

# CORRESPONDENCE

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## Autism, bowel inflammation, and measles

Sir—John Walker-Smith (Feb 23, p 705)<sup>1</sup> states that children have been badly served by the adversarial approach involved in the current legal action against manufacturers, but offers no evidence to explain how and why.

It is the children, via their parents, who have started this action, at huge public expense and at no cost to the families. They will not be exposed to costs in the likely event of the case failing.<sup>2</sup> By contrast, health service professionals and the manufacturers have to meet their own costs.<sup>2</sup>

It shows the generosity of our legal system that this action is publicly funded in the absence of published evidence supporting a causal relation between the measles-mumps-rubella (MMR) vaccine, and mounting evidence to the contrary. In the context of a failing National Health Service, is this good use of scarce public monies?

Although I have every sympathy for these children, can they be said to be badly served by the litigation system compared with the defendants? Moreover, it is difficult to see what this litigation will achieve apart from enriching lawyers.

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- 1 Walker-Smith J. Autism, bowel inflammation, and measles. *Lancet* 2002; **359**: 705–06.
- 2 Lord Chancellor's department. Access to Justice Act 1999—section II.

Sir—I am a partner in one of the firms of solicitors coordinating claims on behalf of families who believe their children have developed autism as a result of receiving the MMR vaccine. John Walker-Smith<sup>1</sup> says that children have been badly served by the adversarial approach involved in the current legal action against manufacturers. I and my colleagues entirely agree.

The present situation has arisen despite our attempts to encourage research of individual cases, not populations. I agree with Walker-Smith's point that much of the criticism of Wakefield's work has been

epidemiological. We deal with hundreds of individual accounts of children's health worsening after receiving the MMR vaccine.

In 1996, I was so concerned about what seemed to be happening that I wrote to chairman of the Committee on Safety of Medicines offering to make available the medical records and other information about children who had apparently been affected by the vaccine.

My offer was put to government representatives on three occasions but was turned down. The only concession was that parents would be sent questionnaires about their children's symptoms. In coordination, we and the Department of Health sent out around 1200 questionnaires.

The Department of Health, without referring to us or our clients, set up a working party to look at the families' questionnaires, and questionnaires they later sent to the treating family physicians. They now use the resulting report<sup>2</sup> as part of the evidence to support the assertion that the MMR vaccine and autism are not linked. They describe it as involving a detailed assessment of more than 100 children's records referred to them by solicitors, yet the report itself states that it took into account only evidence derived from the parental and medical questionnaires.<sup>3</sup> The report's conclusion is that it is impossible to prove or refute the suggested associations between MMR vaccine and autism, pervasive development disorder, or inflammatory bowel disease because of the nature of the information used.

Few would argue with Walker-Smith's sentiments. Those of us who are involved in the litigation are acting only because the families have no other alternative. Clearly, MMR does no harm to most children. The question mark over safety of the MMR vaccine for a minority of children needs proper investigation.

The real issue is that the UK has no adequate vaccine-damage compensation scheme. A one-off payment, currently of UK£100 000, is paid only if parents can prove that their children have been at least 60% disabled by a particular vaccine. No public help is

available to enable parents to present their cases to the Vaccine Damage Payments Unit or Tribunal and the autism is not currently acknowledged as an adverse effect of the MMR vaccine. As a consequence, few payments are made.

If the UK Government were to adopt a more helpful scheme, like that in the USA, the issue raised by Walker-Smith would start to be resolved and some common sense could once again be injected into these important public-health issues.

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- 1 Walker-Smith J. Autism, bowel inflammation, and measles. *Lancet* 2002; **359**: 705–06.
- 2 Report of the working party on MMR vaccine. <http://www.mca.gov.uk/inforesources/publications/mmr1.htm> (accessed on April 10, 2002).
- 3 Measles, mumps and rubella vaccine (MMR). <http://www.doh.gov.uk/mmr.htm> (accessed on April 10, 2002).

Sir—John Walker-Smith<sup>1</sup> recognises that epidemiological studies have shown that MMR vaccine is safe in most children,<sup>2</sup> but he suggests that further non-epidemiological research is required in the subgroup of children who show features of regression and gut disease.

This suggestion follows a report that measles virus genes were present in the intestinal tissue of children who had gut and developmental disorder more frequently than in a comparison group, in which some children had gut disease but all of whom were developmentally normal.<sup>2</sup> Walker-Smith suggests that epidemiological methods are too blunt a tool to solve the newly defined question. We strongly disagree with this opinion.

We agree that if Uhlmann and colleagues' findings<sup>2</sup> are confirmed, further molecular research is required to address issues such as the origin of the measles virus markers and whether their presence is specific to this type of autism or is present in other gut

pathologies. The latter would suggest the persistence of measles virus markers is a result of disease rather than a cause and, therefore, unrelated to autism.

If a small proportion of cases of autism arise because of exposure to MMR vaccine and those cases cannot be distinguished by their clinical or pathological characteristics from all other cases of autism, epidemiological research may not identify or confirm the association. However, such confirmation is not what is being proposed; the key question is whether exposure to MMR vaccine (or other sources of measles virus) is associated with an increased risk of this relatively rare subtype of autism.

Epidemiological research has not addressed this question so far because the question was not previously posed, not because epidemiology itself is a blunt tool. Research focusing on this subgroup of autistic children compared with a suitable control group will assess association and establish the temporal sequence between exposure to measles virus and onset of the disorder, thus addressing causality.

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- 1 Walker-Smith J. Autism, bowel inflammation, and measles. *Lancet* 2002; **359**: 705–06.
- 2 Uhlmann V, Martin CM, Silva I, et al. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. <http://jcp.bmjournals.com/cgi/data/55/1/DC1/1> (accessed April 10, 2002).

Sir—In your Feb 23 editorial,<sup>1</sup> you somewhat belatedly acknowledge that the publicity surrounding MMR and autism has been mainly negative.

When Wakefield and colleagues' work<sup>2</sup> was first reported, many of us doubted the wisdom of the associated hype, for which you must take at least some of the responsibility. Many of us who wrote to point out the real hazards of measles, especially in any child with congenital or acquired immunodeficiency, had our submissions rejected on the grounds that there had been adequate publicity on the topic.

Tensions are inherent in vaccination programmes started for potentially life-threatening diseases, such as measles, or those that can cause severe morbidity, such as rubella in pregnancy. The risk for the individual is balanced against a low but definite risk of abnormal reaction to the

vaccine. Therefore, the topic should be handled with maximum objectivity and sensitivity.

One of the great challenges of modern day medicine is to balance the individual's wellbeing against the overall health of the community. You have provided no objective balance in the argument previously, possibly in the search for headline publicity. In contrast to previous attempts, your current editorial does provide such balance. Media hysteria has done a great disservice to many thousands of parents who are anguishing over what is right to do for their children.

I hope in the future you will be more thoughtful in your search for publicity. Your journal is highly respected and widely read, but its content is taken as authoritative and the media rightly or wrongly assume it is sound and objective. I presume you will not publish this letter but perhaps those responsible within the editorial office will ponder on its message.

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- 1 Editorial. Time to look beyond MMR in autism research. *Lancet* 2002; **359**: 637.
- 2 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637–41.

Sir—John Walker-Smith's call<sup>1</sup> for a programme of non-epidemiological research is justified and timely.

The people who overlook these concerns do not observe the first rule in clinical medicine—listen to the patient. Parents of the children in question have described their children's ailment with extraordinarily little effect on the commissioning of clinical research, which suggests to me a deep resistance to hear what they are saying.

The Department of Health is adamant that autism is typically noticed around the time of vaccination, but presents no cases in which autism was acquired after a normal infancy just before MMR, nor seeks to explain autism developing in older children who received MMR after several years of normal development.

Although no evidence of a link between MMR and autism has been reported in reviews, absence of evidence is not evidence of absence. Confusing the two may yet prove to be medicine's fatal error.

Most of the reviews that are quoted as evidence of non-involvement of MMR in acquired autism have since been overtaken by further clinical research. For example, Singh<sup>2</sup> reported that, in 75 of 125 autistic children, there was an unusual MMR antibody that was related to the measles haemagglutinin antigen of MMR. None of 92 controls had this feature. In addition, more than 90% of MMR antibody-positive autistic sera were also positive for myelin basic protein autoantibodies, which Singh interprets as suggesting a causal association between MMR and brain autoimmunity in autism.

Such findings suggest that the concerns raised by Walker-Smith, and by Wakefield and co-workers,<sup>3</sup> are well founded. These findings are also consistent with the reports of parents.

The US Institute of Medicine's Immunisation Safety Review Committee has stated that it was unable to address the concern about exposure of susceptible children to multiple immunisations in the developmental period, since no epidemiological study addresses this issue.<sup>4</sup> The UK Department of Health does not seem to share their candour about the lack of research. They have slightly increased autism research funding. However, there has been no clinical research. The Scottish Chief Medical Officer, Mac Armstrong, has even stated that calls to fund clinical research into MMR and autism would be resisted.

Increasingly, it has become a battle between the crude science of epidemiology and the forensic science of clinical examination. The cause of those who seek to shore up public confidence in childhood immunisation by placing all their faith in epidemiology, much of it based on children's medical records that probably contain little of relevance to the issue, will be more than ill served if they are eventually proved wrong.

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- 1 Walker-Smith J. Autism, bowel inflammation, and measles. *Lancet* 2002; **359**: 705–06.
- 2 Singh VK, Nelson C. Abnormal measles serology and autoimmunity in autistic children. *J Allergy Clin Immunol* 2002; **109**: (abstr 702).
- 3 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637–41.
- 4 National Vaccine Information Center. Press release. 2002; Feb 20.

## Multidrug resistance and response to antiretroviral treatment

Sir—Jacques Fellay and colleagues (Jan 5, p 30)<sup>1</sup> describe the effect of MDR1 P glycoprotein on plasma concentrations of antiretroviral drugs and on immune recovery. However, their results partly contradict those from previous studies.

Fellay and colleagues' data confirm those for human enterocytes that the MDR1 3435 TT genotype is associated with low MDR1 P glycoprotein expression,<sup>2</sup> but they cannot explain the low concentrations of antiretroviral drugs, being at least partly substrates of MDR1 P glycoprotein. They cite another report in which the 3435 TT genotype was associated with lower plasma concentrations of the MDR1 substrate fexofenadine, but those data were obtained on a different genetic background, linked with a G2677T polymorphism.<sup>3</sup> That polymorphism led to higher MDR1 activity in an in-vitro digoxin assay in the same study. These findings clearly suggest complex, probably substrate-specific, interactions not only in the MDR1 gene.

Fellay and colleagues claim to have investigated two possible explanations for these results: CYP3A up-regulation with increased drug metabolism or up-regulation of ABCC1 (MRP1) or ABCC2 (MRP2) as transport compensation for MDR1. However, they exclude only the first possibility by doing CYP3A activity assays. Analysis of transcription concentrations of MRP1 and MRP2 in blood cells alone is not sufficient to exclude up-regulation of the transport proteins anywhere, especially in the intestine, which is the main determinant for oral bioavailability of antiretroviral drugs.

Furthermore MRP2 is not expressed in unpolarised cells such as blood cells<sup>4</sup> and can be regulated translationally, leaving mRNA concentrations alone with no valid estimate about protein expression.<sup>5</sup> Compensatory up-regulation of MRP1 or MRP2 in blood cells, as postulated by Fellay and colleagues, would not explain the low plasma drug concentrations and the better immune recovery in TT genotype patients.

On the basis of the presented data we favour another explanation for this MDR1 paradox: in the state of lower MDR1 activity, compensatory up-regulation of intestinal MRP2 accounts for the low plasma concentrations, but the complete absence of MRP2 expression in blood cells might explain the better immune recovery even with

lower plasma concentrations. Measurement of drug concentrations in blood cells could support this hypothesis.

Therefore, the non-uniform data in the cited studies might be partly the result of differences in substrate affinity and tissue-specific distribution of several transport proteins.

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- 1 Fellay J, Marzolini C, Meaden ER, et al, for the Swiss HIV Cohort Study. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. *Lancet* 2002; **359**: 30–36.
- 2 Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc Natl Acad Sci USA* 2000; **97**: 3473–78.
- 3 Kim RB, Leake BF, Choo EF, et al. Identification of functionally variant MDR1 alleles among European Americans and African Americans. *Clin Pharmacol Ther* 2001; **70**: 189–99.
- 4 Evers R, Kool M, van Deemter L, et al. Drug export activity of the human canalicular multispecific organic anion transporter in polarized kidney MDCK cells expressing cMOAT (MRP2) cDNA. *J Clin Invest* 1998; **101**: 1310–19.
- 5 Vore M, Hoffman T, Cao J. Translational regulation of rat hepatic MRP2. *Hepatology* 2001; **34**: 476A.

### Authors' reply

Sir—Cristoph Dietrich and colleagues point to the limited published data on the impact of the 3435 TT polymorphism in MDR1 on oral bioavailability of antiretroviral drugs. We list two more useful studies.<sup>1,2</sup> However, the various studies have looked at different cell populations and used different transporter substrates (table). The issue is also confounded by a potential role of protease inhibitors as inducers or inhibitors of the P glycoprotein, and by evidence for tissue-specific and developmental-

specific expression of many transporters.

To approach the paradox, we attempted analysis of the transporters MRP1 and MRP2 in peripheral blood mononuclear cells, to allow for consistency with P glycoprotein data in the same set of individuals. We did note expression of MRP2 in peripheral blood mononuclear cells, although at a 64-fold lower concentration than for MRP1. Dietrich and colleagues suggest a selective functionality of MRP2 in the intestinal epithelium, and propose that it is at this barrier that compensation for P glycoprotein deficiency may take place. Testing their hypothesis will require intestinal biopsy in genotyped individuals. In addition, measurement of intracellular drug concentrations in blood cells could prove important.

We have one word of caution. The ABC family of transporters is one of the largest known protein superfamilies. Although P glycoprotein is the best characterised ABC transporter, new members are being investigated<sup>3</sup> and have the potential for overlapping substrate specificities and for cell-selective expression. Unexpected compensation may also result from up-regulation of renal transporters,<sup>4</sup> from other transporter families, or from induction of cytochrome P450 isoforms such as CYP2C19 or CYP2B6.

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- 1 Hitzl M, Drescher S, van der KH, et al. The C3435T mutation in the human MDR1 gene is associated with altered efflux of the P-glycoprotein substrate rhodamine 123 from CD56+ natural killer cells. *Pharmacogenetics* 2001; **11**: 293–98.
- 2 Tanabe M, Ieiri I, Nagata N, et al. Expression of P-glycoprotein in human placenta: relation to genetic polymorphism of the multidrug resistance (MDR)-1 gene. *J Pharmacol Exp Ther* 2001; **297**: 1137–43.
- 3 Litman T, Brangi M, Hudson E, et al. The multidrug-resistant phenotype associated with overexpression of the new ABC half-

Study	Cell type	Expression/function of MDR1 3435 TT	Plasma drug concentrations
Hoffmeyer et al	Enterocytes	↓MDR1 mRNA	↑Digoxine
Kim et al	Transfected murine NIH-3T3	↑PGP function in vitro for MDR1*2 haplotype	↓Fexofenadine
Hitzl et al	CD56 natural killer cells	↓MDR1 mRNA ↑rhodamine efflux	NA
Tanabe et al	Placenta	↓PGP expression for MDR1*2 haplotype	NA
Fellay et al	Peripheral blood lymphocytes	↓MDR1 mRNA and PGP expression	↓Nelfinavir and Efavirenz

PGP=P glycoprotein; MDR1\*2 haplotype=G677T/C3435T; NA=not available.

### Cell populations and transporter substrates in studies of MDR1 3435 TT

transporter, MXR (ABCG2). *J Cell Sci* 2000; **113**: 2011–21.

- 4 Smit JW, Schinkel AH, Weert B, Meijer DK. Hepatobiliary and intestinal clearance of amphiphilic cationic drugs in mice in which both *mdr1a* and *mdr1b* genes have been disrupted. *Br J Pharmacol* 1998; **124**: 416–24.

## Intestinal involvement in children with Behçet's disease

Sir—Gianluca Terrin and colleagues (Jan 26, p 316)<sup>1</sup> report one case of paediatric Behçet's disease with severe clinical intestinal involvement and with a partial response to the conventional treatment for Crohn's disease. In an international collaborative study, gastrointestinal symptoms arose in a low number of patients,<sup>2</sup> whereas 69% of Japanese children showed intestinal involvement.<sup>3</sup>

We followed up nine paediatric cases of Behçet's disease according to the criteria proposed by the International Study Group for Behçet's disease.<sup>3</sup> Of the four major diagnostic criteria, eight patients had recurrent aphthous stomatitis, six had skin lesions, and five had genital ulcers, but only four had eye disease. Of the five minor criteria, severe gastrointestinal symptoms (diarrhoea, abdominal pain, and perforation that required surgery) occurred only in one patient.

To assess the sensitivity of nuclear medicine procedures in the diagnosis of gastrointestinal involvement of Behçet's disease in symptom-free patients,<sup>4</sup> we did monoclonal antibody technetium-99 (<sup>99</sup>Tc) leucocyte scintigraphy in the other eight patients. Despite the absence of gastrointestinal complaints, in six cases there was scintigraphic evidence of inflammation in the distal gastrointestinal tract, confirmed by ileocolonoscopy, that showed substantial endoscopic and histological signs of inflammation. In three cases, the diagnosis made was based on two major criteria of Behçet's disease plus two minor criteria, and one of these was the presence of gastrointestinal scintigraphic and endoscopic involvement.

As in the cases reported by Terrin and colleagues, and in agreement with other paediatric experiences,<sup>5</sup> three patients were successfully treated with thalidomide for severe steroid-dependent systemic symptoms unresponsive to other treatment.

In our experience, gastrointestinal involvement in patients with Behçet's disease is common, even in the absence

of specific gastrointestinal symptoms, and in some cases are important for early and complete diagnosis. Monoclonal antibody <sup>99</sup>Tc scintigraphy can be a useful diagnostic tool for detecting gastrointestinal involvement before symptoms become evident.

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- 1 Terrin G, Borrelli O, Di Nardo G, Pacchiarotti C, Cuccchiara S. A child with aphthae and diarrhoea. *Lancet* 2002; **359**: 316.
- 2 Konè-Paut I, Yurdakul S, Bahararbrri SA, et al. Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. *J Pediatrics* 1998; **132**: 721–25.
- 3 Tabata M, Tomomasa T, Kaneko H, Morikawa A. Intestinal Behçet's disease: a case report and review of Japanese reports in children. *J Pediatr Gastroenterol Nutr* 1999; **29**: 477–81.
- 4 Kucuk O, Aras G, Soylu A, et al. Evaluation of gastrointestinal involvement of Behçet's disease by nuclear medical techniques. *Ann Nucl Med* 1999; **13**: 211–14.
- 5 Kari JA, Shah V, Dillon MJ. Behçet's disease in UK children: clinical features and treatment including thalidomide. *Rheumatology* 2001; **40**: 933–38.

## Dynamic epidemiology of group A streptococcal serotypes

Sir—James Dale and Stanford Shulman (March 9, p 889)<sup>1</sup> attempt to use our report on group A streptococcal serotypes<sup>2</sup> to provide support for the type-specific M-protein group A streptococcal vaccine strategy being promoted by ID Biomedical Corporation. Unfortunately, they incorrectly represent our results and conclusions in a way that may be misleading.

They state that serotype-specific natural immunity was clearly evident in the population we studied, since, they further state, apparently none of the individuals became infected a second time with type 1 streptococci during the observation period. There is no basis for such a statement. We did see such individuals but we did not present these data because of a request for brevity and because this information was not pertinent to the major point of our report—a rapid change in prevalent M types.

Dale and Shulman also comment that the potential for such vaccines to elicit broad protection against the serotypes circulating in the population could prevent the rapid spread of

highly virulent strains, which they claim we note in the report. They imply that our data support their M-specific vaccine strategy, but we did not address this effect in our report.

Dale and Shulman suggest, without any supporting epidemiological evidence, that future shifts in serotype prevalence in a population will probably occur slowly over long periods of time and can be predicted by continuing surveillance, thus allowing a vaccine to be reformulated. However, intensive and comprehensive, long term prospective epidemiological observation has shown the striking rapidity with which serotypes may enter into and then disappear from a population.<sup>3</sup> Furthermore, we are unaware of any current sufficiently comprehensive surveillance programme that would provide the required data for timely reformulation of such a group A streptococcal vaccine. Shulman himself, in the surveillance study they cite, described large geographical and seasonal variation in serotype distribution with implications for vaccine development.<sup>4</sup> Furthermore, other published reports indicate that natural immunity is group A streptococcal strain specific, not simply serotype specific.<sup>5</sup>

Dale, an accomplished streptococcal vaccine investigator, could be considered the inventor of this multivalent vaccine, and, according to the company website, the patent, currently licensed to ID Biomedical Corporation, is held by the University of Tennessee, where he is employed. Shulman, also an experienced streptococcal researcher, is currently listed on this same company website as a collaborator. Given Dale and Shulman's extensive experience, we are disappointed that their response to our report was based essentially on an incorrect representation of our data and on unsupported conjecture.

The issue of a group A streptococcal vaccine is complex, especially because of the many questions about the epidemiology of the spread of the currently more than 130 recognised group A streptococci types worldwide. We wrote our original report to emphasise these issues and to stimulate thought. We did not aim to specifically endorse any one of the several candidate vaccine strategies.

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- 1 Dale JB, Shulman ST. Dynamic epidemiology of group A streptococcal serotypes. *Lancet* 2002; **359**: 889.
- 2 Kaplan EL, Wotton JT, Johnson DR. Dynamic epidemiology of group A streptococcal serotypes associated with pharyngitis. *Lancet* 2001; **358**: 1334–37.
- 3 Anthony B, Kaplan E, Wannamaker L, Chapman S. The dynamics of streptococcal infections in a defined population of children: serotypes associated with skin and respiratory infections. *Am J Epidemiol* 1976; **104**: 652–66.
- 4 Shulman ST, Tanz RR, Kabat W, Kabat K, Beall B. US nationwide streptococcal pharyngitis serotype surveillance. San Francisco: IDSA 39th Annual Meeting 2001: 87 (abstr 277).
- 5 Eriksson BKG, Villaseñor-Sierra A, Norgren M, Stevens DL. Opsonization of TIMI group A streptococcus: dynamics of antibody production and strain specificity. *Clin Infect Dis* 2001; **32**: E24–30.

## Near-death experiences

Sir—Many of the elements of the near-death experiences described by Pim van Lommel and colleagues (Dec 15, p 2039),<sup>1</sup> are also described by patients after episodes of awareness or unintended consciousness occurring during general anaesthesia.<sup>2–4</sup>

These episodes of recovery of consciousness are invariably attributed to an insufficient supply of anaesthetic, for various reasons, and are not generally associated with hypoxia. They occur despite the fact that patients have received a cocktail of potent, centrally acting drugs—specific general anaesthetic agents, opioids (eg, fentanyl), benzodiazepines, and other psychotropic drugs (eg, droperidol)—given with the object of preventing consciousness. Many of van Lommel and colleagues' patients received a similar cocktail of drugs during resuscitation. I suggest that their patients' near-death experiences were simply an episode of consciousness modulated by drugs, hypoxia, hypercarbia, or other physiological stressors.

There does seem one element of such near-death experiences, however, that is not so commonly reported during anaesthesia, namely the out-of-body experience. Given the circumstances of their awareness, the anaesthetised patient generally has a clear insight into their situation and their role in it. Is it possible that patients with a cardiac arrest have a poorer understanding of their predicament and impose a different interpretation upon events, possibly one that the subsequent interview and the interest of the interviewer may have inadvertently moulded?

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- 1 van Lommel P, van Wees R, Meyers V, Elfferich I. Near-death experience in survivors of cardiac arrest: a prospective study in the Netherlands. *Lancet* 2001; **358**: 2039–45.
- 2 Evans JM. Patients' experiences of awareness during general anaesthesia. In: Rosen M, Lunn JN, ed. Consciousness awareness and pain in general anaesthesia. London: Butterworths, 1987: 184–92.
- 3 Moerman N, Bonke B, Oosting J. Awareness and recall during general anaesthesia: facts and feelings. *Anaesthesiology* 1993; **79**: 454–64.
- 4 Cobcroft MD, Fosdick C. Awareness under anaesthesia: the patient's point of view. *Anaesth Intensive Care* 1993; **21**: 837–43.

Sir—Pim van Lommel and colleagues<sup>1</sup> ask, how could a clear consciousness outside the body be experienced at the moment that the brain no longer functions during a period of clinical death with flat electroencephalography?

Evidently, they assume that the brain may not function at this time. This assumption, however, is erroneous. Normal electroencephalography techniques can detect electrical activity in only one half of the area of cerebral cortex. Possible activity in the other half and deeper structures cannot be observed.

Electroencephalography is not a reliable indicator of brain death.<sup>2</sup> Before clear consciousness has been proven to occur in people without cerebral blood flow, there is no need to reconsider the nature of mind-brain relation.

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- 1 van Lommel P, van Wees R, Meyers V, Elfferich I. Near-death experience in survivors of cardiac arrest: a prospective study in the Netherlands. *Lancet* 2001; **358**: 2039–45.
- 2 Paolin A, Manuali A, Di Paola F, et al. Reliability in diagnosis of brain death. *Intensive Care Med* 1995; **21**: 657–62.

Sir—Pim van Lommel and colleagues' study<sup>1</sup> reminds me of an apocryphal comment attributed to Kerry Packer, Australia's wealthiest man.

Packer had a myocardial infarction while riding a polo pony. A nearby ambulance crew resuscitated him. Packer reported his experience with the telling comment: "Mate, I tell you there is nothing there". He was obviously not keen to repeat the experience and promptly equipped the New South Wales ambulance service with defibrillators.

The most fascinating part of van Lommel and colleagues' study, which is noted by the researchers, although it subsequently attracts little attention, is the association of these events with spiritual beliefs and subsequent

strengthening of these beliefs. Taking this association further, I wonder whether some of these experiences have led to some of the myths, legends, and religious beliefs we hold today.

Paranormal phenomena such as ghosts, and religious events such as reincarnation could be explained through distortion over the ages of near-death experiences. Bruno Bettelheim<sup>2</sup> drew our attention to the importance of myth, legend, and fairytale as a roadmap to overcoming adversity on the pathway to maturity. Near-death experiences may prove to be a fountainhead for these devices and, as such, be central to spirituality rather than stemming from it.

The other element that does not attract comment is the overwhelmingly positive nature of the near-death experience. This positivity could represent the optimism of the human spirit, or maybe it ensures that the experience is subject to recall and recounting. It may also underpin one of the most quoted biblical phrases from Psalm 23: "Yea, though I walk through the shadow of the valley of death, I will fear no evil".

It is a pity that Kerry Packer, who, in his rare public utterances tells it as he sees it, could offer no further insight into the presence of the human soul.

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- 1 van Lommel P, van Wees R, Meyers V, Elfferich I. Near-death experience in survivors of cardiac arrest: a prospective study in the Netherlands. *Lancet* 2001; **358**: 2039–45.
- 2 Bettelheim B. The uses of enchantment. New York: Knopf, 1976.

Sir—In his Dec 15 Commentary, C C French<sup>1</sup> states that any report of veridical perception during out-of-body experiences would represent a strong challenge to any non-paranormal explanation of the near-death experience.

Another context in which out-of-body experiences have been described is the dissociated rapid-eye-movement (REM) sleep state, defined as sleep paralysis. Cheyne and colleagues<sup>2</sup> reported 17 cases of autoscopic experiences associated with sleep paralysis, in which the individuals viewed themselves lying on the bed, generally from a location above the bed.

I previously reported the results of a survey of people experiencing sleep paralysis.<sup>3</sup> Of 264 participants, 28 (11%) had had some kind of out-of-body experiences. Some of them reported recurrent episodes of such experiences. I invited these people to do

the following simple reality tests: trying to identify objects put in unusual places; checking the time on the clock; and focusing on a detail of the scene, and comparing it with reality.

I received a feedback from five individuals (unpublished data). Objects put in unusual places (eg, on top of the wardrobe) were never identified during out-of-body experiences. Clocks also proved to be unreliable: a woman with nightly episodes of sleep paralysis had two out-of-body experiences in the same night, and for each the clock indicated an impossible time. Another participant stated "I look at my alarm clock to check, and if the bright green LED is not there, then I immediately know that it is a sleep disorder experience . . . my bedroom seems the same as it is during waking, only the lights don't work". Finally, in all cases but one, some slight but important differences in the details were noted: "I looked at 'me' sleeping peacefully in the bed while I wandered about. Trouble is the 'me' in the bed was wearing long johns . . . I have never worn such a thing".

On the whole, out-of-body experiences in people who experience sleep paralysis seem not to pass reality tests. Therefore, what is seen should be thought of as a recollection of information stored in the person's memory of his or her surroundings.

A clue about the origin of such experiences may come from neuroimaging studies of brain activation during REM sleep. By use of positron emission tomography, Maquet and colleagues<sup>4</sup> noted a significant negative correlation between regional cerebral blood flow (rCBF) and REM sleep in a large area of the dorsolateral prefrontal cortex and the parietal cortex, and a significant positive correlation between rCBF and REM sleep in limbic-system structures implicated in the formation and consolidation of memories. In dissociated REM sleep states, activation of such limbic structures during inhibition of the neocortex may lead to an oneiric recollection of images concerning the individual's sleeping environment.

Likewise, in near-death experiences, out-of-body visions, and possibly other phenomena, such as flashes of recollection from the past, and even life reviews reported by some patients, may represent a disinhibition of limbic-system structures due to hypoxic suppression of the neocortex,<sup>5</sup> rather than paranormal phenomena or false memories.

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- 1 French CC. Dying to know the truth: visions of a dying brain, or false memories? *Lancet* 2001; **358**: 2010–11.
- 2 Cheyne JA, Rueffer SD, Newby-Clark IR. Hypnagogic and hypnopompic hallucinations during sleep paralysis: neurological and cultural construction of the night-mare. *Conscious Cogn* 1999; **8**: 319–37.
- 3 Buzzi G, Cirignotta F. Isolated sleep paralysis: a web survey. <http://www.sro.org/2000/Buzzi/61/> (accessed Feb 27, 2002).
- 4 Maquet P, Pétters JM, Aerts J, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature* 1996; **383**: 163–66.
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## Blood pressure and cardiovascular risk in the HOPE study

Sir—Peter Sleight and colleagues (Dec 22/29, p 2130)<sup>1</sup> do not take account of an important confounding factor in their re-examining of the Heart Outcomes Prevention study (HOPE) data.

More individuals with high cardiovascular risk were randomly assigned placebo than ramipril. The placebo-group outcome would, therefore, have been worse even with no active treatment in the angiotensin-converting-enzyme (ACE) inhibitor group. Use of only the relative risk magnifies the apparent drug effect on cardiovascular outcome because of the baseline imbalance.

Specifically, the placebo group contained more individuals with each of the major risk factors: existing peripheral vascular disease ([PVD] 119), previous myocardial infarction (72), stable angina (74), unstable angina (nine), previous cerebrovascular disease (13), left-ventricular hypertrophy (27), raised total cholesterol (53), and microalbuminuria (52). There were also more men, more smokers, and a longer duration of disease in patients with diabetes. Hypertension and diabetes were under-represented in the placebo group.

No risk factor considered in isolation differs significantly between the placebo and drug-treated groups. However, existing vascular disease is the most potent risk factor for future vascular events and the cumulative preponderance of vascular disease in the placebo group is striking.

The excess risk characteristics at baseline cannot simply be summed to establish how many individuals were at increased risk because they had coronary artery disease, PVD, or cerebrovascular disease, or a

combination of these. Many individuals will have these in combination, and hence, comparison of relative risk between the placebo and active groups in the presence and absence of each factor in isolation will be misleading. For example, assessment of outcome in individuals without previous myocardial infarction gives a relative risk statistic that does not take account of the imbalance of, say, PVD between the placebo and ACE inhibitor groups.

The most unbalanced characteristic was PVD, with 119 more individuals in the placebo group. The primary event rate was 30·8% in patients with PVD and 17·1% in those with no PVD (personal communication, H Gerstein and S Yusuf). Given this almost two-fold difference in outcome, small imbalances in study groups at baseline will produce disproportionately great effects on outcomes. The HOPE study data were reported to show absolute risks of a primary event of 17·8% (ACE inhibitors) and 14·0% (placebo) over 4·5 years. An estimation based on stated assumptions to correct for the baseline imbalance suggested that the absolute risks of a primary event were around 16·7% and 14·0%, respectively.<sup>2</sup> Hence, the drug-associated relative risk reduction may have been overestimated by about a third.

Researchers in the Hypertension Trialists Collaboration<sup>3</sup> and a meta-analysis<sup>4</sup> showed no effect of different antihypertensive agents on vascular outcome. Similarly, the UK Prospective Diabetes Study<sup>5</sup> showed no difference between ACE inhibitors and  $\beta$ -blockers in lowering blood pressure or the risk of fatal and non-fatal complications in people with type 2 diabetes over a median of 8·4 years. The baseline imbalance of vascular risk in the HOPE study could account for the conflicting observations reported by Sleight and colleagues.

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- 1 Sleight P, Yusuf S, Pogue J, Tsuyuki R, Diaz R, Probstfield J, for the Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Blood pressure reduction and cardiovascular risk in HOPE study. *Lancet* 2001; **358**: 2130–31.
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- 4 Staessen JA, Wang J-G, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; **358**: 1305–15.
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Sir—Peter Sleight and colleagues<sup>1</sup> attempt to provide evidence that the benefits seen in the HOPE study are not due to reduced blood pressure alone. However, two major points of concern have not been addressed.

First, blood pressure was measured only at baseline, 1 month, 2 years, and at the end of the study. It is unclear at what time of the day these blood-pressure measurements were taken—presumably during the first half of the day. Even when based on these daytime measurements, blood pressure was significantly different between the ramipril and the placebo groups. Since adjustment of antihypertensive drug therapy is generally based on daytime office measurements, differences in blood pressure between the ramipril and placebo groups were probably even more pronounced during the rest of the day, especially at night, even in these so-called normotensive participants.

Second, no information is provided on blood-pressure-lowering medications other than ramipril or any other drug treatments relevant for cardiovascular outcomes during the study period. Thus, assessment of an important source of treatment bias is impossible. Significant differences in treatment other than the study intervention between the two groups cannot be excluded.

The HOPE study does not convincingly show that the effects of ramipril are additive to other proven treatments. Therefore, a comparison with another blood-pressure-lowering drug rather than with placebo is required. In the UK Prospective Diabetes Study,<sup>2</sup> atenolol and captopril were similarly effective in reducing the risk of macrovascular and microvascular complications in people with type 2 diabetes.

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- 1 Sleight P, Yusuf S, Pogue J, Tsuyuki R, Diaz R, Probstfield J, for the Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Blood-pressure reduction and cardiovascular risk in HOPE study. *Lancet* 2001; **358**: 2130–31.

- 2 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; **317**: 713–20.

#### Authors' reply

Sir—Roy Taylor speculates that the benefits seen with ramipril in the HOPE study may have been overestimated because of baseline imbalances in risk factors. None of these selected imbalances was significant. Randomisation balances known or measured risk factors as well as unmeasured or unknown factors. In the companion vitamin E paper<sup>1</sup> we showed similar minor non-significant differences; 72 more people with PVD were assigned active vitamin E, but this did not lead to a worse outcome. We therefore disagree with Taylor's conclusion. Many regulatory authorities have carefully assessed the full data, and have not raised these issues.

He notes that in neither the UK Prospective Diabetes study (UKPDS) nor the Hypertension Trialists Collaboration meta-analysis were differences in outcomes identified between different drugs. The UKPDS compared atenolol and captopril in few patients; it lacked power to detect moderate but worthwhile differences. Similarly the Blood Pressure Trialists' Collaboration noted that their meta-analysis lacked power to discriminate between classes of drugs in subgroups. Patients randomised in those trials had baseline coronary disease in around 5%, compared with 80% in HOPE. ACE inhibitors, particularly ramipril, may be especially useful in high-risk subgroups with coronary heart disease. The Losartan Intervention For Endpoint reduction in hypertension study (LIFE)<sup>2</sup> supports the HOPE conclusion; it clearly shows that the angiotensin-I-receptor blocker is better than atenolol in hypertensive patients with left-ventricular hypertrophy, despite identical reduction in blood pressure by the two agents.

Ingrid Mühlhauser noted the low number of times when blood pressure was measured, but this does not bias the difference in blood pressure from the placebo group. The blood pressure measurements are at least the equal of the epidemiological measurements (often only two or three in number) that form the basis of our knowledge of the effects of blood pressure on risk. Because in some people (but not all) ramipril was taken at night, the difference in blood pressure may have

been greater between placebo and ramipril. A 38-patient study of ambulatory blood pressure in patients in Sweden with peripheral vascular disease<sup>3</sup> showed a greater fall in blood pressure at night. These patients differed importantly from the main HOPE study; they had higher blood pressure, known peripheral vascular disease, and notably fewer blood-pressure-lowering drugs. The PROGRESS study<sup>4</sup> showed very comparable falls in blood pressure with the ACE inhibitor, perindopril, alone. We agree that (as in similar studies) other blood pressure medications will be different between the placebo and the ramipril groups.

Mühlhauser questions the additive effects of ramipril on top of other proven blood-pressure-lowering drugs. Again we disagree. We gave the relative risks for the benefit of ramipril with and without  $\beta$ -blockade, diuretics, and calcium-channel blockers. These are almost identical for patients prescribed non-study  $\beta$ -blockade or not, or diuretics or not, and do not differ significantly between calcium-channel blockers and no calcium-channel blockers. We stated that in each case there was significant benefit from ramipril for the primary outcome ( $p < 0.01$ ), with no significant evidence of heterogeneity.

We received grant support for the HOPE trial from Hoechst-Marion-Roussel (now Aventis), AstraZeneca, and the Natural Vitamins Association (as well as the Canadian Medical Research Council, and the Ontario Heart and Stroke Foundation). The trial was designed, analysed, and published independent of all sponsors.

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## Climate change: the new bioterrorism

Sir—I write in sorrow in response to the uncritical science and anti-Americanism of your Nov 17 editorial.<sup>1</sup>

This is sadly the second occasion, the first being your unfortunate foray into genetic modification in agriculture, on which you have opted for ecochondria rather than the cautious assessment of environmental science and economics. I do not think your role is to engender mass sociogenic illness by proxy through using the term, bioterrorism, so disingenuously.

All serious scholars remain cautious about the science of climate change, even those who believe some action needs to be taken. The Intergovernmental Panel on Climate Change admits publicly that it knows next to nothing about 75% of the main proxy variables involved.<sup>2</sup> There are also hundreds of physicists, chemists, meteorologists, and climate historians who remain totally unconvinced by the current climate models and their virtual predictions; such scientists, however, are little reported in the UK media, although they are elsewhere in the world.<sup>3,4</sup>

In the past year alone, such scientists<sup>4</sup> have questioned the whole relation between carbon dioxide and temperature; the role of that most important greenhouse gas, water vapour; the accuracy of temperature measurements on land and sea in relation to satellite measurements; the importance of newly considered variables, such as black carbon (soot), aerosols, waves, and so-called Pacific vents; and our understanding of climate history, bearing in mind the fact that we are currently emerging from a Little Ice Age which ended around 1880.

You, however, exhibit ignorance of this work. Moreover, in your attempt to link the worst of climate predictions with the worst of medical outcomes, you also do not take into account the medical consequences of cold and damp and the fact that disease epidemiology is rarely, if ever, monocausal.<sup>5</sup>

Likewise, you have ignored the critical economics and politics of the Kyoto Protocol, including the deep economic black hole of carbon trading, totalling anything up to US\$190 billion, represented by the Ukraine and Russia. Russia was represented at the latest meeting, COP7 in Marrakech, demanding yet more. In general terms, the Kyoto Protocol is conservatively estimated to cost between \$100 billion and \$1000 billion, with a mean around \$350 billion. This amount of money could pay off the public debt of the

49 poorest countries in the world and provide clean drinking water for all. Imagine the comparative medical advantages of that course of action.

Yet more importantly, you do not recognise that climate change is, always has been, and always will be, the norm. Climate is the ultimate coupled non-linear chaotic system; we can no more predict the outcome of doing something (emitting gases) than of not doing something (stopping emitting gases). This central truth must be stated without equivocation: control of the emission of human-induced greenhouse gases will not halt climate change. You should be helping us to develop international medical frameworks for adaptation to this constant change, whatever its direction—hot, wet, cold, dry, or all at once—not just falling for uncritical ecohyge.

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- 1 Editorial. Climate change—the new bioterrorism. *Lancet* 2001; **358**: 1657.
- 2 IPCC. Climate change 2001, the scientific basis: contribution of Working Group 1 to the Third Assessment report of the IPCC (table 6.11 and fig 6.6). <http://www.ipcc.ch/pub/tar/wg1/index.htm> (accessed Feb 20, 2002).
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## Is the NICE process flawed?

Sir—The National Institute for Clinical Excellence (NICE) has published the technology appraisal of irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer.<sup>1</sup> We believe that the long-delayed result is a mixed blessing.

Although the decision by NICE shows courage and foresight in endorsing the use of oxaliplatin to down-stage patients with metastases confined to the liver, it discourages the use of these drugs in a wider, first-line setting, despite strong evidence of clinical benefit.<sup>2</sup> Failure to use new cancer treatments is likely to impede improvements in UK survival rates,<sup>3</sup> and will ultimately detract from the government's own agenda, as stated in *Our Healthier Nation*,<sup>4</sup> to reduce cancer deaths by 10% by 2010.

We are concerned about the NICE

process, and the apparently inconsistent approach to appraisals. It is surely a requirement for a systematic and evidence-based institute to provide thresholds of clinical effectiveness and cost-effectiveness that it deems acceptable for technologies to be recommended. These definitions should form the basis of all appraisals.

The colorectal cancer appraisal for example, which rejected first-line use of drugs on balance of clinical and cost-effectiveness, assessed four randomised controlled trials on the use of irinotecan, and seven on the use of oxaliplatin as first-line treatment, in which significant clinical benefits were reported. It is unclear from the guidance why these benefits were not judged sufficiently worthy for a more widespread recommendation of these drugs. In addition, although cost-effectiveness was clearly a factor in the guidance, the level at which this factor was deemed worthy is not transparent and seems to be affected by measures not actually calculated (eg, quality-adjusted life-years).

We are also concerned that the appraisals committee included no oncologists or colorectal-cancer specialists. Two individuals provided expert opinions to the NICE committee at the preliminary appraisal stage, but withdrew before the committee debated changes to the guidance.<sup>5</sup> A wider consultation that included colorectal cancer specialists from the start might have resulted in a more acceptable outcome for practising oncologists.

Oncologists treating patients with advanced colorectal cancer are now in a difficult position when facing patients and their families, having to deny them treatments that they know to be the best option available. The pragmatic options open to patients will be to accept less-effective treatment or to consider funding treatment privately. Is it to be the case that NICE delivers guidance that indirectly leads to rationing of non-NICE-approved treatments and to a two-tier health system? In the current climate of media speculation around the future of the National Health Service, this move can only prompt further concern that evidence-based recommendations by NICE may reduce rather than assist patients' choices. Surely informed choice is the ultimate goal of evidence-based medicine and is what we and our patients should expect.

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- 1 Technology appraisal no. 33. London: National Institute for Clinical Excellence, 2002.
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- 4 Saving lives: our healthier nation. London: Stationery Office, 1999.
- 5 Minutes of the appraisals committee meeting, 7 February, 2001. [www.nice.org.uk/article.asp?a=15823](http://www.nice.org.uk/article.asp?a=15823) (accessed April 8, 2002).

Sir—As a group of surgeons with an interest in the management of advanced colorectal cancer, we welcome the long-delayed decision by NICE to approve the use of combination chemotherapy with oxaliplatin and 5-fluorouracil in selected cases of metastatic disease.<sup>1</sup> This decision will be of benefit to patients who have non-resectable liver metastases at diagnosis or relapse.

The role of surgery for liver metastases is now well established; indeed, surgery is the only potentially curative treatment for such lesions. Resection of liver metastases is associated with low mortality and morbidity, and potential 5-year survival of up to 50% for otherwise uniformly fatal cases. Although the potential benefits of liver resection are increasingly recognised by surgeons and oncologists alike, only 10–20% of patients initially presenting with liver metastases are suitable candidates for liver surgery.<sup>2</sup> For many patients, therefore, resection is not technically feasible without preceding chemotherapy.

NICE's decision takes into account important studies from France<sup>3</sup> and the USA,<sup>4</sup> in which significant proportions of initially non-resectable patients were down-staged by systemic oxaliplatin and 5-fluorouracil and subsequently underwent resection, with results as good as those in patients with initially resectable metastases.

We have assessed the clinical and economic effect of use of chemotherapy followed by resection in the UK.<sup>5</sup> Our findings suggest that long-term survival (average 9 years) could be achieved for more than 260 additional patients per year in England and Wales, none of whom would otherwise survive longer than 1.7 years. The cost of this outcome should be acceptable to the National Health Service.

The welcome judgment by NICE has at last opened the way in the UK for treatment that has been available for many years in continental Europe. We hope that, as a result, many more

patients will be considered for chemotherapy and surgery, and urge clinicians to look at the possibility of curative treatment for most cases of advanced colorectal cancer and to fully investigate the options in the context of multidisciplinary team discussions.

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- 2 Rees M, John TG. Current status of surgery in colorectal metastases to the liver. *Hepatogastroenterology* 2001; **38**: 341–44.
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- 4 Alberts S, Horvath W, Donohue J, et al. Oxaliplatin, 5-fluorouracil, and leucovorin for patients with liver only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. Presented at the 37th annual meeting of the American Society of Clinical Oncology, San Francisco, CA, USA, May 12–15, 2001.
- 5 Poston G, Benjamin IS, Diamond T, et al. Costs of neoadjuvant chemotherapy and surgery in patients with liver metastases from advanced colorectal cancer. *J Med Econ* 2001; **4**: 167–77.

## Striking reduction in medical junk mail

Sir—I reported previously that the medical junk mail I received in 1999 created a 2 m high stack that weighed 122 kg.<sup>1</sup> Some sources suggest that the American Medical Association (AMA) list of members is, in the USA, key to much of this unsolicited mail. I attempted to test the accuracy of this theory.

In October, 2000, I wrote to the AMA by requesting that my name be removed from all of their mailing lists, and they sent me written confirmation that this was done. Surprisingly, although I continued to receive (and read) the *Journal of the American Medical Association*, to which I have never subscribed, the overall amount of my other medical junk mail declined precipitously.

From Jan 1, 2001, to Dec 31, 2001, I again collected all of my medical junk mail, according to the same criteria as previously (unsolicited undesired mail, intended for me as a physician). The cumulative weight dropped from 122 kg in 1999 to 9 kg in 2001, and the height of the stack declined from 2 m

to 30 cm (7.5 cm of which was a box containing a sample prescription laxative). This change was so substantial, I polled colleagues at work to investigate where there was an alternative explanation to the AMA removing me from its marketing lists.

I asked co-workers whether their medical junk mail had increased or decreased strikingly, somewhat, or not at all, in 2001 compared with 1999. Eight reported no difference, six reported some decrease, and five reported some increase. Only one substantial change was reported—a new physician in his first year of full-time employment after training, whose junk mail had increased. Overall, the quantity of the group's medical junk mail had not changed.

This result strongly implies that the decrease in my medical junk mail was not due to overall changes in marketing practices in this area. I therefore conclude that much of the medical junk mail in the USA, which costs more than US\$1 billion yearly, is directly attributable to the commercial practices of the AMA.

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- 1 Montauk L. Medical junk mail. *Lancet* 2000; **356**: 344.

## DEPARTMENT OF ERROR

*Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack*—In this Article by the PROGRESS Collaborative Group (Sept 29, p 1033), the fourth sentence of the section entitled “Duration of follow-up and adherence to study treatment” in the Results (p 1036) should have read: “The main reasons for discontinuation were participant's decision (active 232 [7.6%], placebo 250 [8.2%]), cough (active 66 [2.2%], placebo 12 [0.4%]), hypotension (active 64 [2.1%], placebo 29 [0.9%]), and heart failure requiring treatment with an ACE inhibitor or diuretic (active 47 [1.5%], placebo 69 [2.3%]).”

*HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers*—In this Article by Pamela Sonnenberg and colleagues (Nov 17, p 1690), the second sentence in the last paragraph of the results should have read “At recurrence, four sensitive cases had developed isoniazid resistance (one relapse, one reinfection, two unknown) and two had developed multidrug resistance (one relapse, one unknown).”

*Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndrome: a meta-analysis of all major randomised clinical trials*—In this meta-analysis by Eric Boersma and colleagues (Jan 19, p 189), the second sentence of the section entitled “Treatment benefits in subgroups of patients” (p 194) should have read: “The treatment effect seemed smaller in patients with ST-segment depression than in those without, but the difference did not reach significance”.