

# CORRESPONDENCE

## Screening for congenital dislocation of the hip

Sir—Sara Godward and Carol Dezateux (April 18, p 1149)<sup>1</sup> report on surgery for congenital dislocation of the hip in the UK (1993–94) as a measure of the outcome of screening. Their study is based on only those cases treated by orthopaedic surgeons. They conclude that “in most children congenital dislocation of the hip had not been detected by screening or surveillance before age 3 months” and that “the incidence of first operative procedure for congenital dislocation of the hip in our study similar to that of established dislocation reported in the UK before screening was introduced”. They end with the claim that, “Formal evaluation of current and alternative screening policies, including universal primary ultrasound imaging, is needed”. A review of this report in the *BMJ* had the title “Screening babies for hip dislocation is not effective”.<sup>2</sup>

I believe these statements are unjustified on the basis of the data provided and are seriously misleading. I refer to: the complete absence of data on cases treated by paediatricians without reference to the orthopaedic team; to the few data on age-at-diagnosis (essential to interpretation because prevalence and the need for surgery are age-related); and to the way in which, numerically, minor surgical procedures such as diagnostic arthrograms, the application of plaster casts, and adductor tenotomies (80–90% of all the reported surgical cases) are given the same weight in the final count as is major surgery of the hip or pelvis. Our study in the 1970s showed that 97% of cases of congenital dislocation of the hip were not seen by an orthopaedic surgeon.<sup>3</sup> Of the 3% of cases referred to an orthopaedic surgeon, a third had been diagnosed at birth and required only minor procedures; major surgery was confined to 1.4% of the total series, all diagnosed after age 6 months.

Many studies in the past 40 years have shown that clinical screening for this disorder is effective, provided that the examiners are well-trained and supervised. Unfortunately, this proviso is frequently not met—the screening is left to the most inexperienced members of the team. Thus, a large

number of cases are missed and come to surgery. But this situation is, of course, a failure of organisation and training and not of the process and method of screening as recommended by the Standing Advisory Committee Working Party in 1986.<sup>4</sup> Although early diagnosis and treatment involves light splinting of many infants that might have recovered spontaneously, it is a small price to pay for avoiding the risk of later surgery and possible life-long disability.

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- 1 Godward S, Dezateux C, on behalf of the MRC Working Party on Congenital Dislocation of the Hip. Surgery for congenital dislocation of the hip in the UK as a measure of outcome of screening. *Lancet* 1998; **351**: 1149–52.
- 2 McKee L. Screening babies for hip dislocation is not effective. *BMJ* 1998; **316**: 1265.
- 3 Dunn PM, Evans RE, Thearle MJ, Griffiths HED, Witherow PJ. Congenital dislocation of the hip: early and late diagnosis and management compared. *Arch Dis Child* 1985; **60**: 407–14.
- 4 Standing Medical Advisory Committee and Standing Nursing and Midwifery Advisory Committee. Screening for the detection of congenital dislocation of the hip. London: Department of Health and Social Security, 1986.

### Authors' reply

Sir—Peter Dunn notes that “a large number of cases are missed and come to surgery”. This comment concurs with our conclusion that “a substantial proportion of children with congenital dislocation of the hip were not detected by screening or routine surveillance before age 3 months”. This statement is neither unjustified nor misleading and is based on the finding that 70% of children requiring at least one operative procedure for congenital dislocation of the hip had not been identified through screening. Whether these cases occur as a result of poor test performance or a good test poorly performed cannot be assessed from an observational study.

There are, as Dunn suggests, other outcomes of screening. The number of

children treated non-surgically with abduction splinting by paediatricians (or, increasingly, by orthopaedic surgeons<sup>1</sup>) provides a combined estimate of the true positives and false positives of the screening programme. However, to identify which of these children pay the “small price” of unnecessary abduction splinting is, as Dunn recognises, not possible since we lack a confirmatory diagnostic test, relevant natural history data, and evidence of treatment effectiveness from randomised trials. Paediatricians need no reminding of instances in clinical practice where small prices have turned into large costs that might have been apparent earlier had the interventions been assessed prospectively in randomised trials.<sup>2</sup>

Next year marks the 30th anniversary of the introduction of a clinical screening programme for congenital dislocation of the hip in the UK,<sup>3</sup> with its implicit challenge to reflect on ways to improve the existing limited evidence base for current and alternative screening policies for the disorder.

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- 1 Dezateux C, Godward S. A national survey of screening for congenital dislocation of the hip. *Arch Dis Child* 1996; **74**: 445–48.
- 2 Silverman WA. *Retrolental fibroplasia: a modern parable*. New York: Grune and Stratton, 1980.
- 3 Standing Medical Advisory Committee. Screening for the detection of congenital dislocation of the hip in infants. London: Department of Health and Social Security, 1969.

Sir—I congratulate Sara Godward and Carol Dezateux<sup>1</sup> for describing what many have long feared to be the case. The so-called successful treatment of babies with clicking hips has not translated into a reduction in the number who need orthopaedic procedures later on. The investigators avoid jumping to the erroneous conclusion that screeners must be to blame for “missing” cases, or for “failing” in the treatment given, and instead suggest that the optimistic hopes of the 1950s and 1960s require for their fulfilment a clairvoyance and

an early treatment bullet that are unattainable with current knowledge and techniques.

Your talking point on this paper and the news item in the *BMJ*<sup>2</sup> conclude that alternative screening policies must be evaluated, yet Dezateux and Godward point out that ultrasound screening in other European countries seems to lead to 40 times as many babies being treated as could possibly be destined to have hip disorders.

When bedrest after myocardial infarction turned out to be damaging, did we conclude that safer beds had to be assessed? When episiotomy in normal vaginal delivery turned out to be of no value, did we call for a new design of scissors, or a computer-assisted technique for deciding when and where to make the cut? Would the sky fall down if we explained to parents that the best we can do is to diagnose and treat infants if and when hip disorders become apparent.

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- 1 Godward S, Dezateux C, on behalf of the MRC Working Party on Congenital Dislocation of the Hip. Surgery for congenital dislocation of the hip in the UK as a measure of outcome of screening. *Lancet* 1998; **351**: 1149–52.
- 2 McKee L. Screening babies for hip dislocation is not effective. *BMJ* 1998; **316**: 1265.

## Prevalence of hay fever and consumption of margarine in East Germany

Sir—Erika von Mutius and colleagues (March 21, p 862)<sup>1</sup> describe in their report of an increasing prevalence of hay fever and atopy among children in Leipzig, in former East Germany, a possible relation between the rise in hay fever and atopic symptoms and increased consumption of margarine in that country.

The frequency of asthma and allergies was examined in two cross-sectional studies with schoolchildren in Leipzig in 1991–92 and 1995–96. In both studies, the children were investigated with a skinprick test, and a self-administered questionnaire was distributed to the parents. However, true consumption of margarine by children was not measured.

The actual sale of margarine in 1991–92 and 1995–96 (GfK Panel Services, Gesellschaft für Konsumforschung, Nürnberg, Germany) does not support the relation between the prevalence of atopic disorders and the

increased consumption of margarine because less margarine was consumed in 1995–96 than in 1991–92. Furthermore, an obvious increase in the consumption of low-fat margarine containing by definition 50% less linoleic acid was recorded. Thus, the intake of vegetable fat fell in this period.

Therefore a connection cannot be made between the changes in consumption of margarine and the prevalence of hay fever in East Germany.

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#### Authors' reply

Sir—Ingo Witte, from the Margarine Institute for Healthy Diet, argues against a potential role for the consumption of margarine for the development of hay fever and atopy in East-German children by referring to decreasing sales of margarine in Germany in recent years (according to the National Bureau of Statistics, Berlin, Germany, by about 10% between 1991 and 1996 in eastern Germany). The GfK Panel Services started to collect data on the purchase of food per household in Eastern Germany only about 3 years after the fall of the Berlin wall in 1989, after which most western food products became rapidly available in East Germany. No information on fat consumption in former East Germany (GDR) can be obtained from this source.

Other reports investigating earlier periods<sup>1,2</sup> suggest a striking increase in the consumption of margarine since 1989. For example, the results of repeated dietary surveys in random samples of adults in Erfurt, East Germany, in 1987–88 and 1991–92 show a significant increase in the mean daily intake of margarine (6 vs 40 g,  $p=0.0001$  in men; 5 vs 22 g,  $p=0.0001$  in women) and a concomitant significant reduction in the intake of butter (40 vs 17 g,  $p=0.0001$  in men; 26 vs 13 g,  $p=0.0001$  in women), as assessed by 3-day weighted dietary records. However, the interpretation of trends in consumption at the population level is of limited value for causal inference because of its potential for bias, known as ecological fallacy. Thus, the assessment of dietary intake on an individual level is clearly preferable.<sup>3</sup>

In our study, we asked parents about changes in the consumption of 22 different food items before and after unification of East and West Germany. Only changes in the intake of margarine and butter were significantly associated with hay fever or atopic sensitisation. This explorative approach has obvious limitations, which we acknowledge in the discussion of our findings. However, we feel that the hypothesis linking the intake of certain polyunsaturated fatty acids, such as linoleic or linolenic acid, to the development of childhood atopy deserves further investigation because of its biological plausibility<sup>4</sup> and supportive evidence from other studies.<sup>5</sup>

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- 1 Winkler G, Brasche S, Heinrich J. Trends in food intake in adults from the city of Erfurt before and after the German reunification. *Ann Nutr Metab* 1997; **41**: 283–90.
- 2 Jaross W, Bergmann S, Wahrburg U, Schulte H, Assmann G, DRECAN Team. Dietary habits in Eastern Germany; changes after unification and their relation to CHD risk profiles (DRECAN). *Rev Environ Health* 1996; **11**: 27–32.
- 3 Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven, 1998.
- 4 Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997; **10**: 6–12.
- 5 Hodge L, Salome CM, Peat JK, Haby MM, Xuan W, Woolcock AJ. Consumption of oily fish and childhood asthma risk. *Med J Aust* 1996; **164**: 137–40.

## Prevalence of tuberous sclerosis in UK

Sir—Finbar O'Callaghan and co-workers (May 16, p 1490)<sup>1</sup> estimate the prevalence of tuberous sclerosis in Wessex, UK, at 8 per 100 000 people. Their range of prevalence rates, from 0.7 per 100 000 people in Northern Ireland to 3.8 per 100 000 people in Wessex, is misleading. The Northern Ireland prevalence figure reported by Stevenson in 1956, was a gross underascertainment. Such studies relied on ascertainment of genetic disorders with the complete phenotype at a time when understanding of the disease genetics and clinical features was limited. Similar estimates for Huntington's disease in Northern Ireland, also by Stevenson, in 1957,<sup>2</sup> give a prevalence figure of 8 per million people, almost ten times

smaller than the current accurate figure.<sup>3</sup> This figure is similar to historical estimates in South Wales in 1937,<sup>4</sup> which were also out by a factor of ten. When the same rule of thumb is applied to the Northern Ireland figure, a current prevalence of 7 per 100 000 people, close to the 8 per 100 000 people figure projected for Wessex, is derived.

The correct way to calculate prevalence in autosomal dominant diseases is to carry out a thorough survey, maximise contact with clinicians, family doctors, patients' support groups, and other health professionals, concentrate on case ascertainment from multiple sources with careful secondary tracing, and, finally, leave the survey for 5–10 years and then repeat it again.

O'Callaghan and colleagues also mention that "many people with tuberous sclerosis do not receive either genetic counselling or specialist medical supervision". This situation reduces ascertainment and does not allow secondary tracing in the proportion of families without new mutations. Our surveys of Huntington's disease in two similar populations with and without a genetics service showed that the population without the service had less than 50% of the prevalence found in the area with the service.<sup>3,5</sup>

One of the functions of a genetics service is data gathering, and repetition of the Wessex survey in the future after careful family tracing, improvements in molecular genetic diagnosis within families, and prospective record-keeping through combined multi-disciplinary tuberous sclerosis clinics, such as our own, will increase the minimum prevalence, since there are currently no complete prevalence figures for this disorder.

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- O'Callaghan FJK, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. *Lancet* 1998; **351**: 1490.
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### Authors' reply

Sir—The prevalence rates we quoted represent the range of published prevalence estimates for tuberous sclerosis in the UK. We agree that Stevenson's figure for Northern Ireland is likely to be a gross under ascertainment. Indeed, our study suggests that the figure produced by the Wessex study (the highest prevalence rate published for the UK) is also a substantial underestimate.

The methods used by Webb and colleagues<sup>1</sup> in the Wessex survey were similar to what Patrick Morrison and colleagues call the correct method of ascertaining prevalence. But our capture-recapture analysis showed that this survey, which used up-to-date diagnostic criteria, maximised contact with clinicians and the relevant patients' support group, used multiple sources, and adopted careful secondary tracing, probably still missed more than 50% of cases.

One conclusion to be drawn from this analysis is that traditional methods of ascertaining prevalence, however rigorously applied, fail to identify all cases. Capture-recapture methods are useful to verify estimates produced by traditional prevalence studies. It would be interesting to do a similar analysis on the most up-to-date prevalence estimates for Huntington's disease in Northern Ireland.

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- Webb DW, Fryer AE, Osborne JP. Morbidity associated with tuberous sclerosis: a population study. *Dev Med Child Neurol* 1996; **38**: 146–55.

### "Buffalo hump" in HIV-1 infection

Sir—Joan Lo and colleagues (March 21, p 867)<sup>1</sup> and others<sup>2</sup> have reported the accumulation of adipose tissue in the dorsocervical region (buffalo hump) in HIV-1 infected patients receiving protease inhibitors. Although evidence for the association between these drugs and increased fat accumulation is strong, the underlying mechanism has not been elucidated. In Lo and colleagues' report, four of the eight HIV-infected patients were not taking protease inhibitors. In our centre, a 38-year-old man, who had been infected with HIV-1 since

January, 1989, developed a buffalo hump 9 months after the initiation of the nucleoside analogues stavudine and lamivudine.

This patient gained 3 kg in the first 6 months of treatment. His weight was then stable for the 3 months preceding the development of buffalo hump. He had normal basal morning cortisol, and measurement of plasma cortisol over 24 h confirmed normal circadian rhythm. His serum concentrations of amylase, cholesterol, and leptine were normal. He had abnormally high triglyceride at 4.19 mmol/L (normal 0.5–2.00 mmol/L) and mildly raised serum fatty free acids (FFA) at 0.59 mmol/L (0.13–0.45 mmol/L). His viral load was 338 RNA copies per mL and CD4 count was 296 (12%) cells/μL. Blood glucose was normal but serum C-peptide remained high at 9.0 μg/L, 11.8 μg/L, and 11.1 μg/L, at 30, 90, and 100 min, respectively, after oral glucose challenge with 75 g glucose, indicating insulin resistance. The patient was chemically hypogonadal with a low serum testosterone of 33.8 ng per 100 mL (360–1170 ng per 100 mL). The patient received testosterone cypionate intramuscularly every 2 weeks for 4 months. During this treatment we noted a substantial reduction in cervicodorsal fat accumulation and abdominal girth, and an increase in lean body mass. The patient also consistently reported greater physical strength, sense of wellbeing, good mood, and improved sexual function. Simultaneously with testosterone substitution, insulin sensitivity was restored, serum C-peptide returned to normal, and FFA fell to concentrations still above the normal range.

The aetiology of buffalo hump in HIV-1 infected patients taking antiretroviral therapy is unclear and probably multifactorial.<sup>1,3</sup> Notably, visceral fat is associated with various metabolic abnormalities. These disorders include hyperlipidaemia, increased FFA concentrations, glucose intolerance, insulin resistance, and testosterone abnormalities. These metabolic and endocrine abnormalities might affect regional lipogenesis and lipolysis, and could probably direct a larger than usual proportion of body fat to visceral and cervicodorsal fat depositions. We postulate that combined endocrine and metabolic abnormalities have profound effects on body-fat distribution and may contribute to insulin resistance. In rats, castration is followed by severe insulin resistance due mainly to a lessened insulin sensitivity of the glycogen synthase system. Again with

testosterone substitution, insulin sensitivity is fully restored.<sup>4</sup> Further, when cervicodorsal or visceral fat has accumulated in excess, metabolic disturbances might be exaggerated by delivery of excessive FFA (which are powerful inducers of insulin resistance) from visceral adipose tissue.

Is buffalo hump a consequence of hypertriglyceridaemia and what is the role of androgen concentrations in fat accumulation? To resolve these questions, we need prospective studies of patients on antiretroviral therapy, before fat accumulation has developed, and especially of those on protease inhibitor therapy.

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Sir—Kirk Miller and co-workers (March 21, p 871)<sup>1</sup> describe 11 HIV-infected patients taking the antiretroviral HIV-1 protease inhibitor indinavir (Crixivan, Merck, Hoddesdon, UK), who developed increased abdominal girth despite stable body weight, with abdominal distension, fullness, and bloating. These patients were shown by computed tomography to have more intra-abdominal fat than controls. This symptomatic visceral fat accumulation has been termed crixbelly, because of its association with indinavir. Nevertheless, the number of patients is too small for conclusions about an association with this protease inhibitor, as James Lipsky notes in his accompanying commentary.<sup>2</sup> Causality needs to be verified before decisions can be made on whether to switch to other protease inhibitors in affected patients.

In our outpatient clinic, 115 consecutive HIV-1-seropositive individuals taking antiretroviral combination therapy, including protease inhibitors, were asked about the presence of increased abdominal girth with concomitant abdominal symptoms. We examined them to exclude increased body weight,

hepatosplenomegaly, ascites, or a major intra-abdominal mass. 88 (77%) patients were men, the median age was 37 years (25-75%, IQR 33-40 years), the median CD4 cell count was 294/ $\mu$ L (190-401), median plasma HIV-1-RNA was 1000 copies/mL (<500-7250). 76 patients (66%) were taking indinavir 800 mg thrice daily, and 39 (34%) other protease inhibitors (16 ritonavir 600 mg twice daily, ten saquinavir hard-gel capsules 400 mg twice daily plus ritonavir 400 mg twice daily, 12 saquinavir 600 mg thrice daily, and one nelfinavir 750 mg thrice daily plus saquinavir 600 mg thrice daily). Overall, the median time of exposure to protease inhibitors was 28 weeks (12-52). All patients were concomitantly receiving various combinations of nucleoside analogues, which included stavudine (79 cases), lamivudine (89), zidovudine (nine), and didanosine (nine). Baseline CD4 cell counts, HIV-1-RNA, age, sex, and time of exposure to protease inhibitors did not differ between patients taking indinavir and those taking other protease inhibitors.

A symptomatic picture suggestive of intra-abdominal-fat syndrome was recorded in 29 (25%) patients: 24 (31%) of 77 taking indinavir, and five (13%) of 38 taking other protease inhibitors (relative risk 2.37 [95% CI 0.98-5.72], Mantel-Haenszel,  $p=0.03$ ). Mean time of exposure to indinavir was significantly higher in patients with the syndrome than in those without (25 [SD 21] vs 38 [20] weeks,  $t$  test,  $p=0.02$ ). No significant differences in sex, age, CD4 cell count, and HIV-1-RNA were recorded between patients with or without the syndrome. With logistic regression, patients taking indinavir had a relative risk of intra-abdominal fat syndrome of 3.90 times (1.26-12.06;  $p=0.02$ ) higher than those taking other protease inhibitors, after controlling for sex, age, CD4 count, and time of exposure to protease inhibitors. The time patients were on protease inhibitors was independently associated with the syndrome, with relative risk of 1.03 (1.01-1.05;  $p=0.004$ ) times per week of exposure. One severely affected patient decided to stop indinavir and was switched to ritonavir: after 4 weeks he no longer had symptoms and after 8 weeks his abdominal girth was measurably reduced.

Our findings suggest that this syndrome is more frequently, though not exclusively, associated with indinavir. Time of exposure to the drug greatly increases the risk of this effect. Rarely, symptoms are severe enough to require discontinuation of the drug.

In such instances, a switch to other protease inhibitors should be considered.

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Sir—Keith Henry and colleagues (May 2, p 1328)<sup>1</sup> report two cases of HIV-protease-inhibitor-induced hyperlipidaemia leading to premature coronary artery disease. A similar case of a 41-year old man with ritonavir-induced hypercholesterolaemia and myocardial infarction was reported to the Swiss pharmacovigilance centre. These cases clearly show that drug-induced hyperlipidaemia, a well-known adverse drug reaction (ADR) of ritonavir,<sup>2</sup> can have important clinical consequences. The other implicated protease inhibitor was indinavir, which is known to cause lipodystrophy associated with metabolic abnormalities. As far as we are aware, however, lipid alterations have not been recorded with the use of saquinavir and nelfinavir.

We extracted all reports from the national and international database of spontaneous ADR reporting that included one of the terms hyperlipidaemia, hypertriglyceridaemia, hypercholesterolaemia, or HDL decrease as the suspected ADR for protease inhibitors. For comparison we also obtained the corresponding reports for zidovudine. The table summarises the reports for lipid alterations and other ADRs and shows clearly that lipid alterations have been reported substantially more often for all protease inhibitors than for zidovudine. Since

	Number of ADRs		Number of patients	
	Lipid alterations	Other	Lipid alterations	Hypercholesterolaemia
Ritonavir	115	1880	82	40
Saquinavir	10	611	7	5
Indinavir	40	3370	30	15
Nelfinavir	1	15	1	1
Zidovudine	15	4037	13	3

\*Based on the international and Swiss pharmacovigilance database. ADR-reporting odds ratios<sup>3</sup> are: ritonavir vs zidovudine 16.5 (95% CI 9.6-28.3); saquinavir vs zidovudine 4.4 (2.0-9.8); indinavir vs zidovudine 3.2 (1.8-5.8).

**Comparison between spontaneously reported ADRs of lipid alterations for protease inhibitors and zidovudine**

five of the seven cases associated with saquinavir use did not receive any other drug known to affect serum lipids (for example, other protease inhibitors or didanosine), confounding by comedication can be excluded. The only case on nelfinavir was reported recently from Switzerland in a 51-year old man who developed hypercholesterolaemia 3 months after starting the drug.

Plasma cholesterol was raised in 50% of the patients with protease-inhibitor-induced lipid alteration, irrespective of the protease-inhibitor used. Lipid disorders were diagnosed after a median exposure time of 8 (range 1–40) weeks. 13 patients on ritonavir recovered without sequelae after stopping this drug and one positive rechallenge was reported. For the other protease inhibitors no follow-up data were available.

The ADR reporting odds ratio for saquinavir and indinavir is lower than for ritonavir. A possible explanation for these differences is that plasma lipids are checked more frequently in ritonavir-treated patients and reporting is more complete, because physicians are aware of this effect only for ritonavir.

The fact that plasma cholesterol fell to normal values after changing from ritonavir to nelfinavir in one of the Swiss cases, and that one other patient was successfully switched from ritonavir to indinavir, suggests that changing the protease inhibitor could prevent lipid alterations despite the fact that they can occur with all protease inhibitors. If treatment with a lipid-lowering drug is necessary, it is important to consider that most protease inhibitors strongly inhibit cytochrome P450 3A4 and that severe ADRs have been reported for fibrates and most statins in combination with CYP 3A4 inhibitors.<sup>4</sup> Hence, by contrast with Henry and colleagues, a statin that is not exclusively metabolised by CYP3A4 such as, for example, pravastatin or fluvastatin, should be chosen for the safe treatment of protease-inhibitor-induced hyperlipidaemia.

KEF was supported by a fellowship from the Swiss National Science Foundation (32-51955.97).

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### Simvastatin treatment in cholesterol emboli syndrome

Sir—Robin Woolfson and Helen Lachmann (May 2, p 1331)<sup>1</sup> report a patient with renal cholesterol emboli syndrome and clinical improvement after simvastatin treatment. Their observation is important since prognosis in this syndrome is poor and no effective treatment is available, especially with respect to the renal damage which usually has an inexorably progressive downhill course. The disease, which is commonly caused by invasive diagnostic or therapeutic procedures, is not rare and treatment options are urgently needed. Nevertheless, we doubt that the restoration of renal function in Woolfson and Lachmann's patient was due to simvastatin treatment.

These investigators should have discussed the possibility of spontaneous remission of the disease; several others have claimed renal function improvement in patients with cholesterol embolisation syndrome. Smith and colleagues<sup>2</sup> described a patient (number 3) whose renal function was greatly impaired and who had to have haemodialysis for 4 months before recovering renal function. Another patient recovered renal function after 2 months of peritoneal dialysis,<sup>3</sup> and Siemons et al<sup>4</sup> report a patient (number 2) who had peritoneal dialysis for 7 months before recovering renal function. The same researchers cite several other claims of spontaneous amelioration of renal function. Most, if not all, of these reports, however, may easily be explained by reversal of other renal lesions—for example, concomitant acute tubular necrosis.

Whatever the mechanism by which patients regain renal function, it is hardly likely that fully established renal damage from cholesterol emboli

lasting for several months is reversible: the permanent feature of cholesterol embolism is not vessel obstruction by cholesterol crystals (which might possibly be reversed by resolving cholesterol crystals) but vessel occlusion by thrombus formation, and infiltration by monocytes and macrophages followed by endothelial proliferation and fibrosis of the whole vessel lumen. According to laboratory data, this last process takes place in 2–7 days.<sup>5</sup> Thus, during the subsequent chronic stage of the disease, damage to end organs such as the kidney is probably irreversible. If amelioration of kidney function is seen, other factors (such as reversal of an accompanying acute tubular necrosis)—not revascularisation and resolution of cholesterol emboli—are probably involved.

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- 1 Woolfson RG, Lachmann H. Improvement in renal cholesterol emboli syndrome after simvastatin. *Lancet* 1998; **351**: 1331–32.
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#### Author's reply

Sir—Wolfgang Rumpf and colleagues rightly comment that spontaneous remission in cholesterol emboli syndrome has been reported. We described the apparent association between introduction of statin therapy and the subsequent cessation of systemic cholesterol emboli. The possibility of spontaneous remission of a disease which, on the basis of available clinical information, had been active for several years cannot be excluded. Indeed, maintenance of remission in years to come will only provide further circumstantial evidence.

They also comment that recovery from renal failure in patients with cholesterol emboli syndrome is recognised,<sup>1–3</sup> which probably indicates recovery from a concomitant injury,

usually acute tubular necrosis (ATN), secondary to ischaemia or nephrotoxic injury. We agree that recovery from ATN probably underlies renal restoration in our patient in whom the diagnosis was proven by the presence of a characteristic cholesterol cleft in an interlobular artery. The final destination of cholesterol emboli is determined by particle size with proximal impaction leaving the distal microcirculation intact. The severity of the tubular epithelial response to resultant hypoperfusion (and potential for recovery) depends initially on the available collateral blood supply and then on subsequent improvements (for whatever reason) in local blood flow. In severe disease, ischaemic injury is irreversible.

Finally, Rumpf and colleagues describe the rapid obliterative vasculopathy that follows renal cholesterol emboli syndrome,<sup>3</sup> and note that, on histological grounds, this should be irreversible. However, recanalisation of occluded vessels occurs in other conditions, such as vascular rejection, and could presumably also take place in vessels occluded as a result of cholesterol embolisation. Ultimately, the capacity to recover renal function depends on preservation of the uninvolved distal microcirculation.

Although we wish our report to be viewed in the context of the emerging evidence of statin-induced plaque stabilisation and regression, we are well aware that it provides only circumstantial evidence of benefit from statin therapy in renal cholesterol emboli syndrome. There is no substitute for a proper prospective study in this group of patients, who will otherwise continue to have a dismal outlook.

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## Hazards of white asbestos

Sir—Mark Cullen's perceptive comments, in his May 9 commentary,<sup>1</sup> on the attempts by some doctors and scientists to rehabilitate Canadian chrysotile, or white asbestos, are topical. On May 28, the Canadian Government announced that it was to make a complaint to the World Trade Organisation about the 1997 French Government's total ban on all forms of asbestos. An accompanying dossier, detailing their worldwide lobbying on behalf of so-called safe Canadian asbestos, revealed that they had met the UK Prime Minister Tony Blair on several occasions, and this meeting had delayed the UK asbestos ban that had been promised in June, 1997.<sup>2</sup>

Cullen believes the good news is that the predicted<sup>3</sup> third wave of disease from very low levels of exposure to asbestos, largely chrysotile in the environment, has shown little evidence of materialising. If the history of this 100-year-old public-health disaster tells us anything, it is to be wary of making complacent assumptions.

Millions of tons of asbestos are currently in our homes, schools, hospitals, and workplaces, and must be removed safely at some time in the future. 1996 Health and Safety Executive (HSE) research<sup>4</sup> showed the safest asbestos face masks can leak (protection factor was 40, not 2000!), and asbestos removers have thus been exposed to asbestos when they thought they were safe. 768 asbestos-removal firms are licensed to remove asbestos in the UK, and each one receives less than one site visit from the HSE each year.<sup>5</sup> Since 1983, only 13 licences have been revoked. During the past 5 years, the average fine<sup>2</sup> for breaking asbestos laws has been a mere £1120. Do your readers really feel protected against the deadly, and invisible, hazards of asbestos dust?

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- 1 Cullen MR. Chrysotile asbestos: enough is enough. *Lancet* 1998; **351**: 1377–78.
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Sir—In his commentary, Mark Cullen,<sup>1</sup> states that inhabitants of asbestos-laden facilities, largely chrysotile, are at minimum exposure and at low risk of malignant disease. Clinical, epidemiological, and pathological surveys and in-vivo and in-vitro work show that asbestos is responsible for the aetiology of mesothelioma of the pleura and peritoneum, cancer of the lung and larynx, and gastrointestinal cancers.<sup>2</sup> All forms of asbestos are carcinogenic. Although crocokolite seems to be two to four times more potent than chrysotile in its capacity to induce mesothelioma, all forms of asbestos have the same capacity to cause cancer of the lung.<sup>3</sup>

In Turkey there is a high incidence of lung cancer and mesothelioma in many villages in an area of Central Anatolia known as Cappadocia.<sup>4</sup> The inhabitants of these villages are exposed throughout their lives to unusually high concentrations of inorganic dust, from local rocks and soils. Detailed examination showed that environmental samples contained several different kinds of fibrous minerals, including chrysotile asbestos and other non-asbestos fibers such as fibrous zeolite.

A team from our institute carried out a survey in this region.<sup>5</sup> In all villages more than 50% of men were current smokers or ex-smokers, whereas for traditional reasons, less than 0.5% of women were smokers. Our estimates indicated an increased mortality from lung cancer of about 17-fold in men and four-fold in women, when compared with the general population. The ages of these individuals at the time of diagnosis tended to be unusually young, which supported the working hypothesis that an aetiological agent existed in the environment, with exposures beginning at birth. In two control villages near Cappadocia no cases of cancer were recorded. Environmental samples from the two villages showed that there was no asbestos in the specimens, whereas the content of the other fibrous minerals were found to be similar to the villages in Cappadocia. Our findings indicate that there is a direct relation between non-occupational environmental exposure to chrysotile asbestos and the risk of lung cancer. I disagree with Cullen and believe that to live in an asbestos-laden facility should be regarded as a high-risk exposure. I agree with Cullen's conclusion that any relaxation of vigilance against asbestos exposure would be unacceptable.

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- 1 Cullen MR. Chrysotile asbestos: enough is enough. *Lancet* 1998; **351**: 1377-78
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## Fetal malformation and failed medical termination of pregnancy

Sir—Claudette Gonzalez and colleagues (May 30, p 1624)<sup>1</sup> describe birth defects after failed illegal abortion in 42 infants who were exposed to misoprostol at doses of 200-1600 µg during the first 3 months of gestation. This report underscores both the risk of misuse of misoprostol used as a sole agent to procure abortion and the social consequences of the restrictive laws on abortion in Brazil.

Misoprostol is registered for use in association with mifepristone for legal termination of early pregnancy (up to 49 days of gestation) in France. The licensed regimen has proved over 95% effective in inducing complete abortion.<sup>2</sup> In the UK and Sweden, the prostaglandin PGE1 analogue gemeprost is registered for use in association with mifepristone for termination of early pregnancy of up to 63 days' gestation, and efficacy has been shown to be about 95%.<sup>3</sup> The regimens of oral misoprostol or vaginal gemeprost in association with mifepristone are associated with a complete failure rate of between 1.5% and 0.3%, respectively.<sup>2,3</sup>

The Exelgyn (the French company set up by ES to further develop and

market Mifegyne [mifepristone] outside the USA) datasheet indicates that it is essential that termination of pregnancy by another method be undertaken in the event of failure. Nevertheless, if a woman changes her mind or the clinician fails to follow-up or make a diagnosis, some pregnancies will continue.

We reviewed 71 cases of continuing pregnancy after failed early medical termination of pregnancy. The cases occurred between 1987 and 1998, and in that time we estimate that about 405 000 early medical terminations of pregnancy had been done in the UK, France, and Sweden. In 21 of these cases mifepristone was used alone, in the remaining cases mifepristone was associated with a prostaglandin analogue: misoprostol 400 µg orally (22), sulprostone 0.25-0.5 mg intramuscularly (four), gemeprost 1 mg vaginally (ten), and an unspecified prostaglandin (14). In eight of the 71 cases, malformation of the fetus or baby was reported. The table shows details of the drug regimen used, age of pregnancy, and outcome in those for whom abnormality was reported. There were no reported cases of malformation associated with use of misoprostol when used with mifepristone.

Our findings show the safety of legal, early, medical termination of pregnancy in association with mifepristone and prostaglandin, but also provide information on the risk associated with continuing a pregnancy to term after a failure of the method. The apparent risk should be viewed with respect to the rate of spontaneous fetal malformation or non-viability, which might be as high as 34% at the stage of gestation appropriate for early medical termination of pregnancy.<sup>4</sup> We emphasise the need for rigorous adherence of the recommended procedure and counselling of women who change their minds about termination after a failed medical procedure should be undertaken to explain the possible risks to the fetus and the high rate of naturally occurring

abnormalities that may lead to later miscarriage or non-viability.

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## Conceptions and terminations after the 1995 warning about oral contraceptives

Sir—Susan Jick and colleagues (May 9, p 1404)<sup>1</sup> report that the General Practice Research Database showed no change in the frequency of pregnancies or terminations in women using. Third-generation oral contraception after the warning letter from the Committee on Safety on Medicines in October, 1995, or in the database as a whole. This finding seems to contradict claims that the 1995 so-called pill scare led to an increase in unplanned pregnancy and abortion. By contrast, national data suggest a strong association between the scare and a substantial increase in conceptions and legal abortions in 1996. Quarterly conception figures recorded by the Office for National Statistics show an increase of 1% in the last quarter of 1995, and of 7%, 4%, and 2%, respectively, in the first three quarters of 1996, compared with the same quarters in 1995.<sup>2</sup> There were 26 000 more conceptions in England and Wales in 1996 than in 1995. The notification of 13 601 additional abortions in 1996 suggests that at least half of the additional conceptions did not result in a birth.

One reason why Jick and co-workers did not detect an increase in pregnancies is that those that resulted in births would not appear in their

Case	Gestation	Mif dose (mg)	PG type	Outcome	Defect
1	7 weeks	400	None	TTOP	Sirenomelia, cleft palate
2	8 weeks	600	Gemeprost	ABN	Bilateral talipes equinovares
3	9 weeks 2 days	600	Gemeprost	ABN	Fingernail defect 3
4	8 weeks	600	Gemeprost	TTOP	Talipes equinovares
5	9 weeks	600	Gemeprost	TTOP	Acheiria, talipes equinovares
6	7-8 weeks	600	Gemeprost	TTOP	Anencephalia, talipes equinovares
7	8 weeks 4 days	600	Gemeprost	ABN	Heart malformation
8	6-7 weeks	200	Gemeprost	TTOP	Cerebellum atrophy

Mif=mifepristone, Pg=prostaglandin, TTOP=therapeutic termination of pregnancy, ABN=abnormality at term.

## Fetal malformation associated with failed medical termination of pregnancy

database until the last quarter of 1996. They acknowledge that their data are limited in other ways, particularly, that they relate only to women who had oral contraception prescribed by their general practitioner (GP) and that some women may have obtained abortions from private clinics. These are serious limitations that prevent their findings being extrapolated to the women of England and Wales as a whole.

Women who seek contraceptive advice from their GP are not representative of women nationally. McGuire and Hughes<sup>3</sup> found that, in 1993, almost 50% of 6.1 million women who used family-planning services in the UK did not make use of GP services. These women tend to be under the age of 25 and unmarried—the categories of women in whom the increase in conceptions and legal abortions was particularly significant in 1996. Of women aged 16–19 years resident in England, 19% attended family planning clinics in 1995–96 and 20% in 1996–97.<sup>4</sup> In 1996, 60 390 women aged under 16 were registered with family planning clinics; 26 521 were registered with GPs.

Women have direct access to NHS abortion services of some health authorities and also to private providers. In 1996, about 30% of legal abortions were obtained privately by women in England and Wales<sup>5</sup> some of whom will have requested that their GP should not be informed of the termination.

The General Practice Research Database was designed primarily to record the prescribing practice of the collaborating sample of GPs. It is unrepresentative of the UK population as a whole in relation to rates of conception and abortion.

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## von Willebrand factor proteolysis and doxycycline in thrombotic thrombocytopenic purpura

Sir—Thrombotic thrombocytopenic purpura (TTP) is characterised by widespread microvascular thrombosis with end-organ injury. The pathophysiology of this disorder is poorly understood. S Tarantolo and colleagues<sup>1</sup> reported a series of five TTP patients with Bartonella-like erythrocyte inclusions. All five patients received doxycycline; three of the patients received no plasma therapy, and were treated successfully with doxycycline alone or doxycycline with steroids.

Two groups of investigators<sup>2,3</sup> described a proteolytic activity present in normal plasma that cleaves von Willebrand factor (vWf) resulting in decreased multimer size. Under the hypothesis that in TTP high-molecular-weight vWf multimers may accumulate as a result of impaired vWf proteolytic activity, each group analysed the plasma of patients with TTP for presence of the activity. In both studies, most TTP patients exhibited deficiencies of vWf proteolytic activity suggesting that impaired vWf proteolysis may be important in the pathophysiology of TTP.<sup>2,3</sup>

Tsai and colleagues<sup>4</sup> showed that doxycycline inhibits plasma vWf proteolytic activity.<sup>4</sup> Although at therapeutic concentrations the inhibitory effect of doxycycline may be slight, this finding seems paradoxical—if impaired activity of vWf proteolysis is critical in the pathophysiology of TTP, treatment with any inhibitor of this activity should be contraindicated. Moreover, it seems unlikely that treatment of TTP could be as successful as Tarantolo and colleagues report with a drug that exacerbates a critical pathophysiological defect.

In 1969, Mettler<sup>5</sup> described two patients with haemolytic uraemic syndrome and one with TTP in whom erythrocyte-associated organisms identified as belonging to the *Bartonellaceae* spp were identified.<sup>5</sup> Although Tarantolo and colleagues did not confirm the presence of Bartonella in any of their patients with molecular and serological techniques, the re-emergence of this observation indicates a need for diligent efforts to clarify the possible role of Bartonella-like micro-organisms in the aetiology of TTP.

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## Measurement of serum cytokines

Sir—Several recent reports in *The Lancet* have discussed serum concentrations of cytokines and the correlation of these measurements to clinical progression. These reports and many other studies treat cytokine measurement as a straightforward application of the analytical technique of sandwich-format immunoassay. This assumption is incorrect, and the lack of understanding of this problem is leading to the incorrect education of a generation of medical scientists.

Cytokine molecules are seldom found in the unbound state in serum or other complex biological fluid. They are almost always bound to one or more of the following molecules, and are usually found in excess: soluble receptors, binding or carrier proteins, autoantibodies. These binding molecules block the effective and predictable formation of the antibody sandwich needed to measure all cytokines present. As such, the sandwich immunoassay can often provide a precise measurement of a subset of the cytokine present, but is seldom capable of measuring all of it.

This inability of sandwich immunoassay to recover 100% of the analyte has been well documented in analytical biochemistry publications, but this understanding has not transferred well to the journals most read by research and clinical physicians. Such articles consist of the naive direct measurement of cytokines with these assays, followed by publication of the data without comment by peer reviewers. The concentrations detected are then used as facts when the authors and the

readers attempt to create causal models. These models, taught as dogma, often have little in common with reality.

The sad truth is that most measurements of cytokine made during the past 15 years are probably wrong in an analytical sense. Sandwich immunoassay recovers free and some predictably bound cytokine, but misses other cytokine bound by unpredictable binding entities and cytokine not revealed by the kinetics of the assay protocol. Bioactivity measures the stimulation of cytokine in a given system, which is dependent on binding protein, receptor avidity and kinetics, and cell status of the test system and its relevance to the in-vivo system under study. Competitive cytokine assays reproducibly measure the total amount of cytokine (both free and bound) in a system, but they have been used only in a few studies.

More importantly, the models of the immune system developed with these assays are also probably incomplete or wrong. Before we continue to conjecture about how measurements are linked to illness progression, we need to come to an agreement as to what independent variable best signifies the amount of cytokine present in a given state. Only with standardisation on a repeatable measurement can the science move forward reliably.

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## Hepatitis A and vigorous physical activity

Sir—A rare course of hepatitis A that Raymond Koff (May 30, p 1643)<sup>1</sup> does not include in his seminar, is long-term hepatitis, in which serum alanine aminotransferase (ALT) is raised for many months without recurrence of the disease,<sup>2</sup> as seen in relapsing hepatitis.

A 31-year-old, previously healthy, white fireman presented at our hospital with malaise, weakness, anorexia, and nausea on Feb 14, 1997. He had not consumed alcohol or taken drugs and had recently travelled to Brazil. He cycled for 60 km, or walked and climbed for 3–4 h every day. On physical examination, he was jaundiced with a slightly enlarged and tender liver. Laboratory values were: ALT 6642 U/L (normal <41 U/L); aspartate aminotransferase 5040 U/L; total bilirubin 100.89  $\mu\text{mol/L}$ ; conjugated bilirubin 86.18  $\mu\text{mol/L}$ ; alkaline phosphatase 381.6 IU/L;  $\gamma$ -glutamyl

transpeptidase 220.8 U/L; prothrombin time 37%; blood glucose 5.43 mmol/L. Elisa HAV IgM antibodies were positive. Before the onset of illness, ALT had been normal in two routine blood tests. Hepatitis B surface antigen and hepatitis C virus antibodies were negative. An abdominal ultrasound revealed an enlarged homogenous liver. The patient rested in bed until the end of February, after which time he was feeling better, his ALT had decreased to 390 U/L, and he decided to restart his usual vigorous physical activity. On March 27, he had no symptoms of hepatitis A, but ALT had increased to 954 U/L, with normal bilirubin. He reduced his exercise again. 6 months from the onset of illness, hepatitis A virus IgM antibodies were positive, and antinuclear, anti-liver-kidney, hepatitis C virus, hepatitis B core, hepatitis G Ig G, and hepatitis E Ig G were negative. 1 month later, hepatitis A virus IgM antibodies became negative, but serum ALT remained raised for more than 16 months.

In a patient with confirmed acute hepatitis A (positive HAV IgM antibodies), the presence of liver-test abnormalities for more than 4 months is troublesome. If relapsing or cholestatic hepatitis are excluded, a simultaneous co-infection by other viruses, as well as autoimmune hepatitis<sup>3</sup> must be considered. The importance of rest in acute hepatitis A is controversial.<sup>4</sup> During exercise, hepatic blood flow decreases, and fulminant hepatitis A has been described with vigorous exercise at the start of the illness.<sup>5</sup>

In our patient, strenuous physical activity just before the diagnosis of acute hepatitis could have induced an high initial serum ALT value, and restarting his vigorous exercise, which coincided with serum ALT increase, could have contributed to the long duration of the disease. We suggest that vigorous physical activity should be avoided in patients with hepatitis A until liver transaminases are normal.

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## Gamow bag for high-altitude cerebral oedema

Sir—David Austin (June 13, p 1815)<sup>1</sup> describes the efficacy of the portable hyperbaric chamber (Gamow bag) for altitude illness. This experience has been reported in several studies<sup>2–4</sup> and is familiar to many physicians (myself included) who work for the Himalayan Rescue Association Aid Post (Pheriche) and for the Himalayan Trust Hospital (Kunde) in Nepal. The Gamow bag has also been used in other high altitude areas of the world.

Austin's report is unusual in the duration of treatment and in the severity of the case. The apparent diagnosis was severe acute mountain sickness, which he correctly identifies as high-altitude cerebral oedema (HACE). I agree that the cause of such a fulminant case after good acclimatisation is unclear, although I would emphasise that 3500 m is at the transition from moderate (or just high) altitude to very high altitude.<sup>5</sup> The long duration of illness Austin describes is also unusual. He is to be commended for continuing to use hyperbaric treatment and adjunctive therapy with dexamethasone until evacuation was possible. Some authorities would recommend a magnetic-resonance imaging of the brain (rather than computed tomography) for follow-up to rule out underlying disease.

I recently cared for a patient with a sudden onset of HACE at 4300 m on Denali (Mount McKinley) in Alaska after 10 days of acclimatisation. The course was also fulminant, but fortunately a helicopter was available within hours. The patient's mental status cleared as the helicopter descended through 3000 m. Both this case and the one described by Austin show that descent is the treatment of choice and produces rapid improvement in HACE.

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## Acute treatment of stroke

Sir—We would like to reply to some points raised by K Lees' May 16 commentary.<sup>1</sup> In his table, Lees mentions piracetam without reference to PASS (piracetam acute stroke study).<sup>1</sup> PASS-I has been completed, but the results of the early treatment group (<7 h) need examination in a new prospective study of piracetam in acute stroke with selective criteria to define the apparent responders in PASS. Therefore PASS-II has started.<sup>2</sup>

PASS<sup>3</sup> showed non-conclusive results for neurological and functional outcome of the total population (n=927) treated within 12 h of stroke onset, but significantly more patients recovered from aphasia (piracetam 33%, placebo 23%, p=0.04). Analysis in the early treatment group (<7 h) showed differences favouring piracetam relative to placebo in mean Orgogozo scale scores after 4 weeks (piracetam 60.4, placebo 54.9, p=0.07), and Barthel index scores (piracetam 58.6, placebo 49.4, p=0.02) and recovery from aphasia (piracetam 37%, placebo 21%, p=0.02) at 12 weeks.

We agree that reduction of mortality at the expense of increased vegetative survival is undesirable, but there seems no agreement on how to assess functional disability or how to define complete recovery. Is complete recovery a complete neurological and functional recovery or simply a Barthel score of 100? Is a good or fair outcome a Barthel greater than 85 or greater than 60? Is an excess of deaths acceptable if on the other hand many more people recover completely? Moreover, at which timepoint should functional status be evaluated—after 3 or 6 months, or even after 1 year?

In clinical trials, neurological scaling can offer a valuable tool for evaluation of a drug effect because it has true validity to measure the consequences of focal brain lesions. Neurological recovery is very fast during the first month, with a ceiling effect between 1 and 3 months, which allows evaluation of the drug effect after 1 month when there are fewer factors to

take into account such as family support, other illnesses, and late complications.

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## Risk of cerebral vein thrombosis and oral contraceptives

Sir—A strong association between cerebral vein thrombosis and use of oral contraceptive use has been established in case-control studies in Dutch and Italian women of reproductive age.<sup>1,2</sup> S de Bruijn and J P Vandenbroucke (May 9, p 1404)<sup>3</sup> have extended their original study by evaluating the risk conferred by third-generation oral contraceptives that contain gestodene or desogestrel. The investigators found that among patients who developed cerebral vein thrombosis, 56% of oral contraceptive users were taking third-generation products, compared with 38% in the control population, which yields a two-fold increased risk of cerebral venous thrombosis for third-generation compared with other types of oral contraceptives.

We assessed the type of oral contraceptives used at the time of cerebral vein thrombosis by the women included in our original study.<sup>2</sup> Our analysis was limited to patients who had had thrombosis from November, 1993, to June, 1998, since in the control-group information on the type of oral contraceptive used was obtained only during this period. 28 women with cerebral vein thrombosis and 196 controls (friends or partners of patients referred to the thrombosis centre) aged 15–50 years were assessed. 26 (93%) patients and 55 (28%) controls were using oral contraceptive at the time of thrombosis and at the visit (odds ratio 3.3 [95% CI 1.6–7.1]). The prevalence of third-generation oral contraceptives was 81% in patients (21 of 26) and 82% in controls (45 of 55), which yielded an odds ratio of 32.9 (7.2–151.0) with respect to non-users. The prevalence of first-generation or

second-generation products was 19% in patients and 18% in controls (35.3 [5.4–228.0]).

There are obvious differences between these findings and those of the Dutch investigators, who found a higher prevalence of third-generation pills in patients with cerebral vein thrombosis than in controls. One possible explanation for these differences is that our control group might not be representative of the Italian female population of reproductive age. To assess this possibility, we analysed the type of oral contraceptive used by women included in an Italian cohort study which has been underway since 1993, as part of the European Prospective Investigation into Cancer and Nutrition.<sup>4</sup> Information on oral contraceptive was obtained from 4024 women of reproductive age. In 1993, 80% of those who used oral contraceptives took third-generation products, and in 1997, the figure was 90%, with no substantial differences in age categories (<40 years 75%; >40 84%). Therefore, our control group is representative of the Italian female population, but there are clear differences in the pattern of oral contraceptive use between Italy and the Netherlands, with the market share of third-generation pills still increasing in Italy, whereas in the Netherlands it started to fall in 1994.

We concluded that third-generation oral contraceptives are associated with an increased risk for cerebral vein thrombosis, but by contrast with the report of the Dutch investigators, in Italy, the magnitude of such risk is the same as that conferred by the older and less frequently prescribed types of oral contraceptives.

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## Refugee-assistance programme in Guinea

Sir—Wim Van Damme and colleagues (May 30, p 1609)<sup>1</sup> report that a refugee-assistance programme improved the health-care system, transport infrastructure, and led to positive economic changes for the host population in Guinea. Their findings have important implications for other similarly affected developing countries, especially in Africa.

The Guinean approach towards refugee settlement and the manner in which the United Nations High Commissioner of Refugees (UNHCR) and other non-governmental organisations (NGOs) worked together with the government of Guinea to provide assistance to the self-settled refugees and the host population is exemplary.<sup>2</sup> This approach differs from the operations of UNHCR and NGOs elsewhere, in which refugee assistance primarily focuses on refugee communities to the virtual exclusion of the host populations, even when refugees are not confined to camps.

In sub-Saharan Africa, policies towards refugees confine them to camps, usually situated in the most remote, inaccessible, and under-developed parts of their countries. In Uganda, the policy is for refugees to stay in settlements where they engage in some income generation, mainly small-scale farming. This approach leads to some degree of sustainability of refugees. However, provision of refugee health services by NGOs runs in parallel with limited integration of services. As Van Damme and colleagues point out, the non-directive approach and the integration of refugee services is cost effective, besides creating harmony between refugees and the host population. Such integration may avert the negative effect that may be brought about by programmes that divert human and financial resources towards health services for refugees.<sup>3,4</sup>

As long as the refugee question shows no sign of abating, strategies pursued by UNHCR and its partners will succeed only if they build on local commitment and capacities.<sup>5</sup> Integration of services is a suitable and sustainable option for refugee-assistance programmes, humanitarian agencies, and the host nations to pursue.

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Sir—We have been actively involved in the development of the health district of Gueckédou (supported by the German Technical Cooperation Agency, GTZ). Our research supports Wim van Damme's call<sup>1</sup> for a non-directive refugee-policy in Guinea, but also shows there are different ways to address the same issue. We agree with Van Damme that the most important issue was the decision of the Guinean Government not to isolate refugees in huge camps but to focus on integration. Resources that became available through the refugee-assistance programme were partly invested to strengthen the overall health system. Consequently, the district health management team developed a cross-sectoral approach at an early stage, which included both populations as the target population of the same programme.

This approach substantially increased the workload in the existing health services and one would have expected a drop in the health service output data for the host population, but the opposite seems to be the case. Van Damme stated that economic changes in the refugee-affected areas, improvement in transport, and a "refugee-induced demand" for health care may improve the use of services by the host population. The rates of major obstetric interventions are good indicators of improvement in the health-delivery system.<sup>2,3</sup> But the impact of such a massive influx of refugees and of an assistance programme on an existing health system cannot be assessed by a single indicator, because of the complexity of the situation, it can show only a trend.

However, other service data from Gueckédou support Van Damme's hypothesis. It is astonishing that in Gueckédou, despite the influx of 250 000 refugees, output indicators such as vaccination coverage, bed

occupancy rate, accessibility, and first contact rates for the Guinean population have been stable or have even improved between 1992 and 1994.<sup>3</sup>

From 1992 to 1994, vaccination coverage (completely vaccinated children aged 0–11 months) rose from 60% to 69%, the first curative contact rate per year and per inhabitant from 0.29% to 0.4%, bed occupancy rate at the Gueckédou Hospital from 62% to 70%, and accessibility (people living within 5 km of a health centre) from 33% to 60%.<sup>4</sup>

It would also be interesting to compare the health-service data of Gueckédou with data from the neighbouring district of Kissidougou, which was also assisted by the GTZ and was affected only marginally by refugees. For example, the rates of caesarean sections in the Kissidougou district hospital rose from 0.6% to 1.3% in the years 1992–96.<sup>5</sup>

Borderline situations underline the need for new ways to bridge the gap between emergency aid and development activities. Because of a continuous flow of refugees with no prospect of repatriation, middle-term planning was required in Gueckédou. A participative approach that involves the refugees and the national professional staff right from the start of an assistance programme strengthens the refugees' own coping mechanisms and facilitates the transition from acute relief to development. This approach will also help to create a sense of ownership of an assistance programme among the health professionals of the host country and the refugees, keep to a minimum the victimisation of the refugees, and prepare the way for their reintegration.

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## Improving health in India

Sir—Your country profile of India (25 April, p 1265)<sup>1</sup> raises the question why a country with “technically sound scientists and doctors” continues to fare poorly in the provision of adequate health to most of its citizens. An important reason for this situation is the inadequate number of scientists and doctors who are willing to persevere in translating their technical excellence into benefit for the majority of the society. This reason is perhaps more important than is readily obvious from this profile. The lack of political will and inadequate health planning will continue unless more of the bright scientists and doctors from India take it upon themselves to fight against these inadequacies rather than watch passively from a distance. To get to a stage where more scientists and doctors can take up this cause in a well-informed manner, the vital role of reliable epidemiological information has to be taken up seriously.

It is puzzling that in a culture that originally emphasised looking at issues in a holistic manner, the need for sound epidemiological information about the health of the population has been given low priority. Without a clear overall picture of the health issues of the population, there is no way that a systematic effort to improve the health of the nation can be developed. A few good epidemiological studies, for example, those mentioned in the profile and the study done by us on blindness (May 2, p 1312),<sup>2</sup> are not enough. A sound approach to deal with the epidemiological features of health would have to be developed in India if we are to go beyond merely talking about improving health. This approach would have to be practical, outcome-oriented, and take account of the important social issues related to health such as education and the economy.

If enough motivated scientists and doctors in India are armed with reliable information about how to prioritise the health needs of India's people in a realistic way, and they struggle to develop a systematic approach to deal with the priorities, there is no good reason why a nation that can develop nuclear power cannot develop an effective strategy to improve the health of its people.

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## Waking up a sleeping sensibility

Sir—In his book, *The man who mistook his wife for a hat*, Oliver Sacks<sup>1</sup> describes a congenitally blind woman with cerebral palsy who was convinced that she could not do anything with her hands. Her hands were mildly spastic but without objective impairment of sensation, yet she could not recognise or identify objects that were placed in her hands because she had been brought up in an environment in which normal exploratory use of the hands was prevented. Functional reorganisation can rapidly occur in the somatosensory cortex of the brain as a result of changes in afferent input from the hand, such as restricted use of the hand, and areas for reception of afferent impulses may be downregulated as a result of non-use of the hands.

Individuals with cerebral palsy find it difficult to explore the environment and manipulate different objects because typical deformity includes elbow flexion, forearm in pronation, wrist in ulnar deviation, and flexion and thumb adducted and flexed into the palm. Cooper and colleagues<sup>2</sup> reported that 30–97% of patients with cerebral palsy have defective stereognosis—the ability to identify objects without vision. The deformity of the upper extremity in cerebral palsy can be corrected by surgical reconstruction and the technique of such tendon transfers is well established. Perhaps correction of a deformity in cerebral palsy would lead to a more efficient use of the hand, including exposure of the touch areas of the hand to the environment, and thereby leading to an improved stereognosis.

We surgically reconstructed the deformities of 36 patients with hemiplegic cerebral palsy by means of various tendon transfers to improve supination, wrist extension, and to correct the thumb-in-palm deformity.<sup>3</sup> After immobilisation, a comprehensive hospital occupational therapy was initiated. We assessed stereognosis by asking the patient to identify and describe the physical characteristics of different objects; assessment was done before and up to 18 months after the operation. During the follow-up, the patients showed an improved ability to describe and identify objects with the operated hand without vision (stereognosis).<sup>3</sup>

This improvement in stereognosis could be explained by the simple fact that the objects are more easily exposed to the palm and finger pulps after the surgical reconstruction, but also by such factors as cerebral plasticity. The specific cortical projectional areas of the hand can expand because tactile stimulation of the hand is increased,<sup>4,5</sup> and formation of new synapses may even occur. We suggest that stereognosis can be improved after reconstructive surgery of the hand in cerebral palsy because of a modified afferent inflow leading to a functional reorganisation of the somatosensory cortex, which result in an improved capacity of the central nervous system to interpret information from the periphery provided by tactile stimuli.<sup>3</sup> The strategy for the treatment of these patients includes surgical reconstruction followed by an intensive life-long postoperative training.

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## DEPARTMENT OF ERROR

*First-trimester transabdominal fetal echocardiography*—In this early report by Julene S Carvalho and colleagues (April 4, p 1023), in the last paragraph of the Results section (beginning “In the remaining four fetuses”) the case numbers given are incorrect. All references to cases 3 and 12 should be to cases 4 and 11.

*Relation between laboratory test results and histological hepatitis activity in individuals positive for hepatitis B surface antigen and antibodies to hepatitis B e antigen*—In this article by Frank ter Borg and colleagues (June 27, p 1914), the first equation and the following sentence on page 1917 should have been:

$$P_{CAH} = \frac{1}{1 + e^{-Z}} \quad \text{where } Z = 5.01(\pm 0.51) - 4.4(\pm 0.90) \times \sqrt{\frac{ULN_{ASAT}}{ASAT}}$$

and  $P_{CAH}$  is the probability of having chronic active hepatitis.