CORRESPONDENCE

Acetazolamide in posthaemorrhagic ventricular dilatation

Sir—The message of the randomised controlled trial of acetazolamide in posthaemorrhagic ventricular dilatation presented by the PHVD Drug Trial Group (Aug 8, p 433)[1] is clear cut. Therapy with acetazolamide and furosemide is not only unhelpful, but probably even harmful in preterm babies with posthaemorrhagic hydrocephalus, and can no longer be recommended. However, their study design and the findings preclude a final conclusion on drug therapy in neonatal posthaemorrhagic hydrocephalus.

Long-term furosemide therapy frequently causes nephrocalcinosis, osteopenia, or both in preterm babies.[2,3] Thus, furosemide has been replaced by other diuretics for chronic lung disease[2] and is judged unnecessary in hydrocephalus.[3] The PHVD Drug Trial Group chose to ignore this work and investigated acetazolamide combined with furosemide rather than acetazolamide alone, thus inevitably increasing the likelihood of significant side-effects in the treatment group.

The investigators used sodium bicarbonate solution and potassium chloride instead of citrate alkaliser, which provides an equivalent base intake with half the amount of sodium.[4] A high intake of potassium chloride and sodium is potentially harmful to preterm infants who have limited renal acid excretion and are susceptible to hypertension and acidosis. Administration of sodium bicarbonate increases gastrointestinal gas volume and partial pressure of carbon dioxide. These effects are particularly undesirable in preterm infants who frequently have chronic lung disease with carbon dioxide retention, or gastro-oesophageal reflux. This use of such agents may have contributed to the acidosis and the gastrointestinal symptoms that frequently led to discontinuation of the drug in the trial.

Removal of cerebrospinal fluid (CSF) by lumbar or ventricular tap is ineffective in neonatal post-haemorrhagic hydrocephalus, and increases the risk of infection in the central nervous system.[5] Nevertheless, most patients in both groups underwent procedures to remove CSF, even as early as a few days after the start of drug therapy, and often repeatedly.

Acetazolamide may alter the outcome of hydrocephalus in early infancy by reducing production of CSF over a long period, to allow fibrosis of the sutures and establishment of a new CSF equilibrium.[4] Historical data show that a high proportion of infants had lasting normalisation of head growth and avoided shunting after 6 months or longer of drug therapy.[4] Clearly, the duration of therapy is critical. In the PHVD trial, acetazolamide was given for a median of only 38 days, and weaning as early as 4 weeks after the start of treatment was encouraged. If acetazolamide was discontinued after 4 weeks in babies who tolerated and responded to it, then recommended once a rebound of ventricular dilatation was observed, swings of CSF pressure would undermine establishment of a CSF equilibrium. Discontinuation and reintroduction tends to reduce the effect of acetazolamide and increase its side-effects.[3]

Standard therapy was not defined in the trial but was “at the discretion of the referring clinician” across many centres. The standard treatment group included three babies on acetazolamide and 14 on furosemide. This loose definition must jeopardise the quality of this “standard treatment group” for statistical comparison.

The key question is whether a significant proportion of babies with posthaemorrhagic hydrocephalus would tolerate long-term treatment (over at least 6 months) with acetazolamide (plus citrate alkaliser), and benefit by avoiding later CSF shunting. Earlier reports, albeit on smaller samples, suggest that such a subpopulation exists.[4] The study design in the trial by the PHVD Drug Trial Group makes it impossible to answer this question.

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5 Ventriculomegaly Trial Group. Randomised trial of early trapping in neonatal posthaemorrhagic ventricular dilatation: results at 30 months. *Arch Dis Child* 1994; **70:** F129–36.

Authors' reply

Sir—With regard to Peter Raupp's questions on efficacy, experimental evidence suggests that acetazolamide and furosemide are synergistic in reducing production of CSF. The only study to suggest a benefit of diuretic therapy (albeit uncontrolled) used the two drugs in combination.[1] Adverse effects of furosemide are not likely to compromise the efficacy of diuretic therapy. Nephrocalcinosis, which may also follow acetazolamide monotherapy, was the only such adverse effect noted in our trial and led to termination of drug therapy in two (3%) infants. There is no published evidence (other than from our trial) that furosemide is “unnecessary” in the treatment of hydrocephalus. Raupp cites one uncontrolled study,[2] in which two infants did not tolerate acetazolamide but their progress is not further described; in the other three, Mercuri and colleagues postulated that had the infants not received the drug, their ventricular size might have increased at a faster rate.

We recommended continuation of drug therapy for 6 months, but accepted cautious weaning from drug therapy in infants whose ventricular size had decreased or not changed over more than 4 weeks on drug therapy. Only five (7%) infants required a second course of drug therapy. Had insufficient duration of drug therapy added to the number who required shunt placement, this effect would have been apparent as an increase in the time between trial entry and shunt placement, compared with infants given standard therapy, but this was not the case (mean interval 58·1 *vs* 61·5 days).

Furosemide can cause osteopaenia and nephrocalcinosis in infants although adverse long-term effects are not reported.[3] Acetazolamide is also a cause of nephrocalcinosis and renal stones. Far from ignoring the literature, we required participating centres to obtain a renal ultrasound scan after 12 weeks of drug therapy. Raupp implies that carbon dioxide retention would be reduced by the use of polycitra, instead of sodium bicarbonate and potassium chloride, but cites no evidence. This adverse effect results from the production of carbon dioxide when bicarbonate ions are added to correct an excess of hydrogen ions and are likely to pose similar problems with both alkalising agents. Sodium retention is rarely a problem in this population of infants who frequently require sodium supplements to correct leak of sodium from the kidneys.

Previous trials have not shown that CSF taps were ineffective, but rather that early taps (before excessive head growth) were no more effective than late taps.[4] We, therefore, recommended that CSF taps were delayed until head growth was greater than 1·5 cm per week for at least 2 weeks. We also provided treatment guidelines for shunt placement. Our use of CSF taps was not a confounding factor since there were no significant differences in CSF taps between treatment groups.

Correspondence between intention to treat and treatment given was good in the trial with acetazolamide given to 96% of infants assigned drug therapy plus standard therapy, compared with 4% of infants assigned standard therapy alone. The use of furosemide for cardiac or respiratory indications in a further 14% of infants in the standard therapy group was inevitable in a pragmatic study, but is presumably of no relevance to Raupp's argument if he believes that furosemide is of no benefit in hydrocephalus.

We found maximum tolerable doses of acetazolamide and furosemide were ineffective in delaying or preventing shunt placement for neonatal posthaemorrhagic ventricular dilatation. That either of the two drugs alone is effective is improbable. The question of keeping adverse effects to a minimum by reducing the diuretic therapy does not arise.

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1 Shinnar S, Gammon K, Bergman EW, Epstein M, Freeman JM. Management of hydrocephalus in infancy: use of acetazolamide and furosemide to avoid cerebrospinal fluid shunts. *J Pediatr* 1985; **107:** 31–37.
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Hypoglycaemic avoidance, technology, and knowledge

Sir—In her Aug 15 commentary Stephanie Amiel[1] states that "hypoglycaemia is almost unavoidable with existing insulins". She attributes the problem to pharmacokinetics, insulin being absorbed from its molecular moiety, instead of, as in non-diabetic people, being secreted by pancreatic islet cells, depending on blood sugar concentration.

The study cited, which compares human and porcine insulins,[2] omits a possibly important difference between animal pancreas-derived insulin and the newer (20 years or so) semisynthetic insulin. Cattle, porcine, and cadaver insulin, produced by an acid-alcohol extraction of whole pancreas, contains insulin from β-cells and glucagon from α-cells. The German physiologist Buerger in the last century called glucagon the counter-regulatory hormone. It is little wonder that the newer insulin produces a sizeable number of hypoglycaemic reactions, because of the absence of glucagon.

The makers of the newer insulin, and their clinical consultant associates, strenuously oppose such views, since the large firms that produce insulin throughout the western world have abandoned porcine-derived and cattle-derived insulin. This issue requires systematic and independent research studies, which need to be supported by national organisations.

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Ventrolateral medullary decompression in essential hypertension

Sir—The study by Helmut Geiger and colleagues (Aug 8, p 446)[1] should be seen as an uncontrolled experiment on a group of poorly treated hypertensive patients, which probably achieved no lasting benefits and cannot be used as evidence to support the existence of this unproven syndrome. Two major difficulties are obvious: the rationale for surgery is invalid; the evidence for benefit from surgery is tenuous.

Geiger's series consisted of eight patients whose hypertension was judged uncontrollable by medical therapy. Only one was on a long-acting diuretic, four were receiving short-acting diuretics (the dose frequency given), and three were on no diuretic.

Uncontrollable hypertension is generally related to inadequate control of intravascular volume—in many cases compounded by reactive sodium retention when non-diuretic agents begin to lower blood pressure—and the use of either no diuretic or inadequate doses of short-acting diuretics.[2] Therefore, these patients can hardly be described as having hypertension uncontrollable by medical therapy for justification of surgery.

Many non-specific surgical interventions such as appendicectomy have been falsely claimed to relieve hypertension.[3] Figure 4 in Geiger and colleagues' report shows the percentage of high blood-pressure readings before and after surgery, but time after surgery is not stated. The table, however, documents a continued need for medications in all patients.

Jannetta and colleagues[4] have also claimed relief of hypertension by ventrolateral medullary decompression. Neither that study nor Geiger's provided any assessment of autonomic nervous dysfunction before surgery or changes after surgery. Yet Geiger and colleagues state, "We showed a direct causal relation between raised blood pressure and irritation of cranial nerves IX and X". In support of their hypothesis they quote only positive radiological studies but none of the negative ones,[5] even though purely coincidental increased tortuosity of cerebral vessels would certainly be unsurprising in chronic hypertensives.

Before this technique can be taken to "offer an alternative for patients with intractable hypertension", we need proper, scientifically valid evidence for the existence of this syndrome and the benefits of decompressive surgery.

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Authors' reply

Sir—We agree with Norman Kaplan that our study provides no controlled data, however, sham-operations were not possible for ethical reasons.

Before surgery in these patients, many treatment modalities had been tested over periods of at least 4 weeks. Diuretics had been tried in all eight patients but the recorded treatment regimen was that found to be most effective and was the actual therapy before surgery. When short-acting diuretics were used, they were given twice daily. We emphasise that the effect on blood-pressure reduction was independent of the use of diuretics. Even patients who were receiving diuretic treatment before surgery benefited from decompression. We included not only patients without adequate control of blood pressure but also those with intolerable side-effects. Kaplan is correct in stating that many non-specific interventions have been tried to cure hypertension without underlying rationale. But there are many experimental data from animals supporting a role of the ventrolateral medulla for initiation and maintenance of high blood pressure.[1] Blood pressure tends to fall spontaneously for the first 6–12 weeks after an intervention, however our follow-up study time was at least 19 weeks (reported in the paper) and is now up to 144 weeks. We agree that some unspecific blood-pressure-lowering effects should be considered, such as relief of pain, anxiety, or stress, and we cannot exclude these effects in our patients. Obviously long-standing hypertension is difficult to cure because secondary events can perpetuate hypertension to some degree, as seen in renovascular hyper-tension. We have shown that blood pressure can be reduced substantially, together with a significant reduction of anti-hypertensive drugs. Jannetta's group has published new data which indicate that most patients who had a significant blood-pressure response to surgical intervention had long-term relief from autonomic dysregulation.[2]

Kaplan states that tortuosity of cerebral vessels may be purely coincidental in chronic hypertension. One reason why we undertook this study was to prove a causal relation and to show a pathophysiological link. We found a close correlation between findings on preoperative magnetic resonance imaging (MRI) and in-situ findings at the ventrolateral medulla confirming our MRI technique and the assessment of the MRI sequences. By contrast, Watters and colleagues[3] retrospectively analysed MRI scans that had been done by a standard technique (5 mm sections with 7 mm intervals) and were not primarily for investigation of hypertension.

To date we have no tools to show whether pulsatile compression is a crucial factor for hypertension. Obviously, surgical intervention is not successful in all patients with neurovascular compression but to identify preoperatively the patient who will benefit, is not yet possible.

We emphasised that microvascular decompression should be undertaken only in prospective protocols. In the meantime, other groups have reported successful lowering of high blood pressure by microvascular decompression.[4] Data about a family with brachydactyly, hypertension, and neurovascular compression seem to point to a genetic background of this neurogenic form of hypertension.[5] We should put forward this concept and should not neglect it because of prejudice.

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Interferon beta for Guillain-Barré syndrome

Sir—In their report on the treatment of Guillain-Barré syndrome with interferon beta, Alain Créange and colleagues (Aug 1, p 368)[1] claim that the 47-year-old patient with axonal type of Guillain-Barré syndrome improved after interferon beta therapy. I have difficulty in reaching the same conclusion, knowing that the patient had received a full course of plasma exchange (four exchanges of 50 mL/kg over 8 days) directly before the interferon therapy.

The response to plasmapheresis does not occur immediately, but during the first few weeks after the exchange. In the patient described, Créange and colleagues state that the patient started to improve on day 12, upon the start of the interferon therapy, and improved less after day 28. This period actually corresponds to day 4, up to day 20, after stopping the plasma exchange.

I do not think one can conclude that the interferon beta-1a was the reason for the patient's motor improvement when it was preceded by a course of plasmapheresis. The clinical improvement may well be the result of the plasma exchange or the expected course in some cases of Guillain-Barré syndrome.

I agree that there may be a potential usefulness for interferon beta in Guillain-Barré syndrome, since it is used in other motor neuropathies and in experimental allergic neuritis, but I do not believe this case proves any benefits from this therapy.

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1 Créange A, Lerat M, Meyrignac C, et al. Treatment of Guillain-Barré syndrome with interferon-β. *Lancet* 1998; **352:** 368–69.

Author's reply

Sir—We agree with Raja Sawaya that it is not possible to conclude that interferon beta is effective in Guillain-Barré syndrome. This conclusion would have also been true if plasma exchanges had not been undertaken. However, interferon beta could have been included in the recovery soon after its introduction. Effects of both interferon and plasma exchanges are different and could be complementary. Plasma exchanges may remove humoral inflammatory factors, such as antibodies and cytokines, whereas interferon beta is an immunomodulator that decreases T-cell and monocyte activations, and increases T-cell suppressor functions.[1] Breakdown of the blood-nerve barrier is an early and crucial event in Guillain-Barré syndrome, and it has been shown that treatment could restore disruption of its central nervous system equivalent, the blood-brain barrier.[2] We believe that this open study was a prerequisite to a randomised placebo-controlled trial of interferon beta in this syndrome, the design of which should take into account the efficacy of the reference treatment. However, a trial of interferon beta in Guillain-Barré syndrome, as an isolated treatment, could be of interest for countries with poor facilities for plasma exchange and intravenous immunoglobulins.

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1 Liblau RS, Fontaine B. Recent advances in immunology in multiple sclerosis. *Curr Opin Neurol* 1998; **11:** 293–98.
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Outbreak of chlamydia infection in rural Australian town

Sir—Joanne Williams and colleagues' (June 6, p 1697)[1] report an outbreak of psittacosis in a rural Australian town, and identify mowing lawns as a risk factor for psittacosis by means of a case-control study.

The case definition included positive serology for *Chlamydia psittaci*. They state in the methods section that serology was done with the Spot IF test (BioMerieux, Lyon, France). However, in referring to the serological results given in table 3, they state that the titres shown refer to a complement fixation test. The complement fixation test detects genus-specific antibody response and therefore cannot be used to distinguish between infections with different species of *Chlamydia*.[2] The species specificity of fluorescent antibody tests, such as the Spot IF test, is not very high, because a mixture of genus-specific and species-specific antibody responses are usually detected in these tests. It is therefore possible that the outbreak of pneumonia they describe was due to *C pneumoniae* rather than *C psittaci*.[3] These workers do not seem to have measured serological responses to *C pneumoniae*. The parallel measurement of antibody responses to *C psittaci* and *C pneumoniae* in these serum samples and the demonstration of a four-fold rise in IgG titres against *C psittaci* but not against *C pneumoniae* would have provided far more convincing evidence for implicating *C psittaci* as the cause of this outbreak.

Several outbreaks of acute respiratory infection caused by *C pneumoniae*, which has no known animal reservoir, have been described in Europe and North America.[4,5] As in Williams' study, there is usually an excess of male cases. In selecting their controls, Williams and co-workers do not match for sex: 15 of 16 cases and 29 of 54 controls were male. It is therefore not surprising that cases were more likely to mow lawns. From the data provided in table 2, it seems that 36 of 44 men and 13 of 33 women in the study mowed lawns. This difference is significant (χ^2 test, $p<0{\cdot}001$). On the other hand, if the analysis of the case-control data is restricted to males, it is evident that 14 of 15 cases mowed lawns, compared with 22 of 29 controls—a non-significant difference ($p=0{\cdot}23$, Fisher's exact test).

Thus, an outbreak of acute respiratory infection has occurred in a rural Australian town which could have been caused by *C pneumoniae* or *C psittaci*; there was an excess of male cases and men are more likely than women to mow lawns in this community.

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High-dose chemotherapy in high-risk breast cancer

Sir—The conclusions in Lajos Pusztai and Gabriel Hortobagyi's Aug 15 commentary[1] are not justified by the evidence presented. The report by Sjoerd Rodenhuis and colleagues (Aug 15, p 515)[2] refers only to high doses of cyclophosphamide, thiotepa, and carboplatin. It is unscientific to extrapolate conclusions from this specific protocol to high-dose chemotherapy in general. There are several studies under way that use a greater number of different drugs and more effective induction protocols.[3,4] The results of randomised studies that use cyclophosphamide, etoposide, thiotepa, and cisplatin will not be available until the year 2000, and alternative protocols, while promising, are still being investigated.[5] A more balanced view is that the place of treatment with this combination of drugs in the therapy of breast cancer is unknown and awaits further investigation.

The idea that such treatments should be given only as part of randomised controlled clinical trials is naive. No new protocol can be entered into a randomised trial until there is evidence that it can be given safely with encouraging results to fully informed patients with advanced disease whose only option is imminent death and nearly all of whom have already relapsed on standard treatment. I believe it is unethical to enter such patients into a randomised clinical trial because if assigned the standard treatment only, they would die. It is disappointing that such a commentary should come from one of the world's leading centres of excellence on cancer medicine.

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Authors' reply

Sir—There has been no published randomised study to date showing that high-dose chemotherapy with stem-cell support (HDC) has better clinical outcome than adequate standard therapy in patients with high-risk early breast cancer. However, two reported randomised studies reported identical outcomes for both the conventional and high-dose groups.[1,2] Several non-randomised studies have shown impressive results in highly selected patients.[3] However, similarly impressive results can be achieved with more conventional combined-modality therapy in a selected group of patients.[4] Each HDC trial used different drug combinations and schedules—one of the two randomised studies in the adjuvant setting used cyclophosphamide, thiotepa, and carboplatin,[1] the other used cyclophosphamide, etoposide, and cisplatin in high doses.[2] No obviously superior regimen has emerged from these and previous studies. We agree that the drugs used are commonly not the most active agents against breast cancer. We do not advocate that research with HDC should be abandoned. Indeed, innovative new strategies that use more active drugs are a promising research direction. We advocate, however, an open-minded approach in clinical research and this includes consideration of the possibility that HDC, as it has been administered in the past decade, may not be as effective as we expected it to be. Unfortunately, an important part of the evidence for both high-risk early-stage patients and for metastatic disease points to this direction and motivates future research.

According to the North American Autologous Blood and Marrow Transplant Registry, which tracks about half of haemopoietic stem-cell transplants done in North America, HDC has been used for the treatment of stage II–III breast cancer in 5886 patients between 1989 and 1995.[5] Only 11% of these patients received treatment in randomised studies. If 50% of these patients had received treatment as part of a randomised clinical study, we would be closer to knowing which group of patients benefits to what extent, from which type of HDC. To enter most adult patients into clinical trials is a challenge. Our colleagues in paediatric oncology did rise to this challenge; 60% of children with cancer in North America are entered into clinical trials. We recognise the differences between paediatric and adult oncology and accept that many patients could receive HDC without protocol for several reasons. We do maintain, however, that when an investigational treatment is considered, treatment is best given within the framework of an organised clinical study. We believe that at the current stage of research, although continued phase I and II studies with HDC are necessary, priority should be given to randomised trials.

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Is oxygen an antibiotic?

Sir—Katsuro Kuroki and colleagues (Sept 5, p 782)[1] describe a man with colitis and toxic megacolon who improved after hyperbaric oxygen therapy. They postulate that hyperbaric oxygen may have reduced colonic dilatation by compressing intestinal gas or by increasing the diffusion gradient for nitrogen. Instead or in addition to their hypotheses, could hyperbaric oxygen have been therapeutic as an antibiotic?

Toxic megacolon commonly results from infectious colitis, for example, pseudomembranous colitis due to the anaerobe *Clostridium difficile.*[2] Antibiotics are a component of standard treatment for toxic megacolon.[2] Oxygen is toxic to anaerobic bacteria, whether by production of the free radical superoxide or by increasing the redox potential.[3] Hyperbaric oxygen kills anaerobes, suppresses toxin production in *C perfringens*, and inhibits the growth of escherichia and other aerobes.[4] Because of these and other properties, hyperbaric oxygen is used as adjunctive therapy for tissue infections such as clostridial myonecrosis and necrotising fasciitis.[5]

The hypothesis that hyperbaric oxygen therapy is beneficial in toxic megacolon through a bactericidal or bacteriostatic effect of oxygen could be tested. Levels of pathogenic stool bacteria before and after hyperbaric therapy could be compared. In future controlled trials of hyperbaric oxygen, additional treatment groups could receive 100% oxygen at 101 kPa to exclude any pressure gradient compressing the colon, and hyperbaric room air or other measures to exclude a nitrogen gradient. Unravelling these factors would have immediate practical applications. Most hospitals could provide normobaric hyperoxia by rebreathing mask or endotracheal tube to patients with toxic megacolon, whereas only a few (<300 facilities in the USA in 1996[4]) have hyperbaric chambers.

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Glutamine-enriched enteral nutrition in patients with multiple trauma

Sir—Alexander Houdijk and colleagues (Sept 5 p 772)[1] claim to have shown a reduction in the incidence of pneumonia, sepsis, and bacteraemia in patients with multiple trauma who received glutamine-supplemented enteral nutrition. However, their results are difficult to interpret.

The investigators used the infection rate in bone-marrow transplant patients, who are not directly comparable with patients who have multiple trauma, and a historical group of trauma patients from 1985–89 to predict an infection rate of 43% in their control group. This rate is more than twice that reported in two large studies of infection in intensive care,[2,3] thus, the observed rate of infection in the control group was inexplicably and inappropriately high. Moreover, in small groups with differing lengths of stay in the intensive care unit (ICU), the rate of infection needs to be corrected for the number of patient-days spent in the ICU (episodes of infections per 1000 patient-days). This omission alone may account for the differences of infection rates found between the two groups.

The researchers provide no evidence that the volume of enteral feed delivered and absorbed in the first 3–5 days was equal in the two study groups. Previous studies have shown a dose response of some forms of immune-enhancing enteral nutrition.[4] In addition, more than 80% of infections in the control group noted by Houdijk and colleagues occurred early, between the fifth and seventh day after admission to the ICU. No information is provided about the use of antimicrobial prophylaxis, specifically selective decontamination of the digestive tract, and no reduction in the use of antimicrobials in the glutamine group was reported.

The differences in infection rates between the two groups did not influence the duration of mechanical ventilation and length of ICU stay. Thus, the reduction of infection in the treatment group neither reduced true morbidity nor influenced the main determinants of cost per patient-episode. In our view, other forms of immune-enhancing nutrition are more effective.[5]

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1 Houdijk AP, Rigusburger ER, Jansen J, et al. Randomised trial of glutamine-entriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998; **352:** 772–76.
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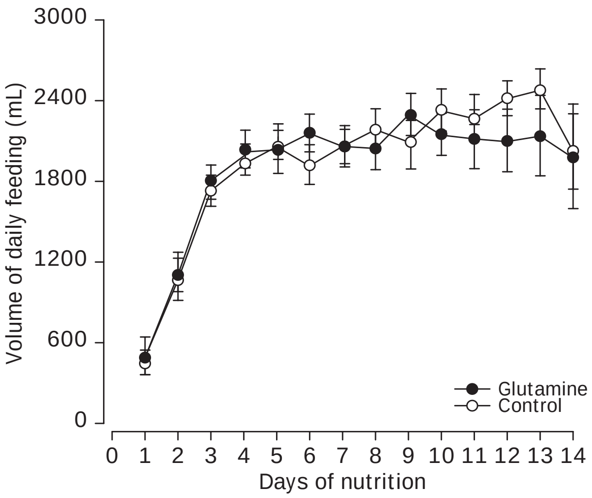
4 Atkinson S, Seiffert E, Bihari D, on behalf of the Guy's Hospital Intensive Care Group. A prospective, randomised, double blind, controlled clinical trial of enteral immunonutrition in the critically ill. *Crit Care Med* 1998; **26:** 1164–72.
5 Zaloga GP. Immune-enhancing enteral diets: where's the beef? *Crit Care Med* 1998; **26:** 1143–46.

Authors' reply

Sir—Imogen Mitchel and David Bihari's interpretation of our results is obscured by inappropriate comparison with previously reported results. The rate of infection in a homogeneous group of trauma patients cannot be compared with that in a heterogeneous intensive care population.[1] Furthermore, to predict morbidity from infection before undertaking a single centre randomised study, the best statistical precision is reached by the use of results from that centre. In our study, both the control and glutamine group had similar length of ICU stay (16·5 [0·21] and 14·5 [1·9] days) and therefore different lengths of ICU stay does not explain the difference in infections. There were no differences in the volume of feeding per day between both groups. At the end of the third day, patients already received a mean of 1800 mL of nutrition (figure).



Amount of enteral nutrition in both groups

Antimicrobial prophylaxis was given for 24 h perioperatively, selective decontamination of the gut was not used. Antimicrobial strategy was not predefined in the study. An important number of patients in both groups had chest trauma and long-term mechanical ventilation is frequent. The healing of fractured ribs and contused lungs in patients with chest trauma are independent factors in addition to pneumonia that prolong the duration of ventilation. Nutritional supplementation is not likely to speed up fracture healing.

Our study shows that enteral glutamine lowers the rate of pneumonia, bacteraemia, and sepsis in trauma patients. The strength of the study is that the effect of a single nutritional supplement is studied in a homogeneous group and comparison to studies that use immunonutrition with multiple supplements in a heteregeneous population of patients is inappropriate.[1] Conclusions as to whether one or the other form of immunonutrition is more effective in trauma patients cannot be based on present facts.

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1 Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. *Crit Care Med* 1998; **26:** 1164–72.

Polychemotherapy for early breast cancer

Sir—I read the Early Breast Cancer Trialists' Collaborative Group's long-awaited report (Sept 19, p 930)[1] with great interest and note that the absolute benefit in 10 years survival among postmenopausal women is estimated to be 2–3%, irrespective of nodal status. Previous reports showed that the relative risk reductions were constant across all prognostic subgroups. Therefore, the absolute benefits would be likely to be greater among node-positive patients than among node-negative patients. This view is clearly no longer the case, so selection of patients to receive systemic therapy could be assessed by the pathological and biological characteristic of the primary cancer alone. Can anyone out there remind me of any other reasons why we should be dissecting the axilla?

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1 Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998; **352:** 930–42.

Carcinoid tumour

Sir—Martyn Caplin and colleagues (Sept 5, p 799)[1] present a classification of carcinoid tumours, but do not mention pancreatic carcinoid. In 1986, we observed a 45-year-old man with fulminant Cushing's syndrome caused by a hormonally active maligant pancreatic carcinoid.[2] The clinical picture of hypercortisolaemia appeared about 4 weeks before the patient's admission to our department. Severe myasthenia, hypokalaemia (K^+ 1·8 mmol/L) and diabetes mellitus were the main features of the adrenal disease, accompanied by an acute pancreatitis. Cortisol concentrations ranged from 3588 to 4537 nmol/L (normal range 138–690 nmol/L). Aminoglutethimide administration resulted in a remission of Cushing's syndrome, however, the patient died from pancreatic necrosis. After histological examination, we made a diagnosis of a pancreatic carcinoid, with metastatic infiltration in the abdominal lymph nodes.

In our experience bronchial carcinoid is more common than pancreatic carcinoid. In 1995–96, we observed two patients (patient 1, a 39-year-old woman and patient 2, a 26-year-old man) with an ectopic adrenocorticotropic hormone (ACTH) syndrome caused by bronchial carcinoid. The excision of the tumour with local lymph nodes resulted in a rapid recovery in both patients.[1] The surgery is a treatment of choice for carcinoid tumours, but the detection of tumour localisation may not be easy. We had treated three other patients with ectopic ACTH syndrome and increased 5-hydroxyindoleacetic acid excretion, in whom imaging of the carcinoid tumour was not possible. In patient 1, multiple round lesions were found on pulmonary radiography, most of them seemed to be flat pleural lipomas (surgical investigation). Scintigraphy with labelled somatostatin allowed us to localise a single carcinoid tumour in the right lung. Carcinoids that produce ACTH manifest themselves by the features of hypercortisolaemia, although the differential diagnosis and detection of the tumour can be difficult.

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1 Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. Carcinoid tumours. *Lancet* 1998; **352:** 799–805.
2 Kasperlik-Załuska AA, Rolonowska E, Migdalska B, et al. The syndrome of ectopic ACTH excretion. *Pol Arch Med Wewn* 1987; **78:** 355–62.
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Sir—Martyn Caplin and colleagues[1] discuss the newer modalities of diagnosis and management of patients with carcinoid tumours. An important association not mentioned is that between duodenal carcinoids and Von Recklinghausen's neurofibromatosis (VRNF).[2]

The duodenum is a common site of origin for gastrointestinal carcinoids in patients with VRNF and there seem to be some differences in histology and hormone-secretion compared with similar tumours not associated with VNRF.[2] Almost 90% of duodenal carcinoids in patients with VRNF are pure somatostatinomas. By contrast, similar tumours not associated with VRNF are frequently multi-hormonal.[3] This difference may be important for follow-up, treatment, and outcome of these patients.

The detection of a pure somatostatinoma in the duodenum should at least alert one to the possibility of coexistent VRNF. Also, histologically, psammoma-bodies tend to be more common in carcinoids associated with VRNF.[4]

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1 Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. Carcinoid tumour. *Lancet* 1998; **352:** 799–805.
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Sir—The review of carcinoid tumours by Martyn Caplin and colleagues is excellent. One aspect that deserves further comment, however, is the statement that "measurement of 24 h urine 5-hydroxyindoleacetic acid [5-HIAA] by high-performance liquid chromatography is highly specific". This statement is accurate from an analytical standpoint, but does not take into account that a large number of patients with high 5-HIAA results do not have carcinoid tumours. Physicians commonly are unaware of this fact when they assess patients' results.

The large number of high 5-HIAA results when patients are tested illustrates the difficulty. The clinical reference laboratory at the University of Utah receives about 400 urine specimens per month for 5-HIAA analysis, and these are tested with high-performance liquid chromatography with electrochemical detection.[2] Even with this highly specific method, however, about 8% of patients' results are raised (>15 mg daily, of these 6% >25 mg daily, and 3% >100 mg daily.[3]) Since carcinoid tumours are rare, only a small fraction of these high results are from patients with carcinoid tumours.

Although the origins for physiological increases of 5-HIAA excretion in specific cases are usually unknown, there are many possible sources: foods that contain 5-hydroxytryptamine (serotonin) such as bananas and avocados,[1] and malabsorption syndromes such as coeliac disease.[4] Other possible sources include medicines such as melatonin (N-acetyl-5-methoxytryptamine) and 5-hydroxytryptophan.[3] Long-term use of drugs such as omeprazole might increase the density of gastric endocrine cells,[5] and thus raise 5-HIAA release. Carcinoid tumours are probably the least frequent cause of rises in 5-HIAA.[3]

24 h-urine collection for HIAA is a commonly used screening test for carcinoid tumours. Most patients with high 5-HIAA will not have a carcinoid tumour, and further evaluation is necessary to identify those who do. False-negative 5-HIAA results also occur, particularly in association with drugs such as aspirin, levodopa, and phenothiazines.[1] The best way to decide when to assess possible carcinoid tumour is to use clinical judgment.

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1 Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. Carcinoid tumour. *Lancet* 1998; **352:** 799–805.
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Prediction of hepatic inflammatory activity in hepatitis B

Sir—We appreciate that the data presented by François Habersetzer and colleagues (Sept 12, p 907)[1] are consistent with our proposals for the assessment of patients with hepatitis B surface antigen (HBsAg) and antibodies to hepatitis Beautgen (anti-HBe). Three of their four neural net models (although without prospective validation) suggest that, in a population of HBsAg positive and mostly (70%) HbeAg positive patients with increased aminotransferase concentrations, serum hepatitis B virus (HBV) DNA measurements with the branched DNA assay, might facilitate more accurate prediction of histological hepatitis activity and hepatic fibrosis.

We recommend measurement of serum HBV DNA concentrations, preferably by a branched DNA assay[2] if the concentration of aspartate aminotransferase is greater than 1·2 times the upper limit of the normal range in a patient positive from HBsAg and anti-HBe.[2] Predictions of hepatic fibrosis could be clinically important; however, this issue was beyond the scope of our study. Habersetzer and colleagues data do not support a role for expensive serum HBV DNA assays in the initial assessment of HBsAg-positive, anti-HBe-positive patients.

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1 Habersetzer F, Trépo C, Minor J, Comanor L. Activity of hepatitis B surface antigen and antibodies to hepatitis Be antigen. *Lancet* 1998; **352:** 907–08.
2 ter Borg F, ten Kate FJW, Cuypers HTM, et al. Relation between laboratory test results and histological hepatitis activity in individuals positive for hepatitis B surface antigen and antibodies to hepatitis Be antigen. *Lancet* 1998; **351:** 1914–18.

Quality of reports of randomised trials and estimates of treatment efficacy

Sir—The study by David Moher and colleagues (Aug 22, p 609)[1] is an excellent investigation of the mechanisms that underlie the conduct and reporting of randomised trials. However, their results can be partly explained by a process completely different from the causality that they imply in their title. Not only trial quality affects trial results, but also trial results affect the quality of reporting them.

The report of a study that had negative results is more likely to be rejected by a journal than is one of a study that found a significant treatment effect (publication bias). Thus, the report of the negative trial will be rewritten according to the reviewers' suggestions and then be submitted to another journal, where other reviewers again refine the quality of trial reporting. When the paper is finally published, more people have spent more time and effort on reviewing and reformulating it than would happen for a report of a positive study. A better and more detailed description of methods (eg, allocation concealment) is a likely outcome. Thus, negative trials possibly score higher on any checklist designed to measure the quality of the trial report.

We believe that this mechanism may have had a strong influence on the results reported by Moher and colleagues. To date, there are no data to prove our hypothesis, but negative trials are known to be published with longer delay—the so-called time-lag bias.[2] This time-lag can be expected to originate mainly from submission/resubmission loops. A prospective study on how a paper on its way towards publication is altered would be interesting. Without any data, we can only conclude that the world of scientific publications should not be mistaken for a measure of clinical reality.

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1 Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352:** 609–13.
2 Ioannidis JPA. Effect of statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA* 1998; **279:** 281–86.

Author's reply

Sir—Stefan Sauerland and Rolf Lefering pose an interesting hypothesis. At the centre of their argument is the notion that peer review improves the quality of trial reports. Are there any data to help address this possibility? Peer review and editing improve the quality of reports that are submitted for publication, especially in areas that are used by readers to judge the importance and generalisability of the findings. Goodman and colleagues[1] investigated whether peer review increased the quality of papers which had been initially accepted for publication in the *Annals of Internal Medicine* but had not been revised. 44 peer reviewers assessed by means of a 34-item instrument the quality of 111 original research articles. All papers were assessed on acceptance and again after publication. Five of the 34 items showed a statistical improvement from baseline—discussion of study limitations, generalisations, use of confidence intervals, and tone of conclusions. This study showed, however, only slight agreement between reviewers (intraclass correlation 0·12 [95% CI −0·22 to 0·44]). Similar evidence has been reported elsewhere.[2]

Sauerland and Lefering assume that reviewers' suggestions are helpful to authors. In general, authors disagree with the comments made by peer reviewers. Sweitzer and Cullen[3] surveyed 209 authors of unsolicited papers and assessed six characteristics of peer review: timeliness, quality, manuscript, process, specificity, and overall assessment. The survey was made at the *Journal of Clinical Anesthesia*. 95 (45%)

authors responded to the questionnaire; the proportion responding was highest among authors of papers that had been categorised as "accept with revision". Authors reported most satisfaction with the specificity of the peer reviewers' comments. Overall, authors rated the review process slightly positive to neutral across all categories. Surprisingly, 28% of authors of articles accept with revision reported disagreements with peer reviewers' comments.

Sauerland and Lefering's hypothesis is important and the best way to address whether peer review is effective at improving the quality of published research is a randomised trial.

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1 Goodman SN, Berlin J, Fletcher SW, Fletcher RH. Manuscript quality before and after peer review and editing at *Annals of Internal Medicine. Ann Intern Med* 1994; **121:** 11–21.
2 Pieric JPEN, Walvoort HC, Overbeke AJPM. Readers' evaluation of effect of peer review and editing on quality of articles in the *Nederlands Tijdschrift voor Geneeskunde. Lancet* 1996; **348:** 1480–83.
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Is uric acid really an independent cardiovascular risk factor?

Sir—In his Aug 29 commentary Harry Ward[1] implies that uric acid might be responsible for vascular injury in hypertension, and that angiotensin-II receptor antagonists (losartan in particular) could have beneficial effects in hypertension because of their uricosuric activity. This same issue was raised in 1979 when tienilic acid—a uricosuric non-sulphonamide diuretic with antihypertensive effects similar to thiazides—was first investigated.

Whereas at first sight serum uric acid seems to predict cardiovascular mortality, the evidence must be regarded as shaky. The difficulty with the association between uric acid and cardiovascular risk is that uric acid is itself closely related to obesity, glucose intolerance, blood pressure, alcohol intake, plasma lipids, and packed cell volume. After taking these factors and the effects of drug therapy into account, the Coronary Drug Project Research Group[2] concluded that uric acid probably was not an independent risk factor but rather a marker for other risk factors.

Then tienilic acid was withdrawn because of hepatotoxicity and the debate was largely forgotten. The finding that losartan, unlike other angiotensin receptor antagonists, has uricosuric properties meant that this debate has been reintroduced.[1] The speculation about several mechanisms whereby uric acid might be harmful is no proof and only long-term epidemiological studies can show whether uric acid is an independent cardiovascular risk factor. Careful analysis of the evidence strongly suggests that it is not.

In both the Framingham project and the British Regional Heart Study,[3] serum uric acid ceased to be an independent cardiovascular risk factor after taking into account all the possible confounding variables. The results of the NHANES-1 study[4] suggest that uric acid might be a risk factor, but only in women; however, many possible confounders were not measured in that study.

In trials of hypertension treatment, thiazide diuretics, with their uric acid raising properties proved more effective at coronary prevention than β-blockers. The shortfall in coronary prevention highlighted by Harry Ward[1] can largely be explained by non-use of thiazides rather than their use.[5] The impressive coronary prevention achieved in the SHEP study,[5] might lead to speculation that coronary prevention by thiazide diuretics was greater than expected, and that the small rise in serum uric acid, with its antioxidant properties, might even be beneficial.

We hope that losartan will not have the same fate as tieniltic acid, but we conclude that its success can only be proved by long-term outcome studies, such as the LIFE and ELITE-2 trials, rather than by stating possible mechanisms which are not adequately supported by sound clinical or epidemiological proof.

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1 Ward HJ. Uric acid as an independent risk factor in the treatment of hypertension. *Lancet* 1998; **352:** 670–71.
2 The Coronary Drug Project Research Group. Serum uric acid: its association with other risk factors and with mortality in coronary heart disease. *J Chron Dis* 1976; **29:** 557–69.
3 Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. *Heart* 1997; **78:** 147–53.
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Registration of refugee and asylum-seeking doctors

Sir—J B Eastwood and colleagues' viewpoint (Aug 22, p 647)[1] on registering refugee and asylum-seeking doctors is factually incorrect. The General Medical Council (GMC) has not recommended revocation of the right of the United Examining Board to award a registrable medical qualification, nor has it any powers to do so.

The statutory functions of the GMC's Education Committee include the inspection of qualifying examinations. The Committee is required to report to the Privy Council and may make representations if there seem to be serious deficiencies. The Privy Council, not the Education Committee or the GMC, decides whether the examination should cease to be a qualifying examination. The Education Committee has submitted the Inspector's report and its representations. The Privy Council will consider all the evidence, including any objections from other bodies.

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1 Eastwood JB, Fiennes AGTW, Cappuccio FP, Maxwell JD. Registering refugee and asylum-seeking doctors. *Lancet* 1998; **352:** 647–48.

Authors' reply

Sir—We thank Finlay Scott for his comments. We hope that he has accepted our arguments that there is a continuing need in the UK for a requalifying examination within a structured educational framework. Currently, the United Examining Board provides the only suitable route. We accept his point that the GMC has made representations to the Privy Council rather than recommendations, as well as submitting their Inspector's Report. We hope that the Privy Council will also appreciate that these are not recommendations.

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Trends in prescribing calcium-channel blockers

Sir—Malcolm Maclure and co-workers (Sept 19, p 943)[1] show that changes in the antihypertensive treatment prescribing pattern by general practitioners in British Columbia during 1995–96 were a consequence of the controversy about safety and efficacy of calcium-channel blockers. The database of the GIFA (Gruppo Italiano di Farmacovigilanza nell'Anziano) study[2] allows us to analyse trends in the use of antihypertensive medications every 2 months for alternative years from 1988 to 1997 in 22 general medicine wards and 19 geriatric wards of 36 acute care hospitals in Italy. 29 wards were in university hospitals. We analysed drug prescription at discharge in 3852 hypertensive patients, (mean age 72·1 [SD 11·7] years, 42% men). For patients admitted more than once we included only the prescription at first discharge.

Inhibitors of angiotensin-converting enzyme (ACE) have gained a leading role among antihypertensive drugs, whereas use of calcium-channel blockers increased until to 1993 and had declined thereafter. Use of diuretics declined between 1988 and 1991, did not change until 1995, and then rose to 41·5% in 1997, compared with 42% and 39·5% for ACE inhibitors and calcium-channel blockers, respectively. The frequency of use of β-blockers was uniformly low, although 40·7% of patients had at least one condition that contraindicated use of these drugs. Long-acting preparations accounted for 33·7% of all calcium-channel blockers prescribed in 1993, 47·8% in 1995, and 60% in 1997 ($p<0{\cdot}001$).

Our findings probably reflect a real modification of the prescribing pattern because prevalence of comorbid diseases, which can influence the use of some antihypertensive drugs did not change in the study period. Thus, our data confirm the observations by Maclure and colleagues, with some differences, such as greater use of ACE inhibitors, which probably reflects the fact that we did not select hypertensive patients who were free from cardiovascular disease. By contrast with our findings and those of Maclure, Moser[3] observed that prescription of diuretics as antihypertensive agents had steadily decreased in the past 15 years. However, the studies cited by Moser describe practice patterns until 1995 thus, cannot reflect the most recent data.

Future studies will clarify whether our results mark the start of a well-defined trend in the use of antihypertensive agents. Indeed, the observed increase in the use of long-acting calcium-channel blockers might herald a renewed interest in this category of drugs.[4]

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1 Maclure M, Dormuth C, Naumann T, et al. Influence of education interventions and adverse news about calcium-channel blockers on first-line prescribing of antihypertensive drugs to elderly people in British Columbia. *Lancet* 1998; **352:** 943–48.

2 Carbonin PU, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? *J An Geriatr Soc* 1991; **39:** 1093–99.

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Oral sildenafil in erectile dysfunction

Sir—The study by I Goldstein and colleagues[1] provides the much needed data for scrutiny by the medical community with regard to the efficacy, mechanism of action, pharmacokinetics, dosing, and side-effects of sildenafil. Their findings are promising. Since its approval by the Food and Drug Administration on March 27, 1998, sildenafil (marketed by Pfizer as Viagra) has been a pharmaceutical phenomenon. Its appeal stems from the fact that sildenafil is the first effective and safe oral therapy for men with erectile dysfunction.[1–4]

Pfizer's stock has risen by 50%, primarily because of aggressive marketing and the tremendous expectations for sildenafil.[3] New prescriptions have increased almost exponentially—from 546 in the week ending April 3, to 269 842 in the week ending May 1.[3] Urologists and non-urologists alike have been swamped with requests for the drug. The associated media frenzy has been fuelled by endorsements from prominent individuals. Such reports stoke the already intense public demand for information about and prescriptions for sildenafil.

In the midst of these developments, it is crucial to recognise and deal with the potential problems. First, sildenafil is no panacea; not all patients with erectile dysfunction will benefit from it. Second, there is substantial risk that many patients will receive little or no evaluation before treatment; the potential for ill-informed and inappropriate prescribing is high.[4] Third, sildenafil is not an aphrodisiac,[3,4] nor does it increase sexual desire or libido.[1–4] The drug has the potential for abuse by thrill-seekers. Fourth, the known side-effects may not be transient, as current data suggest. Sildenafil may also have other, as-yet-unknown, adverse effects that will become evident only over time.

In the first few weeks after sildenafil's release, physicians' only information source was the package insert.[2] Goldstein's study[1] supplied data that physicians should use to make informed decisions in the work-up and treatment of patients with erectile dysfunction. Physicians who prescribe sildenafil should do so only after a comprehensive work-up (history and physical examination, with diagnostic tests if indicated) has been completed.

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1 Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998; **338:** 1397–404.

Transient global amnesia after sex

Sir—In his intriguing hypothesis on the pathophysiology of transient global amnesia, Steven Lewis (Aug 1, p 397)[1] suggests that a Valsalva manoeuvre may be a common triggering event among patients with this syndrome. In support of Lewis' hypothesis, we report two patients who presented with transient global amnesia immediately after sexual intercourse, an activity that has been associated with other untoward effects consequential to Valsalva manoeuvre.[2]

A 72-year-old man with new onset thrombocytopenia had an episode of transient loss of memory 2 years previously. The patient was otherwise healthy and had a normal complete blood count at age 70. Within 30 min after sexual intercourse with his wife, the patient sat on his bed completely conscious, but was confused. He was taken to hospital by his wife and found to be disoriented. He misidentified the current US President as Jimmy Carter. A neurological examination revealed no focal signs and magnetic-resonance imaging of the head was normal. He was discharged home and regained orientation within 12 h. The patient resumed usual sexual relations with his wife and has remained symptom free.

A 75-year-old retired physician with mild leucopenia, who was otherwise healthy, had sexual intercourse with his wife and within 30 min he became disoriented and talked continuously without making sense. He was brought immediately to hospital, where he misidentified the current US President. The neurological examination revealed no focal deficits. Computed tomography of the head was unremarkable and he was admitted for observation. He regained orientation within 15 h, but did not recall events that occurred within the 6 h after sexual intercourse. He has resumed his usual activities including sexual relations with his wife without any sequelae.

These cases and those previously reported show a link between sexual intercourse and transient global amnesia that can potentially recur.[3–5] Both cases lend support to Lewis' hypothesis and may also provide an explanation for many cases of this syndrome, in which only a careful medical and social history will identify the inciting event. The sympathetic activation and Valsalva manoeuvres during sexual intercourse may lead to retrograde transmission of high venous pressure to the cerebral venous system, resulting in venous ischaemia and transient global amnesia, as postulated by Lewis.[1] As with our patients who did not recall the current US President, a presidential Valsalva manoeuvre during each of his recent escapades may have legally allowed him to not recall specific events and may thereby help maintain international stability during the current transient global economic fluctuation.

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Diagoras of Melos (500 BC): an early analyst of publication bias

Sir—Publication bias refers to the tendency for researchers to fail to submit for publication negative study findings, and the failure of journal editors to consider such papers for publication: one book of advice on doing research recommended destruction of negative findings as "a commendable custom".[1] One solution to this difficulty involves coaxing hidden trials from their dark file drawers with promises of an amnesty.[2] The prospective registration of trials should also help .

This difficulty is not new.[4] Some investigators have been tempted to seek early mentions of publication bias, perhaps because scientific firsts are interesting in themselves, but also because even science requires creation myths. Medicine is full of them and often traces the study of a particular idea to an early founding figure. Dickersin and Min's[4] brief history of the study of publication bias supplies two early examples highlighting its perils. One is a 1909 editorial from the *Boston Medical Journal* which describes the selective citation of successful cases in medicine. The other much earlier quotation is by chemist Robert Boyle (1661): "Many excellent notions or experiments are, by sober and modest men, suppressed." The example by Boyle is perhaps not directly relevant to publication bias, because it suggests the suppression of excellent ideas rather than negative results: the example from the *Boston Medical Journal* is comparatively recent, and the investigation of publication bias can perhaps be tracked further back.

The writings of Francis Bacon (1561–1626) are a good starting point. In his 1605 book *The advancement of learning*,[5] he alludes to this particular bias by pointing out that it is human nature for "the affirmative or active to effect more than the negative or privative. So that a few times hitting, or presence, countervails oft-times failing or absence". This is a clear description of the human tendency to ignore negative results, and Bacon would be an acceptable father figure. Bacon, however, goes further and supports his claim with a story about Diagoras the Atheist of Melos, the fifth century Greek poet.

Diagoras was the original atheist and free thinker. He mocked the Eleusinian mysteries, an autumnal fertility festival which involved psychogenic drug-taking, and was outlawed from Athens for hurling the wooden statue of a god into a fire and sarcastically urging it to perform a miracle to save itself. In the context of publication bias, his contribution is shown in a story of his visit to a votive temple on the Aegean island of Samothrace. Those who escaped from shipwrecks or were saved from drowning at sea would display portraits of themselves here in thanks to the great sea god Neptune. "Surely", Diagoras was challenged by a believer, "these portraits are proof that the gods really do intervene in human affairs?" Diagoras' reply cements his claim to be the "father of publication bias": "yea, but . . . where are they painted that are drowned?"

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DEPARTMENT OF ERROR

Exporting tobacco addiction from the USA—In this letter by John Britton (July 11, p 152), the second from last sentence should end: "tobacco will account for 10 million deaths worldwide".

Chronic obstructive pulmonary disease: don't forget the gatekeeper—In this letter by Samuel Coenen and colleagues (Aug 22, p 649), Joke Denekens should have been included as an author.

Peanut allergy—In this letter by Deborah Fox and Gideon Lack (Aug 29, p 741), the first sentence of the last paragraph should read: "Associations between exposure to environmental processes and disease risks are not necessarily linear, and simplistic all or nothing public health measures may have unintended effects."

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)—In this article by the UK Prospective Diabetes Group (Sept 12, p 854), part of the key for figure 9 was incorrect. That part should read as follows:

····□···· Sulphonylurea alone (n=126)

- - ■ - - Sulphonylurea plus metformin (n=127)

Shrinks in the sack—We regret the publication of the cartoon that went with this Jabs and Jibes column (Oct 31, p 1484).