# CORRESPONDENCE

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## SARS, lay epidemiology, and fear

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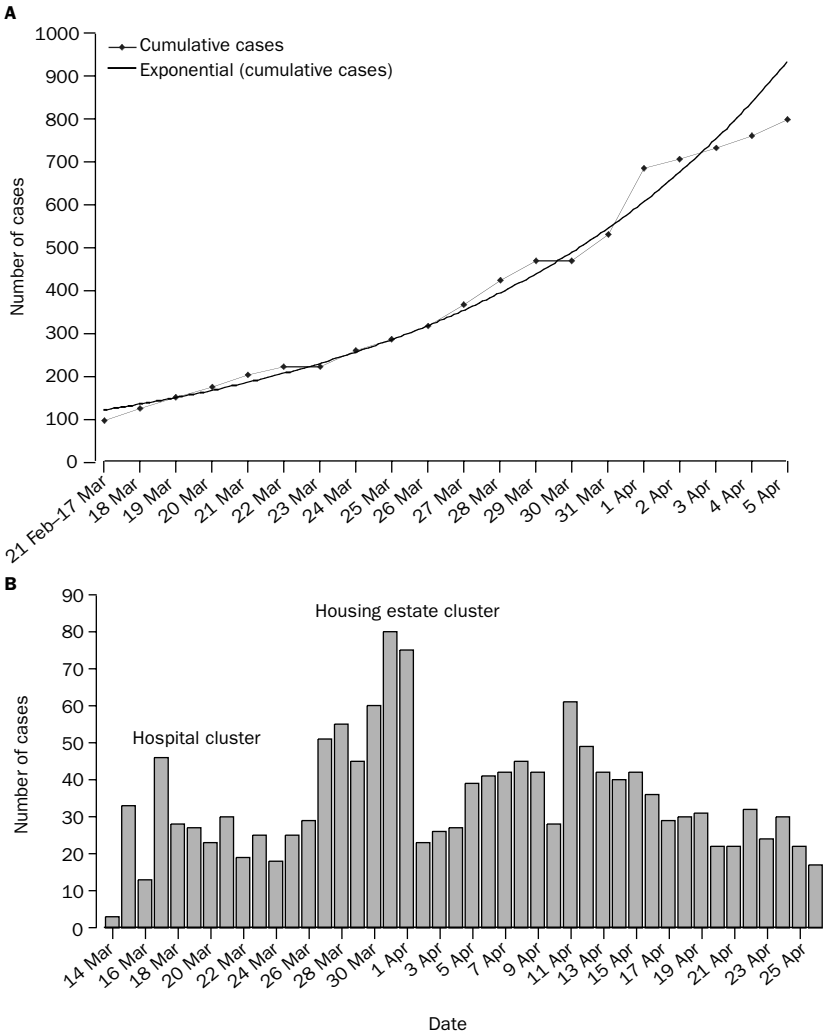
Sir—Ann Falsey and Edward Walsh (published online April 8)[1] describe the fears that surround severe acute respiratory syndrome (SARS). In the past few weeks, our outpatient department in Germany has received numerous calls from worried doctors of companies doing business in Asia. These calls have increased since the claim was made that within 2 years every citizen of Hong Kong will be infected with SARS. A German newspaper[2] fitted an exponential curve to the cumulative number of probable SARS cases (as reported by WHO[3]), forecasting a progressively steeper increase in case numbers. Such predictions can have enormous economic repercussions, so they should be scientifically tenable; we do not believe they are.

To illustrate why, we have fitted curves to the cumulative cases reported from Hong Kong between Feb 21 and April 5, 2003. Microsoft Excel calculates an $R^2$ of 0·98 for an exponential curve, indicating an excellent fit (figure, A). Using the function of the curve, we can predict a total of 71 583 cases 60 days later. The exponential curve matches the dynamics of an epidemic in a closed population with a high basic reproductive number $R_0$, which corresponds to the average number of new cases that one infectious case is expected to produce. Under such conditions, almost everyone will become infected during the epidemic.[4] However, a linear curve can be fitted to the same data, yielding an equally impressive $R^2$ of 0.96, but predicting only 2410 cases 60 days later. Moreover, $R^2$ statistics are invalid with cumulative data because the assumption that observations are independent is violated.

Making predictions early in an outbreak by fitting simple curves is dubious for another reason—doing so ignores interventions to decrease contact rate and transmission probability. If successful, such efforts reduce $R_0$ and thereby case numbers.[4] An emerging herd immunity would also reduce $R_0$. This effect might only be temporary, however, since antibody levels diminish rapidly in other coronavirus infections.[5]




**Cumulative number (A) of reported cases of SARS in Hong Kong up to April 5, 2003, and daily number (B) of reported new SARS cases in Hong Kong up to April 26, 2003 (total n=1527)**

Part B of the figure shows an alternative way of presenting the data, which we think is more informative. That there has not been a great increase in the average number of new cases per day in the past weeks becomes immediately apparent. Furthermore, the outbreak in a housing estate in late March is not followed by a pronounced peak of secondary cases 2–7 days later, as would be expected if $R_0$ was generally high. These data are compatible with the hypothesis of uncommon but effective modes of transmission, in combination with an overall $R_0$ that is not exceptionally high. Given the possibility of waning immunity, the data are also consistent with an emerging endemic situation in which a part of the population will be affected seasonally.[4,5]

Attempts to model the dynamics of an epidemic early on can lead to untenable conclusions, especially when based on worst-case scenarios such as a persistently high $R_0$. Although we wholeheartedly support the policy to publish case numbers, a format that can be easier understood by lay people

should be used—namely, daily case numbers instead of cumulative figures.

*Oliver Razum, Heiko Becher, Annette Kapaun, Thomas Junghanss

Department of Tropical Hygiene and Public Health, University Hospital, Im Neuenheimer Feld 324, 69120 Heidelberg, Germany (e-mail: oliver.razum@urz.uni-heidelberg.de)

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## Atypical presentations of SARS

Sir—Singapore reported its first imported cases of SARS on March 13, 2003. By March 17, 21 secondary cases had been identified at Tan Tock Seng Hospital, which was then designated the national SARS hospital in an attempt to contain the epidemic.

At the National University Hospital, we developed screening protocols similar to those reported by William Ho.[1] All patients meeting WHO criteria[2] for probable or suspect SARS were transferred to Tan Tock Seng hospital. However, four individuals admitted to our hospital with atypical presentations of disease were later diagnosed with SARS. Their clinical and epidemiological features (table) emphasise some of the difficulties in identifying SARS without a reliable diagnostic test.

Individuals are defined, according to WHO, as having had contact with SARS if they have cared for, lived with, or had direct contact with respiratory secretions and body fluids of a person with the disease. Three of our four patients became infected simply by visiting affected wards of other hospitals; only children or dangerously ill patients can now be visited in hospital.

Our patients might not have had the characteristic fever (>38°C) associated with SARS[3] on admission because of chronic comorbidities, raising questions about the sensitivity of temperature monitoring as a screening tool. All our patients became febrile with clinical and radiological deterioration, and eventually met the criteria for transfer.

The four patients had lymphopenia and raised serum concentrations of lactate dehydrogenase. These non-specific abnormalities have been previously reported[4] in individuals with SARS, and could alert doctors in affected areas to atypical presentations of SARS. Other laboratory variables were not helpful in our cases.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Age (years) | 71 | 43 | 78 | 63 |
| Sex | Woman | Woman | Woman | Man |
| Date of admission | March 19, 2003 | March 23, 2003 | March 31, 2003 | April 8, 2003 |
| Time to isolation (h) | 3 | 8 | 4 | 12 |
| Type of contact | Visitor* | Visitor* | Recent inpatient | Visitor* |
| Contact identified on admission | No | No | No | No |
| Temperature on admission (°C) | 38·7 | 37·3 | 36·3 | 36·0 |
| White blood cell count/ lymphocytes ($10^9$/L) | 4·5/0·78 | 19·3/0·94 | 11·2/0·69 | 9·3/0·63 |
| Lactate dehydrogenase (IU/L) | 747 | 2513 | 1032 | 1770 |
| Chest radiograph | Increased right basal markings | Bilateral lower lobe consolidation | Bilateral lower lobe infiltrates possibly acute | Bilateral lower zone haziness |
| Initial diagnosis | Possible congestive cardiac failure | Pneumonia, bilateral, possibly bacterial | Exacerbation of chronic lung disease, possible congestive cardiac failure | Congestive cardiac failure |
| Comorbidities | Diabetes, ischaemic heart disease | Hypertension | Connective tissue disease on steroids, ischaemic heart disease | Ischaemic heart disease |
| Outcome | Survived | Died | Died | Died |

*Attendance in a hospital ward later found to be accommodating a patient with SARS.

**Characteristics of four patients with atypical presentations of SARS**

Early in the epidemic, a single non-isolated case of SARS led to dozens of secondary and tertiary cases, many fatal.[5] The contagious nature of the disease justifies early isolation of individuals with low grade fever, chest radiograph abnormalities, or respiratory symptoms alone. In the first 3 weeks of adopting this policy, we had admitted 275 individuals who did not meet WHO criteria to our isolation wards, where full respiratory and contact isolation is provided in single rooms. 49 patients and 17 staff have since been referred to the SARS hospital. At the time of writing, six more typical probable cases have been transferred, without having caused any secondary infections.

Unfortunately, nosocomial transmission did result from two of our atypical cases, since they spent up to 12 h in open ward areas before full isolation precautions were taken. Two doctors, three nurses, three visitors, and two other patients have been infected by them, and a further 100 individuals who came into contact with these two cases remain under surveillance.

Atypical presentations of SARS are a threat to patients, staff, and visitors. The WHO case definition is a useful epidemiological device. However, it is no substitute for daily, thorough clinical, laboratory, and radiological assessment of patients with symptoms of this emerging disease. Doctors cannot afford rigid adherence to epidemiological criteria when caring for individual patients.

*Dale A Fisher, Tow-Keang Lim, Yean-Teng Lim, Kamaljit S Singh, *Paul A Tambyah*

National University Hospital, Singapore 119074
(e-mail: mdcpat@nus.edu.sg)

1 Ho W. Guideline on management of severe acute respiratory syndrome (SARS). *Lancet* 2003; **361:** 1313–15.

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## Admission cardiotocography

Sir—Observer variation in visual analysis of cardiotocograms was not taken into account by Lawrence Impey and colleagues (Feb 8, p 465).[1] However, such variation does arise, including admission cardiotocography,[2] and makes randomised controlled trials impossible to interpret.[3]

For example, for an observer variation with a proportion of agreement of 0·33 and 0·71 for abnormal and normal tracings, respectively, and an assumed sensitivity and false positive rate of 50% and 17%, respectively, the latter can vary between studies from 0% to 100% and 0% to 33%, respectively.[3] In the same way, for a proportion of agreement of 0·33 and 0·71 for intervention and no action, respectively, and an assumed efficacy and rate of unnecessary interventions of 50% and 17%, respectively, the latter can vary between studies from 0% to 100% and 0% to 33%, respectively. This variation leads to discrepancies in randomised controlled trials and could also result in poor average results in multi-observer studies and meta-analyses.[3]

Therefore, we believe that Impey and co-workers' results should be considered as an absence of evidence rather than an evidence of absence of effectiveness of admission cardiotocography. In our opinion, the above difficulties can only be overcome if we focus the research on more objective cardiotocogram analysis[3–5] and then undertake randomised controlled trials based on reproducible methods.

J Bernardes and A Costa-Pereira are involved in the development of SisPorto, a computer based system for cardiotocogram analysis.

*João Bernardes, Altamiro Costa-Pereira

Porto Faculty of Medicine, 4200 Porto, Portugal
(e-mail: joaobern@med.up.pt)

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Sir—Lawrence Impey and colleagues[1] report that routine use of admission cardiotocography does not improve neonatal outcome. As the investigators acknowledge, the practice in Dublin is to rupture the membranes when the patient is admitted to the ward in labour. However, in most obstetric units in the UK there is now a midwife-driven policy to preserve the membranes unless there is delay in labour, so that presence or absence of meconium is not ascertained.

The outcomes measured by Impey and colleagues (moderate or severe neonatal morbidity or perinatal mortality in the absence of a major congenital malformation) only arose in about 1·3% of their patients in the UK and are not all indicators of severe morbidity. Obstetricians are concerned, among other things, to prevent rare but serious events, for example, severe hypoxic ischaemic encephalopathy leading to fetal death or cerebral palsy. Yudkin and co-workers[2] found that, in 1984–85, this type of event occurred at an estimated rate of 0·63 per 1000 neonates. For 1997–2001 in Dublin, the expected incidence of such events is probably lower than the rate reported by Yudkin and co-workers. Therefore, even a study the size of the one done by Impey and colleagues, which consisted of 8580 women, would be too small to detect any differences occurring as a result of treatment. It is difficult to examine rare, serious events in a randomised controlled trial because such a study would have to be so huge. We, therefore, have to fall back on methods such as case control or case analysis. Case analysis is used in the Confidential Enquiry into Maternal Death in the UK, and in the Confidential Enquiry into Stillbirths and Deaths in Infancy.

The one disaster fully described in the Impey paper was a neonatal death in the usual care group of the study. Fetal monitoring might well have discovered this case. The babies who died or were damaged in Yudkin and co-workers' study[2] were either not monitored or had abnormal ominous signs that did not give rise to action.

Whether asphyxia is a rare cause of cerebral palsy depends on the definition of rare. Cerebral palsy is not common; about 1–2 per 1000 neonates. Most cerebral palsy is not caused by labour-related asphyxia. The suggestion by Pschirrer and Yeomans[3] that asphyxia might cause about 10% of cases of cerebral palsy seems reasonable. Does that make it a rare cause? Hypoxic ischaemic encephalopathy, a strong risk factor for death or cerebral palsy, is almost unheard of after elective caesarean section.[4]

The available methods we use to identify all high-risk patients—eg, growth-restricted pregnancies—are not good. For these reasons, I believe electronic fetal monitoring, for all its faults, remains an essential tool for admission to and in the labour ward.

*W A Liston*

Department of Obstetrics, Royal Infirmary of Edinburgh, Little France, Edinburgh EH16 4SA, UK
(e-mail: liston@btinternet.com)

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### *Authors' reply*

Sir—We thank João Bernardes and W A Liston for their comments.

In reply to Bernardes, there is indeed interobserver and intraobserver variation in interpretation of cardiotocography. Standardised interpretation by means of a computer program would overcome this difficulty. Success has been achieved in the antepartum period,[1] but extending this achievement to the start or duration of labour is very different. We await developments in this area with interest.

The use of admission cardiotocography is widespread. In its current form, interpretation is almost exclusively by individuals. Our trial was designed to answer the question: "Does what we currently do benefit our patients?" Our findings suggest that it does not. Evidence with respect to the potential benefits

of a computer-interpreted admission cardiotocogram remain absent. Such a tool should also be assessed by means of a randomised controlled trial. But that would be answering a different question.

In response to Liston, we acknowledge, as we did in our report, that we show admission cardiotocography to be unhelpful only in women with clear amniotic fluid. Importantly, however, much of the evidence about continuous electronic fetal monitoring (EFM) in labour has also been collected in such women.[2]

Likewise, we tested admission cardiotocography only, not continuous (EFM) itself. Those who use admission cardiotocography aim to reassure themselves that they do not need to use EFM. Yet EFM reduces neonatal encephalopathy, certainly in women whose amniotic fluid is clear.[2] As far as the baby is concerned, therefore, a policy of EFM for all is probably safer than one of admission cardiotocography, because the latter is a poor screening test.

EFM is a sensitive, but non-specific test for hypoxia. But many babies with so-called hypoxic ischaemic encephalopathy do not have hypoxia; and most babies with hypoxia do well. Moreover, prediction is not the same as prevention. Thus, although an admission cardiotocogram might have discovered, or predicted our neonatal death, the evidence suggests that it would not have prevented it.

A common assumption is that hypoxia/acidosis is the only way in which a baby can be adversely affected by labour. The emerging data on maternal pyrexia[3] points to other mechanisms, which might explain the apparent protective effect of prelabour elective caesarean.[4] The benefits of electronic monitoring in trials and in practice have been, at best, small and at a heavy price in terms of operative delivery. The time has come for a rethink.

*Lawrence Impey, on behalf of co-authors*

Oxford Feto-Maternal Medicine Unit, Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK
(e-mail: Lawrence.Impey@orh.nhs.uk)

1 Dawes GS, Moulden M, Redman CW. Computerized analysis of antepartum fetal heart rate. *Am J Obstet Gynecol* 1995; **173:** 1353–54.
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## Hepatic artery chemotherapy and colorectal liver metastases

Sir—David Kerr and colleagues (Feb 1, p 368)[1] have made a valuable contribution to the debate on the role of hepatic artery chemotherapy in colorectal liver metastases. We agree with their conclusion that the intra-arterial regimen they used should not be used outside of a clinical trial. However, there are three crucial issues that need to be understood when reviewing the disappointing results of their study.

First, fluorouracil was used as the intra-arterial drug. In previous trials[2] that have shown a survival advantage for hepatic artery chemotherapy, floxuridine was used as the chemotherapeutic agent. Unfortunately, this drug was not available to Kerr and coworkers.

Second, no data is presented on the carcinoembryonic antigen response to the chemotherapy regimen and, therefore, the efficacy of the regimen cannot be compared with those used in other studies, in which response rates of 75% have been noted.[3] In a trial[4] in which we used an alternative fluorouracil-based regimen, we noted a median survival of 15·2 months and a carcinoembryonic antigen response in half the study group.

Finally, the controlled trials referred to in the accompanying Commentary[5] used pumps rather than ports for the delivery of the chemotherapy agents. We have noted large differences in complication rates between port-delivered fluorouracil and pump-delivered floxuridine systems in the 430 patients we have treated with hepatic artery chemotherapy; early catheter loss hardly ever arises in the latter group. We will report data on this shortly.

We believe that further assessment of the role of hepatic artery chemotherapy in the management of colorectal liver metastases is needed.

*Adam Brooks, Philip Clingan, *David Morris*

University of New South Wales, Department of Surgery and Medical Oncology, St George Hospital, Sydney, Australia
(e-mail: david.morris@unsw.edu.au)

1 Kerr DJ, McArdle CS, Ledermann J, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. *Lancet* 2003; **361:** 368–73.
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Sir—In their study, Kerr and colleagues[1] did not note the differences in progression-free or overall survival between individuals who received regional intra-hepatic chemotherapy with fluorouracil and those who received intravenous fluorouracil for unresectable colorectal liver metastases. Although randomised studies are of great importance for the comparison of chemotherapy regimens, several issues need to be addressed to properly interpret the trial.

In the intra-arterial chemotherapy group, a large proportion of patients (37%) did not start the regional chemotherapy, and only a third of them completed all six cycles. Additionally, fluorouracil was used as the chemotherapeutic agent. Floxuridine, a metabolite of fluorouracil, would have been preferable, since it is associated with an increased response rate due to its higher hepatic extraction (>95%) and hepatic first-pass effect; floxuridine is associated with decreased toxicity and improved survival.[2]

Furthermore, only patients without extra-hepatic diseases would benefit from selective intra-arterial chemotherapy. Since survival of patients is improved after liver resection for colorectal metastases by exclusion of those with occult extra-hepatic diseases,[3] we routinely search for extrahepatic tumours with positron emission tomography (PET)-scanning.

Last, we believe that administration of intra-arterial chemotherapy by an implantable pump is better than using a port system, since it offers the possibility of bolus injection combined with continuous treatment on an outpatient basis. Implantable pumps have been used successfully for adjuvant chemotherapy[2] or downstaging of non-resectable liver tumours.[4]

Although Kerr and colleagues' study provides some novel insight, we believe that further studies are warranted with a focus on drugs with high hepatic extraction rates given by a continuous intrahepatic infusion system, and possibly in combination with systemic chemotherapy.

*P A Clavien, F Dahm, N Selzner, M Selzner

Department of Visceral and Transplantation Surgery, University Hospital Zurich, Zurich, Switzerland
(e-mail: pierre-alain.clavien@usz.ch)

1 Kerr DJ, McArdle CS, Ledermann J, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. *Lancet* 2003; **361:** 368–73.
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Sir—Efficacy and compliance are two separate components related to how treatment works in the population, and they should not be routinely combined in a single intention-to-treat analysis.

One of the major justifications for undertaking an intention-to-treat analysis in a randomised study is that, by ignoring compliance when the data are analysed, the way treatments will function in the population is suggested. When compliance shows great imbalance in a phase 3 study, however, this result counts against the treatment efficacy of the non-compliant group. Moreover, compliance during an efficacy trial might be quite different from compliance of the same treatment once it has been proven to be efficacious.

Kerr and colleagues[1] report that 34% of patients in the intra-arterial group did not receive the planned treatment due to catheter issues, and the effect of worse compliance in the experimental group was mistakenly translated into treatment efficacy of the standard group. The investigators assumed that because similar outcomes were noted for those who followed the standard intravenous treatment more closely, the intrahepatic arterial therapy was not more effective.

Additionally, 45 of 145 patients in the intra-arterial group, who did not start treatment or received fewer than six cycles, were swapped to the intravenous group, meaning that two-thirds of the trial patients were eventually allocated to the intravenous standard treatment. Hence, the potential efficacy results of the experimental group vanish in an intention-to-treat analysis. To emphasise the difficulty of such an analysis in this setting, the authors should ask themselves how many patients out of the 145 in the intra-arterial group actually received more than 1 month of intra-arterial chemotherapy.

Based on these considerations, the intention-to-treat analysis undertaken by Kerr and colleagues is not the proper test to answer the research efficacy question. Since the efficacy of a treatment is often of great scientific importance irrespective of compliance issues, we believe that additional statistical analyses should be presented to the reader for a complete and correct interpretation of the data, such as using compliance as a covariate so that it is not confounded with treatment, or by doing an on-treatment analysis also. The authors' interpretation of the study, as it seems in the summary of their article, is not correct and could lead to misleading conclusions.

*Emiliano Calvo, Manuel Sureda

Department of Oncology, Hospital San Jaime, Partida de la Loma, 03180 Torrevieja, Alicante, Spain
(e-mail: calvo@hsanjaime.com)

1 Kerr DJ, McArdle CS, Ledermann J, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. *Lancet* 2003; **361:** 368–73.

### *Authors' reply*

Sir—Brooks and Clavien and their colleagues make similar points, reporting their experience with implantable arterial pumps and the cytotoxic drug floxuridine. No trials have been done to compare fluorouracil with floxuridine. Their assumptions that floxuridine is better than fluorouracil are, therefore, not based on randomised evidence. Floxuridine does have a higher hepatic extraction rate but, as discussed in our report, many patients with macroscopic hepatic metastases have pulmonary micrometastases, making the lungs a common site of cancer progression. We can generate effective systemic concentrations of fluorouracil with our arterial regimen without having to resort to complex combinations of arterial and venous regimens.[1]

The published work on complication rates with implantable pumps is variable and we await publication of Brooks and colleagues' work with interest.

PET was not generally available in the UK during our trial and, although several centres did measure carcino-embryonic antigen response rates as a surrogate of tumour response, this test was not a formal trial requirement since the analysis was powered to detect survival differences.

Calvo and Sureda made a series of points about intention-to-treat analyses. They pose a question, which was asked by several of our investigators—what was the survival in the intra-arterial group who received more than 1 month's therapy? We resisted then (and now) the temptation to undertake subgroup analyses because we believe that doing so would not provide any additional insight; better that we test the experimental group in its entirety, than select an arbitrary and potentially unrepresentative subpopulation who might, by chance, have a different natural history. Patients could cross over from the intra-arterial to the intravenous chemotherapy group (not vice versa), but this action was predefined in the trial protocol and in keeping with the observation that conventional chemotherapy offers a survival benefit compared with observation alone.

*David Kerr, Colin McArdle, Jonathan Ledermann, Irving Taylor

*University of Oxford, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE, UK (DK); Cancer Research UK and UCL Cancer Trials Centre, London (JL); University Department of Surgery, Royal Infirmary, Glasgow (CM); and Department of Surgery, Royal Free and University College Medical School, London (IT)
(e-mail: david.kerr@clinical-pharmacology.oxford.ac.uk)

1 Kerr DJ, Ledermann JA, McArdle CS, et al. Phase I clinical and pharmacokinetic study of leucovorin and infusional hepatic arterial fluorouracil. *J Clin Oncol* 1995; **13:** 2968–72.

## Does VaxGen hide the breakthrough infections?

Published in the last week of February, 2003, the latest report from the UN Population Division[1] indicates that by 2050, the population of the hardest hit nations will have risen by 400 million people fewer than previously estimated because of AIDS. This estimate could be the first sign that HIV-1 will cause extinction of human beings in this millennium unless an effective AIDS vaccine is developed.

The results of an efficacy trial[2] of the only AIDS vaccine to progress past phase 3 trials—a gp120-based vaccine made by VaxGen (Brisbane, CA, USA)—have however, confirmed that

an effective vaccine is not on the horizon. According to VaxGen's report, after 5 years of trials, involving 5108 men who have sex with men and 309 women, all negative for HIV-1, the vaccine was ineffective.

Commenting on this report, many mainstream AIDS researchers concluded that the results were disappointing but not unexpected. So why was so much effort, time, and money, allowing further evolution and spread of HIV-1, not prevented?

During the past 10 years, we have been studying the properties of the HIV-1 envelop protein and the molecular mechanisms that prevent the immune system from mounting an efficient response to infection.[3] We noted that after infection deceptive imprinting[4] takes place—a process that we postulated would be accelerated in individuals vaccinated against AIDS. Reports of fast breakthrough disease progression among volunteers who participated in clinical trials of HIV-1 gp120-based vaccines lend support to this notion.[5]

These findings raise important questions about the safety of VaxGen's AIDS vaccine. During the efficacy trial, 191 vaccinated volunteers and 98 controls were infected with HIV-1. To properly assess the safety of the vaccine, the HIV-1 status of the breakthrough-infected vaccinated volunteers and controls need to be compared. Our work[5] indicates that the vaccine would increase the likelihood of infection and disarm the immune system's antiviral response, thus resulting in accelerated disease progression. It is noteworthy that in 3003 white and Hispanic volunteers who received VaxGen's vaccine, the proportion of breakthrough infections was higher than in 1508 corresponding controls (6% *vs* 5%). Although this difference is not significant, it could indicate a dangerous trend.

A thorough analysis of the VaxGen trial and its results is necessary to prevent possible harm to volunteers and further money wasting in the future.

*Veljko Veljkovic, Sybille Müller, Heinz Köhler

*Center for Multidisciplinary Research, Institute of Nuclear Sciences VINCA, PO Box 522, 11001 Belgrade, Yugoslavia (VV); Immpheron, Lexington, KY, USA (SM); and Department of Microbiology and Immunology, University of Kentucky, Lexington, KY, USA (HK)
(e-mail: veljko01@hotmail.com)

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## Inequities among the very poor: effect of young age on care-seeking

Sir—We fully agree with the findings of Joanna Armstrong Schellenberg and colleagues (Feb 15, p 561) on inequities among the very poor in rural Tanzania.[1] From our own experience, we would like to add some comments, which in our opinion are also crucial for the understanding of adequate care-seeking behaviour.

Haydom Lutheran Hospital is in a remote rural, semi-arid area close to Lake Eyasi in Mbulu District, northern Tanzania. People are at least as poor as in Schellenberg's study, quite a few of them being nomads. As part of a study on the usefulness of providing emergency ambulances in our area, we noted that children were four to ten times less likely than adults to be brought in by ambulance (table). The only exceptions were infants, who were transported 2·5 times more often than older children.

These results surprised us, since ambulances are usually called only in emergency situations, and mortality rates indicate that neonates (many of whom are born at home), infants, and children are at high risk. Since all patients and caregivers can call ambulances via radio from the surrounding villages, and since the price to transport a child is the same as that for an adult per km (300 Tanzanian shillings in 1999 [US$0·4] to be paid at the end of treatment), there must be some other explanations for this striking difference.

One reason is probably the direct and indirect cost of transport. Parents will try to save money by transporting even very sick children to hospital themselves. Furthermore, in a very poor family, resources might be allocated to individual members differently, to ensure the economic survival of the family.[2] A care-giver's knowledge about neonatal and childhood diseases might also play a part, as might local beliefs and habits in child health care.

Together, these factors could explain in part why even seriously ill infants and children are brought in for appropriate care very late or not at all.[3,4] The higher rates of use of ambulances for neonates and infants in our study compared with others' experiences[3,4] might indicate the efforts of the mother and child health outreach programme provided by the hospital, and the good reputation of its neonatal services in the community.

Can Schellenberg and colleagues confirm our observation of age-dependent care-seeking behaviour on the basis of their data? We strongly believe that health-care programmes need to be refocused not only on the poorest but also on the youngest patients to improve health equity for all. Education of caregivers, provision of free emergency transport for young children, and so-called community-based programmes,[3,4] could improve the situation.

*Carsten Krüger, Ole Halgrim Evjen Olsen

Haydom Lutheran Hospital, PO Mbulu, Haydom via Mbulu, Tanzania (CK, OHEO); and *Department of Paediatrics and Neonatology, St Vincenz Hospital, Suedring 41, D-48653 Coesfeld, Germany (CK)
(e-mail: carsten.krueger@krankenhaus-coesfeld.de)

| | Individuals transported (n=798) (number, %) | Mortality (%) | Age distribution of total population in the catchment area (%)* | Relative chance of using ambulances† |
|---|---|---|---|---|
| **Age (years)** | | | | |
| <1; subgroup <1 month | 14 (2%)‡; 4 (0·5%)‡ | 21%; 75% | 4% | 0·24 |
| 1–5 | 20 (3%)‡ | 20% | 14% | 0·09 |
| 5–15 | 45 (6%)‡ | 7% | 31% | 0·09 |
| ⩾15 | 719 (90%) | 9% | 52% | 1·00 |

*1988 Tanzania National Census data adjusted for 1999. †Age 15 years and older defined as relative chance=1. ‡No sex differences noted.

**Age-dependent use of ambulances at Haydom Lutheran Hospital, Tanzania, in 1999**

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## Recombinant activated factor VII and perioperative blood loss

Sir—Philip Friederich and colleagues (Jan 18, p 201)[1] found that 40 μg/kg of recombinant activated factor VII can reduce perioperative blood loss and eliminate the need for transfusion in patients undergoing major surgery. Median perioperative blood loss was 2688 mL in placebo-treated patients, 1235 mL in patients treated with 20 μg/kg recombinant factor VIIa, and 1089 mL in those who received 40 μg/kg recombinant factor VIIa.

Standard requirements for transfusion do not support the use of packed red blood cells above a haemoglobin concentration of 4·5 mmol/L or 5·5 mmol/L in otherwise healthy patients. The Transfusion Requirements in Critical Care Investigators[2] showed that transfusion in patients with a haemoglobin concentration of 4·35 mmol/L may be associated with increased survival. Therefore, it would be informative to know the lowest haemoglobin concentrations in all groups in Friederich and colleagues' trial, and to see how many patients would have reached standard transfusion requirements.

We have found that the haemostatic effect of recombinant factor VIIa can be seen immediately.[3] We may thus assume that in Friederich and colleagues' study transfusion requirements were restricted to the intraoperative period. Furthermore, it is unclear from their discussion why the duration of operation in the placebo group was significantly longer than in the treatment groups. If less bleeding was associated with better conditions in which to operate, than we would expect surgeons to have seen the effect of recombinant factor VIIa during surgery. Perhaps in this trial, therefore, blood loss during surgery meant that surgeons were aware of study treatment.

As Guillonneau and co-workers[4] report, laparoscopic prostatectomy is associated with significantly less blood loss and less requirements for blood transfusions than radical retropubic prostatectomy or Millin prostatectomy. At our institution we do not routinely prepare blood for laparoscopic radical prostatectomies because we normally have no blood transfusion requirements.[5]

Friederich and co-workers state that 2 units of packed red blood cells could be saved by giving 40 μg/kg of recombinant factor VIIa. However, this is not a cost-effective option since the estimated additional cost for recombinant factor VIIa is €2550, compared with €200 for additional packed cells. We suggest that patients should be identified who will tolerate low transfusion thresholds, that laparoscopic methods should be used for prostatectomy, and that recombinant factor VIIa should be restricted to patients with refractory bleeding.

*Thomas Volk, Christian von Heymann, Wolfgang J Kox

Department of Anaesthesiology and Intensive Care Medicine, University Hospital Charité Campus Mitte, Humboldt University, Berlin, 10117 Berlin, Germany
(e-mail: thomas.volk@charite.de)

1 Friederich PW, Henny CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003; **361:** 201–05.
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Sir—Although we agree with Philip Friederich and co-workers[1] that recombinant factor VIIa can reduce perioperative blood loss and need for transfusion, there are several points that need further clarification.

Friederich and colleagues suggest that the only clinical benefit is a reduction in the need and number of units of blood transfused with 40 μg/kg recombinant factor VIIa. However, there was no reduction in length of hospital stay among patients who received recombinant factor VIIa. Furthermore, are the investigators able to comment on the cost benefit of using recombinant factor VIIa to save transfusion of 2 units of packed cells?

Was the significant reduction in duration of operation between placebo and treatment groups related to differences in time before administration of the intravenous bolus of recombinant factor VIIa and placebo, or to time spent achieving haemostasis in the placebo group alone?

One of the specified aims of the study was to assess the safety of administering recombinant factor VIIa in patients without pre-existing coagulation disorders who undergo major surgery. As Friederich and colleagues acknowledge, the study was not large enough to offer definite conclusions about the incidence of serious adverse events, specifically thromboembolic complications, in these patients. The incidence of thromboembolic events within this population of patients is well documented.[2,3] Surely, therefore, such a serious complication should have been included in the initial power calculation, since it is an important clinical endpoint in the use of procoagulant factors.

*David Williams, Robert McCarthy

Department of Vascular Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK
(e-mail: davidj.williams@ubht.swest.nhs.uk)

1 Friederich PW, Henny CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003; **361:** 201–05.
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### *Authors' reply*

Sir—Thomas Volk and colleagues correctly state that current guidelines recommend transfusion with haemoglobin concentrations as low as 4·5–5·5 mmol/L. In our trial, red-cell transfusion was administered only if the haemoglobin concentration was below 4·5 mmol/L intraoperatively or 5·5 mmol/L postoperatively, which is identical to the threshold mentioned by Volk. We are not sure whether the slightly lower transfusion threshold that was studied by the Transfusion Requirements in Critical Care Investigators[1] is relevant to intra-

operative and postoperative bleeding, since that trial assessed critically ill patients without bleeding in an intensive care unit, most of whom were not even surgical patients.

We did not specifically investigate why the administration of recombinant factor VIIa resulted in a shorter duration of the operation. We can only postulate that this effect was due to better intraoperative haemostasis. We systematically asked our surgeons after the operation whether they were satisfied with the surgical haemostasis and the intraoperative blood loss; we did not find any correlation with measured blood loss or the duration of the operation. Thus, Volk's suggestion that the surgeons were not adequately blinded seems unlikely.

Volk and David Williams and Robert McCarthy ask about the cost benefit of recombinant factor VIIa and prevention of transfusion. Although we judge Volk's projected cost of a transfusion to be an underestimate, administration of recombinant factor VIIa will undoubtedly result in increased costs. We are currently undertaking a detailed cost analysis on the basis of the findings in our trial. Whether the additional costs will justify the reduced need of blood transfusion will be a matter of debate.

We can confirm that the time between the start of the operation and administration of recombinant factor VIIa was identical in all three study groups, which makes the suggestion of an effect of recombinant factor VIIa on surgical haemostasis more likely. We agree with Williams and McCarthy that the size of our trial does not allow for any unequivocal conclusion on the safety of recombinant factor VIIa in these patients. Our trial was designed to test the hypothesis that improvement of haemostasis could lead to a reduction in blood loss and transfusion requirements in patients without a coagulation disorder. Further studies are needed to investigate whether prophylactic treatment in surgical patients with expected major blood loss or treatment on demand in case of severe perioperative bleeding (as suggested by Volk) is justified.

*Marcel Levi, Philip Friederich, C Pieter Henny

Departments of *Internal Medicine/Vascular Medicine (ML,PF) and Anaesthesiology (CPH), Academic Medical Centre, University of Amsterdam, 1105 AZ Amsterdam, Netherlands (e-mail: m.m.levi@amc.uva.nl)

1 Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340:** 409–17.

## Churg-Strauss syndrome

Sir—Imre Noth and colleagues (Feb 15, p 587)[1] provide an excellent review of Churg-Strauss syndrome, but after 5 years of realisation, one can still only speculate on how the association with use of leukotriene antagonists has occurred. Dendritic cells produce and are responsive to leukotriene B4,[2] but that does not seem to offer an answer. I could speculate that, since eosinophils produce 15-hydroxyeicosatetaraenoic acid (15-HETE), which is implicated in endothelial-cell proliferation in some circumstances, leukotriene-receptor blockade might influence that. Some precise measurements are needed.

In the specialty of glomerulonephritis, we now have a whole series of potentially useful drugs that are not being used. They are the antithromboxanes such as picotamide, antileukotrienes, anti-PAF (platelet activating factor) agents, pentoxifylline, rolipram PDE4 phosphodiesterase inhibitor, antiendothelins, heparins, prostaglandin E1, interleukin-1-receptor antagonists, and thiazolidinediones. The point is that assessment of efficacy requires dedicated measurements and thus hard work by highly trained personnel. It is not enough to contemplate some statistics in an evidence-based quest.

*E N Wardle*

37 Princess Road, London NW1 8JS, UK

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## Cancer patients' anxiety

Sir—In their Correspondence letter, Max Dahele and Ross Camidge (March 8, p 882)[1] call for tumour marker reference ranges to be expressed in smaller units to allay the anxiety of patients with cancer. We do not feel that this action would be helpful and believe that it could, at worst, be counterproductive and undermine patients' confidence in the oncologists' clinical skills and judgment. Our experience suggests that a detailed explanation about tumour markers rather than a spin on numbers is more likely to reassure patients.

A patient of ours with prostate cancer queried why his prostate specific antigen (PSA) concentrations were still detectable at less than 0·2 μg/L (upper limit of normal 4·5 μg/L) even though he had had his prostate removed. We had to explain that 0·2 μg/L is the lowest limit of PSA measurable by our test. Another patient with early stage ovarian cancer who had both her ovaries and uterus removed by surgery asked a similar question, even though her CA125 concentrations were within normal range. We reassured her with the explanation that tissues other than ovaries such as peritoneum could produce CA125.[2] Expression of tumour marker values in smaller units of measurement would not have in any way reassured these patients.

There are other reasons why quoting tumour marker reference ranges in smaller units is unlikely to have any effect on degree of anxiety. First, tumour marker reference ranges are derived from a healthy population and are not necessarily applicable to patients who have already been diagnosed with cancer. A normal tumour marker concentration provides limited if any reassurance with respect to the absence of tumour activity.[3,4] Second, not all tumours secrete markers. In particular, poorly differentiated cancers produce scant amounts of markers, and tumour markers could be within the normal reference ranges in histologically proven recurrences. Third, patients with prostate and ovarian cancer can have microscopic and macroscopic residual disease, even after previously high tumour maker concentrations have returned to normal with treatment.[3,4] Finally, the kinetics of serial tumour marker values is more important than the actual values themselves.[5] For instance, a doubling of nadir values after treatment, even if the tumour markers are within normal range, might indicate a relapse of cancer. Furthermore, the anxious patient who places an unduly high emphasis on tumour marker concentrations is likely to overestimate the value of monitoring with tumour markers.

Hence, the psychological morbidity of patients with cancer is unlikely to be reduced by expressing tumour marker reference ranges in smaller units.

*Santhanam Sundar, Paul Symonds

Department of Oncology, Leicester Royal Infirmary, Leicester LE1 5WW, UK (e-mail: sundar.santhanam@uhl-tr.nhs.uk)

1 Dahele M, Camidge R. Tumour marker reference ranges and patients' anxiety. *Lancet* 2003; **361:** 882.

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## Mortality, morbidity, and injury of children living with single parents

Sir—Gunilla Ringbäck Weitoft and colleagues (Jan 25, p 289)[1] report that children living with a single parent in Sweden show greater mortality, a greater risk of severe morbidity including psychiatric disorders, and more injuries than their peers growing up in a two-parent household.

With respect to psychiatric morbidity, these findings reflect data only from children and young adults who received inpatient treatment for their psychiatric disorders. Although the authors concede that single parents might be more likely to seek inpatient care for their offspring, their data do not address the occurrence of psychiatric disorders that could be treated in the community. In our study of patients with chronic schizophrenia who received treatment in inpatient and outpatient settings,[2] we found a correlation between parental absence and long-term inpatient stay, which did not hold true for the community sample. This finding was not mediated by other differences between the groups, such as ethnic origin, sex, socioeconomic status, or age. In a further study of the same sample,[3] we found that a family's rating of the patient's problem behaviours was the most powerful predictor of inpatient status, followed by cognitive functioning, severity of illness, and family burden.

Taken together, these findings indicate that long-term consequences of living in a single parent family, rather than simply increasing the occurrence of psychiatric disorders, might include adverse effects on the course and outcome of such disorders, particularly an increased risk of institutionalisation.

*Peter Stastny*

Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461, USA
(e-mail: corapxs@omh.state.ny.us)

1 Ringbäck Weitoft G, Hjern A, Haglund B, Rosén M. Mortality, severe morbidity, and injury in children living with single parents in Sweden: a population-based study. *Lancet* 2003; **361:** 289–95.
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Sir—Gunilla Ringbäck Weitoft and colleagues[1] suggest that living in single-parent households causes children to become adults with more frequent health problems and a higher risk of suicide, alcoholism, and drug abuse. However, is it possible that inherently troublesome children, who might well have developed psychiatric problems in the future regardless of their environment, could themselves be the cause of their family's split?

A study of statistical data can only be regarded as scientific when the researchers explore every possible association, and do not limit themselves to the most popular and comfortable interpretation of their findings.

*Andras Hernadi*

Sköldgatan 6, 3 tr S-118 63 Stockholm, Sweden
(e-mail: frequentwriter@hotmail.com)

1 Ringbäck Weitoft G, Hjern A, Haglund B, Rosén M. Mortality, severe morbidity, and injury in children living with single parents in Sweden: a population-based study. *Lancet* 2003; **361:** 289–95.

## Mortality in parents after death of a child

Sir—In their study of bereaved parents in Denmark, Jiong Li and colleagues (Feb 1, p 363)[1] found that the death of a child is associated with increased mortality in mothers and increased early mortality from unnatural causes in fathers. This finding differs from that observed by one of us (IL) in a study of bereaved parents of adult sons in Israel, which showed no increased parental mortality.[2] An accompanying editorial by Rogers and Reich[3] on Levav and colleagues' findings concluded that clinicians owe it to the bereaved to emphasise human resilience rather than the harmful health effects of stress.

Li and colleagues' Danish study[1] controls for a range of variables, whereas the Israeli study[2] only included information on parental sex and age. Despite the positive findings, table 4 in Li and colleagues' study shows that only three of six analyses on maternal mortality were significant, and that only one of six analyses on paternal mortality was significant. Only four of these 12 analyses had significant results, which suggests that the effect of bereavement on mortality was not sufficiently large or consistent to be observed in both parents across time. The Danish study included 21 062 parents, compared with two Israeli groups of 1830 and 4470. The Israeli study may have been underpowered to identify small effects.

The Israeli study involved adult sons, whereas the Danish study included boys and girls younger than 18 years. The parents included in the Israeli study were, therefore, much older than the parents in Li and colleagues' study. Furthermore, the Israeli study only addressed the sudden, unexpected death of a child, whereas the Danish study included unexpected and other causes of death. Thus, in Li and colleagues' study some of the children may have been sick for a long time. The effects of caring for a child for an extended period could have exhausted parents and might explain why mortality was mostly increased among mothers, who are traditionally the caregivers. The Danish authors do not state whether they included mortality during the first year of bereavement when grief is greatest—an ideal time to investigate the health consequences of bereavement.

Is the observed increased parental mortality evidence that the stress of bereavement causes mortality? Stress may not be the sole cause. Genetic factors and shared environment may determine mortality among children and their parents. The strong association in the Danish study between unnatural death in children and subsequent death of their mothers might point to suicide or accidents in both children and parents.

Li and colleagues suggest that there may be increased relative risk of parental mortality after the death of a child. However, the absolute risk seems small and may only be partly caused by the stress of bereavement. Human beings can be resilient after all.

**Mark Van Ommeren, Itzhak Levav*

*Department of Mental health and Substance Dependence, WHO, CH 1211, Geneva, Switzerland (MVO); and Ministry of Health, Mental Health Services, PO Box 1176, Jerusalem 91010, Israel (IL)
(e-mail: vanommerenm@who.int)

1 Li J, Precht DH, Mortensen PB, Olsen J. Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* 2003; **361:** 363–67.
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*Authors' reply*

Sir—We agree with Mark Ommeren and Itzhak Levav that many bereaved parents are able to live through this stressful life event and eventually resume a normal life, even though they have been deeply affected by the loss of their child.[1] However, the death of a child will affect the health outcomes of some parents. We did not expect that all our analyses would be significant. We did examine the effect of cause and type of death of child on parental mortality (table 3), and found that unexpected death (mostly unnatural death) had a more pronounced effect. Unfortunately, the registration data did not allow us to investigate mortality during the first year of bereavement. We could, however, compare the acute effects with long-term effects when we stratified follow-up time into three intervals.

The absolute risk of death in parents whose child died was small, although the relative risk of violent death was substantially increased in the first years after bereavement. Our finding of increased mortality in some parents underlines the need to recognise the health effects of substantial grief and provide appropriate care to bereaved parents.

*Jiong Li, *Jørn Olsen*

Danish Epidemiology Science Centre, University of Aarhus, DK-8000, Denmark
(e-mail: jo@soci.au.dk)

1 Stroebe MS, Hansson RO, Stroebe W, Schut H, eds. Handbook of bereavement research. Washington DC: American Psychological Association, 2001.

## Staining for cell death

Sir—Alexander Woywodt and colleagues (Jan 18, p 206)[1] report the presence of dead circulating endothelial cells in patients with small-vessel vasculitis. I would like to challenge the interpretation that cell death had occurred by necrosis.

16% of these cells stained with annexin V alone—a feature suggestive of an early stage of apoptosis—whereas 84% stained with both annexin V and propidium iodide. The authors interpret the double staining as evidence of a necrotic form of cell death. However, double annexin V and propidium iodide staining is a feature of necrosis and the late stages of apoptosis. This is especially true for apoptotic cells that are not promptly engulfed by adjacent cells. Cell fragmentation is another feature of apoptosis, and fragmented circulating endothelial cells were seen by the authors.

TUNEL (terminal deoxynucleotide transferase-mediated dUTP nick-end labelling) staining is also characteristic of apoptosis. No TUNEL-positive endothelial cells were seen by Woywodt and colleagues, despite the fact that 16% of cells were in an early stage of apoptosis. Previous reports by others[2] have shown up to 60% TUNEL positivity among circulating endothelial cells. TUNEL is a technically demanding technique. Necrotic and transcriptionally active cells can both stain with TUNEL, and morphology should be assessed concurrently.[3,4] Careful morphological studies might identify features of apoptosis, such as the characteristic nuclear morphology, in circulating endothelial cells. The issue of the mode of cell death is important, since apoptosis can be manipulated therapeutically.

*Alberto Ortiz*

Unidad de Dialisis, Fundacion Jimenez Diaz, 28040 Madrid, Spain
(e-mail: Aortiz@fjd.es)

1 Woywodt A, Streiber F, de Groot K, Regelsberger H, Haller H, Haubitz M. Circulating endothelial cells as markers for ANCA-associated small-vessel vasculitis. *Lancet* 2003; **361:** 206–10.
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*Authors' reply*

Sir—We are fully aware of the limitations of the assays we used in assessing the morphology of circulating endothelial cells. However, we believe that our TUNEL staining technique was accurate in its inability to detect apoptotic cells, because we used positive controls side-by-side. It is therefore highly unlikely that all cells positive for annexin and propidium iodide staining in our study were in late stages of apoptosis.

With regard to cell morphology, we feel that such criteria are difficult to apply to our cells, particularly since the Dynabeads used for isolation remain attached to the cells. Apoptotic changes in the cell membrane, such as blebbing, might well be obscured by these particles. Detachment of the Dynabeads is feasible, but might affect the cells. Moreover, the isolation procedure could change the cell morphology. As we described, we were able to show that the isolation procedure does not induce necrosis in endothelial cells. However, this finding does not imply that the cell morphology remains unchanged. We therefore believe that comments on cell morphology would be rather premature at the present stage.

Finally we think that findings in other vascular disorders, such as sickle-cell anaemia,[1] are difficult to compare with those in ANCA-associated vasculitis. In our opinion, reports of apoptotic circulating endothelial cells in sickle-cell anaemia are no contradiction to our findings in a very different inflammatory disease. The morphology of circulating endothelial cells can vary greatly between disorders.[2]

In conclusion, we believe that our circulating endothelial cells were necrotic, rather than apoptotic. Further studies are certainly needed to clarify the phenotype of these cells, elucidate the pathogenesis of endothelial detachment, and delineate possible interactions of circulating endothelial cells with other cell subsets.[3]

**Alexander Woywodt, Kirsten de Groot, Heide Regelsberger, Hermann Haller, Marion Haubitz*

Division of Nephrology, Department of Medicine, Hannover Medical School, 30625 Hannover, Germany
(e-mail: Woywodt.Alexander@MH-Hannover.de)

1 Solovey A, Lin Y, Browne P, Choong S, Wayner E, Hebbel RP. Circulating activated endothelial cells in sickle cell anemia. *N Engl J Med* 1997; **337:** 1584–90.
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## Private medical education takes off in India

Sir—Medical colleges in India were once funded exclusively by the state, but now private medical colleges are becoming an integral part of medical education. Charitable organisations, religious or minority groups, or trusts are largely managing such colleges. Their main source of income is student fees. Until recently, their intake of medical students was regulated strictly by the government. Typically, 50% of students are mandatory merit students, usually selected on the basis of a common entrance test, who pay minimal fees. A further 35% of students pay a higher fee and 15% of medical students pay substantially higher fees than merit students. The government regulates the fee structure for all

categories. However, most colleges find it difficult to comply with all staff and infrastructure requirements of the Medical Council of India and subsist on the current fee structure.

A judgment of the Supreme Court of India in 2002 is set to radically change the prevailing scenario (T M A Pai Foundation and Others *vs* State of Karnataka and Others and related judgments).[1] The court ruled that all citizens and religious denominations have a right to establish and maintain educational institutions. This ruling has upheld the right of private professional educational institutions to charge fees higher than those set by government to ensure their viability and generate revenue surplus for development and expansion. The court also observed that many of the students who pay higher fees come from lower socioeconomic groups and, in fact, subsidise the education of the mandatory merit students, contrary to the ideology of the scheme.

Further, there is an obvious need for private colleges in India—in the state of Karnataka, for example, there are 19 medical colleges of which only four are governmental. The court observed that maximum autonomy be given to the management of these colleges with respect to admission procedures, fees, and staffing, without disregarding the principle of merit. Such institutions could also devise their own selection methods. The court underlined the importance of autonomy, non-regulation, and excellence of educational standards. The authorities could regulate the educational and academic matters for affiliation and licensing. The ruling allowed greater regulation for government-aided institutions. Minority-run institutions are also given greater freedom, whereas state governments are to regulate and ensure transparency for government-aided institutions.

These judgments should radically improve the medical education sector in India and introduce an element of market competition. There seems to be no logic for one student to subsidise the higher education of another student, especially when the student who is being subsidised is from a richer family. The quality of medical teachers and facilities available at various private colleges could now dictate the proportion of fees chargeable and yet receive adequate applicants. All merit students have an opportunity to enrol at government medical colleges with a low fee structure or pay fees for education imparted at private colleges.

Since health is a social good essential for the development of a country, it is to be hoped that the increasing commercialisation of medical education in India ultimately improves health care, without having any adverse effect on the charity services provided by many doctors.

*R K Bansal*

Department of Community Medicine, Municipal Institute of Medical Education and Research, PO Box 1030, Bombay Market PO, Surat, 395010 Gujarat, India
(e-mail: rajkumar_bansal@hotmail.com)

1 TMA Pai and others *vs* State of Karnataka. Writ Petition (Civil) Number 317 of 1995. New Delhi: October, 2002.

## Primary-care research is not a lost cause

Sir—In one sense you are right in your Editorial (March 22, p 977)[1] about simply getting on with doing better research in primary care, and focusing on testable hypotheses. After all, in this discipline-versus-discipline competitive environment, good research—that which improves how we care for people—is the only thing that counts in the end. But in another sense, you are distressingly wrong, for the end is not yet nigh. As society has become enthralled with the quick fix for all their health problems, so it expects something equally magical for science: a paradigm shift to serve up exciting cures for everything. If this shift lures us to concentrate almost only on the basic sciences for research investment, we will miss out on careful process and empirical research—at the applied end of the research spectrum—that primary care is best at.

We think we have good reasons for feeling undervalued. A strong self-sufficient primary care workforce seems to be the mainstay of the good health of a country.[2] Expert generalism and academic excellence are hard to reconcile, when academics have traditionally focused on becoming specialised. Yet making high quality judgments about how best to advise people (patients) enmeshed in complex systems arguably necessitates a willingness to think of innovative solutions.[3] We have tended to be very pragmatic in primary care. Our current attention to theory is aiming to define and organise relevant research questions.

Primary care needs the kind of self-inspection that the World Organisation of Family Doctors (WONCA) conference on research afforded (www.globalfamilydoctor.com). We need the opportunity to gather the resolve to unite internationally (as, incidentally, do many other disciplines), and formulate plans to improve the quantity and quality of primary-care research. If at the same time we extend a helping hand to developing countries (the sort of effort heavily championed in these columns), is that not laudable? Rather than sneering, we should be congratulating Chris van Weel and Walter Rosser for making such an event happen, as well as for exposing our vulnerable underbelly to *The Lancet* for ridicule.

But another thought: perhaps your Editorial was designed to provoke us, to have us rise up in indignant response, to focus our vision and redouble our efforts. If so, well done. We are one step behind.

**Chris Del Mar, George Freeman*

*University of Queensland, Queensland, Australia (CDM); and Imperial College London, London, UK (GF)
(e-mail: c.delmar@cgp.uq.edu.au)

1 Editorial. Is primary-care research a lost cause? *Lancet* 2003; **361:** 977.
2 Starfield B. Is primary care essential? *Lancet* 1994; **344:** 1129–33.
3 Aron DC, Lindberg C. Health care's new periodic table. *Lancet* 2003; **361:** 1141.

## Randomised controlled trials and quality of journals

Sir—Randomised controlled trials are thought to be the best way of comparing treatments, yet such studies make up only a small proportion of the published work.[1] Given the rise of evidence-based medicine, we postulated that researchers cite randomised controlled trials in preference to other sources. Thus, the more randomised studies a journal contains, the more times it will be cited, having implications for journal editors and readers alike.

Journal quality is a difficult characteristic to define objectively. Perhaps the most often quoted indicator of quality is impact factor, a measure of the number of times the average article in a journal is cited. This method has several well described weaknesses, since citation could relate to numerous factors not necessarily associated with journal quality, including the journal language and the size of its distribution.[2,3]

We believe that the volume of randomised controlled trials a journal publishes is another such factor, which could have little to do with journal quality. In view of the fact that the quality of methodology and reporting of such trials is highly variable,[4] publication of a large number of trials does not necessarily mean a high number of good quality trials or a high quality journal, though it could lead to a higher citation rate.

We identified the impact factor for all journals classified under the subject headings of "surgery" (n=139) and "medicine, general and internal" (n=112) in the Institute for Scientific Information journal citation report of 2001. We then used the Ovid Medline database to ascertain the number of journal articles and number of randomised controlled trials each journal published in 1999–2000. We excluded journals that were not included on the Ovid Medline database (n=25) or that were first published after 1999 (n=6).

120 surgical and 100 medical journals were analysed. The median impact factor for 2001 was 0·793 (IQR 0·504–1·806). The journals studied published a median of 245 articles (124–416), with five randomised controlled trials per journal (1–14), in 1999 and 2000. Randomised controlled trials accounted for a median of just 2·3% (0·7-4·3) of all journal content during the study period.

We noted significant weak correlations (Spearman rank correlation) between 2001 impact factor and the total number of all journal articles ($r$=0·258, p=0·01), the number of randomised controlled trials ($r$=0·383, p=0·01), and the proportion of randomised controlled trials ($r$=0·319, p=0·01) published in the previous 2 years (1999–2000).

Worryingly, journals that simply publish more than others seem more likely to be cited, notwithstanding the fact that there is a large amount of redundancy in the published work, with numerous articles never being cited.[3] Journals with a higher number of randomised controlled trials are also more likely to have a higher impact factor than other journals.

We believe our findings greatly weaken the validity of using impact factor alone to assess a journal's quality. This fact should be borne in mind by authors, readers, and editors when trying to discern which journals are of highest quality.

*A R Weale, P A Lear

Southmead Hospital, North Bristol NHS Trust, Westbury on Trym, Bristol BS10 5NB, UK
(e-mail: andy@weale.org.uk)

1 McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *BMJ* 2002; **324:** 1448–51.
2 Opthof T. Sense and nonsense about the impact factor. *Cardiovasc Res* 1997; **33:** 1–7.
3 Rennie D. The present state of medical journals. *Lancet* 1998; **352:** 6–13.
4 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357:** 1191–94.

## Importance of language

Sir—Your article on depression (Feb 22, p 653)[1] travelled far, and its language was, with one exception, exemplary. The one exception was when you deviated from naming the illness, depression, to "the mentally ill patients"; reverting to the generic stereotype was an error. "The physically ill patients", its corollary, would not appear, the illness would be named.

As I tracked the newspapers that picked up your article, most adhered to the respectful language you used. Congratulations: the media does not as readily stereotype when they have a model to copy. Your language is of great importance in overcoming negative public attitudes toward people with unnamed mental disorders. The public reacts with far less discrimination when the illness has a name and the person with that illness is not conflated with it.

*Harold A Maio*

International Association of Psychosocial Rehabilitation Services Publications Committee, 8955 Forest Street, Fort Myers, FL 33907, USA
(e-mail: khmaio@earthlink.net)

1 Geddes JR, Carney SM, Davies C. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003; **361:** 653–61.

Sir—We draw your attention to the worrying fact that the term plasma apheresis (or plasmapheresis) is increasingly used in the published work as a synonym for, or instead of, the term plasma exchange.[1]

The term apheresis derives from the Greek word aphairesis, meaning taking out or removal. Thus, the word plasmapheresis refers to the act of removing plasma from an individual; so long as the individual can tolerate the volume of plasma removed (generally up to an acute plasma volume reduction of about 600 mL), no replacement fluid needs to be used.

When plasma removal is indicated for therapeutic reasons, however, the efficacy of the procedure can only be attained by the extraction of huge volumes of plasma (at least one plasma volume—ie, about 3000 mL in an adult weighing 70 kg), which necessitates replacement of the removed plasma with a liquid solution. The replacement solution in the case of thrombotic microangiopathies is fresh frozen plasma, inactivated or not, or cryoprecipitate-poor plasma. The procedure is complex because of the volume of blood processed, and the need to control volume balance, and to prevent and treat adverse effects, such as citrate toxicity, allergic reactions, neurovegetative reactions, electrolyte disturbances, vascular access complications, and transfusion-related acute lung injury.[2] As such, replacement acquires such importance that plasma removal is overshadowed. Moreover, in the case of thrombotic thrombocytopenic purpura, the therapeutic effect is actually attained through the infusion of plasma with a normal content of ADAMTS 13, the von Willebrand factor-cleaving metalloprotease defective in this condition; the parallel removal of plasma simply allows infusion of greater amounts of the defective metalloprotease that would otherwise be impossible.[2]

To define this process as plasmapheresis is, therefore, inaccurate, despite the addition of the adjective therapeutic, which only creates ambiguity. The term plasma exchange would be much more suitable, since it describes exactly what is done: removal and, at the same time, infusion—ie, exchange of plasma for a replacement solution.[3,4] We feel, as do others,[5] that the term plasmapheresis should be reserved to describe situations in which only plasma removal is undertaken—ie, plasma donation, usually in a shorter time (about 45 mins) and using blood-cell separators that, in general, are much simpler than those used in plasma exchange.

*Miguel Lozano, Roberto Mazzara*

Department of Haemotherapy and Haemostasis, Biomedical Diagnostic Center, Agustí Pi i Sunyer Biomedical Research Institute (IDIBAPS), Hospital Clínic, University of Barcelona, Villarroel 170, 08036 Barcelona, Spain
(e-mail: mlozano@clinic.ub.es)

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2 Moake JL. Mechanisms of disease: thrombotic microangiopathies. *N Engl J Med* 2002; **347:** 589–600.
3 McMinn JR, Thomas IA, Terrell DR, Duvall D, Vesely SR, George JN. Complications of plasma exchange in thrombotic thrombocytopenic purpura, hemolytic uremic syndrome: a study of 78 additional patients. *Transfusion* 2003; **43:** 415–16.
4 Clark WF, Rock GA, Buskard N, et al. Therapeutic plasma exchange: an update from the Canadian Apheresis Group. *Ann Intern Med* 1999; **131:** 453–62.
5 Bier-Ulrich A, Haubelt H, Anders C, et al. The impact of intensive serial plasmapheresis and iron supplementation on iron metabolism and hemoglobin concentration in menstruating women: a prospective randomized placebo-controlled double-blind study. *Transfusion* 2003; **43:** 405–10.

## DEPARTMENT OF ERROR

*Ladner J, Cartoux M, Dauchet L, Van de Perre P, Czernichow P. Teenage African women and HIV-1 prevention.* Lancet *2002;* ***360:*** *1889*—Philippe Van de Perre was incorrectly listed as an author of this Correspondence letter (Dec 7).