

CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Travel and risk of venous thrombosis

Sir—We find it surprising that Roderik Kraaijenhagen and colleagues (Oct 28, p 1492)¹ question a well established concept in venous thromboembolic disease that is supported by published work.

The method they use does not seem to be suited to the end result. The population with suspected but non-confirmed deep-vein thrombosis (DVT) does not constitute an ideal control group. The signs or symptoms that led to the suspicion of DVT are not analysed. Furthermore, the mean age of this group is lower than that of patients with DVT (61 *vs* 64 years), which could have meant better mobility.

More than 50% of the DVTs assessed were secondary events (22% related to known malignant disease, 20% to recent surgery, 11% to recent trauma), which were good reasons for not travelling. To take these biases into account would lose a proportionate quantity of statistical validity since less than half the patients would remain.

The patients asked about recent travel were all outpatients. In our study,² we asked about recent travel when patients were admitted to hospital, in the first few days of their stay, and before discharge. Moreover, the assistance of the patient's family was often necessary to obtain details of journeys completed several weeks previously to avoid memory bias related to stressful situations (pain, emergency consultation, &c).

Finally, in Kraaijenhagen and colleagues' study, the frequency of travel in the two groups is quite low (5% and 7%), which suggests a low chance of difference between the two groups. In our study, the prevalence of travel was 24.4% in the DVT group.

We do not believe that Kraaijenhagen and colleagues' report invalidates the established concept. As reported by R Sarvesvaran,³ pulmonary embolism is one, and probably the main, cause of sudden death among travellers.

*Emile Ferrari, Georges Morgan

Cardiology Department, Hôpital Pasteur, 06002 Nice, France
(e-mail: ferrari.e@chu-nice.fr)

- 1 Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. *Lancet* 2000; **356**: 1492–93.
- 2 Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease: a case control study. *Chest* 1999; **115**: 440–44.
- 3 Sarvesvaran R. Sudden natural deaths associated with commercial air travel. *Med Sci Law* 1986; **26**: 35–38.

Sir—In their report, Roderik Kraaijenhagen and colleagues¹ conclude that venous thrombosis is not associated with long travelling time, including air travel, based on 186 patients with DVT and 602 without. I believe that their study was underpowered to reach this conclusion.

The patients and controls were taken to have travelled a long time if they had travelled continuously for 3 h in the past 4 weeks. The investigators also analysed patients in subgroups of 3–5 h and 5 h or longer. The number of patients in the subgroups are not given nor the number of patients who had travelled by air in economy class, the number on long-haul flights (>7 h), or on overnight flights when travellers would sleep.

Venous thrombosis spontaneously lyse. Patients who had travelled weeks earlier and had clots that spontaneously lysed would have been assigned to the control group and not the DVT group, which could have confounded the results. To check for confounding, data could be presented for people who had travelled in the week before presentation to the hospital, those that had travelled 1–2 weeks earlier, and those that had travelled 2–4 weeks earlier.

The number of people in the different subgroups would be very low, with maybe only one or two in the control group. Since the number of patients in the DVT group was less than a third of that in the control group, the expected number in the DVT group would be less than one patient. Even a large increase in the frequency of venous thrombosis in the DVT group (eg, two or three times the risk), would not give a significant difference.

Kraaijenhagen and colleagues show that in most patients who present at hospital, DVT cause is not related to

travel. The only way to find out whether long-duration economy air travel is associated with DVT would be by a prospective study of long-duration travel by different forms of transport to compare frequencies of DVT, diagnosed by objective testing.

Stots B Reeve

Sutton, Macclesfield SK11 0HR, UK

- 1 Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. *Lancet* 2000; **356**: 1492–93.

Sir—The report by Kraaijenhagen and colleagues¹ adds nothing to the debate on travel risk and DVT. The study was poorly designed, retrospective, and biased.

Many patients with DVT develop no signs or symptoms of their thrombosis and, therefore, never attend outpatient clinics. The investigators do not tell us the age of the thrombus, which may have preceded clinical symptoms, and makes their 4-week cut-off for travel history invalid.

The D-dimer results are not provided but are probably not useful without a previous sample for comparison. Concentrations could have returned to normal 4 weeks after the event. Compression ultrasonography cannot detect calf thrombus accurately.² These investigations seem to have been grouped together with clinical follow-up to confirm presence or absence of DVT.

Only 17 of 788 participants had a recent history of plane travel and only four of 186 with proven DVT had been on a plane within 4 weeks of presentation. Flights longer than 3 h were assessed, but Kraaijenhagen and colleagues give no information about the distribution of flight times. DVT risk is probably higher on long flights. The small number of passengers studied and the inclusion of short flights make a type II error probable. No data on coexisting thrombophilia is provided.

Few prospective studies on this topic have been done and we are concerned that this report replaces a balanced review of air travel and DVT. We have not been able to mount a proper prospective study,

despite the promise of funding, because we would need access to airline passengers as opposed to staff and pilots. In our proposed study we intended to measure D-dimer concentrations in the UK and Australia at the beginning and end of 24 h flights. People with substantial rises would be offered full assessment of deep-vein and thrombophilia status.

We believe that airline travellers will be reassured only by knowing the true incidence of thrombosis, in relation to seat design, cramped conditions, dehydration, and the presence of pre-existing thrombophilia.

*Kevin Burnand, Matthew Waltham, Alberto Smith

Department of Surgery, Guy's, King's and St Thomas' School of Medicine, London SE1 7EH, UK

- 1 Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. *Lancet* 2000; **356**: 1492–93.
- 2 Simons GR, Skibo LK, Polak JF, Creager MA, Klapac-Fay JM, Goldhaber SZ. Utility of leg ultrasonography in suspected symptomatic isolated calf deep venous thrombosis. *Am J Med* 1995; **99**: 43–47.

Sir—Roderik Kraaijenhagen and colleagues¹ address a specific null hypothesis that travel has no influence on the likelihood of confirmed DVT in patients presenting to hospital with a swollen leg. Their findings are compatible with this null hypothesis, but cannot exclude an association between any type of travel and the risk of thrombosis.

The investigators made an implicit assumption that travelling has no association with swelling in the leg that is negative on venography or ultrasonography. The choice of controls does not allow this association to be explored, and no supporting evidence is provided to refute the possibility that travel increases the incidence of all types of swollen leg.

Until the relation between travel and the control group is known, Kraaijenhagen and colleagues' study cannot tell us whether there is any extra risk of thrombosis in travellers.

Christopher Cates

Manor View Practice, Bushey Health Centre, Watford WD23 2NN, UK (e-mail: chriscates@email.msn.com)

- 1 Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. *Lancet* 2000; **356**: 1492–93.

Authors' reply

Sir—At the start of our study in 1997, we purported that travelling would increase the risk of thrombosis, since this effect is theoretically plausible. Unbiased and properly controlled studies with a similar observation time in patients and controls were lacking. We set out to objectively quantify the real risk. Surprisingly, we found no scientific confirmation for the theoretical assumption that travel increases the risk for thrombosis.

We did a prospective investigation with individuals coming through the same referral filter (ie, via their family physician) because of clinically suspected DVT. We obtained information on travel in a standard way before and independently of diagnostic testing for DVT. The presence or absence of an objectively confirmed symptomatic DVT provided us with a clinically relevant outcome measure. This approach for identifying new causal factors is sensitive and avoids several biases that have flawed previous investigations.^{1,2} Our finding that cancer and previous surgery, well known risk factors for thrombosis, yielded significant odds ratios consistent with other studies is reassuring.

The median duration of travel was 7 h (range 4–36) in patients with DVT and 10 h in those without (3–32). Hence, our data suggest no risk related to regular travelling. Adjustment for sex, age or duration of symptoms did not alter these odds ratios. Also, after exclusion of patients and controls with known malignant disorders, previous thromboembolism, surgery, and immobilisation, the odds ratio for recent travelling remained the same.

For air travel alone we saw no increased risk for DVT, but the upper limit of the 95% CI was 3.0. We have therefore extended our study to investigate whether this subset of patients or patients with pulmonary embolism are at increased risk on long-duration flights (>15 h) or in combination with thrombophilia.

Although swelling might occur during travelling it is unlikely to have biased our findings, since patients were seen an average of 1 week after onset of symptoms, and most of them had unilateral symptoms. The odds ratio of 0.4 for travel longer than 5 h makes it unlikely that we missed an important effect.

*Roderik A Kraaijenhagen, Harry R Büller

Department of Vascular Medicine, Academic Medical Centre, 1105 AZ Amsterdam, Netherlands

- 1 Voorberg J, Roelse J, Koopman MMW, et al. Association of idiopathic venous thromboembolism with single point mutation at ARG⁵⁰⁶ of factor V. *Lancet* 1994; **343**: 1535–36.
- 2 Bloemenkamp KW, Rosendaal FR, Büller HR, et al. Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias. *Arch Intern Med* 1999; **159**: 65–67.

Sir—Although Roderik Kraaijenhagen and colleagues¹ found no relation between thromboembolism and travel, some evidence suggests an increased risk for travellers. A Mercer and J Brown² found that 50% (33 of 66) of patients with thromboembolism admitted to hospital had flown in the previous 30 days, and B Arfvidsson and colleagues³ reported the same for 23% of patients. The proportion of travellers among patients admitted for thromboembolism or for another cardiovascular disease was 24% for the thromboembolism group, compared with 8% for controls in E Ferrari and colleagues' study.⁴

On the other hand, the Aéroports de Paris emergency medical unit (ADP) have reported 109 proved pulmonary embolisms since 1990, with 29 in 2000 including four deaths. This number is underestimated, since only symptomatic pulmonary embolisms on disembarkation were registered, which represent 26% according to published data (mean delay of diagnosis 2–8 days). The 21 deaths thought by the airport's physicians to be due to pulmonary embolism were not included. R Sarvesvaran⁵ noted that 20% of deaths were caused by pulmonary embolism on arrival at Heathrow airports, ten times more than on departure.

We identified the main risk factors. First was flight duration, 95% of passengers had travelled for more than 6 h, and 70% for at least 12 h, although only 8% of the passengers had been on long-haul flights. Second was female sex, 83 women and 24 men were affected. Women represent less than 35% of all passengers, but 55% of the pulmonary embolism register. Third was age. Affected passengers had a mean age of 57.3 years, which is older than the estimated mean for all passengers at 38 years. Fourth is immobility: 80 passengers did not move during the entire flight and only eight did. Finally is antecedents. 25 passengers had a history of thromboembolism or venous insufficiency, 24 with miscellaneous risk factors—eg, injury, hypertension, smoking,

obesity, malignant disorders—and 24 women taking oral contraceptives. However, 38 passengers had no risk factors or history, and the only triggering factor seemed to be the flight itself.

These 109 cases, currently the most common serious emergencies on arrival at Paris airports, convince us of this pathology, which relates to economy and business or first class. Perhaps we should refer to traveller's thromboembolism or long-term seated position syndrome.

This potential life-threatening disorder needs prevention. We insist on safe and easy physical measures, (movement during flights and regular deep breathing, ample hydration, avoidance of smoking and alcohol). Medical measures (compression stockings, low-molecular-weight heparin, or aspirin) are still disputed but we think they should be used for high-risk patients.

*G Caillard, M Clerel

Service Médical d'Urgence, Aéroports de Paris, 95711 Roissy, France
(e-mail: gcaillard@club-internet.fr)

- 1 Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. *Lancet* 2000; **356**: 1492–93.
- 2 Mercer A, Brown J. Venous thromboembolism associated with air travel: a report of 33 patients. *Ariat Space Environ Med* 1998; **69**: 154–57.
- 3 Arfvidsson B, Eklof B, Kistner RL, Masuda EM, Sato D. Risk factors for venous thromboembolism following prolonged air travel: a "prospective" study. *Vasc Surg* 1999; 537–44.
- 4 Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease. *Chest* 1999; **115**: 440–44.
- 5 Sarvesvaran R. Sudden natural deaths associated with commercial air travel. *Med Sci Law* 1986; **26**: 1.

Sir-Roderik Kraaijenhagen and colleagues' findings¹ support my conclusion that DVT after air travel is frequently confused with jet flight leg.²

Oedema, which can be severe, might be related to the drop in cabin pressure at altitude.³ Unlike DVT, jet flight leg can be easily controlled by compression stockings, and is without sequelae.²

The number of patients with DVT who had travelled by air was small in Kraaijenhagen and colleagues' study, but this finding does not show no risk of DVT for air travel, rather that the risk must be small. Quantification of the risk is still required.

Such a study should compare the rate of DVT and jet flight leg in economy, business, and first class air travellers with that of mobile cabin staff, and include some simple

capillary filtration studies in an altitude simulator.

Sam Shuster

42 Double Street, Suffolk IP13 9LBN, UK
(e-mail: samshuster@compuserve.com)

- 1 Shuster S. Jet flight leg. *Lancet* 1996; **347**: 832–33.
- 2 Shuster S. Jet flight leg and hypobaric pressure. *Lancet* 1997; **348**: 970.

Cancer survival

Sir—J B Cookson (Nov 4, p 1611)¹ interprets the comparative analyses of European lung cancer survival in the EURO CARE study^{2,3} as showing an evident lack of basic epidemiological principles, and questions whether the UK government's cancer strategy "is built on sand".

Cookson's comments and his selective presentation of data are, however, misleading. He argues that unless the age structure of lung-cancer patients accurately reflects that of the general population, the lower survival rates in England and Scotland, where lung-cancer patients are somewhat older than elsewhere, must indicate systematic registration bias. Yet he does not recognise that the age distribution of cancer patients differs between countries and, as a result, the survival rates were standardised to a common age structure. The rates were also adjusted for the age-specific background mortality to keep to a minimum the effect of age and competing causes of death on the overall comparisons. Even without such adjustment, the survival rates in each age-group still show a deficit in the UK.

Cookson is further concerned that the results elsewhere in Europe might be biased by small selective movement of patients across the boundaries of smaller cancer-registry areas, if they are not tightly defined. If such loss to follow-up were more common outside the UK and if it preferentially affected patients with poor outlook survival rates might be artefactually improved in the registries concerned, as Cookson suggests. But the cancer registries contributing to EURO CARE have rigidly defined population boundaries, losses to follow-up have been minimal, and there is no evidence that these are biased to patients with poor outlook. The impact of 5-year survival from lung cancer has been quantified as part of the extensive quality control procedures in the EURO CARE study.⁴ Survival rates are changed by around 1.5% but, in the UK, the effect is to lower these rates further.

In his selective tabulation of lung-cancer results from EURO CARE,

Cookson omitted the Finnish data, which cover the entire country: migration across regional borders is not an issue. Data linkage and follow-up procedures in the Finnish Cancer Registry are among the best in the world, and selective loss of subgroups of patients can be discounted. The all-ages, 1-year, and 5-year relative survival rates for Finnish men with lung cancer diagnosed in 1985–89 were 40% and 10% respectively, compared with 23% and 7% in England.^{2,3} Similar differences were seen in all age-groups. For example, in people aged 55–64 years, the corresponding rates were 45% and 13% in Finland and 27% and 9% in England. Even without the rest of Europe, the UK population has a right to know why it cannot expect lung-cancer survival rates equivalent to those obtained in Finland.

The EURO CARE findings are in accord with what is known about international variation in the use of diagnostic procedures and appropriate therapeutic interventions for lung cancer. Indeed, the lower proportion of microscopically verified cases, noted by Cookson, shows that fewer cancer patients receive investigations and surgery in the UK than in other European countries. Cancer survival in European countries can be broadly correlated with the proportion of the gross national product, spent on health.³ There are also differing medical cultural attitudes within the UK about the treatability of certain cancer patients.⁵ It is time for some UK doctors to take their heads out of the sand.

*David Forman, Gemma Gatta,
Riccardo Capocaccia,
Maryska L G Janssen-Heijnen,
Jan W W Coebergh

*Northern and Yorkshire Cancer Registry and Information Service, Leeds LS16 6QB, UK; Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy; Istituto Superiore di Sanita, Rome, Italy; and Eindhoven Cancer Registry, Eindhoven, Netherlands

- 1 Cookson JB. Cancer survival. *Lancet* 2000; **356**: 1611.
- 2 Janssen-Heijnen MLG, Gatta G, Forman D, Capocaccia R, Coebergh JWW, and the EURO CARE Working Group. Variations in survival of patients with lung cancer in Europe 1985–1989. *Eur J Cancer* 1998; **34**: 2191–96.
- 3 Berrino F, Capocaccia R, Estève J, et al, eds. Survival of cancer patients in Europe: the EURO CARE-2 study. No 151. Lyon: International Agency for Research on Cancer, 1999.
- 4 Sant M, Gatta G. The EURO CARE database. In: Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Esteve J, eds. Survival of cancer patients in Europe: the EURO CARE study. No 132. Lyon: International Agency for Research on Cancer, 1995.
- 5 Crawford SM. Cancer in the UK: a question of culture. *Eur J Cancer* 2000; **36**: 1909–12.

Caesarean section and litigation

Sir—Your Nov 18 editorial¹ suggests reasons for the rise in the rate of caesarean sections in UK, including “the threat of malpractice lawsuits”. Most medical negligence cases are legally aided and most fail.

Legal aid is normally granted on the advice of the claimant’s lawyer, who has a direct financial interests: there is, a conflict of interest. A successful health-service defendant cannot generally recover legal costs. Cases may be settled, irrespective of merit, to avoid irrecoverable legal costs. The legal-aid system is unfair and biased. Resources intended for patients’ care are diverted by the state-funded litigation process, in which the main beneficiaries are lawyers.

The operation of legal aid thus affects clinical practice and the economics of the health service. These concerns are about patients’ care, not medical professional protectionism. Yet the UK medical establishment seems incapable of formulating any coherent policy to address the clinical and economic implications of medical negligence litigation.

Anthony Barton
London N1 0RB, UK

1 Anon. Caesarean section on the rise. *Lancet* 2000; **356**: 1697.

Fetal death and radiation exposure

Sir—Pat Doyle and colleagues (Oct 7, p 1293)¹ report the association between fetal death (ascertained by self-report in postal questionnaire) and parent’s radiation exposure in the nuclear industry. Unfortunately, fetal death has been substantially under-reported by fathers.

Doyle and colleagues note that 12% of pregnancies reported by male radiation workers and 15% reported by female workers ended in fetal death. However, the female workers were on average 10 years younger than the male workers at the time of the survey (mean

ages 39·8 and 49·6 years, respectively) and, in addition, pregnancies reported by female workers were more recent than those reported by men (62% during 1985–96 *vs* 32%, table). Both of these factors contribute to a much lower expected fetal death rate in female workers than in male workers, especially for late events such as stillbirth.

The magnitude of this under-reporting for stillbirths can be estimated by use of the proportion of births to male and female workers in each of the three time periods presented by Doyle and colleagues and the mid-period stillbirth rates published for England and Wales (table).² After adjustment for the different proportion of births reported in each of the time periods and the published mid-period stillbirth rates, the predicted male/female worker stillbirth rate ratio for the cohort should be around 1·50.

The male/female worker stillbirth rate ratio reported by Doyle and colleagues was 1·05, suggesting an under-reporting of stillbirths by male workers of around 50%. This estimate is conservative, since it does not take into account the lower rate expected in women because of their younger age at reporting.

I also compared the stillbirth rates reported by Doyle and colleagues with those reported by Parker and colleagues,³ who ascertained stillbirths to male Sellafield workers (some of whom were included in Doyle et al) by record linkage, which was around 98% accurate. Parker and colleagues’ stillbirth rate was 14·1 per 1000, compared with 7·1 reported by Doyle and colleagues. Part of the difference between the two studies is accounted for by the higher proportion of pregnancies in the years when stillbirth rates were higher in Parker and colleagues’ study (table). With adjustment, however, the rate ratio of stillbirths for Doyle and colleagues should be about 1·19, but is 1·98, which suggests under-reporting of about 60%. The difference in stillbirth definition between the two studies (24 weeks’ gestation onwards *vs* 28 weeks’ for Doyle and colleagues and Parker and colleagues, respectively) make this estimate conservative.

The reliability of adverse pregnancy outcome data reported by fathers is questionable. Such unreliability might

explain why they found an association between paternal preconceptional irradiation and stillbirth risk of only borderline statistical significance, compared with the significant association found by Parker and colleagues.

Louise Parker

Department of Paediatric Epidemiology,
Sir James Spence Institute of Child Health,
Newcastle University, Newcastle upon Tyne
NE1 4LP, UK
(e-mail: Louise.Parker@ncl.ac.uk)

- 1 Doyle P, Maconochie N, Roman E, Davies G, Smith PG, Beral V. Fetal death and congenital malformation in babies born to nuclear industry employees: report from the nuclear industry family study. *Lancet* 2000; **356**: 1293–99.
- 2 Macfarlane A, Mugford M, Henderson J, Furtado A, Stevens J, Dunn A. Birth counts: statistics of pregnancy and childbirth, 2nd edn. London: Stationery Office, 2000.
- 3 Parker L, Pearce MS, Dickinson HO, Aitkin M, Craft AW. Stillbirths in offspring of male radiation workers from Sellafield nuclear reprocessing plant. *Lancet* 1999; **354**: 1407–14.

Authors’ reply

Sir—We show in the table that Louise Parker’s assertion that our findings differ from hers because men are less likely than women to report stillbirths (fetal deaths \geq 24 weeks’ gestation) has no foundation. The 3·2% gap for all gestations (11·5% in pregnancies reported by men and 14·7% reported by women) is created by the difference in early, not late, fetal loss (table). In our study, this variation in early fetal loss largely reflects the fact that, at the time of the survey, the women were younger than the men, their pregnancies more recent, and more recent pregnancies are detected earlier in gestation. This well-known temporal trend has been seen in many similar datasets, as has the fact that losses soon after a missed period are more likely to be reported by women than men.

Furthermore, because Parker and colleagues’ study population differs from ours in many crucial respects, crude comparisons are likely to be misleading. Parker and colleagues’ data were compiled by probabilistic record linkage (primarily parental names and addresses) of Cumbrian registered births with British Nuclear Fuels Sellafield staff files of male workers, whereas we obtained information directly from male and female radiation and non-radiation workers employed at nuclear establishments throughout the UK. Among other things, the two study populations have markedly different socioeconomic distributions: only 35% of the radiation workers included in Parker and colleagues’ study were classified as non-manual workers,

Year of pregnancy end	Proportion pregnancies reported (%)			Mid-period stillbirth rate
	Doyle and colleagues		Parker and colleagues	
	Male workers	Female workers	Male workers	
<1965	26	8	37	23/1000 (1957)
1965–84	42	29	47	11/1000 (1975)
1985–96	32	62	..	5/1000 (1990 for Doyle et al)
1985–89	16	5/1000 (1987 for Parker et al)

Temporal distribution of births to male and female workers in nuclear industry

	Number reported by men (n=23 676)	Number reported by women (n=3285)
Livebirths	20 899 (88.3%)	3048 (85.0%)
Fetal deaths	2723 (11.5%)	526 (14.7%)
<12 weeks gestation	1189 (5.0%)	295 (8.2%)
12 to <16 weeks gestation	1059 (4.5%)	165 (4.6%)
16 to <24 weeks gestation	264 (1.1%)	37 (1.0%)
>24 weeks gestation	211 (0.9%)	29 (0.8%)
Termination of pregnancy for medical reasons	54 (0.2%)	11 (0.3%)

Outcome of study pregnancies

compared with 72% (radiation and non-radiation) in ours. Since socioeconomic status has such a profound effect on stillbirth risk, our overall rate is, as expected, lower than that seen by Parker and colleagues.

The critical issue of why the scientific inference of the two studies is not the same remains to be resolved. We have raised queries previously,¹ and would like to take this opportunity to suggest a way forward. Our childhood cancer data have already been successfully compared with those for another study.² A similar cross-check against Parker and colleagues' Cumbrian birth cohort is surely the most sensible way to proceed.

*Pat Doyle, Noreen Maconochie,
Eve Roman

Epidemiology Unit, Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

- 1 Doyle P, Roman E, Maconochie N. Stillbirths among offspring of male radiation workers. *Lancet* 2000; **355**: 492.
- 2 Draper GJ, Little MP, Sorahan T, et al. Cancer in the offspring of radiation workers: a record linkage study. *BMJ* 1997; **315**: 1181–88.

Hepatitis C detection

Sir—In her response to Gregory Dore, Marianne Leruez-Ville (Oct 28, p 1520)¹ suggests that “HCV [hepatitis C virus]-infected patients with potentially HCV-infected gametes could lead to contamination of a couple's embryos” and that this information “should be considered when deciding the management of HCV-infected infertile couples”. To date, there are contradictory reports^{2,3} that HCV RNA is present in a fraction of seminal plasma samples from men infected with HCV, but no evidence that it can be detected in male or female gametes.

Since 1989, we have done more than 2300 intrauterine insemination or in-vitro-fertilisation attempts with washed spermatozoa from men infected with HIV, 62% of whom were co-infected by HCV, with no case of seroconversion for either disease in the women assisted. Our data are therefore against the

possibility that HCV can infect spermatozoa. No data exists on the possibility that HCV can infect the oocyte. Moreover, homologous embryos obtained from oocytes of a woman infected with HCV are returned in uterus, which makes it impossible to find out whether vertical transmission occurred at the embryonic stage or later in prenatal life.

We think that all couples with HCV asking for assisted conception should be informed about these uncertainties rather than counselled about or offered treatment against potential risks for which no scientific evidence exists.

*Augusto E Semprini, Alessandra Vucetich,
Tiziana Persico

via Carlo Crivelli 20, 20122, Milano, Italy
(e-mail: e.semprini@libero.it)

- 1 Leruez-Ville M, Rouzioux CH, Chaix ML. Detection of HCV RNA in semen. *Lancet* 2000; **356**: 1520.
- 2 Semprini AE, Persico T, Thiers V, et al. Absence of hepatitis C virus and detection of hepatitis G virus/GB virus C RNA sequences in the semen of infected men. *J Infect Dis* 1998; **177**: 848–54.
- 3 Leruez-Ville M, Kunstmann JM, De Almeida M, Rouzioux CH, Chaix ML. Detection of hepatitis C virus in the semen of infected men. *Lancet* 2000; **356**: 42–43.

Authors' reply

Sir—We and others have shown that HCV RNA can be recovered from seminal plasma of HCV-infected men by sensitive PCR methods.^{1–3} There is indeed no evidence that HCV can be detected in male gametes. However, the presence of HCV in spermatozoa fraction has not yet been searched with an appropriate and sensitive method. Indeed, HCV was not detected in 56 studied spermatozoa fractions but the sensitivity of the method used was low compared with the PCR method actually available (600 copies/million of spermatozoa tested to <100 copies/million).⁴ We are currently assessing the validity of HCV undetectability in spermatozoa fractions with such a highly sensitive PCR method.

Augusto Semprini and colleagues show impressive clinical experience with intrauterine insemination and in-vitro fertilisation done to assist

couples infected with HIV or HCV who wish to have children. The detailed long-term follow-up of these cases, if at all available, should prove invaluable to help the medical community to answer such a difficult question. There is a lack of up-to-date data on the presence of HCV in the spermatozoa fractions used in in-vitro fertilisation and peer-reviewed data on the follow-up of HCV-infected couples treated with in-vitro fertilisation. Therefore, we strongly suggest that the spermatozoa fraction of HCV-infected men should be virologically tested for HCV before being used in this way.

*Marianne Leruez-Ville, Christine Rouzioux,
Marie-Laure Chaix

Service de Bacteriologie, Virologie Parasitologie, and Hygiene, Groupe Hospitalier Necker-Enfants Malades, 75743 Paris, France

- 1 Leruez-Ville M, Kunstmann JM, De Almeida M, Rouzioux CH, Chaix ML. Detection of hepatitis C virus in the semen of infected men. *Lancet* 2000; **356**: 42–43.
- 2 Levy T, Tardy JC, Bourlet T, et al. Transmission risk of hepatitis C virus in assisted reproductive techniques. *Hum Reprod* 2000; **15**: 810–16.
- 3 Paquier C, Daudin M, Right L, et al. Sperm washing and virus nucleic acid detection to reduce HIV and hepatitis C virus transmission in serodiscordant couples wishing to have children. *AIDS* 2000; **14**: 2093–99.
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Melatonin secretion after surgery

Sir—In their study of melatonin secretion after surgery in seven patients, A J Cronin and colleagues (Oct 7, p 1244)¹ measured nocturnal melatonin concentrations on nights 1, 2, and 3. They noted a low amplitude of melatonin secretion during night 1 in all the patients compared with secretion on nights 2 and 3.

According to the investigators, the low amplitude of melatonin secretion seen on the 1st night is due to the normal postoperative loss of sleep time. However, they present no sleep records of these patients. Workers in several studies have shown that melatonin is indispensable for sleep induction, and loss of sleep is generally attributed to disturbance of melatonin secretion from the pineal gland.²

Whether the melatonin concentrations on nights 2 and 3 represent the basal secretion of melatonin in these patients is unknown. Each individual's

melatonin secretion is genetically determined. Since night-time peaks can be reproduced most accurately, measurement of melatonin concentrations in these patients only on complete recovery from surgery would show their basal melatonin secretion.

Stress of any kind, whether acute or chronic in nature increases melatonin secretion in normal people and patients.³ In a study done on 23 pregnant women V Katz and co-workers⁴ reported an increase of 6-sulphatoxy melatonin concentrations in people on working days compared with on non-working days. Those investigators attributed the increased melatonin concentrations to the effects of acute psychological stress induced by work. On the basis of these observations the increased melatonin secretion reported nights 2 and 3 after surgery in Cronin and colleagues' patients could be mainly related to the effects of acute surgical stress and might not represent their basal melatonin secretory values.

Our own observations on the effects of surgical stress on pineal-gland activity in rats show that surgical stress increased pineal nucleic acid and indole concentrations 24 h and up to 1 week after the operation.⁵ Control rats did not reveal any such changes during the period of study.

These observations on the effects of stress on melatonin production and secretion in animals or human beings suggest that organisms can adapt to stressful situations by increasing melatonin secretion. Hence Cronin and colleagues might more appropriately attribute increased melatonin secretion on nights 2 and 3 after surgery to the effects of acute psychological stress and not to changes in patients' basal melatonin values.

V Srinivasan

PSG Institute of Medical Sciences and Research, Coimbatore 641 004, Tamil Nadu, India (e-mail: saivsr@yahoo.com)

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Authors' reply

Sir—We also disagree with the contention that stress of any kind increases melatonin secretion. Sleep deprivation does not inhibit melatonin secretion in normal human volunteers,¹ and we doubt it inhibits melatonin secretion in postoperative patients. Rather, we expect that the lowered melatonin secretion either directly decreases sleep or, more likely, reflects an underlying weakening of the circadian rhythm, thereby decreasing nocturnal sleep. We did not design our study, however, to test these hypotheses.

We also disagree that stress acute or chronic of any kind increases melatonin secretion. In human beings, the stress of one night's sleep deprivation raised cortisol concentrations but did not alter melatonin secretion on the night of the sleep deprivation nor on the recovery night.¹ In patients with panic disorder, urinary excretion of cortisol was increased but excretion of melatonin was normal.² Nevertheless, we also expect that surgical stress influences melatonin secretion in postoperative patients. Although not included in our report, the concentrations of urinary free cortisol in the patients in this study were several fold higher on the first postoperative night than on the next 2 nights. By the 3rd night, the urinary free cortisol and 6-sulphatoxy-melatonin concentrations were normal, which suggests that the body responded to the acute stress by decreasing melatonin secretion. Consistent with our findings, other studies have shown decreased melatonin secretion in human beings after the administration of corticotropin-releasing hormone (CRH).³ The melatonin decrease did not, however, seem to be caused by a rise in cortisol, since cortisol was not raised by CRH. Additionally, adrenocorticotropin hormone administration, which did increase the cortisol concentrations, did not alter the melatonin concentrations.

The nocturnal melatonin concentrations we saw on the 3rd postoperative night are similar to those other workers have reported in normal people.⁴ Therefore, we think the lower melatonin concentrations on night 3 represent suppression of melatonin secretion.

Our data do not necessarily conflict with V Srinivasan's view that melatonin secretion is increased after surgery. We maintain that melatonin secretion is abnormally low on the first postoperative night, but that secretion

rises and might reach supranormal peaks by night 4.

*Arthur J Cronin, Tonya S King, John C Keifer, Edward O Bixler, Matthew F Davies

Departments of *Anesthesiology, Health Evaluation Sciences, Psychiatry, and Obstetrics and Gynecology, Milton S Hershey Medical Center, Hershey, PA 17033, USA; and Department of Anesthesiology, Duke University Medical Center

- 1 von Treuer K, Norman TR, Armstrong SM. Overnight human plasma melatonin cortisol, prolactin, TSH under conditions of normal sleep, sleep deprivation, and sleep recovery. *J Pineal Res* 1996; **20**: 7–14.
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Postoperative nitric oxide

Sir—Owen Miller and colleagues (Oct 28, p 1464)¹ have done a well designed study showing a decrease in the incidence of pulmonary hypertensive crises (PHTC) in patients treated with inhaled nitric oxide after congenital heart surgery. Miller and colleagues have provided a valuable contribution about the safety and efficacy of inhaled nitric oxide. Yet, we showed no significant decrease in the incidence of clinically important PHTC.² I believe difference in the selection of patients, the classification of PHTC, and the analysis of results might explain the reported conflicts in our conclusions.

Miller and colleagues enrolled patients with high flow or high pressure in the pulmonary circulation before surgery. Patients who had increased pulmonary vascular resistance would have been more appropriate. Many of their patients had low pulmonary vascular resistance. The probability of developing a PHTC is low during the postoperative period in such patients.³ We enrolled patients with an early postoperative systolic pulmonary arterial pressure higher than 50% of the systolic systemic pressure.

Although Miller and colleagues did a double-blind study with uniform standards for postoperative care, in a clinical setting many of their patients

would be unlikely to require muscle relaxants or assisted ventilation for longer than 70 h.

Miller and colleagues define PHTC as episodes in which the pulmonary to systemic arterial pressure ratio exceeded 0.75. Major episodes were associated with a decrease in systemic arterial pressure or systemic oxygenation, and minor episodes with haemodynamic stability. In our study, the definition was an acute episode of suprasystemic pulmonary-arterial pressure associated with a decrease in blood pressure, heart rate, or oxygenation. Thus, all our reported episodes would be major episodes in Miller and colleagues' study. Nitric oxide did not significantly decrease the incidence of major episodes in either study. We are unclear as to why minor episodes were thought clinically important by Miller and colleagues. Several of our patients had a systolic pulmonary to systemic arterial pressure ratio higher than 0.75 for extended periods, with no evidence of haemodynamic instability.

The report of Miller and colleagues focuses on their positive results, and the importance of negative results seem understated. Nitric oxide did not prevent severe episodes of increased pulmonary vascular resistance, nor improve the duration of assisted ventilation and intensive care. They report only the number of PHTC. The number of major PHTC in each group would be useful, as well as the number of episodes per patient. They should provide evidence that nitric oxide decreases the probability that individual patients will have a major PHTC.

Nitric oxide can save lives or prevent the need for extracorporeal support in patients with severe pulmonary hypertension.⁴ However, we need evidence that nitric oxide decreases mortality or clinically important adverse events before we promote its routine use in postoperative care. Miller and colleagues' data are not sufficient to support the prophylactic use of inhaled nitric oxide.

Ronald Day

Primary Children's Medical Center, 100 North Medical Drive, Salt Lake City, UT 84113, USA

- 1 Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celemajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet* 2000; **356**: 1464–69.
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Authors' reply

Sir—We no longer routinely catheterise neonates at high risk of postoperative pulmonary hypertension and, therefore, did not routinely measure preoperative pulmonary vascular resistance. However, all patients underwent preoperative echocardiography to estimate preoperative right ventricular pressure.

On the basis of the underlying diagnosis and echo findings patients thought to be at risk of pulmonary hypertension were included prospectively. The preoperative randomisation allowed for an equal balance of patients who might have had reactive and labile pulmonary vasculature in the postoperative phase. Although we agree that patients classified as minor cases might be at lower risk of postoperative pulmonary hypertension, which we first reported some time ago,¹ we also think that postoperative randomisation answered a different (and possibly less relevant) clinical question.

As with many controlled clinical trials, the degree of monitoring and intervention probably does not exactly mirror daily practice, but our aim was to integrate a tightly controlled study into everyday practice in a busy tertiary-referral paediatric intensive care unit. We used a structured treatment protocol because of the constraints of the double-blind design.

We agree with Ronald Day that minor and major PHTC should be managed differently and, therefore, prospectively defined and separated the events in all patients. However, the overall clinical management of such infants is influenced not only by the occurrence of major crises. High pulmonary artery pressure (or, in our study, pulmonary vascular resistance if cardiac output has been consistently measured) is important even in the absence of major crises. Pulmonary vascular lability is a continuum to be assessed throughout the postoperative course. We analysed major PHTC separately to better understand the effects of inhaled nitric oxide in these patients.

To analyse results, we prespecified two major endpoints—risk of all PHTC and time to extubation criteria—which were positively affected by nitric-oxide administration. Although the number of patients with major PHTC was similar in the two groups, the number was small and we caution against post-hoc analysis.

Low dose inhaled nitric oxide lowered the incidence of PHTC and time to extubation readiness. The study was not powered to demonstrate an effect on mortality. Day and colleagues, and our findings should be considered when deciding about the routine prophylactic use of inhaled nitric oxide.

Owen I Miller

Eastern Heart Clinic, Prince of Wales Hospital, Randwick NSW 2031, Australia (e-mail: ovhmmiller@one.net.au)

- 1 Miller OI, Celemajer DS, Deanfield JE, Macrae DJ. Very low dose inhaled nitric oxide: a selective pulmonary vasodilator after operations for congenital heart disease. *J Thorac Cardiovasc Surg* 1994; **108**: 487–94.

Helium/oxygen and severe COPD

Sir—A H Morice, in his Nov 25 commentary,¹ outlines his view on the use of helium-oxygen breathing mixtures. Is Morice's commentary the light at the end of the tunnel or an oncoming train?

Tasseaux and colleagues' trial² of 70/30 helium-oxygen breathing mixture resulted in halving the incidence of trapped gas and intrinsic positive end-expiratory pressure. Their work is all but discounted on the grounds that the cost of the helium-oxygen mixture is too high. Two other areas of research are offered as alternatives: one requiring high inspiration pressures and another for ventilator weaning. However, before methods are discounted because of cost, the cost of helium-oxygen gas mixture in the UK is, notably, much lower than Tasseaux and colleagues quote. 79% helium 21% oxygen is a readily available preparatory medical gas mixture. Based on my calculation of 8.4 L/min × 60 min = 504 L/h × 24 h = 12 096 L/day, use of this mixture with the addition of oxygen to establish any required oxygen concentration, as would be a normal procedure for air and oxygen, the cost per day for gas would be less than half that quoted by Tasseaux.

As with all treatments, the cost/benefit is an important feature. For helium/oxygen mixtures the information entered into such an

equation must be accurate for a valid conclusion to be drawn.

Gerard Laden

Clinical Hyperbaric Facility, Hull and East Riding Hospital, Anlaby, Hull HU10 7AZ, UK (e-mail: gerardladen@cs.com)

- 1 Morice AH. Helium/oxygen and severe COPD. *Lancet* 2000; **356**: 1785–86.
- 2 Tassaux D, Jolliet P, Roeseler J, Chevrolet J-C. Effects of helium-oxygen on intrinsic positive end-expiratory pressure in intubated and mechanically ventilated patients with severe chronic obstructive pulmonary disease. *Crit Care Med* 2000; **28**: 2721–28.

Malaria eradication on islands

Sir—Akira Kaneko and colleagues (Nov 4, p 560)¹ describe the successful eradication of malaria on a small southwest Pacific island with 718 inhabitants through implementation of short-term mass-drug administration. Despite their encouraging report, short-term mass-drug administration is generally not effective in larger populations or geographic areas.

Successful malaria eradication requires cure of every infected host by antimalarial agents and complete interruption of the transmission chain by vector control. Incomplete coverage is a major pitfall of short-term mass-drug programmes. This difficulty increases with increasing size of population or geographical area. Another serious drawback is unidentified and unmanaged treatment failures because of poor case-finding and monitoring systems, which leads to incomplete cure of infected hosts. Elimination of mosquito vectors in large geographic areas is difficult to achieve in a short period of time, and resurgence of malaria and emergence of drug resistance can ensue.²

In 1965, malaria was successfully eradicated in Taiwan,^{3,4} a west Pacific island that had been heavily plagued by malaria for centuries. Taiwan has a much larger area and population than the island where Kaneko and colleagues worked. The incidence of malaria was up to 1.2 million cases yearly per six-million population. Instead of mass-drug administration, Taiwan has implemented, since 1952, a control programme of antimalarial drugs and pesticides, with an epidemiological and entomological surveillance system. Island-wide dichlorodiphenyltrichloroethane (DDT) 2-g/m² indoor spraying was done once yearly from 1952 to 1957, simultaneously with mass screening of

the population. Infected patients were given appropriate curative drug therapy. The incidence of malaria rapidly decreased and use of DDT was restricted to residual foci of transmission. It took until 1965, however, to completely eliminate parasite reservoirs, since then surveillance has effectively counteracted the continuous threat of imported malaria, and Taiwan has remained free from malaria.

We strongly advise a global malaria control programme of this type rather than mass-drug or pesticide administration.

*Chi-Tai Fang, Hui-Li Chang, Wei-Chuan Hsieh

*Section of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei 100, Taiwan; and Center of Diseases Control, Department of Health, Executive Yuan, Taipei (e-mail: fangct@ha.mc.ntu.edu.tw)

- 1 Kaneko A, Taleo G, Kalkoa M, Yamor S, Kobayakawa T, Björman A. Malaria eradication on islands. *Lancet* 2000; **356**: 1560–64.
- 2 Wernsdorfer WH. The biological and epidemiological basis of drug resistance in malaria parasites. *Southeast Asian J Trop Med Public Health* 1992; **23** (suppl 4): 123–29.
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Risk score for treatment of upper-gastrointestinal haemorrhage

Sir—Oliver Blatchford and colleagues (Oct 14, p 1318)¹ propose a recidive prediction system for patients who have an upper-gastrointestinal haemorrhage on the basis of clinical and laboratory variables, to avoid the need for endoscopic data.

Many workers have reported their own triage systems based on scores obtained from the analysis of series of patients. Non-endoscopic variables that compose a score frequently vary from system to system, even in very similar studies, probably because of different methods of work and treatment used by the different groups in their own hospitals. Dependent on analysed data, medical or laboratory variables such as age, previous use of non-steroidal anti-inflammatory drugs, presence of comorbidity, or haemoglobin concentrations are significant risk predictors in

some series, but are excluded from others because of lack of significance.

Endoscopic variables are, however, more homogeneous than those of the triage systems: type of ulcer base, size and location of the bleeding ulcer, and the presence of active bleeding during the endoscopy. We did a prospective study in our hospital on 317 patients with an upper-gastrointestinal haemorrhage secondary to a gastroduodenal ulcer.² We have analysed the clinical and laboratory data and the endoscopic variables of recidive risk presented by our patients. Our four variables were independent predictors of risk, just one of which medical (presence of clinical findings of low cardiac output: syncope, angor pectoris, or systolic arterial pressure ≤ 100 mg Hg), the other three being endoscopic ulcer size, ulcer base feature, and presence of haematic rests in the tract explored by the endoscopist. By contrast with Blatchford and colleagues, age, the presence of melaena, cardiac frequency, and concentration of haemoglobin or blood urea were not independent risk variables.

Subsequently, we have validated our score with another prospective series of 175 patients, and even if we used a triage system of greater complexity that incorporated endoscopic data, 8% of patients had unpredicted rebleeding episodes (of 13 recidives, 12 were predicted by our score and one was not).³

We believe that Blatchford and colleagues' results are interesting, since their data contribute to a better knowledge of the behaviour of another series of bleeders, and their findings, once externally validated, could be of interest for hospitals without an available endoscopist. On the other hand, we believe that the score they propose, although valid in the context of their own hospital and working methods, is not applicable to other hospitals since it does not include the essential data offered by the endoscopy.

*Joan Vidal, Antoni Obrador

*Servei d'Urgències, and Servei de Digestiu, Hospital Universitari Son Dureta, 07014 Palma de Mallorca, Balearic Islands, Spain

- 1 Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet* 2000; **356**: 1318–21.
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Adverse drug reactions

Sir—Sandra Knowles and colleagues (Nov 4, p 1587)¹ discuss the possibility of cross reactivity between sulphonamides and other related drugs such as sulphonylureas. They note that sulphonylureas are not recommended for patients with a history of an adverse drug reaction to a sulphonamide but suggest that this precaution is unwarranted. We did a small survey of patients attending the diabetic clinic at our hospital and our results lend support to this conclusion.

We asked 82 patients who were taking, or had previously taken, some form of sulphonylurea to complete a questionnaire. Of these, 34 had at some time taken a sulphonamide, most commonly as a sulphamethoxazole-trimethoprim formulation. Of these 34 individuals, seven had had a hypersensitivity reaction to the sulphonamide and one needed hospital admission. Two of the 34 had a mild rash as a reaction to a sulphonylurea but only one of these had previously had a reaction to a sulphonamide. Hypersensitivity reactions might, therefore, be more common with sulphonamides than with sulphonylureas; A E Cribb and colleagues² suggest that only sulphonamide compounds that are aromatic amines and, hence, can be oxidised to nitroso derivatives, are likely to have cross-allergic reactivity with the antimicrobial sulphonamides.

Many diabetes specialists advise patients with a history of sulphonamide allergy not to take sulphonylureas and could be depriving patients of potentially important treatment.

*Gillian M Shenfield, Justin Jacka

*Department of Clinical Pharmacology, Royal North Shore Hospital, St Leonards, NSW 2065, Australia; and Department of Pharmacy, University of Sydney, Sydney

- 1 Knowles SR, Uetrecht J, Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndromes. *Lancet* 2000 **356**: 1587–91.
- 2 Cribb AE, Lee BL, Trepanier LA, Spielberg SP. Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis. *Adverse Drug React Toxicol Rev* 1996; **15**: 9–50.

Sir—We appreciate I Ralph Edwards and Jeffrey Aronson's timely review of adverse drug reactions (Oct 7, p 1255).¹ The risks of adverse events in rheumatology can be high because of the common use of immunosuppressive agents and frequently associated comorbidity and polypharmacy.

Rheumatic diseases can involve

multiple systems. Therefore, attribution of causality for adverse events can be especially difficult. We believe that formal surveillance systems do not record, and thus lose the opportunity to learn from, many adverse events for which there are clinical uncertainties. Furthermore, well known drug-related serious adverse events even though they are rare and little is known about optimum management, are seldom reported to regulatory authorities.

Having been frustrated and, frankly, bored by numerous audits of drug monitoring of disease-modifying antirheumatic drugs (DMARDs) that report on proportions of patients attending for scheduled blood monitoring visits, we established a surveillance and assessment system for severe adverse events related to DMARDs. We established a network of 21 consultant rheumatologists in the West Midlands region. All are sent a monthly postcard and asked to report relevant adverse events. For reported cases, we prepare a detailed report. Two researchers check details of the reports. The format of the report is standard and is based on the US Food and Drug Administration's reporting form for adverse events (available at www.fda.gov/medwatch/safety/3500.pdf accessed on Feb 13, 2001). Case reports are sent, without identifying the patient or their doctor, to four senior rheumatologists (consultants or final-year trainees) for peer review. Doctors are asked to complete a questionnaire that aims to elicit opinions on issues of causality, whether the adverse event was preventable, and opinions about management of such events. By this means we hope to obtain consensus on these issues.

So far 25 serious events, over 10 months, have been reported for patients on DMARDs, including two deaths while on active treatment, dyspnoea in five patients taking methotrexate, blood dyscrasias in seven patients, malignant disease in two patients, and serious bacterial infections in five patients. To our knowledge, only one of these events has been reported to the Committee on Safety of Medicine via the yellow card system. Our methods have much in common with the Confidential Enquiry into Perioperative Deaths (www.ncepod.org.uk accessed on Feb 13, 2001), on which we have modelled our approach.

Although we recognise the important role of regulatory agencies in assessing adverse events, we believe that our methods offer additional means of investigating potential drug-related

adverse events in a systematic way. Involvement of local specialists, we believe, is essential. We believe that specialist knowledge, a familiarity with local approaches and health-care systems is more likely to identify preventable errors in any given specialist area.

*Paresh Jobanputra, Dawn Homer

Department of Rheumatology, Selly Oak Hospital, University Hospital Birmingham NHS Trust, Birmingham B29 6JD, UK

- 1 Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**: 1255–59.

Sir—I Ralph Edwards and Jeffrey K Aronson¹ report on management of adverse drug reactions. We describe the US Department of Veterans Affairs' development of a common terminology and schema for adverse drug events (ADEs). The aim of this effort is to promote consistency and a common base of understanding for improving system-wide Veterans Health Administration (VHA) reporting efforts.

VHA analysed spontaneous reports of adverse drug reactions submitted by VHA health-care facilities to the Food and Drug Administration for fiscal year 1999. Signals of drug-safety issues emerged after a review of the adverse-drug reaction database, including preventable reactions. This approach allowed rapid-turnaround notification to VHA centres of events and recommended preventable measures.

The preliminary analysis showed a wide variation in the use of certain terms and definitions relating to adverse events, including medication errors and adverse drug reactions, by frontline health-care practitioners. Our review of the medical and pharmacy literature mirrored these internal findings and revealed that the area of research into adverse drug reactions was in a period of dynamic positive change. VHA clearly needed to reconcile terminology differences and diffuse this information throughout the organisation to effectively further its safety agenda.

The findings led to a charge by the Under Secretary for Health for the creation of working groups to focus on the identification and possible prevention of ADEs. To lay the necessary framework, the taxonomy and nomenclature working group aimed to create a consensus during a conference in Washington, DC, USA, in September 2000. Stakeholders oriented the group on views and needs of use of the VHA system and the Food and Drug Administration. National experts on ADEs and VHA leaders

were given a compilation of evidence on adverse events, descriptions of safety efforts, and a table of literature definitions, and asked to apply adverse event case studies to show use of terms. The group used suggested straw man definitions and schemata and, through an iterative process of development, arrived at a consensus on definitions (table 1), schematic representations, and taxonomies and abbreviations.

The VHA envisions that the proposed definitions will accommodate the broad reporting of adverse events by front-line staff (laypeople and practitioners), allow for analysis of events, and provide a universal framework for understanding medication-related disorders. The definitions might require refinement over time after data are collected and analysed. Two working groups are

planned to assess VHA computer systems and work processes to further accommodate reporting and analysis of ADEs.

The definitions and schema will help training to improve reporting and reduction of adverse events, which will improve the care of patients since more than half of all practising physicians in the USA are trained in the VHA system.

*Robert Roswell, Louise R Van Diepen, Judith K Jones, Wanda E Hicks

*Department of Veterans Affairs, Veterans Health Administration, 810 Vermont Avenue NW, Washington, DC 20420, USA; and The Degge Group Ltd, Arlington, VA, USA

1 Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**: 1255–59.

Consensus definitions for adverse drug events

First tier: perspective of a layperson

Problem: something that looks funny.

Second tier: perspective of health practitioner/professional

Medication-related problem: a problem discovered in patient care that appears to be related to a medication, and/or the medication use process, and outcome (including ordering, transcribing, dispensing, administering, and monitoring).

The medication use process: intends to provide the five R's: right patient, right drug, right route, right dose, right frequency. The problem may have, but may not have caused injury to the patient. The problem may have, but may not have been preventable.

Third tier: perspective of analyst

Adverse drug event: an injury associated with use or non-use of a drug. This is an overarching term for the terms described below.

Medication error: a preventable event in the medication use process (eg, ordering, transcribing, dispensing, administration, adherence, or monitoring) that resulted in (or could have resulted in) an outcome other than intended. An event in the process includes events of admission or omission.

Potential adverse drug event: ("close call") a medication error that has the potential to cause injury

Preventable adverse drug event: an adverse drug event associated with a medication error.

Non-preventable adverse drug event: (historically referred to as adverse drug reactions). An adverse drug event associated with appropriate medication use.

Serious adverse drug experience: a regulatory term used by the FDA. The Taxonomy and Nomenclature Working Group acknowledges the use of this term in support of FDA's mission.

Myalgic encephalomyelitis in children

Sir—I was able to spend a few months as an observer at the paediatric department of a hospital in the UK. During my stay, I came across a disease called myalgic encephalomyelitis (ME), which, despite 17 years in general paediatrics, I had never encountered. I contacted French, Belgian, and Swiss colleagues none of whom had ever diagnosed any paediatric case of chronic fatigue syndrome or ME. In my home practice, we see children who are tired, but never to the point of disability. I sought to discover whether, ME is truly a disease.

ME's severe sounding names makes it obvious it should be judged as a disease. Children become non-functioning and even bedridden. Symptoms frequently occur after an infectious disease, and include multiple ache in the muscles, throat, and head that can continue for months to years. Recovery is long-term and requires a multidisciplinary clinical team. Some biological abnormalities have been found in ME, that suggest a viral infection or impairment of the immune system. Many reports are available on this disorder (256 references in the report of a working group in 1996).¹

However, the name of the disease does not correspond to a specific muscle or brain disease. No clinical, biological, radiological, or electrical investigation shows a specific abnormal pattern. No basic treatment leads to a complete cure. After an acute viral illness, ME or chronic fatigue can continue for months or years and renders children incapable of participating in everyday activities. The disorder seems to be a disease, and most children have heard about it before

developing it. They can catch it because it exists, and people can read about it.

Maybe ME should be classed as a disease because its consequences can sometimes in fact be extensive. It may not, however, be an organic disease. ME is unknown in Europe outside the UK. Maybe UK children are genetically different from their European counterparts. Maybe a mysterious unknown virus exists on only one side of the Channel. Or maybe the disease is culturally induced, possibly through medical information, education, or the school system.² The disorder is not a product of children's imagination and requires medical treatment. However, the child cannot be cured because there is no specific disease and, therefore, no specific treatment.

The difference between the UK and France is that no child, parent, or physician has heard of ME, and ME does not seem to exist as a specific disease in France. Perhaps in France we are overlooking ME diagnoses? Or perhaps ME will emerge with a better knowledge of symptoms. Hopefully, further studies will demonstrate a specific infectious cause or a role for substances such as food preservatives. Alternatively, ME might be an example of a culturally induced or culturally worsened disease, similar to neurasthenia in the 19th century.

Olivier Mouterde

Paediatric Department, Rouen University Hospital, 76031 Rouen, France (e-mail: Olivier.Mouterde@chu-rouen.fr)

1 Report of a joint Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners: chronic fatigue syndrome. London: Royal College of Physicians Publications Unit, 1996: 1–158.

2 Pliophly AV. Chronic fatigue syndrome should not be diagnosed in children. *Pediatrics* 1997; **100**: 270–71.

DEPARTMENT OF ERROR

Statins and the risk of dementia—In this Article by H Jick and colleagues (Nov 11, p 1627), there were a number of errors in table 1: the third category under body-mass index should be " ≤ 23 "; there should be no "+" sign after the 95% CI for coronary-artery disease; and there should be a "S" sign after the 95% CI for coronary-artery bypass surgery. In table 2, the p value for current use of statins should be " 0.002 ".

Holmes-Adie syndrome—In this Eponym by Paolo Martinelli (Nov 18, 2000, p 1760), the legend to the figure should be "**Basal assessment and pharmacological assessment.** A: basal assessment under room light... B: pharmacological assessment."

Safety of insulin glargine—In this Correspondence letter by Michael Berger (Dec 9, p 2013), the first sentence should have read "The Aug 5 commentary of Gerencia Bolli and David Owens requires some additional information on the safety of insulin glargine."