immunological stages of disease. Children seem particularly vulnerable; in the absence of overt cardiac risk factors, apart from possible in-utero exposures, they frequently have evidence of accelerated arteriosclerosis,⁴ with intimal proliferation and microthrombosis of small vessels, which may become clinically manifest with cerebral and myocardial infarctions.⁴ Fragmentation of elastic fibres and arteriosclerosis at the ventricular septum have been described on necropsy, changes rarely seen before age 40 years in the HIV-1 population.⁴ Our group has described plasma factors that may be associated with accelerated procoagulant activity and programmed cell death of cardiac endothelium in vitro in the setting of HIV-1 infection.⁵

I believe that cardiac disease should be considered more often in the setting of HIV-1/AIDS. However, there is no direct evidence that any anti-HIV drug, including the protease inhibitors, augments an already substantial frequency of HIV-1-linked cardiac disease. These disorders may represent the end stage of various insults operating concurrently and, perhaps, synergistically. But once heart failure develops, it has a poor prognosis.^{2,3} An understanding of the pathophysiological events that precede overt cardiac dysfunction in the setting of

HIV-1 infection, including the potential role of side-effects of the new anti-HIV medications, may permit early or even anticipatory therapy.

Jeffrey Laurence

Laboratory for AIDS Virus Research, Cornell University Medical College, New York, NY 10021, USA

- 1 Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998; **351**: 1328.
- 2 Anderson DW, Virmani R. Emerging patterns of heart disease in HIV infection. *Hum Pathol* 1990; **21**: 253–59.
- 3 Patel RC, Frishman WH. Cardiac involvement in HIV infection. *Med Clin NA* 1997; **80**: 1493–512.
- 4 Bharati S, Joshi VV, Connor EM, et al. Conduction syndrome in children with AIDS. *Chest* 1989; **96**: 406–13.
- 5 Laurence J, Mitra D, Steiner M, et al. Plasma from patients with idiopathic and human immunodeficiency virus-associated thrombotic thrombocytopenic purpura induces apoptosis in microvascular endothelial cells. *Blood* 1996; **87**: 3245–54.

Meta-analysis

Sir—We share with Matthias Egger and colleagues (May 16, p 1517)¹ the goal of improving the quality of meta-analyses. However, these workers' comments on our article on meta-analysis is inaccurate in three respects.² First, they state that in a previous editorial we had recommended that treatment with magnesium should be implemented without further delay in patients with acute myocardial infarction (AMI). This statement is incorrect and misleading. We were sufficiently encouraged by the promising results of two meta-analyses^{3,4} of the use of magnesium in AMI to participate in the design and conduct of the large ISIS-4 trial (and hoped for a favourable result). Contrary to Egger and colleagues' claim, we stated in the article they cite: "The most appropriate conclusions of these two overviews is that intravenous magnesium is a promising intervention that deserves to be evaluated in large, well designed randomised trials" and "although some physicians might be persuaded by the current data, others may believe that it would be prudent to await the results of the large ISIS-4 trial before routinely using magnesium". Subsequent to the publication of ISIS-4, we stated that "these were no grounds for the routine use of magnesium for patients with myocardial infarction".⁵

Second, in the cumulative meta-analyses of magnesium that Egger and co-workers report, they included at least one trial with promising results that become available in abstract form after the ISIS-4 results were publicly presented. Therefore an appropriate

cumulative analysis should have included ISIS-4, which would have made the analysis non-significant. Our general preference is to use monitoring boundaries that are more extreme (corresponding to $p < 0.01$ or 0.001) and not to rely solely on a temporary crossing of any boundary.

Third, in our methodological essay about meta-analysis,² we recommended the use of both qualitative (similar to those proposed by Egger et al) and quantitative standards for the interpretation of meta-analysis. Unlike Egger's statement, we do not propose "mechanically to apply formal stopping rules" alone or any single statistical or non-statistical criterion. Instead, a range of criteria should be used, which are outlined in panel 1 of our essay. We believe that the usual meta-analyses are retrospective exercises and that developing prospective protocols and exploration of biases should become an integral part of the methodology, with the use of different approaches including funnel plots, &c. However, this by itself is insufficient because even a rigorous meta-analysis (or for that matter, an individual trial) based on sparse data is more likely to find spurious differences (type I error). This can be kept to a minimum (but not wholly eliminated) by the use of quantitative standards and formal approaches to viewing the weight of the evidence, as is done within well-designed, large individual trials. We did not state that once certain boundaries were crossed, no further trials are needed. Instead, we indicated that this approach provides a guidance to the minimum amount of information that should be available. Therefore, to be persuasive, meta-analyses should meet both qualitative and quantitative standards.

*Salim Yusuf, Janice Pogue

Division of Cardiology, McMaster University and Preventive Cardiology and Therapeutics Research Program, Hamilton Health Sciences Research Centre, Hamilton, Ontario, Canada L8L 2X2

- 1 Egger M, Smith GD, Sterne JAC. Meta-analysis: is moving the goal post the answer? *Lancet* 1998; **351**: 1517.
- 2 Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet* 1998; **351**: 47–52.
- 3 Teo KK, Yusuf S, Collins R, Held PH, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: Overview of randomised trials. *BMJ* 1991; **303**: 1499–503.
- 4 Horner SM. The efficacy of intravenous magnesium in acute myocardial infarction in reducing arrhythmias and mortality: meta-analysis of magnesium in acute myocardial infarction. *Circulation* 1992; **86**: 774–79.
- 5 Yusuf S, Flather M. Magnesium in acute myocardial infarction: ISIS 4 provides no grounds for its routine use. *BMJ* 1995; **310**: 751–52.

Effectiveness of pneumococcal vaccine

Sir—Åke Örtqvist and colleagues (Feb 7, p 399) report the results of a randomised trial in Sweden that assessed the efficacy of 23-valent pneumococcal polysaccharide vaccine to prevent pneumococcal pneumonia in persons aged 50–85 years who were discharged from hospital after treatment for pneumonia. Although substantial antibody responses to pneumococcal vaccination had been previously reported for patients with similar characteristics,¹ rates of pneumococcal pneumonia and pneumonia overall were similar for vaccine and placebo recipients. However, the efficacy study has critical limitations.

The study participants represented only a few of all middle-aged and elderly persons (<1% of whom are admitted for pneumonia yearly, D S Fedson, unpublished data); yet, the investigators generalised their conclusions to the total population in this age group. The 120 admissions for pneumonia during the 2.4 years of observation represent an incidence of about 7000 cases per 100 000 persons per year. The annual rate of pneumococcal bacteraemia in the placebo group was 600/100 000. These rates were roughly ten times higher than the rates of admissions for pneumonia and pneumococcal bacteraemia for the general population of similar age in Scandinavia and North America.^{2–4} Whether immunological or other factors were responsible for the greatly increased rate of pneumonia and pneumococcal bacteraemia in this special population is unclear. Despite these high rates, only five patients died of pneumonia and of these none was thought to have had pneumococcal pneumonia. The study design did not allow evaluation for prevention of the first episode of pneumonia.

Most (60%) cases of pneumococcal pneumonia were diagnosed by a two-fold or greater rise in serum antibody to pneumolysin or by detection of pneumolysin immune complexes in serum. Örtqvist and colleagues provide no data or citations to assess the predictive value of these innovative assays for diagnosis of pneumococcal infection in patients with community-acquired pneumonia. An inaccurate case definition of pneumococcal pneumonia would bias the findings of the study toward the null.

Retrospective studies have confirmed the clinical effectiveness of pneumococcal vaccination for

prevention of unquestionable infection (eg, bacteraemia) in immunocompetent persons aged 65 or over. In fact, Örtqvist's data also suggest efficacy against bacteraemia (point estimate of vaccine efficacy 79%, Fisher's exact test $p=0.22$), but the power to detect a statistically significant difference in bacteraemia between vaccine and placebo recipients was only 5%. On the basis of data on vaccine efficacy, pneumococcal vaccination is also cost-effective in prevention of bacteraemia and compares favourably with all other interventions in the care of elderly persons.⁵

We agree that protection against all pneumococcal infection (non-bacteraemic as well as bacteraemic) is an important goal for pneumococcal vaccine development and use; however, to establish policy for vaccination of the elderly with the current 23-valent polysaccharide vaccine, its effectiveness for preventing life-threatening bacteraemia alone justifies its use.

*Jay C Butler, John S Spika,
Kristin L Nichol, Eugene D Shapiro,
Robert F Breinan

*National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA; Laboratory for Disease Control, Ottawa, Canada; Minneapolis Veterans Affairs Medical Center, Minneapolis; Yale University School of Medicine, New Haven; and National Vaccine Program Office, Atlanta

- Hedlund JU, Kalin ME, Örtqvist Å, Henrichsen J. Antibody response to pneumococcal vaccine in middle-aged and elderly patients recently treated for pneumonia. *Arch Intern Med* 1994; **154**: 1961–65.
- Jokinen C, Heiskanen L, Juvonen H, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993; **137**: 977–88.
- Marston BJ, Plouffe JF, File TM, et al. Incidence of community-acquired pneumonia requiring hospitalisation: results of population-based active surveillance in Ohio. *Arch Intern Med* 1997; **157**: 1709–18.
- Sankilampi U, Herva E, Haikala R, Liimatainen O, Renkonen O-V, Leinonen M. Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland. *Epidemiol Infect* 1997; **118**: 7–15.
- Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteraemia among elderly people. *JAMA* 1997; **278**: 1333–39.

Sir—Åke Örtqvist and colleagues¹ study fails to incorporate suitable protection against type II errors (false-negative conclusions) for vaccine protection.² They calculated a sample size (based on local estimates of disease incidence) to detect a protective effect of 40% or more of

pneumococcal vaccine on pneumococcal pneumonia. Nevertheless, they ended the trial well before their design-stipulated 60 cases of pneumococcal pneumonia had accrued in the placebo group. Örtqvist and co-workers report 691 patients; 120 of whom had clinical pneumonia, but only 35 (16 in the placebo group) had pneumococcal pneumonia, according to their definition. In other words, the study was stopped when only a fraction of the target number of pneumococcal cases in the placebo group had been achieved. They claim that an external monitoring committee decided that a reasonable protective effect of the vaccine had been ruled out by the accrued cases, but do not describe the statistical methods used to formulate a stopping rule.

The use of an immunological response to infection to define a pneumococcal endpoint can be questioned, since it is not documented that vaccinees and placebo recipients responded equally vigorously with serum antipneumolysin antibodies after pneumococcal infections.³ If vaccinees responded more vigorously, this would bias estimates of efficacy toward the null. Even if vaccinees and non-vaccinees had an equal antibody response, a bias to the null could have occurred if the serological test had been non-specific, especially since serology was the sole basis for diagnosis of a pneumococcal aetiology in 21/35 cases of so-called pneumococcal pneumonia. A diagnostic test with low specificity can substantially reduce the apparent efficacy of a vaccine.^{4,5} Örtqvist et al should provide an estimate of the specificity of the serological criteria they used, and then estimate the true efficacy of vaccine with available formulae,⁵ with a correction for the specificity of the diagnostic test.

Additionally, it is of concern that patients were selected on the basis of a recent episode of pneumonia. If a substantial fraction of these baseline pneumonias had been pneumococcal, false-positive conclusions about such aetiologies in the recurrences could have occurred as a result of residual nasopharyngeal colonisation by pneumococci or by persisting antipneumococcal immune responses, related to the baseline infections. How many of the 21 cases diagnosed by pneumococcal antibody tests alone were diagnosed with pneumolysin immune complexes in a single serum sample, and how many of this subset were early in the course of the study? A substantial proportion of recurrent pneumococcal pneumonias occurred shortly after baseline. Such false-

positive diagnoses, which would be expected to be equally distributed in vaccinees and non-vaccinees, would have tended to dilute estimates of vaccine protective efficacy. It seems plausible that one or more of these biases toward the null was operative, since the point estimate of vaccine protection was 79% against the few pneumococcal pneumonias diagnosed by blood culture—a gold standard test, with high specificity.

The estimate of a bacteraemia rate of 600 per 100 000 in their population suggests that they studied a special subgroup with an unusually high rate of bacteraemic disease, and they may be overgeneralising their findings to all persons over 50 years.

*Mark C Steinhoff, L Moulton,
John Clemens

*Johns Hopkins University, School of Hygiene and Public Health, Baltimore, M 21205, USA; and National Institute Child Health and Human Development, NIH, Bethesda, MD

- 1 Örtqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet* 1998; **351**: 399–403.
- 2 Clemens J, Shapiro E. The pneumococcal vaccine controversy: are there alternatives to randomized clinical trials? *Rev Infect Dis* 1984; **6**: 589–600.
- 3 Kauppinen MT, Herva E, Kujala P, Leinonen M, Saikku P, Syrjala H. The etiology of community-acquired pneumonia among hospitalized patients during a Chlamydia pneumoniae epidemic in Finland. *J Infect Dis* 1995; **172**: 1330–35.
- 4 Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field, further observations. *Epidemiol Rev* 1988; **10**: 212–41.
- 5 Farrington CP. Quantifying misclassification bias in cohort studies of vaccine efficacy. *Stat Med* 1990; **9**: 1327–37.

Authors' reply

Sir—It is true that less than 1% of persons aged over 50 years are admitted each year for pneumonia, but the total of persons in this age group who have ever been admitted for pneumonia does not represent such a particular minority. Moreover, all patients who were admitted for pneumonia but had a known immunosuppressive disease were excluded.

Part of the explanation for the unusually high incidences for pneumonia, pneumococcal pneumonia, and pneumococcal bacteraemia might be the alertness of the patient and the physician to look for pneumonia as soon as there were any signs of severe respiratory tract infection or fever greater than 3 days'

duration. As many as a third of patients with recurrent pneumonia were treated as outpatients. The low mortality is in accordance with previous Swedish findings.^{1,2}

The most important primary endpoint was pneumonia since without a reduction of the total incidence of pneumonia no substantial improvement in general health would be achieved. If, as indicated by our results, pneumococcal vaccination does not reduce the incidence of pneumonia in this group of patients with a previous pneumonia but without known immunodeficiency, it is doubtful whether the vaccine could have much impact on the total incidence of pneumonia in the community, even if protective in persons who had never had pneumonia.

Thus, the aetiological diagnosis was not crucial for efficacy evaluation. However, efficacy estimation would be more powerful with accurate aetiological diagnoses in a high percentage of cases. We therefore used several methods, being well aware that they could, for practical reasons, not all be applied in every case. The pneumolysin assay has a specificity below that of blood culture.^{3,4} The difficulty in diagnosis of pneumococcal pneumonia is that, although 100% specific, blood cultures have a very low sensitivity. Therefore there is no gold standard to which other methods can be compared, making it difficult to establish their true sensitivity and specificity.

Was our study stopped too early? Only the monitoring committee had access to all data. Their decision to end the study was unanimous and final. Further, after 2.5 years of follow-up, the survival curves of the two groups were similar. Since the efficacy of the vaccine declines with time, especially in the elderly,⁵ a long follow-up may not have shown a true difference between groups. The protection of 79% of patients against bacteraemic pneumococcal disease was based on only six cases. If the difference in bacteraemia rates had remained the same for a long time, which is unlikely,⁵ it would have taken at least another 3 to 6 years to show a significant protective effect against bacteraemic disease.

Nevertheless, our interpretation of these and previous results is that the polysaccharide vaccine protects against invasive pneumococcal disease, but not against pneumonia without bacteraemia. Our results must not be overinterpreted to counteract vaccine usage. It is, however, equally

important to define to what extent the vaccine is protective for different groups of patient and diagnoses.

*Åke Örtqvist, Jonas Hedlund,
Mats Kalin

Infektionskliniken, Danderyds Sjukhus,
S-182 88 Danderyd, Sweden

- 1 Örtqvist Å, Hedlund J, Grillner L, et al. Aetiology, outcome and prognostic factors in community-acquired pneumonia requiring hospitalization. *Eur Respir J* 1990; **3**: 1105–13.
- 2 Örtqvist Å, Julander I, Kalin M, Mufson M. Deaths in bacteremic pneumococcal pneumonia: a comparison of two populations - Huntington, USA, and Stockholm, Sweden. *Chest* 1993; **103**: 710–16.
- 3 Jalonen E, Paton JC, Koskela M, Kerttula Y, Leinonen M. Measurement of antibody responses to Pneumolysin: a promising method for the presumptive etiological diagnosis of pneumococcal pneumonia. *J Infect* 1989; **19**: 127–34.
- 4 Leinonen M, Syrjälä H, Jalonen E, Kujala P, Herva F. Demonstration of pneumolysin antibodies in circulating immunocomplexes - a new diagnostic method for pneumococcal pneumonia. *Serodiagn Immunother Infect Dis* 1990; **4**: 451–58.
- 5 Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991; **325**: 1453–60.

Prophylactic antibiotics before insertion of intrauterine devices

Sir—Terri Walsh and colleagues (April 4, p 1005)¹ conclude that prophylactic antibiotics before insertion of intrauterine devices does not reduce the risk of upper-genital-tract infection. We are concerned that this conclusion will be inappropriately generalised to settings where the prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoea* is substantial (>5%). Their conclusion needs to be qualified to refer to populations with a low prevalence of chlamydia and gonorrhoea.

The investigators note that the risk of pelvic infection with contemporary screening of prospective users of intrauterine devices is low, irrespective of antibiotic prophylaxis. Their conclusion is probably true in the USA, but is questionable in developing countries where the prevalence of chlamydia and gonorrhoea is substantially higher than in the California study sample and where services are over-burdened and screening with laboratory-based tests is rare.

In such settings, screening is commonly based on elicitation of risk factors and clinical examination, which

are poor predictors of chlamydia and gonorrhoea.²⁻⁴ Therefore, physicians' judgments about women's risk of pelvic infection may be inaccurate because the presence of cervical infections increases the risk of pelvic infection for women who use intrauterine devices.

*Christiana Coggins, Nancy L Sloan

Population Council, 1 Dag Hammarskjold Plaza, New York, NY 10017, USA
e-mail: pubinfo@popcouncil.org.
http://www.popcouncil.org

- Walsh T, Grimes D, Freziers R. Randomised controlled trial of prophylactic antibiotics before insertion of intrauterine devices. *Lancet* 1998; **351**: 1005-08.
- Mayaud PH, Grosskurth J, Chagalucha J. Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinic. *Bull World Health Organ* 1995; **73**: 621-30.
- Ronsmans C, Bulut A, Yolsal N, Agacfidan A, Filippi V. Clinical algorithms for the screening of Chlamydia trachomatis in Turkish women. *Gentourin Med* 1996; **72**: 182-86.
- Weinstock H, Bolan G, Kohn R, Balladares C. In: Back A, Oliva G. *Chlamydia trachomatis* infection in women: a need for universal screening in high prevalence populations: *Am J Epidemiol* 1992; **135**: 41-47.

Intrauterine devices in HIV-1-infected women

Sir—I welcome Samuel Sinei and colleagues' report (April 25, p 1238)¹ on the use of intrauterine devices (IUD). As pointed out in the accompanying commentary by D Hicks,² the device is highly effective in the prevention of pregnancy and does not have the undesirable side-effects of oral contraceptives. In almost 30 years' experience of inserting the various devices, I never had an expulsion nor a postinsertion infection. Indeed, insertion of an IUD is a surgical procedure that demands the same sterile preparation and aseptic techniques during insertion as is required during any surgery.³ Expulsion occurred with the earlier devices, and was related in part to the selection of the proper size for each woman. The introduction of the Cu-7 and similar devices obviated the need for this judgment, and expulsions were subsequently much less common.

The removal of these devices from the market in the USA, and their present unpopularity, are the result of greed by the trial lawyers and the resultant monetary awards by the courts. These events were totally without justification. The result has been that patients in the USA have been deprived of the most effective and

safest means of contraception for no logical reason. The disgraceful increase in the numbers of abortions speaks for itself.

Donald E Waite

117 Agate Way, Williamston, MI 48895, USA
(e-mail: waited@com.msu.edu)

- Sinei AK, Morrison CS, Sekadde-Kingondu C, Allen M, Konkonya D. Complications of use of intrauterine devices among HIV-1-infected women. *Lancet* 1998; **351**: 1238-41.
- Hicks DA. What risk of infection with IUD use? *Lancet* 1998; **351**: 1222-23.
- Waite DE. Underused IUDs offer safe, effective contraception. *JAOA* 1998; **1**: 15.

Oral melatonin in neurologically disabled children

Sir—Stephen Sheldon (April 25, p 1254)¹ reports that daily oral administration of 5 mg or 1 mg melatonin to children with multiple neurological deficits results in increased seizure frequency. In a misrepresentation of our animal studies,² he implies that we found an anticonvulsive action of melatonin in pinealectomised rats. On the contrary, we reported that the removal of the pineal gland, a major source of circulating melatonin, did not affect the latency or the severity of kainic acid-induced seizures in rats, but that it increased the extent of seizure of triggered brain damage.² In a separate study,³ we investigated the effect of administration of high-dose melatonin (10 mg per kg bodyweight) to naïve rats on kainic acid-induced behavioural response (a score that also included seizures) and brain damage.

As indicated by Sheldon, several animal studies suggest that melatonin possesses anticonvulsant action. Although we did not observe a clear anticonvulsive effect of melatonin but only a slight diminishing of a total kainic acid-triggered behavioural score, we noticed that even in animals with similar behavioural scores, melatonin was effective in reducing the extent of brain damage.³ Thus, we proposed that different mechanisms might be operative in mediating the anticonvulsive and the neuroprotective actions of melatonin. For example, the anticonvulsive effect might be mediated via the interaction of melatonin with the inhibitory γ -aminobutyric acid (GABA) neurotransmission.⁴ The neuroprotective effect might involve multiple mechanisms, such as the antioxidative action of melatonin, its action on gene expression, or both. Although the effect of melatonin on convulsions may differ between experimental animals

(anticonvulsive) and human beings (proconvulsive), it should be stressed that in Molina-Carballo and colleagues' study,⁵ long-term treatment with high-dose melatonin was used successfully in a 29-month-old child with epilepsy; this treatment effectively diminished seizures. Although the report by Sheldon should be considered seriously when melatonin is taken indiscriminately for the amelioration of sleep disorders, further studies are needed to clarify the role of this hormone in seizure and neurodegenerative disorders.

*Hari Manev, Tolga Uz

Department of Psychiatry, The Psychiatric Institute, University of Illinois, Chicago, IL 60612, USA

- Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998; **351**: 1254.
- Manev H, Uz T, Kharlamov A, Joo J-Y. Increased brain damage after stroke or excitotoxic seizures in melatonin-deficient rats. *FASEB J* 1996; **10**: 1546-51.
- Uz T, Kharlamov A, Joo J-Y, Franceschini D, Giusti P, Manev H. Kainate-induced DNA damage and p53 immunoreactivity in the rat hippocampus: protection with melatonin. *Croatian Med J* 1997; **38**: 205-11.
- Tenn CC, Niles LP. Mechanisms underlying the antidopaminergic effect of clonazepam and melatonin in striatum. *Neuropharmacology* 1997; **36**: 1659-63.
- Molina-Carballo A, Muinoz-Hoyos A, Reiter RJ, et al. Utility of high doses of melatonin as adjunctive anticonvulsant therapy in a child with severe myoclonic epilepsy: two years' experience. *J Pineal Res* 1997; **23**: 97-105.

Sir—Stephen Sheldon's¹ discovery that supraphysiological oral doses of melatonin can have proconvulsant effects in neurologically disabled children provides valuable additional evidence that such doses should be used with great caution, if at all.

The use of melatonin is not supported by the abundant data that would be required if melatonin were upregulated in the USA as a drug instead of as a dietary supplement. Sheldon observed this effect when patients received either 1.0 mg or 5.0 mg of the hormone; both doses are many times greater than those needed to raise blood melatonin concentrations to their normal nocturnal peaks (0.3 mg in adults,² less in children). These doses are also many times greater than those that we found could treat the insomnia of a paediatric neurogenetic disease, Angelman's syndrome (≤ 0.3 mg).³ Perhaps such physiological doses might also have promoted sleep without increasing seizure activity in Sheldon's patients.

*Richard J Wurtman, Irina I Zhdanova

*Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

- 1 Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998; **351**: 1254.
- 2 Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci* 1994; **91**: 1824–28.
- 3 Zhdanova IV, Wagstaff J, Wurtman RJ. Melatonin and sleep in Angelman syndrome children. American Sleep Disorders Association (APSS) Sleep Research Society, 10th Annual Meeting, Washington, 1996: 29 (abstr 58).

Author's reply

Sir—Hari Manev and Tolga Uz's comments are important. Melatonin seems to exert various effects on the brain and different mechanisms might be involved. Whether neuroprotective in experimental animals or pro-convulsant in human beings, melatonin in supraphysiological doses is widely available, minimally controlled, and used indiscriminately. The role of melatonin in the treatment of sleep-related disorders in both neurologically challenged and non-neurologically challenged individuals requires further investigation.

I appreciate the comments by Richard Wurtman and Irina Zhdanova about the use of supraphysiological doses of melatonin. Supraphysiological doses of melatonin are readily available in the USA and may be purchased as a dietary supplement without prescription. We agree that supplemental melatonin should be used with great caution, irrespective of dose, until more is known of its safety and efficacy.

We chose a 5 mg dose because use of 2–10 mg oral melatonin resulted in minimal side-effects in children.¹ After we identified this potential adverse reaction, we rechallenge with one-fifth the initial dose, with similar results. We do not know whether more physiological doses, as stated by Wurtman and Zhdanova, would have produced similar adverse reactions. What effect exogenously administered melatonin has on the electroencephalogram in children with or without neurologically disabling disorders is not known. Further efficacy and safety research is, indeed, needed.

Stephen H Sheldon

Sleep Medicine Center, Division of Pulmonary and Critical Care Medicine, Children's Memorial Hospital, 2300 Children's Plaza, Box 43, Chicago, IL 60614, USA

- 1 Jan J, Espanzel H, Appleton RE. The treatment of sleep disorders with melatonin. *Dev Med Child Neurol* 1994; **36**: 97–101.

Japanese encephalitis virus and poliomyelitis-like illness

Sir—Tom Solomon and co-workers (April 11, p 1094)¹ studied 22 children, aged 0.5–15 years, with acute flaccid paralysis in Vietnam. Serological, virological, and electrophysiological investigations point to anterior horn-cell involvement and Japanese encephalitis virus (JEV) infection episodes in 12 (55%) of afflicted children. The central-nervous-system involvement would be shown by magnetic-resonance imaging (MRI) of different regions of the brain and spinal cord.

MRI of the cervical spine in a 27-year-old man who developed acute flaccid paralysis 3 months after his 2-month-old infant was immunised with trivalent poliovirus vaccine, revealed smooth hyperintense bands;² both sagittal-spin proton-density weighted and T₂-weighted images revealed involvement of regions corresponding to the anatomical location of ventral horns.² Cerebrospinal fluid culture studies were positive for poliovirus type 3, with no isolations from stool cultures, and the serum antibody titres were normal.

Wakamoto and colleagues³ described how MRI revealed lesions in the dorsal region of the pons to the upper part of the thoracic cord in a 7-month-old infant with poliomyelitis-like syndrome; there were hypointense T-1 weighted lesions with bilateral horn involvement.

MRI studies in Vietnamese children with acute flaccid paralysis would help to detect the target neurons in brain and spinal cord that were likely to be affected by Japanese encephalitis virus or enteroviruses other than polioviruses. Such early detection could also guide the clinicians in offering interferon- α which can halt the clinical progression of poliomyelitis within 24 h.⁴ MRI-guided therapeutic intervention in episodes of acute flaccid paralysis could prevent long-term sequelae of damage to target neurons in brain and spinal cord.

An attenuated live vaccine for Japanese encephalitis virus, strain SA 14-14-2, has been produced in baby hamster kidney cells and was licensed in China during 1988. The safety of the vaccine with respect to rare events was reported in 1996.⁵ The disability and muscle wasting attributable to Japanese encephalitis virus should stimulate neurovirulence assays, in monkeys or transgenic mice reported to be sensitive to wild and attenuated polioviruses,

with attenuated vaccine SA 14-14-2, vector-expressed vaccines, and the field isolates associated with acute flaccid paralysis.

Subhash C Arya

Centre for Logistical Research and Innovation, M-122 (of part 2), Greater Kailash-II, New Delhi 110048, India.

- 1 Solomon T, Kneen R, Dung NM, et al. Poliomyelitis-like illness due to Japanese encephalitis virus. *Lancet* 1998; **351**: 1094–97.
- 2 Malzburg MS, Rogg M, Tate CA, Zayas V, Easton JD. Poliomyelitis: hyperintensity of the anterior horn cells on MR images of the spinal cord. *Am J Roentgenol* 1993; **161**: 863–65.
- 3 Wakamoto H, Morimoto T, Nagao H, Matsuda H. MRI in poliomyelitis-like syndrome. *Pediatr Radiol* 1992; **22**: 533–34.
- 4 Levin S. Interferon treatment of poliomyelitis. *J Infect Dis* 1985; **151**: 745–46.
- 5 Hennessy S, Zhengle L, Tsai TF, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA 14-14-2): a case-control study. *Lancet* 1996; **347**: 1583–86.

Opiates for sickle-cell crisis?

Sir—Felix Konotey-Ahulu (May 9, p 1438)¹ highlights the controversy surrounding the clinical management of sickle-cell disease. Population estimates indicate the disease is the second-most common inherited disorder in the UK with a prevalence of 0.23 per 1000 births (*cf* cystic fibrosis 0.41 per 1000 births, B Modell, personal communication);¹ in south-east London and other inner-city areas the birth prevalence reaches one in 300 births. Although there has been progress in the prevention of early deaths due to pneumococcal infection and other acute childhood complications, the morbidity and mortality among adults with sickle-cell disease remains high, with a reported median survival in homozygotes of 42 years in men and 48 years in women.² These stark facts underpin the need to evolve appropriate models of care for patients with this disorder in the UK. Although painful crises account for most hospital admissions, debate over the use and choice of analgesic drugs, though important, diverts attention from the wider need to base the clinical care of sickle-cell disease on relevant research-based evidence that addresses the optimum management of the protean manifestations of sickle-cell disease that contribute to its morbidity.

No large randomised controlled intervention study has been undertaken in the UK. A wide gap exists between our understanding of

the molecular basis of haemoglobin S polymerisation, the primary pathophysiological event that underlies sickle-cell disease, and treatment of its consequences. To harness emerging treatment modalities that include pharmacological induction of fetal haemoglobin, bone-marrow transplantation, and on the horizon, gene therapy, to the maximum benefit of patients a co-ordinated multi-disciplinary approach is needed. This approach could be achieved by adopting a model of comprehensive care that incorporates clinical and basic research, akin to that in North America³ and which was established in the UK over 20 years ago for haemophilia.⁴

*D M Layton, G J Mufti

Department of Haematological Medicine, King's College School of Medicine and Dentistry, London SE5 9PJ, UK

- 1 Konotey-Ahulu FID. Opiates for sickle-cell crisis? *Lancet* 1998; **351**: 1438.
- 2 Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med* 1994; **330**: 1639–44.
- 3 Vichinsky EP. Comprehensive care in sickle cell disease: its impact on morbidity and mortality. *Semin Hematol* 1991; **18**: 220–26.
- 4 Rizza CR, Spooner RJD. Development of a national database to provide information for the planning of care for patients with congenital blood coagulation defects. In: Rizza CR, Lowe GDO, eds. *Haemophilia and other inherited bleeding disorders*. Philadelphia: W B Saunders, 1997: 433–53.

Sir—How comforting to rediscover a time when all that was required in the way of evidence for one's assertions was "80 years of personal experience" attached to a string of unsubstantiated anecdotes, as described by Felix Konotey-Ahulu.¹ How stimulating for UK teams trying to develop effective sickle-pain care, in and out of hospital, that venerable sickle gurus are outdoing each other in therapeutic nihilism.

There is no evidence that sickle-cell patients in the UK are dying or requiring intensive care because of iatrogenic opiate overdose, nor is there evidence that "a cohort of drug addicts" with sickle-cell anaemia is being "created". Sickle pain is underestimated, disregarded, and undertreated by doctors; knowledge of this situation has emerged from the accounts of patients themselves² and from their carers.³ Sickle-cell patients are routinely stigmatised as aggressive and complaining addicts who do not deserve to be in hospital, usually in the patently racist terms Konotey-Ahulu so approvingly reports.

The nihilists must come clean: do they think the pain of sickle-cell crisis is trivial, ephemeral pain? Or do they

think that it is severe, sustained pain? If the latter, why should different analgesia be given than in cancer pain or post-operative pain for which morphine is the standard? What are the standards of postoperative and palliative pain relief in West Africa and Jamaica—should we be pressing hospital managers to import them?

Konotey-Ahulu should say what proportion of his experience has been with sickle-cell haemoglobinopathy and mild phenotype sickle-cell anaemia, disorders likely to have selectively survived to adulthood in West Africa (and probably Jamaica): these patients rarely need opiate analgesia in the UK. His lack of awareness of bias becomes comical in the case of tax-paying patients; has it not occurred to him that patients seen in the private sector are unlikely to be on Disability Living Allowance?

The paternalist model of sickle-pain care in which patients are forced to settle for transient attention, feeble analgesia, and limitless exhortation, is no longer acceptable to UK patients and clinicians.

David H Bevan

Department of Haematology, St George's Hospital, Medical School, London SW17 0RE, UK

- 1 Konotey-Ahulu FID. Opiates for sickle-cell crisis. *Lancet* 1998; **351**: 1438.
- 2 Black J, Laws S. Pain relief and staff attitudes in hospital. In: *Living with sickle cell disease*. London: Sickle Cell Society, 1986: 112–31.
- 3 Alleyne J, Thomas VJ. The management of sickle crisis pain as experienced by patients and their carers. *J Adv Nurs* 1994; **19**: 725–32.

Sir—I was disheartened by Felix Konotey-Ahulu's suggestion¹ that we allow patients with sickle-cell crisis to suffer pain rather than administer opioids, which was not supported by strong data. His point that a haematologist who refuses to administer opioids has an office of patients who are "fully employed, pay their taxes, do not claim disability allowance" may reflect the mind set that no person with severe sickle-cell pain crisis would stay with a haematologist who withholds opioids when pain is present.

I am also surprised that Konotey-Ahulu's "combined experience of 80 years covering thousands of patients in sickle-cell crisis", he has not undertaken an objective analysis of opioids versus non-opioids for pain crisis, or the use of oral opioids for pain crisis in an outpatient basis.^{2,3} Given the poor job that health-care professionals do in the management of pain, it would

be useful to have data that support withholding opioids when other analgesics are ineffective. Of course, close monitoring of patients in pain and the more diligent use of pain-assessment tools are worthwhile in any pain situation.

F Michael Gloth III

Department of Medicine, Johns Hopkins University School of Medicine, Union Memorial Hospital, Baltimore MD 21218, USA

- 1 Konotey-Ahulu FID. Opiates for sickle-cell crisis. *Lancet* 1998; **351**: 1438.
- 2 Report of a Meeting of Physicians and Scientists, University of Texas Health Science Center at Houston, Texas. Management of sickle cell anemia pain crisis. *Lancet* 1995; **346**: 1408–11.
- 3 Jacobson SJ, Kopecky EA, Joshi P, Babul N. Oral morphine for painful crisis in sickle cell disease. *Lancet* 1997; **350**: 1358–61.

Catechol-O-methyltransferase inhibitors in Parkinson's disease

Sir—In his April 25 commentary,¹ John Nutt describes a low incidence of side-effects, mainly related to increased dyskinesic movements, with catechol-O-methyltransferase (COMT) inhibitors in Parkinson's disease. By contrast, we found that some patients develop confusion with this treatment which reversed after withdrawal of tolcapone (Tasmar).

The first patient was a 79-year-old man with severe idiopathic Parkinson's disease (IPD) of 18 years' duration. He was admitted with worsening of his IPD, mainly due to episodes of his IPD, freezing. His antiparkinsonian drug regime was Sinamet Plus one tablet five times daily, and Sinamet CR 125 one tablet at night. Tolcapone was added at a dose of 100 mg three times daily and, within 24 h, he became significantly confused. He remained confused for 3 days until tolcapone was stopped. His confusion then resolved within 24 h.

An 87-year-old woman with severe IPD of 10 years' duration received tolcapone 100 mg three times daily together with her antiparkinsonian drug regimen of Madopar CR 125 four times a day in order to control her disease fluctuations. The following day she became significantly confused; this confusion resolved within 24 h of stopping tolcapone 3 days later.

Our final patient was a 68-year-old woman with severe IPD of 11 years' duration. She was admitted with worsening freezing episodes and a consequent increase in falls. She was noted to be mainly off in the early

afternoon and early evening. Tolcapone 100 mg was added at midday to her existing regimen: Sinamet Plus one tablet at 0800, two tablets at 1200, one tablet at 1600, and two tablets at 2000, with selegiline 10 mg mane. Within 24 h she was significantly more confused. Again, this confusion resolved within 24 h of discontinuation of tolcapone 6 days later.

Tolcapone represents a major breakthrough in the treatment of IPD: it reduces daily levodopa intake, increases on time, decreases off time, and has reported benefits for sleep, mood, and energy.^{2,3} As a result, the drug is likely to become extensively prescribed. Tolcapone also has a favourable profile in stable Parkinson's disease.² Kurth and colleagues³ found that tolcapone's side-effects mainly related to dopaminergic activity in patients with motor fluctuations.³ As remarked in one study, adverse reactions may be a result of potentiation of levodopa effects or the action of COMT inhibitors.⁴ Our cases, however, suggest that tolcapone can cause confusion in frail patients with severe Parkinson's disease.

The recommended starting dose of tolcapone is 100 mg three times daily which can be increased to 200 mg three times daily for a further small increase in levodopa effects. Perhaps in some frail patients with severe disease an initial dose of 100 mg daily would be acceptable. The timing of drug administration in this situation should correspond to the time of the maximum off periods. A single dose of tolcapone at night could also be used to potentiate continuous-release combined levodopa dose preparations in the treatment of early morning akinesia.

*Colm Henry, J A Wilson

Department of Medicine of the Elderly,
St John's Hospital at Howden, Livingston
EH54 6PP, UK
(e-mail: colm.henry@mcmill.com)

Sir—John Nutt¹ reviews the use of catechol-O-methyltransferase inhibitors (COMT-I) as an adjunct therapy for motor fluctuations in Parkinson's disease (PD). However, COMT-I have a potential antidepressant effect that would have benefits in PD. Anecdotal observations suggest that patients feel more energetic and livelier after the administration of COMT-I. Although this effect could be due to an improvement in the control of PD through its levodopa-sparing effect, it is likely to reflect a direct antidepressant effect of COMT-I.

Depression is thought to be related to a deficiency of catecholamine, especially norepinephrine,² and is also linked to decreased concentration of S-adenosyl-L-methionine (SAM) in cerebrospinal fluid.³ Oral or intravenous SAM crosses the blood-brain barrier and was reported to alleviate depression.⁴ COMT-I metabolises a range of catechols, including dopamine and norepinephrine, by the transfer of a methyl group from SAM to the hydroxyl moiety of catechols. The use of central COMT-I, such as tolcapone, would decrease the catabolism of norepinephrine and consumption of SAM; this action will increase concentrations of norepinephrine and SAM which will ameliorate depression.

Depression is frequently ignored and undiagnosed in PD because it is masked by the motor impairment and facial immobility. No psychometric tests for depression have been used in clinical trials of COMT-I on PD, which have mainly focused on the improvement of motor function and activities of daily living. So far, the evidence for the antidepressant effect has been indirect. We advocate prospective controlled studies to study the antidepressant effects of COMT-I.

Tao Xie, Shu-Leong Ho, *David Ramsden

University Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China; and *Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Birmingham B15 2TH, UK

- 1 Nutt JG. Catechol-O-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet* 1998; **351**: 1221–22.
- 2 Waters CH, Kurth MC, Bailey PA, et al. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. *Neurology* 1998; **49**: 665–71.
- 3 Kurth MC, Adler CH, St Hilaire M, et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomised, placebo-controlled trial. *Neurology* 1997; **48**: 81–87.
- 4 Jorga KM, Sedek G, Fotteler B, et al. Optimizing levodopa pharmacokinetics with multiple tolcapone doses in the elderly. *Clin Pharmacol Ther* 1997; **62**: 300–10.

MERLIN and malaria epidemic in north-east Kenya

Sir—El Niño recently caused the worst flooding in the Wajir district of north-east Kenya for over 50 years with virtually uninterrupted rainfall between the end of September, 1997, and the end of January, 1998. Roads to the region were cut off and only limited air links remained. Supplies of food and medicines were badly interrupted and water supplies were affected since wells collapsed or became contaminated. Even after the rains stopped, large areas of land remained underwater for weeks. High mortality rates were reported in this region in February caused by an outbreak of Rift Valley Fever (RVF).¹

Most of the district's 190 000 population are nomadic pastoralists, the average population density being about two people per km. Settlements and towns are located along the few existing roads in the district. The district capital of Wajir has a population of 20 000–30 000. The region has suffered from a 2-year drought, immediately before the rains, which caused widespread malnutrition. Flooding displaced both the human population and its livestock into higher ground where over-grazing and diseases led to substantial livestock losses. With apparently high rates of human mortality in Wajir town and surrounding villages, OXFAM, who were running a large-scale nutritional programme in Wajir, invited MERLIN to assess the medical situation in the region.

MERLIN sent an emergency medical assessment team to Wajir on Feb 10, 1998. The team discovered that the main cause of mortality and morbidity in the region was malaria, not RVF. At that time Wajir town hospital had 88 inpatients, 80% of the inpatients had malaria (57% mild, 28% severe, and 17% cerebral) and an average of 12 deaths daily were reported by hospital authorities. During four days the confirmed minimum mortality rate was ten deaths per 10 000 per day, double the WHO defined catastrophe levels. Three district health facilities reported up to six-fold increases in the number of cases of malaria compared with the same period in 1997. Data from one dispensary (El Das) showed that the numbers of cases of malaria (plus respiratory tract [RTI] and to lesser extent gastrointestinal infections) had risen dramatically with the advent of the rains. Interruption of travel and

- 1 Nutt JG. Catechol-O-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet* 1998; **351**: 1221–22.
- 2 Cooper JR, Bloom FE, Roth RH. The biochemical basis of neuropharmacology. New York: Oxford University Press, 1982.
- 3 Bottiglieri T, Godfrey P, Flynn T, Carney MWP, Toone BK, Reynolds EH. Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. *J Neurol Neurosurg Psychiatry* 1990; **53**: 1096–98.
- 4 Bell KM, Plon L, Bunney WE, Potkin SG. S-adenosylmethionine treatment of depression: a controlled clinical trial. *Am J Psychiatry* 1988; **145**: 1110–14.

temporary closure of the clinics due to flooding probably caused the apparent fall in the number of cases of malaria and RTI in October and November, 1997.

A protracted strike by nurses (which officially ended in January, 1998) left the district with below 30% of the health staff in place at the time of the assessment and severely reduced the ability of the local health services to respond to the crisis. The health facilities in Wajir were barely able to cope with the massive influx of patients. Outpatient monthly attendance at El-Das dispensary increased from 350 in October, 1997, to over 800 in January, 1998.

MERLIN responded immediately, sending emergency medical staff to Wajir on Feb 15 to join the initial assessment team. Working closely with OXFAM and the local-health-authority teams of MERLIN, expatriate and local staff were formed to implement a programme of malaria treatment and control for Wajir district. Logistical supplies and vehicles were brought into Wajir and four mobile clinics were established to reach the most vulnerable communities throughout Wajir district. Between March 6 and April 12, 11 774 patients were treated by the mobile clinics. An impregnated bed net programme has been started to protect 80 000 people, mainly young children and pregnant women. These mobile clinics have been collecting morbidity and mortality data. Between 70% and 98% of the patients seen in communities throughout the district have clinical malaria with fever. Microscopic examination of blood films has confirmed that malaria cases are caused by *Plasmodium falciparum*.

This malaria outbreak is one of the most severe ever recorded in East Africa and has been compounded by widespread food shortages. The high incidence of cerebral malaria has given cause for concern among this low-immune-status population. Although there have been a few confirmed cases of RVF in neighbouring areas to Wajir district, the numbers are small and the extensive publicity given to this disease has obscured the real cause of illness and death in this population of north-east Kenya.

*Richard Allan, Sara Nam, Linda Doull
MERLIN, 14 David Mews, London W1M 1HW,
UK

- 1 WHO. Rift Valley Fever: East Africa 1997-98. Haemorrhagic Fever Task Force. World Health Organisation, Geneva, Switzerland. International Conference on Emerging Infectious Diseases, 6 (abstr).

Antiepileptic drugs in developing countries

Sir—Edwin Trevathan and co-workers (April 18, p 1210)¹ highlight the difficulties with antiepileptic and, indeed, all drug use in developing countries. However, their assertion that the question of best antiepileptic therapy should be addressed before the development of distribution programmes and their belief that “the epilepsy and public-health communities can do better than phenobarbitone or phenytoin for the world’s 34 million people with epilepsy who live in the developing world” is misconceived.

Trevathan and colleagues focus on only a narrow medical viewpoint in their letter and ignore the wider context in which drugs are prescribed in developing countries. Rational and effective use of drugs is limited by weak health-care structures, inadequate financial resources, unreliable supply and quality of pharmaceuticals, lack of drug legislation and policy, and the high rate of inappropriate self-medication.² Even a historical review of mortality rates in the UK shows that the introduction of effective drugs such as antituberculous agents or antibiotics had a negligible effect on overall mortality rates in the first half of this century. Non-medical factors are regarded to have been far more important. The WHO Action Programme on Essential Drugs in developing countries highlighted the lack of basic infrastructure, poor management and co-ordination, inadequately trained personnel, and poor allocation of financial resources as obstacles to the provision of essential drugs.³

The clinical case for the use of phenobarbitone or phenytoin for epilepsy in developing countries is strong. Comparative trials show that efficacy and side-effects are similar to carbamazepine in these settings.^{4,5} The practical case for their use is even stronger. Carbamazepine and valproate are 15–30 times the acquisition cost of phenobarbitone, and the new-generation drugs (lamotrigine) are over 100 times more expensive. Improved purchasing strategies by governments could reduce this differential slightly, but are unlikely to reduce the high opportunity cost of devoting a large proportion of scarce resources to antiepileptic drugs with speculative but unproven small benefits over established therapies.

In developing countries there are many other priorities for health services. Formal economic evaluation

of such therapies is essential to account for financial savings that might accrue from the avoidance of short-term and long-term side-effects and differences in tolerability that may exist for these drugs. Together with the results from clinical trials, the results of economic evaluation will enable those who provide care in developing countries to prioritise rationally.

*Dominic Heaney, Josemir W A S Sander

Epilepsy Research Group, National Hospital for Neurology and Neurosurgery, London WC1N 3BG, UK
(e-mail: dheaney@ion.ucl.ac.uk)

- 1 Trevathan E, Medina MT, Madrid A. Antiepileptic drugs in developing countries. *Lancet* 1998; **351**: 1210–11.
- 2 Bapna JS, Tripathi CD, Tekur U. Drug utilisation patterns in the third world. *Pharmacoeconomics* 1996; **9**: 286–94.
- 3 WHO. Action Programme on Essential Drugs in the South-East Asia Region. New Delhi: WHO South East Asia, 1991.
- 4 Feksi AT, Kaamugisha J, Sander JWAS, Gatiti S, Shorvon SD. Comprehensive primary health care antiepileptic drug treatment programme in rural and semi-urban Kenya. *Lancet* 1991; **337**: 406–09.
- 5 Placencia M, Sander JWAS, Shorvon SD. Anti-epileptic drug treatment in a community health care setting in northern Ecuador: a prospective 12 month assessment. *Epilepsy Res* 1993; **14**: 237–44.

The RAGE litigation

Sir—In 1991, women who had experienced difficulties after radiotherapy for breast cancer came together and formed an organisation called RAGE (Radiation Action Group Exposure). In December, 1994, Russell, Jones, and Walker referring to cases treated in 40 hospitals, successfully applied to the Legal Aid Board for funds to undertake research towards a group action. In March, 1995, the plaintiffs were permitted to select ten cases that might show what they believed to be the generic (common) issues. A “stay” was placed over the processing of the remaining 117 cases.

The defence, led after Sept, 1995, by SM, with CAFJ and SD as expert advisers, came to the view that all ten patients had sustained morbidity due to treatment and that this was severe in eight of the women. Two of the women had been treated in a manner deemed indefensible—both were subsequently settled out of court. In the remaining eight women, the morbidity was judged not to have occurred as a result of negligence.

In May, 1996, a Statement of Claim served by Russell, Jones, and Walker

set out nine generic issues and detailed the individual cases. However, in July and again in August, 1997, the plaintiffs submitted modifications—finally the only generic issue which remained related to radiation dose. The defence fully responded to each.

At the hearing, postponed to Dec 8, 1997, Mrs Justice Ebsworth learnt that the whole generic case had been abandoned—costs were given to the defence. Five of the remaining lead cases had also been withdrawn. On Jan 12, 1998, there were three cases to be tried but in one, in which there was a minor problem in the breast but a major one in the axilla, an offer to settle on the minor issue was accepted.

Despite abandonment of the generic case, most of the 21 days of the hearing focused on the dose and fractionation of radiotherapy, especially aspects of radiotherapy and radiobiology. There was detailed scrutiny of published material; some papers of landmark importance were shown to contain discrepancies and to be imprecise in defining relations between radiation dose and the incidence of morbidity.

Mrs Justice Ebsworth handed down her judgment on May 8, 1998, concerning the remaining two cases, treated in 1980, and concluded that there was no negligence. Costs were given against the plaintiffs.

Generic cases usually involve the use of a drug or appliance but here, uniquely, an attempt was made to use a generic approach to the care of many patients treated in most hospitals within one country that give radiotherapy. The failure by the plaintiffs' team of lawyers and experts to bring a generic case to court may discourage others who, in the future, may consider litigation in similar circumstances.

Although those who acted for RAGE failed in their objective, Russell, Jones, and Walker, have expressed a determination to proceed with further cases. The costs of the litigation, we believe, may have already exceeded £4 million, and whether this route should be followed further should be questioned. Mrs Justice Ebsworth regarded it as unfortunate that litigation in terms of medical negligence was felt to be the only mechanism available to patients with serious and unexpected injury who wanted to understand why and how such injury occurred.

*S Dische, C A F Joslin, S Miller

Marie Curie Research Wing, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, UK; Cookridge Hospital, Leeds; and 1 Crown Office Row, Temple, London

Scaling prison walls

Sir—In her April 4 commentary, Kim Marie Thorburn¹ argues that physicians must take a more active role to ensure that the health and rights of incarcerated individuals are protected. On the basis of our experience of treating HIV-1-positive prisoners in the state of Rhode Island, we have found that noticeable cultural changes occur when medical “outsiders” from the community scale prison walls and work within the correctional setting.

During the past 6 years, the Brown University AIDS Program has sent medical students, resident physicians, nurses, researchers, and clinical and research faculty into the state prison.² The Rhode Island Department of Corrections has become an expanding site for care, research, and teaching, and medical students interact with prisoners, correctional officers, and prison nurses. Researchers coordinate projects with wardens, and joint conferences for prison staff and physicians are held. Documentaries involving prisoners, staff, and community physicians have also been filmed.³ We have found that professionals from the medical community provide an excellent link to the postrelease health care, drug counselling, service housing, and employment training necessary to integrate prisoners back into their communities.

Since the inception of formal community health and referral programmes for prisoners, we have documented a decrease in recidivism and high-risk HIV-1 behaviour, and an increase in postrelease medical follow-up.⁴ With infectious disease specialists working in the prison, the state's mandatory HIV-1 testing programme now has tangible health benefits for prisoners who test HIV-1 positive. We routinely identify inmates with acute HIV-1 infection and start immediate treatment.⁵ Over the years, we have witnessed an increasing recognition by prison personnel of the medical and personal needs of the HIV-1 positive inmates.

This type of sustained work by health professionals backed by the resources of academic medical centres helps bridge the gap between correctional and community values. The mere presence of community outsiders has engendered some change. Prisons can be similar to other organisations in having an institutional tunnel vision which can usually only be altered by the presence of non-members. We strongly encourage other academic, medical, and community-based organisations to strengthen links to the correctional

community and to initiate programmes for incarcerated individuals behind the prison walls. Such efforts would not only benefit individual prisoners but begin to transform prison culture.

*A Feller, B Dickinson, J Mitty, A Spaulding, T Flanigan

*Miriam Hospital, Brown University School of Medicine, Providence, RI 02906, USA; and Medical Program, Rhode Island Department of Corrections, Cranston

- 1 Thorburn KM. Conditions in prisons. *Lancet* 1998; **351**: 1003–04.
- 2 Dixon PS, Flanigan TP, Debuono B, et al. Infection with the human immunodeficiency virus in prisoners: meeting the health care challenge. *Am J Med* 1993; **95**: 629–35.
- 3 Schiffman JD, Ribaldo SE, Spaulding AC, et al. An HIV prevention and treatment video program for incarcerated women by incarcerated women. Twelfth World AIDS Conference, Geneva, Switzerland, June, 1998 (abstr).
- 4 Flanigan TP, Kim JY, Zierler S, et al. A prison release program for HIV-positive women: linking them to health services and community follow-up. *Am J Public Health* 1996; **86**: 886–87.
- 5 Rich JD, Dickinson BP, Lafazia L, et al. Interpretation of indeterminate HIV-1 serology results in an incarcerated population. *J AIDS* 1998; **17**: 376–79.

DEPARTMENT OF ERROR

A woman with nodules in her lungs—In this case report by H Järveläinen and colleagues (Feb 14, p 494), the figures were transposed: the lower figure should have been the upper figure. The figure legend was correct.

Leprosy beyond the year 2000—In this letter by C K Rao (March 7, p 756), the last sentence should have read . . . “and the prevalence rate of seven cases per 10 000 in 1997 should be viewed in the light of the premultidrug therapy prevalence rate of 250 per 10 000 population . . .”.

Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease—In this article by P L Paggiaro and colleagues (Mar 14, p 773) in table 2, the values for mean (SD) bronchodilator reversibility in predicted FEV₁ (%) should have been 4.0 (3.9) and 4.0 (4.0).

Leptin in human plasma is derived in part from the brain, and cleared by the kidneys—In this research letter by Murray Esler and colleagues (March 21, p 879), the authors' affiliations were left out. They are:

Baker Medical Research Institute, Commercial Road, Prahran 3181, Melbourne, Australia (M Esler); School of Nutrition and Public Health, Deakin University, Geelong, Australia; and Department of Kinesiology, University of Colorado at Boulder, Boulder, USA.

Critical ethical issues in clinical trials with xenotransplants—In this article by Professor Harold Y Vanderpool (May 2, p 1347), lines 15 to 20 in the first column of p 1348 should have read, “Most of the brief discussions of risk-benefit thresholds surface in articles focusing on the ‘scientific base’ of xenotransplantation. The authors of these articles are sometimes unaware of the ethical underpinnings of a subject they view primarily in scientific and logistical terms”.