

# CORRESPONDENCE

## Pumactant and poractant alfa in respiratory distress syndrome

Sir—S B Ainsworth and colleagues' results (April 22, p 1387)<sup>1</sup> may have been biased against pumactant. The data sheet says: "pumactant should be given as soon as possible after the baby is intubated. If the baby remains intubated, a second dose should be given 24 h from the time of intubation".

In the study by Ainsworth and colleagues only 45% of pumactant-treated babies had the first dose within 10 min of birth and a second dose was given at 12 h. As suggested by Alan Jobe in his commentary, the design of the study favoured poractant.<sup>2</sup>

The 31% mortality in the pumactant group is too high. In other studies of babies less than 30 weeks' gestation, where prophylactic pumactant treatment was compared with controls the mortality in the pumactant groups was less than 20%.<sup>3,5</sup> The 31% mortality in the pumactant group in the trial by Ainsworth and colleagues is higher than the mortality of 26.5% and 25.4% in the main trial centres, Liverpool and Newcastle, for similar gestational ages when pumactant alone was used. This difference suggests some unexpected adverse influence on the pumactant group.

There must be concern about the standards in some hospitals enrolling very premature babies in this trial. Five have no neonatal intensive care unit and one no paediatric staff. Some babies may have received suboptimum care at birth, which influenced their outcome. It is unclear whether babies in these hospitals were given surfactant at birth or transferred and given surfactant later. The number born in each hospital, the randomisation, and gestational age matching are not presented.

Mortality and morbidity are inversely related to gestational age and are considerably higher in infants born before 28 weeks'. For babies less than 28 weeks there were 21% more treated with pumactant and at 29 weeks' there were 33% more treated with poractant. This will have biased the outcome against pumactant.

The interim analysis was not undertaken at the stated half way point. Target enrolment was 482. Interim analysis should have been done at 241

but was done with data on only 199. No reason is given for this early analysis. It is possible that the investigators were aware of the outcomes when they decided on an early interim analysis. This may have contributed to the unexpected difference in mortality. The trial was stopped because of the difference in mortality. However, deaths are included that were unrelated to surfactant treatment—eg, hydrops, incarcerated hernia, and intrapartum asphyxia. The inclusion of these deaths inflated the difference between the groups and added to the bias against pumactant.

Colin Morley

Neonatal Medicine, Royal Women's and Royal Children's Hospital, Melbourne, Victoria 3053, Australia

- 1 Ainsworth SB, Beresford MW, Milligan DWA, et al. Pumactant and poractant alfa for treatment of respiratory distress syndrome in neonates born at 25–29 weeks gestation: a randomised trial. *Lancet* 2000; **355**: 1387–92.
- 2 Jobe AH. Which surfactant for treatment of respiratory-distress syndrome. *Lancet* 2000; **355**: 1380–81.
- 3 Morley CJ, Bangham AD, Miller NG, Davis JA. Dry artificial lung surfactant and its effect on very premature babies. *Lancet* 1981; **i**: 64–68.
- 4 Wilkinson A, Jenkins PA, Jeffrey JA. Two controlled trials of dry artificial surfactant: early effects and later outcome in babies with surfactant deficiency. *Lancet* 1985; **ii**: 287–91.
- 5 Morley CJ, Greenough A, Miller NG, et al. Randomised trial of artificial surfactant (ALEC) given at birth to babies from 23 to 34 weeks gestation. *Early Hum Dev* 1988; **17**: 41–54.

Sir—The study by S B Ainsworth and colleagues<sup>1</sup> was designed to investigate the difference between the cost of treatment with two surfactants, poractant alfa, a porcine-derived surfactant, and pumactant, an artificial surfactant. Babies born at 25–29 weeks gestation were randomised to receive either poractant alfa or pumactant as soon after birth as possible, and at 12 h with further doses at the discretion of the physician. The results showed an excess mortality in the pumactant treated group and the trial was stopped early by the Data Monitoring Committee. Pumactant has now been temporarily withdrawn from use.

The manufacturer's instructions recommend that pumactant should be given as soon as possible after birth, at 1 h, and again at 24 h. This regimen appears to be based on the Ten Centre Study.<sup>2</sup> It is well recognised that surfactant is most effective if given early. Poractant alfa should be given as soon as possible after birth, at 12 h, and again at 24 h if required. The failure of the present study to apply the manufacturer's recommendations may have contributed to the higher mortality in the pumactant group.

The Ten Centre Study compared pumactant with saline placebo. The pumactant-treated babies in the Ten Centre Study were of similar gestation (mean 27.6 weeks; median 27.8 weeks), though slightly heavier (mean birth weight 1093 g; median 949 g) than the pumactant-treated babies in the Ainsworth study. Mortality in the pumactant-treated group in the Ten Centre Study was 23 (14%) of 199 and 25 (25%) of 100 in the study by Ainsworth and colleagues. The mortality rate in the Ten Centre Study seems excellent, considering that this work was done in the mid-1980s. Neonatal practice has advanced since then. In particular antenatal steroids, known to reduce frequency and severity of respiratory distress syndrome<sup>3</sup> and neonatal mortality, were only used in 11% of cases in the Ten Centre Study (93% in the Ainsworth study).

We agree that the excess mortality in the Ainsworth study was probably a treatment effect but cannot exclude the possibility that had the babies received three doses of pumactant at 0, 1 h, and 24 h, as recommended, there would have been no difference in outcome.

In the past, we have used pumactant on our unit in the three doses as recommended. Recently, we have had the clinical impression that natural surfactant is better because it provides a more rapid improvement. However, we should be wary of drawing too many conclusions from anecdotal experience and the published evidence of differences between outcomes of natural versus synthetic surfactants<sup>4</sup> has been less striking than expected.

There are theoretical concerns about possible long-term side-effects of animal-derived surfactants, in particular, sensitisation to animal proteins and introduction of infectious agents, which may take some years to become apparent.

The only way to answer the question as to whether either pumactant or poractant alfa is superior would be to do a study where both are given according to the manufacturer's recommendations. We doubt whether such a study will now ever be done.

Allan D Wardhaugh, \*Jean W A Matthes  
Department of Child Health, Singleton Hospital,  
Sketty, Swansea SA2 8QA, UK  
(e-mail: jwamatthes@hotmail.com)

- 1 Ainsworth SB, Beresford MW, Milligan DWA, et al. Pumactant and poractant alfa for treatment of respiratory distress syndrome in neonates born at 25–29 weeks gestation: a randomised trial. *Lancet* 2000; **355**: 1387–92.
- 2 Ten Centre Study Group. Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. *BMJ* 1987; **294**: 991–96.
- 3 Crowley P. Prophylactic corticosteroids for preterm birth (Cochrane Review). In: The Cochrane Library, Issue 2, 2000. Oxford: Update Software.
- 4 Jobe AH. Which surfactant for treatment of respiratory distress syndrome. *Lancet* 2000; **355**: 1380–81.

Sir—We did consider using the three-dose regimen defined in the datasheet for pumactant for our trial, but decided to follow the dosing schedule that was in place in Newcastle and Liverpool. We did this because it meant we had the advantage of having a population from which to derive the power of the study and a mechanism to check for an unexpected deviation in mortality. We recognised the potential disadvantage that a two-dose regimen would preclude a direct comparison of mortality in our study with that reported in the only large placebo-controlled trial of pumactant<sup>1</sup> but we considered this to be less important in view of the likely changes in casemix that would have occurred over 10 years. The outcome may have been different if a different regimen had been used, but we do not know the direction of the difference; pumactant is the only surfactant for which a second dose at 1 h is recommended and there are no published data to support its efficacy.

Our trial was one of early treatment rather than prophylaxis. This may in part account for some of the difference between mortality rates in the pumactant arm of our study and those quoted by Colin Morley. There was no statistical difference between the two arms in the median administration time for the first dose; for pumactant this

was 13 (interquartile range 7–34) min and for poractant alfa 16 (7–41) min. Other possible reasons for the differences between times include the higher proportion of more immature babies in our study, different population demographics, and enrolling only intubated infants (11% of the babies in the Ten Centre Study had respiratory disease which was not severe enough to warrant ventilation). Allan Wardhaugh and Jean Matthes compare mortality rates from two trials done 10 years apart, and they fail to take into account the differences in population demographics and risk factors that apply in each trial. There is no doubt that antenatal steroid use has improved the outcome from neonatal respiratory distress syndrome and that neonatal practice has improved since the mid-1980s. By the same token, obstetric practices have also changed and we are faced with babies that previously would have died in utero.<sup>2</sup>

Standards of resuscitation and stabilisation skills in level I units are high across the northern region of the UK. Outcomes of babies born in these units and subsequently transferred are as good as those born in the level III units.<sup>3</sup> Babies enrolled into the trial from level I units received their first dose of surfactant after stabilisation and before transfer.

The difference in the gestational age profile is within the bounds of chance variation. The use of analysis of covariance methods to allow for this imbalance is a widely accepted and effective statistical tool. The logistic regression given in our paper took account of trial centre, sex, gestational age, use of antenatal steroids, plurality, and birthweight. The magnitude of the odds ratio varies between models, but in all cases there was a clear and highly significant difference, always in favour of poractant alfa.

There are no hard and fast rules for when an interim analysis is done. The analysis had originally been planned for the half-way stage of the study. Slower than expected recruitment led to the addition of two further centres and it was hoped that the half-way stage would have been reached by September, 1999. As it was, the process of obtaining local ethical committee approval delayed the start in these units and it was decided for pragmatic reasons to have the analysis later in the year, irrespective of recruitment.

Preadmission mortality (all causes) was significantly lower in the poractant alfa group. If respiratory mortality is studied in isolation the difference

between surfactants was accentuated further.

\*S B Ainsworth, M W Beresford,

\*D W A Milligan, N J Shaw,

J N S Matthes

\*Newcastle Neonatal Service, Royal Victoria Infirmary, Newcastle upon Tyne NW1 4LP, UK; Neonatal Unit, Liverpool Women's Hospital, Liverpool; Department of Statistics, University of Newcastle upon Tyne, Newcastle upon Tyne

- 1 Ten Centre Study Group (1987). Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. *BMJ* 1987; **294**: 991–96.
- 2 Olsen P, Laara E, Rantakallio P, Jarvelin MR, Sarpola A, Hartikainen AL. Epidemiology of preterm delivery in two birth cohorts with an interval of 20 years. *Am J Epidemiol* 1995; **142**: 1184–93.
- 3 Northern Neonatal Network. Emergency pre- and post-delivery transfer and its safety in the very preterm baby. *BMJ* (in press).

## Trypsinogen activation peptide in acute pancreatitis

Sir—J P Neoptolemos and colleagues' study (June 3, p 1955)<sup>1</sup> is of course of interest but deserves further comment. Clinicians in charge of patients with acute pancreatitis still need a simple, single, reliable, and cheap test that gives early prediction of disease severity. Since the mid-1980s, dozens of biological markers have emerged but none proved useful when used alone. However, trypsinogen activation peptide (TAP) is specifically related to the pancreas and to trypsinogen activation into active trypsin and could be one of the first events occurring during the course of pancreatitis, although it may be unrelated to the severity of an attack.

Most observers believe that acute pancreatitis results from the premature, intrapancreatic activation of digestive enzyme zymogens, including trypsinogen.<sup>2</sup> The location in the pancreas of premature trypsinogen activation and the fate of activated trypsin, as well as TAP, during the early stages of pancreatitis are issues of considerable importance, but a clear understanding of these phenomena has not yet been reached. TAP measurement is more a diagnostic marker of pancreatitis than a prognostic one. Indeed, in the light of recent research, the ultimate severity of acute pancreatitis has been postulated to result from subsequent non-acinar cell events,<sup>3</sup> including activation of inflammatory cells (eg, neutrophils, macrophages, and lymphocytes) and an imbalance between the production and release of pro-

inflammatory and anti-inflammatory mediators (eg, interleukin-1, interleukin-6, interleukin-8, tumour necrosis factor  $\alpha$ , platelet activating factor (PAF) to interleukin-10, and interleukin-11. These cytokines, which are produced in response to acinar cell events, have also been considered as predictors of severity because their concentrations were closely correlated to the outcome of the disease. However, the results of these studies provided an incremental advance in the field. In some cases, some of these cytokines, particularly PAF, have been used as potential therapeutic targets<sup>4</sup> but in a European study the efficacy of the inhibition of PAF in improving the severity of the disease was questioned.<sup>5</sup>

In the absence of a clear understanding of the physiopathology of acute pancreatitis, other factors, either pancreatic enzymes or mediators induced by the inflammation in the pancreas, will emerge in the near future but will also prove useless in the early prediction of the severity of an attack of acute pancreatitis.

Jean Louis Frossard

Division of Gastroenterology, Geneva University Hospital, 1211 Geneva 14, Switzerland  
(e-mail: jean-louis.frossard.frossard@hcuge.ch)

- 1 Neoptolemos J, Kemppainen E, Mayer J, et al. Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: a multicentre study. *Lancet* 2000; **355**: 1955–60.
- 2 Hofbauer B, Saluja AK, Lerch MM, et al. Intra-acinar cell activation of trypsinogen during caerulein-induced pancreatitis in rats. *Am J Physiol* 1998; **275**: G352–62.
- 3 Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. *Am J Surg* 1998; **175**: 76–83.
- 4 Kingsnorth AN, Galloway SW, Formela LJ. Randomized, double-blind phase II trial of Lexipafant, a platelet-activating factor antagonist, in human acute pancreatitis. *Br J Surg* 1995; **82**: 1414–20.
- 5 Imrie C. Multiple organ system failure and new approaches to therapy [abstr]. *Gut* 1999; **45** (A 43): 5202.

## Benefits of chemotherapy in head and neck cancer

Sir—I would like to commend the diligence of the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group (March 18, p 949)<sup>1</sup> in completing their detailed meta-analyses of chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma. I am, however, deeply concerned by the conservative nature of the conclusions.

The magnitude of the relative risk reduction in the odds of death in the concomitant chemoradiotherapy group,

compared with the same (or more intensive) treatment without chemotherapy is 19%, representing a 25% increase in 5-year survival from 32% to 40%. The magnitude of this difference is comparable to the incontrovertible benefit noted in patients with lymph-node negative breast cancer who are receiving adjuvant systemic therapy. This improvement in survival should stand alone as an important conclusion of the paper, regardless of trial heterogeneity. A survival curve of this subset should have been included in the paper.

The non-significant negative effect of neoadjuvant chemotherapy in the larynx preservation strategy should indicate that an appropriate but sole role of neoadjuvant chemotherapy in this patient population is for larynx preservation, with proper informed consent regarding survival data.

The emphasis on the subset analysis, while questionable from a statistician's standpoint, is critical and clinically relevant. Multi-agent concomitant chemoradiotherapy was associated with a hazard ratio of death of 0.69. Young patients with a good performance status with stage 4 disease derived the greatest benefit from chemotherapy, and it is precisely this group who are most likely to receive aggressive combined modality therapy outside of the clinical trial setting. Interestingly, the subset of patients receiving neoadjuvant cisplatin and 5-fluorouracil had a survival benefit (HR 0.88 [95% CI 0.79–0.97]).

The results of the last several major publications of concomitant chemoradiotherapy trials are consistent and overwhelmingly in favour of chemotherapy added concomitantly to radiotherapy.<sup>2–5</sup> These results should be flagged for the reader in the discussion.

The discussion concludes that the routine use of chemotherapy remains debatable. There should be no debate at all that medically fit patients with unresectable carcinoma, who want the best opportunity for cure, need to receive some form of chemotherapy added to curative intent radiotherapy.

Since 1965, at least 10 741 people have volunteered to take part in the randomised trials represented in these meta-analyses. Based on these meta-analyses, 223 people may have died as a result of receiving less effective control group treatments. Let us not subject more patients to less effective radiation-alone treatment as a result of the conclusions of this paper, because the data offered clearly shows that radiation alone is an inferior option to concomitant chemoradiation for medically fit patients. Few people would accept radiation alone given true

informed consent. Future trials should investigate the optimum modality of integrating systemic therapy, and quality of life.

Bruce Brockstein

Division of Hematology, Oncology, Evanston Northwestern Healthcare, Northwestern University, Evanston, IL, 60201, USA  
(e-mail: b-brockstein@nwu.edu)

- 1 Pignon JP, Bourhis J, Dromeu C. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta-analyses of updated individual data. *Lancet* 2000; **355**: 949–55.
- 2 Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicentre study. *J Clin Oncol* 1998; **16**: 1318–24.
- 3 Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 1998; **338**: 1798–804.
- 4 Bachaud JM, Cohen-Jonathan E, Alzieu C. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys* 1996; **36**: 999–1004.
- 5 Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *J Clin Oncol* 2000; **18**: 1458–64.

Sir—Overall the benefit of chemotherapy is a 4% increase in 5-year survival from 32% to 36%. Most of Bruce Brockstein's comments focus on the results of subgroup analyses and must be considered as exploratory.

It is true that chemotherapy given concomitantly to radiotherapy leads to an improvement in 5-year survival from 32% to 40%. However this result has to be accepted with caution, given the major heterogeneity between trials, since the absolute treatment effect varied from a detrimental effect of 6% to a beneficial effect of 19%. Despite several exploratory analyses, it was not possible to explain this heterogeneity. The small group of trials in which concomitant chemotherapy appeared particularly beneficial included old and more recent trials and a variety of chemotherapy schedules were used (detailed description and references of the trials are given on the *Lancet* website: www.thelancet.com).

Neoadjuvant chemotherapy in the larynx preservation strategy improved the chance for laryngeal preservation but was associated with a non-significant (6%) increase in mortality. This meta-analysis included 602 patients only and has therefore a low power to detect a small effect on survival. However, the observed negative effect on survival in the larynx preservation strategy would suggest that

this approach should still be investigated.

The larger benefit of multiple agents given with radiotherapy is an interesting observation. However, selecting the largest apparent effect among many subset analyses may be statistically and clinically misleading. Based on the study of variation of treatment benefit according to covariate values in MACH-NC, Brockstein identified the ideal candidate for chemotherapy, namely a young patient with a good performance status and a stage 4 disease. This conclusion appears extremely uncertain since neither performance status nor stage modified significantly the effect of treatment.

Brockstein took results from four positive randomised trials of concomitant chemotherapy as an argument in favour of this treatment. Focusing on positive results can be misleading. Exhaustiveness is an important feature of the meta-analysis. Two of the trials mentioned by Brockstein were carried out before 1993 and were included in the meta-analysis. Between 1993 and 1999, more than a dozen randomised trials of concomitant chemotherapy have been carried out. Some, but not all, led to positive results and the only way to give an unbiased estimation of the long-term benefit of this treatment is to update our meta-analysis by including the recent trials (this study is ongoing).

The value of a 4% survival benefit is a matter of debate; some may consider it large enough to establish chemotherapy as a standard treatment, others will not. While waiting for a clear answer which may arise from the updating of MACH-NC, patients should be invited to participate in randomised trials. We have to keep in mind the uncertainty associated with our results. The 95% CI of the overall survival benefit ranges from 2% to 8%.

\*Jean-Pierre Pignon, Jean Bourhis, Catherine Hill, Christian Domenge

Departments of \*Biostatistics, Radiotherapy, and Head and Neck Oncology, Institut Gustave-Roussy, 94805 Villejuif cedex, France (e-mail: jppignon@igr.fr)

## Long-term inhibition of platelet aggregation

Sir—Clinical trials of prolonged pharmacological inhibition of platelet aggregation with oral glycoprotein IIb/IIIa receptor antagonists were mentioned in a review by James N George (April 29, p 1531).<sup>1</sup> Secondary prevention of recurrent cardiac events and death in patients after acute coronary syndromes with oral

Source	Glycoprotein IIb/IIIa blockers	Clinical outcomes	Adverse events
<b>SYMPHONY*</b> 9233 patients within 7 days of acute coronary syndrome	Sibrafiban low and high doses*	90-day outcomes. No additional benefit over aspirin	Significantly higher rate of bleeding events and transfusions of red cells
<b>2nd SYMPHONY*</b> 6600 patients within 7 days of acute coronary syndrome	Sibrafiban low dose plus aspirin and sibrafiban high dose	90-days outcomes. No additional benefit over aspirin. Significantly high rate of death in the high-dose sibrafiban group	Rate of bleeding events, in particular major bleeding, was almost twice higher
<b>OPUS-TIMI 16*</b> 10 302 patients within 3 days of acute coronary syndromes	2 dosage regimens of orbofiban plus aspirin	The study was stopped prematurely because of excess 30-day mortality in one of the orbofiban groups. Similar trend at 10 months	Significantly increased number of severe or major bleeding events
<b>EXCITE*</b> 7232 patients undergoing percutaneous coronary interventions	2 doses of xemilofiban plus aspirin	No significant difference among treatment groups at 30 days and 6 months	Results were not reported

SYMPHONY=sibrafiban versus aspirin to yield maximum protection from ischaemic heart events post-acute coronary syndromes; OPUS=orbofiban in patients with unstable syndromes; EXCITE=evaluation of oral xemilofiban in controlling thrombotic events.

\*Ticlopidine was added in the low-dose sibrafiban group during the study because of the higher rate of stent thrombosis in this group.

glycoprotein IIb/IIIa blockers have been studied in four large clinical trials with 33 367 observations, which we identified while working on a systematic literature review. Results from one clinical trial were published as a journal article.<sup>2</sup> Findings from the other studies are available as conference material.<sup>3,4</sup>

Oral glycoprotein IIb/IIIa blockers alone or in combination with aspirin were compared with aspirin in patients with acute coronary syndromes and in percutaneous coronary interventions, or with a combination of ticlopidine plus aspirin in patients undergoing coronary stenting (table). None of these studies reported any significant additional benefit over aspirin in preventing death, myocardial infarction, reinfarction, or severe recurrent ischaemia. Although the orbofiban in patients with unstable coronary syndromes-TIMI 16 study showed a decrease in recurrent ischaemic events leading to revascularisation in orbofiban groups, it was associated with excess 30-day mortality.

A significantly higher rate of bleeding events was observed in patients taking oral glycoprotein IIb/IIIa blockers. Most of the reported bleeding events were mucocutaneous, but severe bleeding was also significantly more frequent. The strong antiplatelet effect of these new drugs is not associated with better clinical outcomes.

\*Veronika Kolesnik, André Biskop

\*Medical Academy for Postgraduate Studies, St Petersburg 193015, Russia; Regional Cardiology Centre of Leningrad Oblast, St Petersburg; and Swedish Council for Technology Assessment in Health Care, Stockholm, Sweden

1 George JN. Platelets. *Lancet* 2000; **355**: 1531–39.

- 2 Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. The SYMPHONY Investigators. *Lancet* 2000; **355**: 337–45.
- 3 Newby K. A randomized comparison of sibrafiban, an oral glycoprotein IIb/IIIa receptor antagonist, with and without aspirin versus aspirin after acute coronary syndromes: results of the 2nd SYMPHONY Trial. In: Late-breaking clinical trial results—session II. ACC Scientific Session 2000, March 15, 2000. (<http://www.medscape.com/> accessed July 7, 2000).
- 4 Ferguson JJ. Meeting highlights. Highlights of the 48th scientific sessions of the American College of Cardiology conference. *Circulation* 1999; **100**: 570–75.

## A stinging cause for preventive skin care

Sir—Accumulating evidence supports alcoholic hand disinfection with short-chain aliphatic alcohols, so-called rub-ins, as the method of choice in hand disinfection and cross-infection prevention. Given that a health-care worker in an intensive-care unit may encounter up to 60 disinfection opportunities per hour,<sup>1</sup> the short contact time required with rub-ins makes it the only procedure compatible with actual workload. Moreover, a review of the available literature suggests a lower irritant potential of alcohol hand disinfectants on healthy skin, compared with detergent-based products.<sup>2</sup> Compliance, however, is still a challenge.<sup>1</sup> Whereas current infection prevention strategies reiterate Semmelweis' lesson,<sup>3</sup> the role of skin integrity as a compliance factor in alcoholic hand disinfection has not yet received the attention it deserves.

Irritant contact dermatitis (ICD) is

the predominant cause of occupational skin disease in health-care workers. A survey in two intensive-care units reported a prevalence of ICD between 55% and 70%. However, only one of 126 health-care workers had to stop working as a result of hand dermatitis,<sup>4</sup> supporting the commonplace notion that ICD in health-care environments is clinically low-grade in most cases. We have done a series of exposure tests on low-grade irritated volar forearm skin of 12 volunteers. Low-grade ICD was induced by occlusive overnight exposure to 0.05% to 0.2% sodium laureth sulphate, a common proxy for detergents, and quantified by transepidermal water loss, redness, and cutaneous capacitance. Subsequent exposure to 60% n-propanol, a frequently used alcohol skin disinfectant, induced intolerance in 6 of 12 volunteers. Intolerance was characterised by subjective symptoms of stinging, while the skin sites remained symptom-free when unexposed.

Immediate transient stinging is a well-known property of short-chain aliphatic alcohols,<sup>5</sup> familiar to anyone applying an after-shave on slightly abraded skin. Many health-care workers may share that experience when using a rub-in on their hands. Onset of ICD is insidious and goes often unnoticed: typically, dryness and chapping first develop on the dorsal aspects of the metacarpophalangeal joints, followed by discrete fissuring. At that early stage of ICD, an alcoholic rub-in will already sting. And here is the rub: the usual reaction is to blame the rub-in as the irritant, and switch to non-stinging (but more irritating) detergent-based disinfectants.

The high prevalence of low-grade irritant contact dermatitis in health-care workers should be taken into account when strategies are formulated to improve compliance with hygienic hand disinfection. Promoting awareness that stinging upon contact with an alcoholic disinfectant can be an early sign of ICD, rather than a consequence of the rub-in's irritant action, will help to set the focus on preventive skin care.

\*J Lübke, C Ruffieux, D Perrenoud

Department of Dermatology, University Hospital and DHURDV, Geneva CH-1211, Switzerland  
(e-mail: jann.lubbe@hcuge.ch)

1 Pittet D, Mourouga P, Perneger T. Compliance with handwashing in a teaching hospital. *Ann Intern Med* 1999; **130**: 126–30.

- 2 Larson E. Skin hygiene and infection prevention: more of the same or different approaches? *Clin Infect Dis* 1999; **29**: 1287–94.
- 3 Hand washing liaison group. Hand washing. *BMJ* 1999; **318**: 686.
- 4 Forrester B, Roth V. Hand dermatitis in intensive care units. *J Occup Environ Med* 1998; **40**: 881–85.
- 5 Frosch P, Kligman A. A method for appraising the stinging capacity of topically applied substances. *J Soc Cosmet Chem* 1977; **28**: 197–209.

## Hepatitis B virus mutants and efficacy of vaccination

Sir—In his April 22 commentary,<sup>1</sup> Arie Zuckerman reiterates his concern that mutations in the *a* determinant of hepatitis B virus (HBV) allow replication of the virus in vaccinated people. In particular, the most frequent and stable mutant virus (G145R) has been deemed a vaccine-induced escape mutant and extensively studied as a paradigm of vaccine-escape.<sup>2</sup>

Epidemiological evidence does not support the existence of vaccine-escape mutants. Mixed infections of mutant and wild-type (wt) virus indicate failure of vaccination, not failure of the vaccine. In the study of post-exposure prophylaxis by Nainan and colleagues,<sup>3</sup> an estimated 91% of 94 vaccination failures were infected with wt virus or mixtures of wt and mutant virus (principally G145R). A high rate of mixed infections was shown by employing sensitive strain-specific PCR to detect minor populations of virus. The investigators reanalysed their samples and found additional mixed infections, resulting in comparable prevalences of mutant viruses in all groups studied. They concluded that “the similar frequencies of variants in case-mothers and control-mothers suggest that these variants are not associated with failure of post-exposure prophylaxis to prevent perinatal HBV infection”.<sup>4</sup> Most other studies have failed to look for wt virus coexisting at low concentrations with mutant virus.

The original report of vaccine-escape must also be reinterpreted in the light of additional data.<sup>2</sup> My colleagues and I analysed HBV DNA from serum of the original patient when he was aged 7 years and, using a sensitive and quantitative strain-specific PCR, found a subpopulation of wt HBV.<sup>5</sup> Based on the patient's history of inadequate vaccination<sup>2</sup> and evidence of infection with wt virus,<sup>5</sup> even the original example of vaccine-induced escape must be recognised as merely a

vaccination failure, because adequate vaccination, even of newborns, protects against wt virus for at least 12 years and probably longer.

My colleagues and I showed that the two most widely used commercial hepatitis B vaccines protected chimpanzees against infection by the prototype G145R mutant HBV.<sup>5</sup> Two of the vaccinated chimpanzees had suboptimum anti-HBs titres that approximated the minimum protective concentration (100 mIU) adopted by the UK, but this still completely blocked a high titre of mutant virus, as well as the subpopulation of wt virus, from replication. Thus, direct experimentation confirms that the G145R mutant HBV is not a vaccine-escape mutant. It is heartening, therefore, that, although post-exposure prophylaxis fails 10–15% of the time for various reasons, mostly unrelated to mutants, vaccination of contacts will prevent the transmission of mutant virus, as well as wt virus, to others.

Robert H Purcell

Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA  
(e-mail: rpurcell@niaid.nih.gov)

- 1 Zuckerman AJ. Effect of hepatitis B virus mutants on efficacy of vaccination. *Lancet* 2000; **355**: 1382–84.
- 2 Carman WF, Zanetti AR, Karayiannis P, et al. Vaccine-induced escape mutant of hepatitis B virus. *Lancet* 1990; **336**: 325–29.
- 3 Nainan OV, Stevens CE, Taylor PE, Margolis HS. Hepatitis B virus (HBV) antibody resistant mutants among mothers and infants with chronic HBV infection. In: Rizzetto M, Purcell RH, Gerin JL, Verme G, eds. *Viral hepatitis and liver disease*. Turin: Edizioni Minerva Medica, 1997: 132–34.
- 4 Nainan OV, Khristova ML, Byun K-S, et al. Frequency and significance of hepatitis B virus antibody resistant mutants [suppl]. *Antiviral Therapy* 2000; **5** (1): 29–30.
- 5 Ogata N, Cote PJ, Zanetti AR, et al. Licensed recombinant hepatitis B vaccines protect chimpanzees against infection with the prototype surface gene mutant of hepatitis B virus. *Hepatology* 1999; **30**: 779–86.

Author's reply

Sir—The term vaccine-escape mutant was used in the original publication in *The Lancet* in 1990, but subsequent studies have shown that the G145R mutation and other mutations of the *a* determinant of hepatitis B virus (HBV) are found together with wt virus in carriers<sup>1</sup> and in patients with chronic hepatitis. In the commentary of April 22 I did not use the term vaccine-escape mutant.

The reanalysis of the data published by Nainan and colleagues in 1997 is, of course, of interest but presented thus far only in abstract form. These results do not detract from the observations

made by Robert Purcell of experimental transmission of hepatitis B to chimpanzees by the G145R mutant only, after dilution of the AS serum, which also contains wt virus, indicating that this mutant is replication competent.<sup>2</sup>

Purcell fails to address the important findings made by Hsu and colleagues in Taiwan<sup>3</sup> of an increase in the prevalence of mutants of the HBV *a* determinant over 10 years after the introduction of universal vaccination against hepatitis B, and also that the prevalence of the mutants was higher among those who were fully immunised than among those not vaccinated. Related findings in Singapore, The Gambia, Taiwan,<sup>4</sup> and elsewhere indicate that infections with the mutants are not merely vaccine failures, as are the observations of considerable genetic variability of the *a* determinant of HBV in the German population with anti-HBc (antibodies to HB core antigen).<sup>5</sup>

Finally, while the chimpanzee protection studies described by Purcell and colleagues are reassuring, the challenge experiments with the AS serum did not reflect perinatal transmission, which is the commonest time of infection with HBV in south-east Asia and the Pacific region. Perinatally the infant is exposed to the virus at the time of birth and for a few days thereafter before the appearance of vaccine-induced antibodies. Only post-exposure-challenge experiments to mimic natural maternal-infant transmission of wt and variant viruses can establish whether immunisation can always prevent perinatal infection, or not.

Universal immunisation against hepatitis B with current vaccines is essential and should be implemented in all countries. The addition to the vaccine of immunogenic epitopes, able to elicit antibodies to the common HBV mutants, should be explored, and epidemiological monitoring of viral mutations, particularly those not detected by current screening assays, should continue.

Arie J Zuckerman

WHO Collaborating Centre for Reference and Research on Viral Diseases, Royal Free and University College Medical School, London NW3 2PF, UK

- 1 Yamamoto K, Horikita M, Tsuda F, et al. Naturally occurring escape mutants of hepatitis B virus with various mutations in the S gene in carriers seropositive for antibody to hepatitis B surface antigen. *J Virol* 1994; **68**: 2671–76.
- 2 Ogata N, Zanetti AR, Yu M, Miller RH, Purcell RH. Infectivity and pathogenicity in chimpanzees of a surface gene mutant of hepatitis B virus that emerged in a vaccinated infant. *J Infect Dis* 1977; **175**: 511–23.

- 3 Hsu HY, Chang MH, Liaw SH, Li YH, Chen HL. Changes of hepatitis B surface antigen variants in carrier children before and after universal vaccination in Taiwan. *Hepatology* 1999; **30**: 1312–17.
- 4 Hsu HY, Chang MH, Ni YH, Lin HH, Wang SM, Chen DS. Surface gene mutants of hepatitis B virus in infants who develop acute or chronic infections despite immunoprophylaxis. *Hepatology* 1997; **26**: 786–91.
- 5 Weinberger KM, Bauer T, Böhm S, Jilg W. High genetic variability of the group-specific *a* determinant of hepatitis B virus surface antigen (HBsAg) and the corresponding fragment of the viral polymerase in chronic virus carriers lacking detectable HBsAg in serum. *J Gen Virol* 2000; **81**: 1165–74.

## Hit harder than HAART

Sir—In the introduction to their article on treatment for HIV-1, Mark Harrington and Charles Carpenter (June 17, p 2147)<sup>1</sup> say: “. . . no available regimen can eradicate HIV-1; all currently effective regimens may cause undesirable, sometimes life-threatening, toxic effects; and, unless regimens are strictly adhered to, multidrug resistance can develop, limiting future treatment options.” One would conclude that all three of these features had been confirmed beyond question. This is not the case. Treatment is available for which the second and third features do not apply. This treatment is called topical immune modulation (TIM); the modulator is dinitrochlorobenzene. Many encouraging articles about this treatment have been published in peer-reviewed journals.<sup>2–4</sup> These articles include reports on several pilot studies and two clinical trials. All show that TIM works.

The need for treatments such as TIM was emphasised by Joshua Lederberg, when he wrote “. . . our focus on extirpating the virus may have deflected less ambitious, though more pragmatic, aims, including learning to live with the virus by nurturing in equal measure the immune system that HIV erodes.”<sup>5</sup> TIM does just that. Furthermore, with TIM there are no significant side-effects, there is no multi-drug resistance, and difficulties with compliance are minimised. Perhaps more important, dinitrochlorobenzene costs less than 1% of HAART drugs, so TIM can be afforded worldwide, and no technical or complicated medical delivery system is required.

At a time when the world is wringing its hands about a crisis that is threatening both US national security and the capacity of some African countries to function, one

would think that anything offering some ray of hope would generate intense interest. For this reason I cannot understand why Harrington and Carpenter do not acknowledge TIM. When I ask people why there is so little interest in TIM, a common response is that TIM has not proved itself as a stand-alone treatment. What they mean is that it has not been subjected to controlled, randomised, double-blind clinical trials, which is true. Funding a trial of a substance that does not have a significant profit potential is extremely difficult. Because dinitrochlorobenzene is in the public domain, it lacks that potential. So pharmaceutical companies show little interest in dinitrochlorobenzene and, as a consequence, funds have not been available for the necessary research and clinical trials to establish it as a standard of care. That, in turn, has meant that TIM, the only treatment now available that could make a difference in Africa, has been ignored, with catastrophic consequences.

Until those who have made HAART the standard of care re-examine their emphasis on HAART, there is unlikely to be a change. If Harrington, Carpenter, and others playing a part in defining treatments for HIV disease take a serious look at TIM, particularly for its potential in the developing world, there may be hope for Africa. None now exists.

Richard De Lancie

Cellular Immunity Foundation, San Francisco, CA 94108, USA

- 1 Harrington M, Carpenter CCJ. Hit HIV-1 hard, but only when necessary. *Lancet* 2000; **335**: 2147–52.
- 2 Stricker RB, Goldberg B, Epstein WL. Topical immune modulation (TIM): a novel approach to the immunotherapy of systemic disease. *Immunol Letters* 1997; **59**: 145–50.
- 3 Traub A, Margulis SB, Stricker RB. Topical immune modulation with dinitrochlorobenzene in HIV disease: a controlled trial from Brazil. *Dermatology* 1997; **195**: 369–73.
- 4 Oracion R, Adams M, Sharp K, et al. DNCB treatment of HIV-infected patients leads to beneficial immunological outcomes, reduced viral loads, and improved measures of quality-of-life. *J Invest Dermatol* 1998; **110**: 476.

## High mortality among women with HIV-1 infection in Thailand

Sir—Despite strong evidence from the fields of virology,<sup>1</sup> clinical medicine,<sup>2</sup> and epidemiology (<http://www.niaid.nih.gov/spotlight/hiv00/default.htm>,

accessed July 28, 2000) for the causal role of HIV-1 infection, debate over the aetiology of AIDS continues in some arenas.<sup>3</sup> Alternative explanations for AIDS-related immunosuppression include sexual behaviour, socioeconomic status, concomitant infections with for example herpes simplex virus type-2 (HSV-2) and syphilis, and use of antiretroviral medications and illicit drugs.

HIV-1 infection was introduced into northern Thailand in the late 1980s and spread very rapidly with devastating effects. Here we compare mortality rates among women with prevalent and incident HIV-1 infection to rates among women without infection in an ongoing cohort study of female sex workers.

The Chiang Rai Health Club has been described elsewhere,<sup>4</sup> as have HIV-1 disease progression and mortality in the cohort.<sup>1</sup> Female sex workers of age 16 years and more in Chiang Rai province were eligible for the study. HIV-1 infection was tested for by enzyme immunoassay confirmed with western blot at enrolment and quarterly at follow-up visits. Deaths were confirmed by review of hospital, public health office, and housing registration records, and a national vital status database search.

Of the 500 women enrolled during 1991–94, 160 (32%) were HIV-1 infected. Through to October, 1998, an additional 34 women seroconverted, and 68 women died. Of the women who died, 59 were HIV-infected at enrolment, seven had seroconverted, and two were documented to be uninfected shortly before death. For HIV-infected women, all reported causes of death, including AIDS, tuberculosis, pneumonitis, and cryptococcal meningitis were associated with immunosuppression. The reported causes of death of the two uninfected women were postpartum amniotic embolism and gun shot wound. In a Cox proportional hazards model (left censored at time of enrollment), comparing infected women with uninfected women, the mortality rate ratio for women who were infected at enrollment was 52.7, and for women who seroconverted was 22.5 (table). Results were similar when the following characteristics at enrolment were controlled for type of sex work (brothel or non-brothel), duration of sex work, syphilis and HSV-2 infection, education, and year of enrollment. None of these other factors was significantly associated

HIV-infection status	Number who died	Mortality rate ratio (95% CI)*
Uninfected	2 (0.7%) of 306	Referent
Prevalent infection	59 (36.9%) of 160	52.7 (12.7–219)
Incident infection	7 (20.6%) of 34	22.5 (4.6–110)

\*Cox proportional hazards model.

#### Mortality among 500 female sex workers in northern Thailand

with survival. No antiretroviral use was reported through 1997; use was reported by three women in 1998. Injected drug use was rarely reported (1% of women); use of amyl nitrates is very rare in northern Thailand.

These very high mortality rates among HIV-1-infected women, in comparison with uninfected women, provides additional strong epidemiological evidence that HIV-1 infection causes AIDS and death as a result of immunosuppression. All women in this analysis were sex workers, which minimises confounding because of behaviour, socioeconomic status, or coinfections, and we controlled for differences in these factors when they were present. Furthermore, other putative causes of immunosuppression, such as use of antiretroviral medications were rare in this population. These high death rates among HIV-1-infected women underscore the need for individuals and policy makers worldwide to focus their attention on prevention of HIV transmission and on treatment of HIV infection.

\*Peter H Kilmarx,  
Khanchit Limpakarnjanarat,  
Supachai Saisorn, Philip A Mock,  
Timothy D Mastro

\*The HIV/AIDS Collaboration, Ministry of Public Health, Nonthaburi 11000, Thailand; National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; and Chiang Rai Provincial Health Office, Chiang Rai, Thailand (e-mail: <pbk@cdc.gov>)

- 1 Kilmarx PH, Limpakarnjanarat K, Kaewkungwal J, et al. Disease progression and survival with human immunodeficiency virus type 1 subtype E infection among female sex workers in Thailand. *J Infect Dis* 2000; **181**: 1598–606.
- 2 Hammer SM, Squires JE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus zidovudine in persons with human immunodeficiency virus infection and CD4+ cell counts of 200 per cubic millimeter or less: AIDS Clinical Trials Group 320 Study. *N Engl J Med* 1997; **337**: 725–33.
- 3 Jeter J. Mbeki vs AIDS experts. *The Washington Post* 2000; May 16, 1.
- 4 Limpakarnjanarat K, Mastro TD, Saisorn S, et al. HIV-1 and other sexually transmitted infections in a cohort of female sex workers in Chiang Rai, Thailand. *Sex Transm Infect* 1999; **75**: 30–35.

## Regional hyperthermia for rectal cancer

Sir—Jacoba van der Zee and colleagues (April 1, p 1119)<sup>1</sup> showed that there was an improvement of local control and survival rates in patients with cancers of the uterine cervix or bladder when hyperthermia was added to radiotherapy, but for rectal cancer no improvement in survival was seen. The value of hyperthermia in those patients might have been underestimated for several reasons.

No detailed inclusion and stratification criteria were given for the patients with rectal cancer. Also, much of the data (eg, mean size of pelvic tumours, number of patients with irresectable disease, and haemoglobin concentrations) suggest a higher proportion of patients with advanced or metastatic disease, respectively, in the hyperthermia group. Previous trials of deep hyperthermia have shown that there is a significant correlation between applied thermal dose and clinical outcome.<sup>2,3</sup> In this study by van der Zee and colleagues only 59 of 72 patients with rectal cancer treated with hyperthermia did receive more than three hyperthermia treatments (median not given), whereas two patients in the radiation-only arm also received 4–6 hyperthermia treatments.

Comparing survival of patients who received sufficient (and more) hyperthermia treatments with those treated with radiation only would have been informative, but no analysis of outcome and thermal data is given for any indication. Nevertheless, considering the selection bias and the relevant proportion of patients who did not receive a sufficient heat treatment, a trend in favour of patients with rectal cancer in the combined treatment arm was observed.

Our experience is that rectal cancer is clearly a difficult tumour to heat compared with other pelvic tumours such as cervical cancer, because power densities are on average lower due to the shadowing effect of the sacral bone. More advanced technologies are under development and might improve technical preconditions.

Therefore, the lack of survival benefit reported for patients with rectal cancer by van der Zee and colleagues might result from this imbalance of prognostic factors and technical considerations. Despite this, a trend in favour of deep hyperthermia to attain complete tumour response was observed in patients with rectal cancer. Further investigations that

focus on the different treatment indications (neoadjuvant, recurrent, metastatic) are warranted. Results from a phase II study in patients with locally advanced primary rectal cancer indicate that hyperthermia in the scope of multimodal treatment strategies might improve local control and, thereby, survival rates.<sup>4,5</sup> A neoadjuvant phase III trial comparing radiochemotherapy alone with radiochemotherapy with deep hyperthermia in patients with locally advanced non-metastatic rectal cancer is in progress.

\*Bert Hildebrandt, Peter Wust, Beate Rau, Peter Schlag, Hanno Riess  
Departments of \*Haematology and Oncology, Radiation Oncology, and Surgery and Surgical Oncology, Charité, Medical Faculty of the Humboldt University, D-13344 Berlin, Germany

- van der Zee J, González González D, van Rhooon G, van Dijk JDP, van Putten WLJ, Hart AAM, for the Dutch Deep Hyperthermia Group. Comparison of radiotherapy along with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. *Lancet* 2000; **355**: 1119–25.
- Issels R, Prenninger SW, Nagele A, et al. Ifosfamide plus etoposide combined with regional hyperthermia in patients with locally advanced sarcomas. *J Clin Oncol* 1990; **11**: 1818–29.
- Wust P, Stahl H, Dieckmann K, et al. Local hyperthermia of N2/N3 cervical lymphnode metastases: correlation of technical/thermal parameters and response. *Int J Radiat Oncol Biol Phys* 1996; **34**: 635–46.
- Riess H, Löffel J, Hohenberger P, et al. A pilot study of a new therapeutic approach in the treatment of locally advanced stages of rectal cancer: neoadjuvant radiation, chemotherapy and regional hyperthermia. *Eur J Cancer* 1996; **31**: 1356–60.
- Rau B, Wust P, Hohenberger P, et al. Preoperative hyperthermia combined with radiochemotherapy in locally advanced rectal cancer: a phase II clinical trial. *Ann Surg* 1998; **227**: 380–89.

#### Authors' reply

Sir—The Dutch Deep Hyperthermia Trial was designed to test whether the addition of hyperthermia to radiotherapy improved local control, and thereby survival, in patients with advanced intrapelvic tumours, including rectal cancer. We fully agree with the comment by Bert Hildebrandt and colleagues that our study may underestimate the value of additional hyperthermia in rectal cancer and that further studies in this patient group are warranted.

Patients with rectal cancer who have an inoperable tumour, either primary or recurrent, with or without distant metastases, were eligible for the study, as long as there was an indication for locoregional radiotherapy. It turned out that most of the included patients

had recurrent tumours with relatively large tumour sizes. In such a patient group it is rather unlikely to achieve a complete response, which was one of the primary endpoints of the study, and even more unlikely to influence overall survival. Besides a trend of a better local control rate, we found a trend that palliation following combined treatment was better than that following radiotherapy alone; this finding was not included in our report. A complete palliative effect was achieved in 18 (45%) of 40 patients after combined treatment versus eight (25%) of 32 after radiotherapy. Furthermore, the median duration of palliation was considerably longer following combined treatment: 17 months versus 7 months following radiotherapy alone. Hildebrandt and colleagues rightly noted that the patients in the combined treatment arm had worse prognostic factors than those in the control arm. The number of stratification items, however, was limited because the planned number of patients was relatively low, and because we expected that the distribution of prognostic factors would be balanced by randomisation.

We have not yet reported on an association between thermal dose and clinical outcome, since the most important question of the study was whether the addition of hyperthermia, at the level achievable with the presently available techniques, would improve therapeutic outcome. We do not share the experience of Hildebrandt and colleagues that rectal tumours are more difficult to heat than the other intrapelvic tumours. The temperatures that we have measured within rectal tumour tissue were in fact higher than those measured within cervix or bladder tumour tissues. A relatively large number of patients was not treated according to plan, but to avoid bias, the analysis was done by intention to treat.

We have seen the promising results from hyperthermia added to preoperative radiotherapy, with or without chemotherapy, in patients with rectal cancer, from (among others) the phase II study reported by Rau and colleagues.<sup>1,2</sup> We expect that in the preoperative situation the effect from this additional treatment is more likely to result in better local control and survival and are looking forward to the results from the ongoing German phase II study. In irresectable and recurrent rectal cancer, a prospective randomised study with the endpoints palliation and quality of life is warranted.

\*Jacoba van der Zee,  
Dionisio González González on behalf of  
the Dutch Deep Hyperthermia Group

\*University Hospital, Daniel den Hoed Cancer Center, Department of Radiation Oncology, Subdivision of Hyperthermia, 2651 GD Rotterdam, The Netherlands, and Academic Medical Centre, Department of Radiation Oncology, Amsterdam  
(e-mail: zee@hyph.azr.nl)

- Rau B, Wust P, Hohenberger P, et al. Preoperative hyperthermia combined with radiochemotherapy in locally advanced cancer: a phase II clinical trial. *Ann Surg* 1998; **227**: 380–89.
- González González D, Van Dijk JDP, Blank LECM. Radiotherapy and hyperthermia. *Eur J Cancer* 1995; **31A**: 1351–55.

## Measles virus and autism

Sir—Contrary to supposition by Masahiro Iizuka and colleagues (July 8, p 160),<sup>1</sup> our data from molecular virological studies examining the role of measles virus infection in children with autism and enterocolitis have been peer-reviewed, presented, and published at four international scientific meetings.<sup>2–4</sup> We would have been happy to share this information with Iizuka and colleagues if asked. The antibody used in our studies is not that used by Iizuka and colleagues. For the purpose of clarification, our studies involved the use of in-situ hybridisation, in-cell reverse transcriptase, real-time quantitative Taq Man PCR using complementary RNA standards for quantitation and sequencing of complementary DNA measles virus amplicon. In addition, three genes N, F, and H of measles virus were examined. We have also provided data in relation to sub-cellular localisation of measles virus, concordant with the molecular biological findings.

\*J J O'Leary, V Uhlmann, A J Wakefield

\*Coombe Women's Hospital and Trinity College Dublin, Dublin 8, Ireland; and Royal Free and University College Medical School, London, UK

- Iizuka M, Itou H, Chiba M, et al. The MMR question. *Lancet* 2000; **356**: 160.
- Wakefield AJ, Anthony A, Sim R, et al. Persistent measles virus infection immunodeficiency in children with autism ileo-colonic lymphoid nodular hyperplasia and non-specific colitis [suppl]. *Gut* 1998; **42** (1): A86.
- Uhlmann V, Martin C, Sheils O, et al. Measles virus in reactive lymphonodular hyperplasia and ileo-colitis in children [suppl]. *J Pathol* 2000; **190**: 1A–69A.
- Uhlmann V, Sheils O, Leittich K, et al. Identification of measles virus genomes in ileo-colonic lymphoid hyperplasia in children. *Lab Invest* (in press).

## Medical errors: reporting and punishment

Sir—Your observations in “When primum non nocere fails” (June 10, p 2007)<sup>1</sup> are well said. It is, however, curious to me that the Harvard Study of medical charts in New York Hospitals, in which adverse events of 2.9% were reported, seems to remain the benchmark. We are all aware that we live in a litigious society and workers are reluctant to add all adverse events to the medical record; retrospective reviews of charts, even with present quality assurance programmes, must vastly underestimate the true incidence of adverse events.

A study, which I co-authored,<sup>2</sup> showed that incidence of adverse events, measured prospectively by concurrent observation, was close to 45.8% in surgical units, of which 20% were truly serious. Most of these events were system failures and in only a few would disciplining a single person have changed anything. The comparison with the airline industry is encouraging since health care is the only remaining industry that fails to measure adverse events concurrently and at the point of care. Errors are most often the result of faults in the system and blame rather than changing the system is unlikely to accomplish improvement.

The increased surveillance and demand for reporting to ever higher authorities places all health-care workers on the horns of the dilemma. Few of us are convinced that reporting will not lead to punishment.

Thomas J Krizek

The Ethics Center, University of South Florida, Tampa, FL 33620-5550, USA

1 Editorial. When primum non nocere fails. *Lancet* 2000; **355**: 2007.

2 Andrews LB, Stockling C, Krizek T. An alternative strategy for studying adverse events in medical care. *Lancet* 1997; **349**: 309–13.

## Nevirapine for HIV prevention after rape

Sir—I welcomed the announcement made during the World AIDS Conference, July 9 to July 14, 2000, Durban, South Africa, that nevirapine for the prevention of mother-to-child HIV transmission in developing countries has been offered free of charge by the manufacturer, Boehringer Ingelheim GmbH, Germany. Perhaps this offer could now be taken a step further and the drug also offered free for post-exposure HIV prophylaxis for victims of rape.

HIV transmission through rape is of particular concern in southern Africa. HIV prevalences in the general population are often in excess of 25%, young girls are at very high risk of becoming infected with HIV after a limited number of sexual exposures<sup>1</sup> and, in South Africa, estimates of cases of sexual assault are 200 per day.<sup>2</sup> Although countries in the southern Africa region have so far been reluctant to take up the free nevirapine offer, it is difficult to see how provision of help to victims of sexual assault, in whom there is a very real risk of acquiring HIV, can be refused. Whilst the efficacy of nevirapine in preventing HIV through sexual exposure has not yet been proven, the time for a placebo controlled trial has long since passed. In the west, costly triple-drug regimens for post-exposure prophylaxis for the sexual transmission of HIV have also not yet been assessed formally but are accepted widely. The attraction of receiving the possible benefits of nevirapine in preventing HIV would undoubtedly lead to many more victims of sexual assault in developing countries availing themselves of support services. For this to happen, confirmation of a clear commitment by both government and drug manufacturers to support such a programme is awaited.

Nigel O'Farrell

Pasteur Suite, Ealing Hospital, London UB1 3HW, UK  
(e-mail: ofarrell@postmaster.co.uk)

1 O'Farrell N, Windsor I. Sexual behaviour in HIV-1 seropositive Zulu men and women in Durban, South Africa. *J AIDS* 1991; **4**: 1258–59.

2 Smegmo R. HIV/AIDS—problems, progress, and direction. *South Afr J Epidemiol Infect* 1999; **14**: 90–91.

## Control of legionella in drinking water

Sir—As a representative of the manufacturer of the ionisation system mentioned I feel obliged to respond to the June 17 commentary by Christian Hoebe and Jacob Kool.<sup>1</sup> The ionisation equipment of the European parliament headquarters, Bergmannsheil, Bochum, Germany, was correctly installed by our own engineers, and initially set to give the correct concentrations of silver and copper ions within the hot water circulating loops. The recommended concentrations for effective disinfection were 40 mg/L silver and 400 mg/L copper. Initially, the effect was to kill the high concentrations of legionella bacteria, and to disrupt established biofilm within the water system.

It seems that the outputs of our systems were reduced to comply with the maximum level normally allowed in Germany of 10 g/L silver. Probably because of absorption into debris, silver concentrations had dropped to 5 mg and the copper concentrations only registered the same as the background concentration of copper before the ionisation (Tarn-Pure, High Wycombe, UK) systems had been activated.

The initial correct levels of water treatment had a medium-to-long-term effect, even when the ionisation (Tarn-Pure) systems were running at a very low output. Therefore, we must conclude that this was not a meaningful assessment and it cannot be concluded that there was any build up of resistance to the ionic treatment. The results obtained from our many installations in the USA, Europe, and in the UK clearly indicate the effectiveness of the ionisation systems when operating at the correct concentrations of silver and copper.

The UK Health and Safety Executive regulatory body state that ionisation is effective when operated at silver concentrations of between 20 mg/L and 40 mg/L and copper concentrations of between 0.2 mg/L and 0.4 mg/L.

John Hayes

T P Technology plc, Tarn House, High Wycombe HP12 3HE, UK  
(e-mail: tarnpure@compuserve.com).

1 Hoebe C, Kool J. Control of legionella in drinking water. *Lancet* 2000; **355**: 2093–94.

## TV and cinema underused in HIV prevention

Sir—The statement “. . . it is now axiomatic that knowledge alone is insufficient for most individuals to change a behaviour that they value” by Basil Donovan and Michael Ross (May 27, p 1897)<sup>1</sup> is the typical excuse made by many for not carrying out even a basic education campaign for HIV and AIDS prevention. In particular, television and cinema, the most popular entertainment media for growing children and young people, remain very much underused nearly all over the world.

The regular broadcasting of short dramas or songs with visual scenes of 30 s to a few minutes long to educate people about issues surrounding HIV and AIDS, particularly about safe-sex, could make the issues topics of conversation and thus reinforce changes in behaviour of people in the required direction. Such education is particularly important in developing countries, where much extra-marital sex takes place with prostitutes.

With the assistance of the Nepal Medical Association, I helped to

produce a short drama of 52 s about HIV transmission, which was then broadcast on television and in the cinema in October, 1999.<sup>2</sup> However, we are facing many difficulties in getting the support of bureaucrats for regular broadcasting in television because there is no other short film being regularly broadcast.

I feel that unless, and until, international experts and organisations, such as WHO and United Nations AIDS (UNAIDS) vigorously promote the full use of television and cinema in education campaigns against HIV transmission, local governments and bureaucrats, particularly in the developing countries, will not accept the importance of these media. Repeatedly highlighting limited knowledge as the block to changing behaviour, without experts simultaneously pointing out, in international medical journals, the need to carry out basic education campaigns against HIV transmission, is further adding to the inaction. In this way, children and adults alike are sadly denied their right to know about basic facts concerning their life and death.

Lord protect us from failing in our duty by remaining preoccupied in scientific discussion and proof, or in bureaucratic mesh!

Madhur D Bhattarai

Department of Medicine, Bir Hospital,  
PO Box 3245, Kathmandu, Nepal  
(e-mail: mdb@mos.com.np)

- 1 Donovan B, Ross MW. Preventing HIV: determinants of sexual behaviour. *Lancet* 2000; **355**: 1897–901.
- 2 Drama against HIV/AIDS. *Nep Med Assoc Newsletter* 1999; **1**: 1–3.

## A guide to patient-led good controlled trials

Sir—In your June 24 editorial<sup>1</sup> you note that industry is increasingly using questionable methods to persuade investigators and patients to help it pursue commercial agendas. Such alliances undoubtedly sometimes result in shareholders and patients being better off; they are also one of the most powerful distorting influences on a clinical research agenda which is already failing to meet many of the needs of consumers of research. The costs to the public of this distorted agenda are an outpouring of studies addressing trivial questions,<sup>2</sup> and reduced capacity to do studies which, although of no commercial interest, are of great relevance to the needs of patients and health services.<sup>3</sup>

Among the various actors in this scenario, patients are likely to have the

most unconflicted vested interests in promoting important trials. Recognising this, some consumer groups are working in partnership with researchers to promote participation in trials. For example, Action on Pre-eclampsia—a consumer group—is one of the partners promoting research to assess the effects of magnesium sulphate on severe pre-eclampsia, a potentially useful treatment, of no commercial interest.

Now that an international meta-register of controlled trials has been established ([www.controlled-trials.org](http://www.controlled-trials.org) accessed, Aug 9, 2000), the framework exists for creating a consumer-led, electronic good controlled trials guide, to help people who are considering participating in trials to make well-informed choices. Consumer commentaries on trials in the register could cover, for example, the importance of the questions being addressed, whether these had already been answered satisfactorily by previous research, whether the design of the study was scientifically and ethically robust, whether the primary outcomes chosen mattered to patients, and whether arrangements were in place for communicating the results of the research to those who had participated in it. Mobilisation of consumer influence in this way might help to reorientate the clinical research agenda to serve the interests of patients better, just as Sheila Kitzinger's good birth guide,<sup>4</sup> for example, helped to make British maternity hospitals more aware of the public image of the care each of them was providing.

Researchers and research sponsors will need to realise that one of the preconditions for consumer endorsement of and partnership in their trials is likely to be that protocols and other trial documents should be made public. Researchers—commercial or non-commercial—who wish to compete successfully for the attention of potential partners must therefore be prepared to be far more open about their activities than they have been in the past.<sup>5</sup>

Iain Chalmers

UK Cochrane Centre, NHS R&D Programme,  
Oxford OX2 7LG, UK

- 1 Editorial. Safeguarding participants in clinical trials. *Lancet* 2000; **355**: 2177.
- 2 Soares K, McGrath J, Adams C. Evidence and tardive dyskinesia. *Lancet* 1996; **347**: 1696–97.
- 3 Warlow C, Sandercock P, Dennis M, Wardlaw J. Research funding. *Lancet* 1999; **353**: 1626.
- 4 Kitzinger S. The new good birth guide. Harmondsworth: Penguin, 1983.
- 5 Sykes R. Being a modern pharmaceutical company: involves making information available on clinical trial programmes. *BMJ* 1998; **317**: 1172.

## A US health economist's view of the NHS

Sir—Part of the review of *In pursuit of an improving National Health Service*, by Walter Holland and Alexander Macara (July 1, p 79),<sup>1</sup> reads rather oddly. They state that a two-tier health system is counter to basic British beliefs in solidarity. But surely in Britain there obviously are two tiers, namely the NHS and the private sector. Holland and Macara say that a two-tier health system is the accepted norm in the USA. On the contrary, almost without exception, only one tier exists, and it is the private sector. Health care is decentralised, provided by independent physicians and hospitals, no doubt given according to medical necessity, and in emergencies is not limited to those able to pay. However, most healthcare, but not all, is paid for by the patient's medical insurance policy.

This provision of services to those able to pay for them appears to correspond with one solution to the dilemma mentioned by Holland and Macara. The hospitals in small towns, typically founded by a church, and the teaching hospitals in large towns, publicly funded by states, counties, or cities, and even the large Veterans Administration medical system, are coming to depend more and more on the collection of medical insurance from patients who carry it.

Brian Potter

1100 Surf Road, Unit 110, West Palm Beach,  
FL 33404, USA

- 1 Holland W, Macara A. A critical analysis of a US health economist's view of the National Health Service. *Lancet* 2000; **356**: 79–80.

## DEPARTMENT OF ERROR

*New predictions for total vCJD mortality lower than before*—In this News item by Dorothy Bonn (Aug 12, p 570), the final sentence should be “These results are not incompatible with the predictions of Ferguson's group”.

*Trends in breast cancer incidence, survival, and mortality*—In this Correspondence letter by Michel P Coleman (Aug 13, p 590), the fifth sentence of the fourth paragraph on page 590 should be “the more marked improvements in 5-year survival also indicates the influence of more effective treatment”. The acknowledgment should be, “We thank Bianca De Stavols, Susan Harris, Mike Quinn, and Andy Sloggett for help and advice in preparing this letter”. The authorship should be “Michel Coleman, Penny Babb, Diane Stockton, David Forman, Henrik Møller”. The author affiliations should be “Cancer and Public Health Unit, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK; Demography and Health Division, Office for National Statistics, London; Scottish Cancer Intelligence Unit, Information and Statistics Division, Edinburgh; Northern and Yorkshire Cancer Registry, Leeds; and Thames Cancer Registry, London”.