

# CORRESPONDENCE

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## Use of stem cells in creation of embryos

Sir—In your July 21 editorial,<sup>1</sup> you admirably draw a line in the sand and recognise the ethical unacceptability of creating embryos by somatic nuclear transfer exclusively to use them as a source of stem cells. In discussing alternatives, you have, however, perhaps rather underplayed the potential usefulness of stem cells derived from adult bone marrow.

No discipline in stem-cell science has made more exciting progress over the past 12–24 months than work in bone marrow. Just 6 months ago, I commented<sup>2</sup> that cells obtained from adult bone marrow could develop into hepatocytes, chondrocytes, osteoblasts, vascular endothelial cells, adipocytes, and skeletal and cardiac myocytes (as well as, of course, haemopoietic cells), and neurons and glia cells. Bone-marrow transplantation studies in mouse models of muscular dystrophy showed partial restoration of dystrophin expression in dystrophic muscle, and clinical experimental trials of stromal cell transplantation were already underway in children with osteogenesis imperfecta.

This account is already out of date. The specific stem cell present in bone marrow has now been identified.<sup>3</sup> In rodents, implanted adult marrow-derived stem cells have repaired ischaemic cardiac muscle<sup>4</sup> and demyelinated spinal cord tissue. Mature renal cells have been added to the list of progeny of adult marrow cells.<sup>5</sup> These experiments have added to the growing evidence that bone-marrow cells contribute to normal regeneration after damage,<sup>5</sup> which raises the likelihood that they will prove useful in various treatments.

Reliable witness to this potential use is surely offered by the establishment (one assumes for commercial reasons) of a small number of biotech companies in the

USA and the UK devoted to developing reparative transplantation treatments from adult marrow-derived cells. Bone-marrow aspiration is not a trivial procedure, but stem cells derived from embryos, whether abortion-derived, created by in-vitro fertilisation procedures, or cloned, are anything but conveniently obtained by comparison.

Although these important ethical questions of utilitarianism do not hinge on the attractiveness or viability of alternatives, in practical terms the ability to generate stem cells for therapeutic research by other means is an important consideration.

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- 1 Editorial. Stem-cell research: drawing the line. *Lancet* 2001; **358**: 163.
- 2 Scolding N. New cells from old. *Lancet* 2001; **357**: 329–30.
- 3 Krause DS, Theise ND, Collector MI, et al. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. *Cell* 2001; **105**: 369–77.
- 4 Jackson KA, Majka SM, Wang H, et al. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. *J Clin Invest* 2001; **107**: 1395–402.
- 5 Poulson R, Forbes SJ, Hodivala-Dilke K, et al. Bone marrow contributes to renal parenchymal turnover and regeneration. *J Pathol* 2001; **195**: 229–35.

Sir—You point out that research with human embryonic stem cells, despite its potential benefits, is faced with opposition.<sup>1</sup> The latter has to do with religion and philosophy, not with science. Since things can sometimes be seen more clearly from a distant perspective, it might be worthwhile speculating how that opposition could be viewed by hypothetical aliens studying humankind since its origins.

They might wonder why, since 93% of leading scientists do not believe in

God,<sup>2</sup> religion is still allowed to interfere with the progress of science, as has frequently been seen in human history (the sentence against Galileo is an example).

The aliens might also note that the religious ethics that underpin the opposition to research with embryonic stem cells is in contrast to the biological ethic that evolution fostered in human beings to ensure their survival.<sup>3</sup> This biological ethic, which also guides humans' closest relatives,<sup>4</sup> is aimed primarily at avoiding pain and suffering, because they, as expressions of diseases and physical impairments, constitute a threat to fitness and survival.

Evolution could be said to have taught human beings that actions aimed at reducing human suffering are ethical<sup>3</sup> and that, by implication, deliberate actions to hamper this aim are unethical.<sup>3</sup> The opposition to the promising research with embryonic stem cells therefore emerges as unethical. To save a few microscopic and insensitive embryos at the expense of several suffering human beings would be an evolutionary nonsense.

The aliens could finally suggest that some religious dogmas and philosophical conclusions, as mere products of the last 0.1% of human evolution, should be disregarded if they are at odds with the biological ethics that have wisely guided humankind for millions of years.

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- 1 Editorial. Stem-cell research: drawing the line. *Lancet* 2001; **358**: 163.
- 2 Larson EJ, Witham L. Leading scientists still reject God. *Nature* 1998; **394**: 313.
- 3 Baschetti R. People who condemn eugenics may be in minority now. *BMJ* 1999; **319**: 1196.
- 4 Baschetti R. Evolutionary psychiatry. *J R Soc Med* 1997 **90**: 358–59.

## **PTEN mutations and Proteus syndrome**

Sir—In their report, Xiao-Ping Zhou and colleagues (July 21, p 210)<sup>1</sup> describe a study of nine patients with Proteus syndrome, of whom two had mutations in the *PTEN* gene. They say that patients meet published diagnostic criteria.<sup>2</sup> We raise several issues about their conclusions.

First, the reported results by Zhou and colleagues differ substantially from those of other groups. Barker and colleagues<sup>3</sup> reported eight patients with Proteus syndrome, also said to meet the published criteria, none of whom had *PTEN* mutations. Our preliminary data from 19 patients (examined by at least one of us) who meet the criteria and were similarly screened show no *PTEN* mutations.

Second, Zhou and colleagues provide insufficient clinical data to confirm the diagnosis of Proteus syndromes. The clinical data seem to be unavailable because of barriers of informed consent or issues about protection of human participants. We laud the investigators for protecting the interests of their patients, but the diagnosis of Proteus syndrome described cannot be validated.

Third, our experience suggests that the diagnostic criteria are widely misinterpreted. In a review of nearly 100 cases of patients referred for second opinions or for research eligibility, in our opinion, more than half the patients referred (including those from experienced clinical geneticists) with a diagnosis of Proteus syndrome had a different disorder. We believe that there is a high rate of misdiagnosis because the diagnostic criteria do not sufficiently emphasise the progressive nature of the disorder. Patients with Proteus syndrome have postnatal progressive overgrowth that proceeds at a rapid, frequently alarming, rate.<sup>4</sup> Other common errors include misdiagnosis of hyperostoses and the connective tissue naevus of the foot. In Zhou and colleagues' report, the manifestations listed for patient PS2 in table 2 are insufficient for a diagnosis of Proteus syndrome.

Fourth, Zhou and colleagues also conclude that *PTEN* mutations have been reported in patients with Proteus-like syndrome. We suggest that the term Proteus-like further confuses the issue. Many patients have lipomas, hemihyperplasia, epidermal naevi, vascular anomalies, or a combination of these. An overwhelming number of patients in this heterogeneous group do not have

Proteus syndrome.<sup>5</sup> Attaching even a qualified label of Proteus to such patients is not useful for clinical or scientific purposes. Based on these points, we suggest that a more reasonable conclusion for the work by Zhou and colleagues is that patients with overgrowth syndromes who also have lipomas, vascular anomalies, or other features that overlap with Proteus syndrome may have mutations in *PTEN*. The molecular cause of Proteus syndrome is unknown.

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- 1 Zhou X, Hampel H, Thiele H, et al. Association of germline mutation in the *PTEN* tumour suppressor gene and Proteus and Proteus-like syndromes. *Lancet* 2001; **358**: 210–11.
- 2 Biesecker LG, Happle R, Mulliken JB, et al. Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. *Am J Med Genet* 1999; **84**: 389–95.
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- 4 Biesecker LG. The multifaceted challenges of Proteus syndrome. *JAMA* 2001; **285**: 2240–43.
- 5 Cohen MM Jr, Neri G, Weksber R. Proteus syndrome. Overgrowth syndromes. New York: Oxford University Press, 2001: 75–110.

### *Authors' reply*

Sir—We compared essential clinical features among Cowden syndrome, another difficult clinical diagnosis, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome. Although we were prevented by the conditions of ethical approval from disclosing very detailed clinical findings in our patients, all diagnoses of Proteus syndrome were made by very experienced clinical geneticists specialising in dysmorphology.

Biesecker and colleagues claim that the diagnostic criteria might be only 50% sensitive. When a clinical diagnosis is difficult to make and the diagnostic criteria are less than robust, a more objective means to aid diagnosis is warranted. This lesson must surely be one of the most important learned from the developmental and syndromic insights accrued over the past few years—striking examples are the craniosynostosis syndromes, skeletal dysplasias, and other malformation syndromes, in which several clinically

discrete phenotypes share mutations at a common locus. As a consequence, the limits of clinical definition for malformation syndromes have frequently been exposed.

Ironically, Biesecker and colleagues have contributed substantially to this development in the evolution of syndrome understanding, identifying mutations in the *GLI3* gene in Pallister-Hall syndrome.<sup>1</sup> Mutations in this gene also cause the phenotypically distinct disorders of Greig syndrome<sup>2</sup> and familial hexadactyly.<sup>3</sup>

Thus, no matter what the clinical diagnosis, finding a germline *PTEN* mutation should reclassify the patient or family to the molecular diagnosis of *PTEN* hamartoma tumour syndrome (PHTS).<sup>4</sup> Because of genotype-phenotype associations and the risk of cancer in PHTS, we find this molecular classification useful for clinical management as well.

The argument that Barker and colleagues' and their own unpublished work did not reveal germline *PTEN* mutations in Proteus syndrome does not detract from our observations. We suspect that Proteus syndrome is genetically heterogeneous and only a subset will harbour such germline mutations. We have never claimed that all Proteus syndrome is caused by *PTEN* mutation. Second, the frequency of finding *PTEN* mutations is highly dependent on the mutation detection technology used. We have shown that single-strand conformational polymorphism analysis for this gene is highly insensitive (detection rate was 0%, unpublished data). The gold standard of direct sequencing should detect nearly 100% of mutations. However, for Proteus syndrome, in which an unknown degree of mosaicism could exist, sequencing becomes much less sensitive.<sup>5</sup> The method we use, denaturing gradient gel electrophoresis has a sensitivity of around 100% and the added advantage of being able to detect mutant contributions as low as 1%.

We use the term Proteus-like syndrome to denote cases likely to have Proteus syndrome but who, in the opinion of expert dysmorphologists, do not satisfy that clinical diagnosis as currently recognised. In addition, for our continuing studies, these individuals must also not meet the criteria for the diagnosis of Cowden or Bannayan-Riley-Ruvalcaba syndromes. We have noted that individuals with Proteus-like syndromes have features reminiscent of Cowden or Bannayan-Riley-Ruvalcaba, and Proteus syndromes, or a combination of these, but do not meet the respective

diagnostic criteria. Up to half such individuals harbour germline *PTEN* mutations. Therefore, no matter what their clinical diagnoses, they should be reclassified to PHTS.

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## New thrombolytic regimens in acute myocardial infarction

Sir—Frans J Van de Werf and colleagues (Aug 25 p 605)<sup>1</sup> show that the tenecteplase plus enoxaparin or abciximab regimens reduce ischaemic complications of an acute myocardial infarction (AMI).

The enoxaparin and the abciximab groups did not differ significantly. The benefit of the abciximab group was obtained at the cost of a higher rate of thrombocytopenia, major bleeding complications, and blood transfusion, and no benefit was seen in elderly patients and in diabetics.

A patent infarct-related artery is the most powerful predictor of survival after AMI.<sup>2</sup> Pilot studies that combined reduced-dose plasminogen activator and glycoprotein IIb/IIIa inhibitor have shown better speed, and completeness of the infarct-related artery.

In the setting of percutaneous coronary intervention, most complications arise during and immediately

after the intervention, and effective platelet aggregation inhibition is of particular importance during this period. In patients with an AMI, not undergoing early revascularisation, the temporal window of risk is longer. In these patients, it is thus essential that the dosing regimens of a glycoprotein IIb/IIIa inhibitor provide a consistent and durable antiplatelet effect for the entire duration of treatment.

The goal of establishing and sustaining more than 80% platelet-aggregation inhibition has been universally accepted as a surrogate endpoint to identify dosing regimens of glycoprotein IIb/IIIa inhibitors that would provide sufficient clinical benefit.<sup>3</sup> When assessed under standard conditions, the degree of platelet-aggregation inhibition achieved with dosing regimens of different agents used in clinical trials varies substantially, between individual patients and over time.<sup>4</sup> In the group treated with abciximab, substantial between-patient variability was noted, and the proportion of patients who had subtherapeutic inhibition increased over time.<sup>4</sup>

In Van de Werf and colleagues' study, they note an early benefit for combination therapy compared with full-dose tenecteplase plus enoxaparin, which lost efficacy over time. The early benefit will be caused by achieving the target of platelet-aggregation inhibition with abciximab during the period of the first 6 h, the quick loss of inhibitory effect after the end of infusion may explain the absence of expected benefit in 30-day mortality.

The INTEGRITI investigators<sup>5</sup> showed that reduced-dose tenecteplase plus eptifibatid gave excellent angiographic data. By contrast with abciximab, eptifibatid provided an instant, consistent, and durable antiplatelet effect for the entire duration (48 h) of treatment.<sup>4</sup> Thus we have good reasons to presume that combination therapy with a reduced dose of tenecteplase plus eptifibatid in patients with AMI is more effective than combination therapy with abciximab, and will provide evidence of the better efficacy and the combined efficacy and safety outcome. These hypotheses have to be validated in a large trial.

Van de Werf and colleagues' results should not lead us to give up combination therapy with reduced-dose plasminogen activator and glycoprotein IIb/IIIa inhibitor in patients with AMI, because there are big differences in the pharmacodynamic data within the group of glycoprotein IIb/IIIa inhibitors which

may explain the results of published trials.

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- 1 The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; **358**: 605–13.
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- 5 Giugliano RP, Roe MT, Zeymer U, et al. Restoration of epicardial and myocardial perfusion in acute ST-elevation myocardial infarction with combination eptifibatid and reduced-dose tenecteplase: dose-finding results from the INTEGRITI trial. *Circulation* 2001; **104** (suppl II): 538 (abstr).

## Vasopressin and epinephrine for cardiac arrest

Sir—Ian Stiell and colleagues (July 14, p 105)<sup>1</sup> report a similar outcome and no adverse effects for vasopressin and epinephrine in patients being resuscitated in hospital. They disagree with the recommendation of vasopressin as an alternative treatment for cardiac arrest.

By contrast, we believe these observations are in agreement with laboratory and clinical investigations, and suggest that Stiell and colleagues' results apply only to the subgroup of in-hospital cardiac arrest patients they studied. In pigs, with short duration of cardiac arrest and moderate cardiac ischaemia, we have noted that vasopressin and epinephrine are similarly effective. During severe acidosis, however, vasopressin causes a striking pressor response in vitro, but catecholamines do not; vasopressin might, therefore, be beneficial when the duration of cardiac arrest and cardiopulmonary resuscitation is long.<sup>2</sup>

In a study of asphyxia in pigs, we noted that combined epinephrine and vasopressin, but not epinephrine or vasopressin alone, maintained raised coronary perfusion pressures during cardiopulmonary resuscitation, and significantly improved survival rates.<sup>2</sup> Interactions between vasopressin and epinephrine depend on the presence of each other more than was previously thought. After 4 min ventricular fibrillation, endogenous epinephrine concentrations were extremely high, and when vasopressin was then given during cardiopulmonary resuscitation, coronary perfusion pressure rose strikingly from about 15 mm Hg to about 50 mm Hg.<sup>3</sup> During the asphyxia experiment, in contrast, high concentrations of endogenous epinephrine were released immediately after clamping of the endotracheal tube to maintain cardiocirculatory homeostasis until cardiac arrest finally occurred around 8 min after induction of asphyxia. Under these particular conditions, an effective response might only be achieved with vasopressin when the plasma concentration of epinephrine is high because of either endogenously released epinephrine, or exogenously administered epinephrine.

Morris and colleagues<sup>4</sup> reported that four of ten patients undergoing extended cardiopulmonary resuscitation efforts (about 45 min) with around 18 mg epinephrine had return of spontaneous circulation after subsequent administration of 1 U/kg vasopressin. A combination of epinephrine and vasopressin therefore seems particularly effective during extended cardiopulmonary resuscitation, severe global ischaemia, or both. The same mechanism might also explain the response of patients with vasodilatory shock, when a vasopressin infusion in addition to catecholamines can prevent haemodynamic collapse.<sup>5</sup>

We suspect that, because of the many different causes of cardiac arrest and the varied conditions under which rescue teams have to reach and treat their patients, the numerous features of cardiopulmonary resuscitation management must be carefully differentiated. Accordingly, Stiell and colleagues' approach to extrapolate their findings to the larger proportion of cardiac arrest patients in the emergency medical service might be overly cautious. We agree that new cardiopulmonary resuscitation strategies should be handled prudently. We are, therefore, currently coordinating a multicentre randomised clinical trial of vasopressin versus epinephrine

given up to two times out of hospital, followed by epinephrine. Global ischaemia might generally be more severe in these than in Stiell and colleagues' patients, and vasopressin might be beneficial. Meanwhile, two instead of one vasopressor options are available for the management of cardiac arrest patients, and we must look at how best to use them.

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- 1 Stiell IG, Hébert PC, Wells GA, et al. Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial. *Lancet* 2001; **358**: 105–09.
- 2 Mayr VD, Wenzel V, Voelckel WG, et al. Developing a vasopressor combination in a pig model of adult asphyxial cardiac arrest. *Circulation* 2001; **104**: 1651–56.
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- 5 Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory shock. *Crit Care Med* 1997; **25**: 1279–82.

#### Authors' reply

Sir—We agree that our results might be applicable only to the subgroup of in-hospital patients we studied and not to out-of-hospital patients, as studied by other workers. We also agree that further research is required and we look forward to the results of large and high-quality randomised controlled trials.

We acknowledge and respect the experimental and clinical research done by Volker Wenzel and Karl Lindner. We agree that the existing animal data are tantalisingly supportive of vasopressin and that Lindner's study of 40 patients suggests promise in out-of-hospital cases. However, to paraphrase one of the sentences in their letter, we are dismayed that the American Heart Association has extrapolated the findings of a small group of out-of-hospital patients to the larger population of all cardiac arrest patients. This decision we believe is premature. We estimate that at least 50% of all cardiac arrest resuscitations occur with in-hospital patients and we have yet to see strong evidence that vasopressin is effective for these patients. We hope that individual clinicians will not treat all patients alike irrespective of time from arrest or location of arrest as the

American Heart Association algorithms seem to suggest.

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Sir—Ian Stiell and colleagues' recommendation<sup>1</sup> is contrary to that of the American Heart Association.<sup>2</sup> However, a subtle difference in the studies cited might explain the opposing views.

Vasopressin is made in the hypothalamus but transported bound to its carrier protein down the magnocellular neurons in the pituitary stalk to be stored in vesicles in the posterior pituitary.<sup>3</sup> Once released, its half-life is about 6 min. Its main role at low plasma concentrations (<4 pg/mL) is to stimulate the reabsorption of water through the renal tubule to maintain plasma osmolality and plasma volume. At higher concentrations (>4 pg/mL), after a stronger stimulus, such as vomiting or severe shock, its main role is maintenance of blood pressure by increasing vascular tone, which lessens the capacity of the vascular pool. Under severe stress this mechanism may be associated with plasma concentrations as high as 20–30 pg/mL. Since vasopressin is stored in vesicles, severe and extended stimuli might result in depletion of vasopressin stores along with a fall in plasma concentrations. Associated with this may be a delay in further hormone being processed and transported to replenish the depleted vesicles.

Landry<sup>4</sup> has described two groups of patients. Although similar in presentation, one group had appropriately high concentrations of vasopressin (30–33 pg/mL) and the other had inappropriately low concentrations (4–8 pg/mL). Infusion of vasopressin resulted in an increase in blood pressure, with a suggestion that the response is better in those with low endogenous concentrations of vasopressin.<sup>4,5</sup> We have shown similar blood concentrations in sepsis, with a mean concentration in one group of around 3.7 pg/mL (13 of 16 patients) and a mean of 29 pg/mL (three of 16) in the other (unpublished data). This finding suggests that exhaustion of vasopressin stores may occur in some cases of septic shock.

In Stiell and colleagues' study, rapid resuscitation would be expected with initiation of hospital arrest procedures, before vasopressin stores became depleted. In other studies that they cite, in which vasopressin has given a positive response, there has either been out-of-

hospital arrest or the patients have failed standard epinephrine treatment. This implies that the degree of shock might be longer and, thus, vasopressin stores may be depleted, and plasma concentrations inappropriately low for the degree of shock. It would have been informative if Stiell and colleagues had given stored-blood vasopressin concentrations before the start of treatment, but we appreciate how difficult that might have been to do. Patients who responded best included those who had sepsis (nine), and the least responsive had respiratory depression (21), in whom shock may be less severe, or lethal arrhythmias (five), in whom vasopressin might be the least effective.

An understanding of the physiology of vasopressin and how it differs in production, storage, and release from most other hormones might explain the difference in response. This potentially useful agent should not be dismissed; its role in longer shock might still be important.

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- 1 Stiell IG, Hébert PC, Wells GA, et al. Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial. *Lancet* 2001; **358**: 105–09.
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Sir—We think there are important issues raised in the study by Ian Stiell and colleagues,<sup>1</sup> and the accompanying July 14 commentary by Peter Morley,<sup>2</sup> that merit discussion.

First, the International Guidelines, 2000, recommend vasopressin as an alternative first-line vasopressor in adults with ventricular fibrillation and out-of-hospital cardiac arrest (class IIb).<sup>3</sup> This recommendation is based on the results of a small randomised clinical study and two case series.<sup>4</sup> Therefore, further clinical data on the effects of vasopressin in cardiac arrest need to be assessed. Stiell and colleagues' study of 200 patients is the

largest available. They, however, investigated in-hospital cardiac arrest patients, only 21% of whom had ventricular fibrillation or tachycardia (despite the short time between collapse and treatment). Intriguingly, almost 50% of the patients had pulseless electrical activity. This finding is very different from out-of-hospital cardiac arrest, for which the incidence of pulseless electrical activity is far lower.<sup>5</sup> Outcome in patients with pulseless electrical activity is extremely poor.<sup>3,5</sup> Therefore, these data suggest that the in-hospital patients represent a seriously ill cohort with poor postarrest outcome. In such a cohort, it will always be difficult to show any differences between therapeutic strategies.

Second, Morley presents an interesting analysis of Stiell and colleagues' subgroup with ventricular fibrillation or tachycardia, which allows a more appropriate comparison of these results with those obtained by Lindner and co-workers.<sup>4</sup> However, no baseline characteristics are available from that subgroup, although analysis of such data would provide important information.

Third, in Stiell and colleagues' study, the time between collapse and treatment was short, which probably shows that benefit of vasopressin and epinephrine did not differ in short-term cardiac arrest. On the other hand, in experimental studies, workers have shown that, in contrast to vasopressin, catecholamines are less effective (metabolic derangements might affect  $\alpha$ -adrenergic receptors) when administered after extended periods of cardiac arrest.<sup>3</sup> This issue seems important. Stiell and colleagues report a mean time of 6.1 min to study-drug administration. Lindner and colleagues reported, for a response time of the rescue team, a mean time of 6.1 min for the epinephrine group and 6.5 min for the vasopressin group, and an additional 7.8 min and 8.6 min, respectively, until study-drug administration. Thus, the mean time for out-of-hospital treatment was more than twice that for in-hospital patients.

Therefore, we need to assess vasopressors in large clinical studies. A randomised multicentre study is underway of vasopressin compared with epinephrine for out-of-hospital cardiac arrest. When these results are available, the debate on the current International Guidelines will be based on more solid ground.

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- 1 Stiell IG, Hébert PC, Wells GA, et al. Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial. *Lancet* 2001; **358**: 105–09.
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## Mechanisms of brain injury in infantile child abuse

Sir—P Shannon and L Becker report, in their Sept 1 commentary,<sup>1</sup> on the mechanisms of brain injury in infantile child abuse. There is a differential diagnosis of the shaken-baby syndrome that is not widely known and is not addressed in the commentary.

Subdural bleeding and retinal haemorrhages, which are frequently observed in traumatic head injury, are also common findings in glutaryl-coenzyme A dehydrogenase deficiency (glutaric aciduria type I [GA I]). The disorder is an inborn error of the metabolism of the aminoacids lysine, hydroxylysine, and tryptophan that follows an autosomal recessive trait of inheritance. Subdural haemorrhage has even been emphasised as an initial sign of GA I.<sup>2</sup> Timely diagnosis can lead to the early detection of GA I in symptom-free siblings and is a prerequisite for genetic counselling and prenatal diagnosis.

In several patients who were later diagnosed as having GA I, subdural effusions and haematoma had originally been thought of as signs of child abuse and resulted in severe sociolegal consequences and in a delay of treatment.<sup>3</sup> Although there is much heterogeneity in the clinical presentation of GA I, most patients develop severe neurological disease similar to cerebral palsy after an acute encephalopathic episode before age 18 months, unless GA I is suspected early enough and appropriately treated.<sup>4,5</sup>

The incidence of GA I may be as high as one per 30 000–40 000 in the general population,<sup>4,5</sup> and, therefore, the disorder should be considered in the differential diagnosis of subdural

effusions or haematoma in children, especially, if frontotemporal atrophy, macrocephaly, or both are also present.

Laboratory tests for GA I generally start with the measurement of urinary organic acids and quantification of free carnitine and acylcarnitines in blood. Dependent on the results, and on the clinical features of the patient, enzyme activity of glutaryl-coenzyme A dehydrogenase could be assessed in leucocytes or in cultured fibroblasts; mutation analysis is possible. Samples for diagnosis of GA I can still be obtained at necropsy.

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## Was Bristol an outlier?

Sir—Paul Aylin and colleagues (July 21, p 181)<sup>1</sup> provide a fascinating retrospective view of outcomes in 12 paediatric cardiac surgical centres over a period of 12 years, with lessons for a more general application of the statistical methods used.

One centre, as we now know, seems to have done significantly less well than expected during one epoch, for one subgroup of operations, in one subgroup of patients. Aylin and colleagues allude to issues of multiple significance testing, and we have frequently been warned about the pitfalls of subgroup analysis in clinical trials in reports about statistics for clinicians. A more detailed account of the way in which subgroups were chosen would be of interest.

Why analyse by four epochs of unequal lengths, rather than by running totals of cases, or perhaps by the last 'x' cases at regular intervals? Why the subgroups of less than and more than age 1 year (why not, arbitrarily, 200 days, or 500 days)? What, if anything, is the importance of the

apparent improvement in results during the fourth epoch (table 1; Cardiac Surgical Register data 1995–96; open operations; patients younger than 1 year; Bristol mortality 6%; elsewhere mortality 12%)?

It has taken several years and ten contributors from several leading departments of epidemiology and statistics to publish these data and their analysis. Could the failing centre have reasonably been expected to have identified this problem earlier, and if so, when? Were the data to make the necessary comparisons available earlier, and would it have been possible at that stage to specify which particular subgroup analyses would have led to the problem being spotted? These are key questions for other units wanting to use statistical audit to identify an emerging problem, rather than a retrospective analysis when things have become sufficiently bad to justify expelling the guilty clinicians from the medical profession.

Most doctors would like to recognise the problems of poor outcomes in deficient units at an early stage, while still avoiding passing unfair judgment if results are less than perfect. Ordinary clinicians urgently require authoritative and detailed advice on the methods that should be in place and the "rules of the game". When exactly should a unit stop doing a particular procedure? It seems to me that most units in most hospitals are light-years away from that degree of advancement in audit. Meanwhile, for most of us, when we think of Bristol, it is still very much a matter of "there but for the grace . . .".

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- 1 Aylin P, Alves B, Best N, et al. Comparison of UK paediatric cardiac surgical performance by analysis of routinely collected data 1984–96: was Bristol an outlier? *Lancet* 2001; **358**: 181–87.

Sir—In their statistical analysis of cardiac surgical performance in the Bristol tragedy, Paul Aylin and colleagues<sup>1</sup> have been thorough, particularly in their use of different data sources and the accompanying sensitivity analysis.

While the investigators suggest that their model is suitable for general application, it has some limitations that need to be addressed. First, the model as it has been presented seeks to show excessively high mortality. Aylin and colleagues make no comment on the model's ability to identify centres with very low mortality. To improve quality of care, we need to do both.

Second, their model assumes that

mortality rates are drawn from a normal distribution. Inspection of raw data in our research<sup>2</sup> raises questions about the underlying stability of the distribution over time and between centres, let alone distribution of the mortality. Therefore, assigning a p value based on the normal assumption to the application of control charts is misleading.

Third, Aylin and colleagues constructed their random-effects model with Bristol excluded. Therefore, they can confirm only a prior hypothesis that Bristol is different, but not generate that hypothesis. As Aylin and colleagues acknowledge, in practice we must identify exceptional variation in outcome before, not after, the whistle blows.

Control charts included all centres in the analysis.<sup>2</sup> The control charts identified centres 11 and 7 as exhibiting special-cause variation between 1984 and 1987; centres 10 and 11 between 1988–90; and centre 1 (Bristol) and centre 11 between 1991 and 1995. On three of these six occasions (centre 7 between 1984 and 1987 and centre 11 in the remaining two epochs)—special-cause variation suggested very low mortality. Could these investigators confirm these further findings?

We agree with Aylin and colleagues that performance measurement and management are major issues in the UK National Health Service. How these issues are addressed is equally important. We advocate a method that requires no prior hypothesis about which centres might be different; that does not rely on unrealistic assumptions about the distribution of mortality rates between centres; and that guides us towards low and high mortality rates. We therefore see a place for control charts.

However, readers may be misled by a number of Aylin and colleagues' comments on control charts. They state that control charts seek to identify centres 3 SE from the mean with a two sided p value of 0.003. Calculations of the p value rely on an assumption that the underlying distribution is normal—a rarely afforded luxury in the real world. Control charts are not dependent on assumptions about the underlying distribution, but rely on the Chebyshev inequality,<sup>3</sup> which provides upper limits for the probabilities of deviation from the mean for all probability distributions.

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- 1 Aylin P, Alves B, Best N, et al. Comparison of UK paediatric cardiac surgical performance by analysis of routinely collected data 1984–96: was Bristol an outlier? *Lancet* 2001; **358**: 181–87.
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Sir—Paul Aylin and colleagues<sup>1</sup> confirm documented concerns about the paediatric cardiac surgery service at the time. To what extent would the previous knowledge of clinical concerns relating to the performance of specific procedures, such as arterial repair for transposition of the great arteries, and complete atrial ventricular septal defects, have helped this retrospective analysis and statistical surveillance? We refer especially to the reduced need for multiple significance testing.

We also endorse the conclusions of Aylin and colleagues about clinically valid and meaningful data collections, and the introduction of appropriate statistical procedures for comparisons of institutional and individual clinical performance. We have done a personal-professional monitoring project with the Australian and New Zealand College of Anaesthetists.<sup>2</sup> This initiative provides a simple and automated system of data collection and analysis. Within 6 months of the project's start, we observed a change in the cultural behaviour of trainees, with an open and honest commitment to the collection of high-quality data on performance of teams and individuals.<sup>2–4</sup> Trainees and specialists have achieved the goals of optimising clinicians' performance and patients' outcomes. We should be happy to share details of this project.<sup>5</sup>

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### Authors' reply

Sir—David Carr questions our choice of subgroups. These subgroups were chosen before any data analysis was done. The period we looked at was specified by the Bristol Royal Infirmary Inquiry: unfortunately, Hospital Episode Statistics (HES) were available only from 1991 onwards. The first three epochs within this period were chosen because of the different availability of the data sources, whereas the last epoch was chosen because the surgeons in question had stopped almost all operations on children by the end of the third epoch. The age-groups were chosen because the UK Cardiac Surgical Register source data were already aggregated at this level.

Mohammed and colleagues advocate the use of control charts for monitoring purposes, and claim our analysis may depend on unreasonable assumptions. We need to carefully distinguish two different roles of normality. They justify control charts by appealing to Chebyshev's inequality, which says that, whatever the distribution of a test statistic, there is less than a one-ninth chance of it lying greater than 3 SE from its mean. However, Chebyshev's inequality is very conservative, and the true p value will generally be a lot less than one-ninth. In particular, the normal approximation to the binomial distribution is very good for the sample sizes in our analysis, so 3 SE corresponds to about  $p=0.003$ . Hence their results are equivalent to using our figure 1 but with 50% wider intervals, and declaring a centre to have "special-cause" variation when the interval excludes the overall mean. We believe our figure 1 carries more useful information (and furthermore was made publicly available in 1999).

A separate issue is our assumption, in the random-effects model, of a normal distribution of the logits of the true mortality rates between the hospitals. This standard assumption is, admittedly, more questionable and difficult to criticise on the basis of only 11 non-Bristol centres, but leads to a reasoned degree of conservatism in our stated p values (and Bristol still emerges as an outlier).

One of the key questions we set out to answer was whether or not the mortality statistics in Bristol were unusual compared with other specialist centres. However, our calculations of excess deaths were based on each centre in turn being excluded from the analysis, and, furthermore, our model

can generate negative figures, indicating a better mortality rate. Thus, nothing intrinsic restricts our analysis from confirming a prior hypothesis.

Bolsin and Patrick also raise the issue of prior hypotheses. Thus, findings between 1991 and 1995 could be considered as confirmatory of hypotheses suggested before 1991, although we have not made this interpretation.

All correspondents are concerned about appropriate means for prospective monitoring. Although we suggest that our methods are fit for general application to the analysis of clinical and administrative data in other areas of clinical performance, we do not recommend their direct use for surveillance purposes.

Appropriate statistical methods may include risk adjustment where feasible, and placing intervals on ranks to prevent undue attention to league tables. But, as correspondents point out, a crucial issue is the multiplicity of comparisons that can be made and the accompanying dangers of false-positive results. Apart from sampling variability, which is readily taken into account by standard CI and p values, there seem to be at least four reasons for caution in declaring a centre divergent. First, inevitable between-unit variability due to unmeasured factors unrelated to quality; second, the multiplicity of institutions; third, the multiplicity of potential subgroups; and fourth, repeated testing over time. The control chart method seeks to deal with all these issues by a simple black and white identification of units more than 3 SE from the mean. We believe this approach is naive and potentially misleading.

Formal statistical techniques exist for dealing with each of these issues and we are confident that the attention now being focused on this neglected domain will before long yield the comprehensive advice sought by Carr.

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## Management of intersex

Sir—as an intersexed person and a philosopher of science, I welcome Lisa Melton's timely and balanced assessment of the changing paradigm of intersex management, described in her June 30 news item.<sup>1</sup> However, Melton's unquestioned supposition that "children left to grow up in gender limbo will be teased and bullied" merits further analysis. There are two features to her assertion that I assess here.

First, the presumption that children who do not receive genital surgery, and grow up with sexually ambiguous genitalia, will develop a correspondingly ambiguous gender identity. Evidence for this effect is scarce, but the lassoing together of gender and genitalia is a quintessentially Freudian manoeuvre. Freud contentiously proposed that our gendered lives flow from our childhood experience of genitality. Yet this is not a move that Freud advocated; rather, it is an erroneous manoeuvre that he postulated in the psychology of children.<sup>2</sup>

As adults, we and Freud know that the equation of gender and genitalia is oversimplistic and deterministic. As practitioners of evidence-based medicine in 2001, we should be wary of grounding surgical treatment in the assumption that anatomy is destiny, as Freud famously wrote.<sup>3</sup> In sum, if we are to keep our distance from Freud, we cannot simply take for granted that people with ambiguous genitalia will live in so-called gender limbo. Consequently, if medical treatment aims at gender clarity, we must not discount the possibility that non-intervention may be an effective treatment in itself.

Second, Melton insists unequivocally that untreated intersexual children will be bullied by their peers. There is no published documentation of the extent and nature of such teasing. Children can be cruel; I subscribe to an internet discussion group in which parents of boys with hypospadias articulate considerable anxiety for their sons' psychological welfare at school. These parents worry that negative messages imprinted in childhood will affect their sons for life. Indeed, is not children's ease at learning behavioural patterns a distinguishing characteristic of their psychology? But, crucially, this argument turns back on itself: if children are so impressionable, bullies may too be taught to act differently. To assume that bullying is inevitable and should continue unchecked is

inconsistent with the assumption that bullying is harmful precisely because child psychology is malleable and open to revision. To justify the surgical management of intersex infants in these terms is logically flawed.

I do not mean to suggest that intersexuals never grow up in so-called gender limbo, or that bullying never occurs. Indeed, the bullies—and the institutions that tolerate them—are the problem.<sup>4</sup> Victims of bullying are not at fault, just as a physically impaired person is not inherently disabled; rather, their environment is disabling. In fact, intersexuality could be positively enabling: psychologists have shown that individuals who do have an androgynous gender identity are happier, more socially competent, and more intelligent than those with a fixed, stereotypical gender.<sup>5</sup>

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- 1 Melton L. New perspectives on the management of intersex. *Lancet* 2001; 357: 2110.
- 2 Freud S. The infantile genital organization. In: Richards A, ed. *On sexuality*. Harmondsworth: Penguin, 1991: 303–12.
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### Specialists' reply

*Lisa Melton felt unable to respond adequately to Iain Morland's points, and requested that health professionals be allowed to reply for her.*

Sir—As clinicians working in two UK multidisciplinary adult intersex clinics, we agree with Iain Morland that there is no evidence that children with an ambiguous genital appearance will develop an ambiguous gender identity (sense of being male, female, or intersex). However, from our clinical experience and research work we must endorse Lisa Melton's claim that intersexed children encounter many obstacles in our highly sexually dimorphic society. An example is a girl aged 6 years who has clitoromegaly, who will not attend her swimming classes at school because the other children can see her spontaneous erections.

For babies born with ambiguous

genitalia, surgical, medical, and psychosocial interventions are considered in an attempt to alleviate the difficulties and distress that intersex children potentially face. Many clinicians may still harbour expectations derived from misinterpretations of Freud and may require help to abandon their assumption that anatomy is destiny. For other clinicians, however, victimisation is much more immediate. Teasing, bullying, and discrimination do occur in many forms, from childhood through to adolescence, and into adult life.

Surgery is one of the interventions aimed at promoting a child's self-confidence and reducing vulnerability. Surgery does not purport to eradicate all obstacles and, indeed, may introduce additional ones. We are afraid that many targets of bullies including intersexed people cannot wait for society to be taught to act differently. Societal change should take place, but developments in health care must be concurrent.

We do urge clinicians to reassess genital surgery. Is it ethical to do cosmetic genital surgery on infants? Do parents have the right to choose this surgery for their children? Does genital surgery really not damage sexual function? Should intersex even be deemed a medical condition requiring treatment? Only a few intersex adults have currently found a voice to speak out in answer to these and other questions. We should listen to their views; but the silent majority must also be included. Parents, clinicians, and intersex children and adults face huge dilemmas when making decisions about intersex management, but neither research nor clinical experience have convinced us that the answer is to end consideration of childhood genital surgery at this early stage of review. The option of no genital surgery is as active as that of choosing genital surgery, and each requires careful decision making and long-term support for the child and family.

Morland's final point is that individuals who do have an androgynous gender identity have been shown in studies to be happier and more intelligent than those without. We suggest that these studies were flawed in a similar way to those in which female babies exposed to testosterone in utero had higher intelligence quotients<sup>1</sup>—ie, that only the happier and more intelligent people chose to take part in the research. This bias is one of the major challenges facing long-term outcome

research in intersex disorders. Until it is overcome, parents and clinicians making decisions on behalf of intersexed children will remain faced with dilemma and culpability.

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1 Money J. Prenatal hormones and intelligence: a possible relationship. *Impact Science Society* 1971; 21: 285–90.

## Polyneuropathy in type 2 diabetes mellitus

Sir—Of practical concern is the rather discouraging comment of Simon Eaton and colleagues (July 7, p 35)<sup>1</sup> reiterating a concept that there is no proven rational treatment of distal symmetrical polyneuropathy (DSP) in diabetes mellitus. We have reported<sup>2,3</sup> and others confirmed<sup>4,5</sup> the contrary.

In 25 of our 31 patients with type 2 diabetes, which also affected ten of Eaton and colleagues' DSP patients, the small-fibre and large-fibre sensory motor DSP was moderately to prominently improved by anti-dysimmune treatments, notably with intravenous immunoglobulin G. Benefit became evident in 1–8 weeks and was cumulative in the first 4–10 months of treatment.

Pain, numbness, imbalance, and weakness were noticeably lessened to various degrees. Some patients became completely free of distal burning pain that had required narcotics or nightly ice treatments; had prominent lowering of the degree and intensity of numbness from mid-thighs to only the toes; increased their walking from 6 m to 6 blocks; stopped falling, regained ability to climb steps, squat, or brush teeth; or had disappearance of painful nocturnal muscle cramps. These responses presumably show a dysimmune component of the pathogenesis.

With continuing treatment, improvement was sometimes sustainable for at least 5 years. Attribution of benefit to the intravenous immunoglobulin was confirmed by a gradual increase of symptoms 2–3 weeks after treatment was interrupted, followed by a decrease within a few days of resuming treatment (glycaemia management was unchanged). Such treatable patients commonly have raised cerebrospinal fluid protein. The

type 2 diabetes intravenous immunoglobulin-responsive DSP generally involves Schwann cells, but sometimes is mainly dysneuronal. Although this manifestation could be an unrelated chronic immune dysschwannian/dysneuronal polyneuropathy in patients with type 2 diabetes, our patients, like those of Eaton and colleagues, were neurologically judged to have diabetic neuropathy.

Irrespective of their taxonomic designation, the dysimmune treatability of these patients is commonly overlooked. Our patients' treatable DSP had been progressive for 0.25–18.0 years. Intravenous immunoglobulin is the best and safest treatment, but its necessity to be continued, inconvenience, and expense show the need for a better antidysimmune treatment.

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- 1 Eaton SEM, Harris ND, Rajbhandari SM, et al. Spinal-cord involvement in diabetic peripheral neuropathy. *Lancet* 2001; 358: 35–36.
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- 4 Krendel DA, Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus. *Arch Neurol* 1995; 52: 1053–61.
- 5 Sharma KR, Cross J, Ayyar R, Martinez-Arizala A, Bradley WG. Diabetic demyelinating polyneuropathy responsive to intravenous immunoglobulin therapy. *Neurology* 1999; 52 (suppl 2): A128.

Sir—Simon Eaton and colleagues<sup>1</sup> note changes in the cross-sectional area of the spinal cord in diabetic patients, namely substantial diminution compared with normal individuals, which is so far unexplained, but very important.

The cross-sectional area of the cord is due mainly to the summation of three main components. The area of the white matter that is gathered into well recognised tracts and is maximal in the cervical region, the area of the grey matter, maximal in the cervical and lumbosacral segments, and the area of the blood vessels. The quantitative diminution of the cross-sectional area in patients with diabetes might be explained in terms of simple physics, not previously considered.

I have found that the myelin sheath in peripheral nerve fibres is distended by pressure of 30 mm Hg in pigs, rabbits, and rats.<sup>2</sup> This pressure arises from pumping action or pulsation of myelin-forming cells, the Schwann cells in the periphery, or oligodendrocytes inside the central nervous system, which pump cytoplasm into the myelin sheaths to which they are attached by tubes. This mechanism was seen in tissue culture in a film made by the late D S Russell of cultured oligodendrocytes, and is a mechanical shield that protects the axon from external pressure.

Although the glucose concentration in the myelin sheath has not been measured for technical reasons, it is raised in the spinal fluid in patients with diabetes and, therefore, is also likely to be raised in the myelin sheath, in the central and peripheral nervous systems. Glucose is a viscid substance whose adhesive properties would interfere with the pumping system and lower the pressure in the myelin sheath. The sheath would become partly deflated, making its cross-sectional area less than normal, and consequently would decrease the area of the cross-section of the cord. This effect would explain Eaton and colleagues' findings.

I have suggested<sup>3</sup> that in multiple sclerosis the reverse happens—ie, the pressure is raised,<sup>4</sup> leading to the bursting of the myelin sheath due to raised internal pressure and release of many immunogenic myelin proteins and agents that cause relapses. This theory also explains the black holes seen on magnetic resonance imaging of the white matter in multiple sclerosis. A possible answer to the issue in diabetes might, however, be if an isomer of glucose could be found with less viscosity than normal glucose.

These points raise new questions about the physics of the myelin sheath in patients with diabetes and multiple sclerosis.

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- 1 Eaton SEM, Harris ND, Rajbhandari SM, et al. Spinal-cord involvement in diabetic peripheral neuropathy. *Lancet* 2001; 358: 35–36.
- 2 Colover J. Multiple sclerosis: alleviation of myelin sheath pressure as a basis for therapy. 17th World Congress of Neurology, 2001 (abstr S451).
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## Overseeing of clinical research

Sir—Dan Greenberg offers an unbalanced view in his Aug 4 news item<sup>1</sup> of the multiple efforts underway to strengthen the integrity of clinical research involving human research participants. He contends that academic medicine, universities, the Association of American Medical Colleges (AAMC), and others are deliberately dragging their collective feet and impeding efforts to strengthen the role of institutional review boards and strengthen overseeing and management of financial conflicts of interest.

What Greenberg does not mention is the broadly supported and fast-paced movement to establish an accreditation system for human research protection programmes. In recognition that the protection of human research participants is not the responsibility only of institutional review boards, but of all who do the research, the US research and policymaking communities have come to view accreditation as the next right step toward ensuring a safer and more accountable clinical research enterprise. In April, 2001, a committee of the National Academy of Sciences' Institute of Medicine endorsed accreditation as a necessary component of the clinical research enterprise, saying it has strong potential as a mechanism to strengthen the participant protection system.

In May, 2001, the AAMC and six other non-profit organisations announced the founding of a new accrediting entity, the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In offering accreditation, this body seeks to ensure adherence and to raise the bar in human research protections by helping institutions reach standards that surpass the threshold of state and federal requirements. AAHRPP will soon begin pilot testing of its accreditation standards and plans to be fully operational in early 2002.

Greenberg also took an unfair pot shot at the AAMC's Task Force on Financial Conflicts of Interest in Clinical Research. The task force was constructed to ensure that all human research stakeholders—clinical investigators, patients' representatives, and leaders from medical schools, teaching hospitals, universities, industry, law, and the media—would be represented. The task force is close to completing its deliberations about individual conflicts of interest and will

begin to address institutional conflicts of interest at its September meeting. The goal is to develop policy and guidance that withstand policymaker scrutiny and assuage public concerns that research participants' interests will ever become secondary to financial rewards. Given the frequently judgmental reporting in the media, these are difficult issues, and the task force is working with appropriate sobriety, care, and speed.

Dan Greenberg knows as well as anyone, a quick fix will not strengthen our clinical research enterprise—thoughtful, concerted action will. Far from being behind the curve on working to improve the integrity and accountability of the US clinical research enterprise, the leadership of academic medicine is at the forefront.

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<sup>1</sup> Greenberg DS. Johns Hopkins research returns to normal. *Lancet* 2001; **358**: 393.

### Author's reply

Sir—In recent years, the failings of many institutional review boards have repeatedly been spread on the public record by the Inspector General of the Department of Health and Human Services, the Office of Human Research Protections (and its predecessor), and in congressional hearings. Their findings included rubber-stamp reviews, conflicts of interest, and violation of federal criteria for institutional review board membership.

Nonetheless, progress towards improvement has been little, even despite serious incidents of endangerment of experimental participants that have come to light, including the deaths of two volunteers in questionable circumstances. The AAMC's efforts to contribute to reform of these boards do not suggest urgency. The AAMC task force was announced in October, 2000, came into being 5 months later, whereupon it embarked on a 2-year study.

The Office of Human Research Protections' draft guidelines for conflicts of interest in research were rejected by the AAMC as premature. The accreditation system referred to by Jordan Cohen also does not suggest urgency. Daniel Federman, chairman of the Institute of Medicine committee that endorsed the newly created AAHRPP, has described this system as "an evolving tool, and one that cannot be viewed as a panacea or overnight

solution. It must be part of a longtime strategy".

Many institutions run highly effective institutional review boards. The methods for doing so do not require years of study. What is required is the recognition that protection of patients is at least as important as receiving grants and getting on with research.

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## Further work of Fred Hoyle

Sir—Simon Mitton, in his Sept 8 commentary,<sup>1</sup> skates over a major part of Fred Hoyle's scientific career that Hoyle himself judged important.

Besides applying nuclear physics so successfully to solve astronomical problems, Hoyle also pioneered the introduction of chemistry and even biology into the realms of astronomy. He was the first to propose the existence of molecules in interstellar space, hydrogen in the 1940s, and later in the 1970s (along with myself) he argued for interstellar organic molecules including biochemicals. Such molecules have subsequently been identified in great profusion in interstellar space and in comets, so Hoyle's work in this area too can be seen to have been vindicated.

In a collaboration with me that lasted for more than four decades, Hoyle, more than any other scientist, was instrumental in forging a link between astronomy and biology, arguing from different directions that these subjects are inextricably linked. On this account he could justifiably be called the father of the modern discipline of astrobiology. Our ideas on panspermia—life arriving from comets—were thought heretical when they were first proposed in 1976. But in the intervening years, as new data came along, panspermia has been raised to the status of a major contender in theories of the origins of terrestrial life. The discovery of viable microbial cells in the stratosphere at 41 km altitude has provided some tantalising evidence for micro-organisms arriving from space in the present day.

Whether some of this biomaterial could indeed contribute to the spread of certain epidemics still remains a matter of contention, but the role of global meteorological phenomena in causing the worldwide dispersal of pathogenic bacteria and viruses is coming to be more widely recognised.

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- 1 Mitton S. Fred Hoyle's biggest bang. *Lancet* 2001; **358**: 780.
- 2 Wickramasinghe C. Cosmic dragons. London: Souvenir Press, 2001.
- 3 Hoyle F, Wickramasinghe NC, Watkins J. Legionnaires' disease: seeking a wider cause. *Lancet* 1985; **1**: 1216-17.
- 4 Hoyle F, Wickramasinghe NC. Influenza: evidence against contagion. *J R Soc Med* 1990; **83**: 258.

## When is a literature search done?

Sir—I found Faith McLellan's Aug 25 news item<sup>1</sup> fascinating reading. The report was illuminating too, since many of my medical students and residents did not know that your journal is published in the UK, the relevance of 1066, even when told where your journal is published, and the importance of 1966 in reference to medical publications.

I have often been an advocate of making the search for medical literature easier. In some instances, for example, I have recommended that certain words be added to the abstract of a journal report, words that a future researcher might be expected to use in a MEDLINE search. With the words added, the report, which might have remained invisible to the researcher, will appear on the search.

I have also noticed that there are frequently spelling errors in MEDLINE. If the same spelling errors were in the original reports, and, hence, reproduced, the corrected word should also be included in the database to make the report more visible to researchers. Perhaps, too, this change should be made when UK and US spellings differ, such as for foetus and fetus.

Some journals publish keywords, but MEDLINE searches done on one or more of those keywords frequently do not identify the reports. Keywords should, therefore, be included in the text of the abstract, or MEDLINE should add them to the database.

One final point: I did a search on the term "oldmedline" on PubMed and identified only two references,<sup>2,3</sup> one of which is in Spanish.

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- 1 McLellan F. 1966 and all that—when is a literature search done? *Lancet* 2001; **358**: 646.
- 2 Armon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon:

medical and public health management. *JAMA* 2001; **285**: 1059-70.

- 3 Sousa Escandon MA, Gonzalez Guitian C, Gonzalez Fernandez MM. Which language will MEDLINE speak in the next millennium? *Arch Esp Urol* 2000; **53**: 93-99.

## War and public health in Democratic Republic of Congo

Sir—In a hotel just outside Nairobi in September, 2001, a provincial health director from the rebel-controlled province of Maniema in the Democratic Republic of Congo (DRC) sat working late into the night with government colleagues from the other side of the frontline, even as his base of operations in Kindu was being destroyed in a battle between their two opposing armies.

Joining him at this extraordinary encounter were health officials from three other rebel-controlled areas (Bukavu, Goma, and Kisangani), 12 colleagues from the Kinshasa Government's Ministry of Health, 17 representatives of international non-governmental organisations, and representatives of WHO and the United Nation's International Children's Emergency Fund, and international donors. Their aim was to find a way to reduce the extraordinary rate of mortality in DRC, where millions of lives, many of which are young children's and their mothers', have been lost in the past 2 years alone, marking this conflict as one of the greatest humanitarian disasters of all time.<sup>1</sup>

What they came up with is a unique minimum package of services, designed for war conditions and targeted at the immediate reduction of avoidable mortality.

The best efforts of the international community in countering the humanitarian crisis in DRC have been frustrated by continued fighting. But they have also been hampered by a chaotic approach to health provision typical of medical relief efforts in war zones.<sup>2</sup> The minimum package proposes 30 actions in health zones in crisis, directed at the seven leading causes of mortality and ill health in DRC: malaria, measles, diarrhoeal disease, acute respiratory infection, malnutrition, pregnancy-related problems, and HIV and tuberculosis. To be included, an intervention must satisfy a dual standard: proven cost effectiveness in saving lives and practicality under DRC field conditions.

Actions against malaria, for example, will be limited to correct case management and recognition and referral of non-responders. Insecticide-impregnated mosquito nets are proposed only for the postacute phase. Acute respiratory infection will be addressed by only two interventions: recognition of respiratory distress in the household, and correct case management with antibiotics in the health facility.

A surveillance system limited to the seven priority disorders plus those with the greatest epidemic potential is an essential component of the package, as is a bare-bones support system. Priority has been placed on community-based actions, many of which should be able to continue even if the front line once again engulfs villages.

Nothing in the essential package is new. In some conflict zones in DRC, many of the proposed actions are already being done, in addition to other vital functions beyond mortality reduction such as the prevention and response to sexual violence. The minimum package is just that: a minimum package. But if its provisions are adhered to, the courage of Congolese health workers and their non-governmental organisation partners in facing and surviving death and destruction in DRC will be rewarded with more lives saved and more misery alleviated.

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- 1 Roberts L, Despines M. Mortality in the Democratic Republic of Congo. *Lancet* 1999; **353**: 2249.
- 2 Waldman R. Prioritising health care in complex emergencies. *Lancet* 2001; **357**: 1427-29.

## DEPARTMENT OF ERROR

*Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study*—In this article by J Fellay and colleagues (Oct 20, p 1322), there was an error in table 2. In the column headed three-class-ART, the p value for diarrhoea should have been 0.005, and the p value for lactate should have been 0.048.

*Breastfeeding in HIV-1-positive mothers*—In this Correspondence letter (Sept 29, p 1095) by Marian Tompson, the first sentence of the seventh paragraph should have read "We are concerned that policy may be based on this work, ignoring research by Coutsoudis and colleagues that claimed no risk to the health of mother or child from exclusive breastfeeding".

*Redefinition of myocardial infarction*—In this Correspondence letter by O M P Jolobe (Sept 1, p 764), in the first sentence of the second paragraph, ST segment elevation should have been in two or more contiguous leads.