Management of puffer fish poisoning

Sir,—I was interested in the recent review article on animal toxins by Karalliedde [1]. In Hong Kong puffer fish poisoning occurs sporadically. The most important management is early intubation and assisted ventilation for cases with respiratory failure and circulatory support, with fluid and inotropes for hypotensive patients. Although there is no specific antidote for the tetrodotoxin, certain measures may also be useful in the treatment of such poisoning. Removal of unabsorbed toxin by gastric lavage with 2% sodium bicarbonate is useful as tetrodotoxin is less stable in an alkaline solution [2]. Anticholinesterases drugs such as edrophonium and neostigmine, especially if given early in these poisoning, have been effective in reversing the muscle weakness and hastening spontaneous recovery [3–7]. Cysteine, by opening sodium channels, has been used to antagonize the blocking effect of tetrodotoxin on nerve conduction [2, 8]. However, the roles of anticholinesterases and cysteine in the management of puffer fish poisoning remain uncertain [9, 10] and more clinical studies are required to confirm their therapeutic efficacy.

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Sir,—Tetrodotoxin (TTX) causes interruption of neuromuscular transmission at the motor axons and the muscle membranes. Although during partial block it is possible to elicit brief tetanic contraction by increasing the frequency of stimulation, or eliciting a contraction by perfusing acetylcholine into the arterial supply of muscle, when TTX produces a complete block neither has any effect. Neostigmine and edrophonium do not antagonize the block [1, 2].

The apparent benefit of anticholinesterases observed by some workers would have been in situations of partial block, and obviously therefore clinical results have been conflicting [3]. However, as there is no specific antidote, any therapeutic measure that brings about improvement may be attempted. Anticholinesterases have no effect on the other systems affected by TTX. It was beyond the scope of the review to discuss in detail all forms of therapy that have been found to be of benefit empirically.

If one were to speculate, aminopyridine may be more effective in situations of partial block.

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Tramadol

Sir,—Following the editorial on tramadol by Eggers and Power [1], I wish to comment on their mention of the paper by Lehmann, Horrichs and Hoeckle [2] in which 65% of the patients receiving tramadol were aware of music played during operation compared with patients in the placebo group, all of whom were amnestic.

During extensive use of tramadol for the relief of pain after surgery over the past few years, I have not found any incidence of recall in any patient treated. These patient have received either remant anaesthesia supplemented with a volatile agent and IPPV, or volatile agent breathing spontaneously. In all cases tramadol was given either at induction in addition to the perioperative and postoperative periods or only in the perioperative period.

Because of our awareness of the article by Lehmann, Horrichs and Hoeckle [2], we have been particularly careful to assess any recall of operative events. We have had no incidences of recall and the dose of tramadol used varied between 2 and 800 mg in more than 600 patients undergoing a variety of operative interventions.

A recent report from South Africa (Coetzee, personal communication) has failed to reproduce the findings of Lehmann, Horrichs and Hoeckle and I feel that these must be brought into question, and before the drug is labelled as problematic because of this potential adverse event, the study of Lehmann, Horrichs and Hoeckle should be reproduced.

K. BUDD
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Sir,—We thank Dr Budd for his interest in our editorial and for the new information he has given on the use of tramadol; we hope that this study will be published soon as it may well challenge the findings of Lehmann, Horrichs and Hoeckle that tramadol used during general anaesthesia can enhance intraoperative recall [1]. The personal communication from “Coetzee” referred to by Dr Budd also interests us and we trust that this will also appear in the literature soon.

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L. KARALLIEDDE
Queen Elizabeth Military Hospital
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Sir,—We wish to comment on the editorial on tramadol [1].

(1) Intraoperative use. It is stated incorrectly that tramadol “is not licensed for intraoperative use”. In fact there is nothing within the terms of the UK product licence to preclude such use, however, the data sheet does include a precaution pointing out that in one study Zydol was reported to enhance intraoperative recall. This study is unconfirmed and it is likely that recall occurred because of the anaesthetic technique used in this particular study, which does not reflect current anaesthetic practice.

Further, despite extensive perioperative clinical use in other countries such as Germany (where it has been on the market for 18 yr), there have been no spontaneous reports of recall.

(2) Nausea. The authors say “…tramadol has a significant incidence of nausea of 30–35%…” and support the statement with two references [2, 3]. Unfortunately, their comment does not give the full picture, and it is clearly important to consider the rate of side effects of comparative agents in these studies. In the study of Vickers and colleagues [2], nausea occurred in 30% of tramadol patients, but in the control (pethidine) group, it occurred in 40% of patients; in the second study quoted [3], nausea was 35% with both tramadol and ketorolac, but 45% in the group treated with metamizole.

In other studies there has either been no statistically significant difference in the rates of nausea between tramadol and other opioids [4, 5] or in some cases it has been reduced (e.g. tramadol 14% vs morphine 22%) [6]. It is therefore fair to state that the rates of nausea are similar when tramadol and opioids are used as comparative agents.

We therefore believe that the clinical data as a whole do not support the authors’ conclusions that nausea and intraoperative awareness “represent significant disadvantages of tramadol”. We also do not understand the authors’ final comment “Further clinical studies are required to determine the role of tramadol for relief of acute postoperative pain”. This statement seems to contradict an earlier one (“Tramadol has now been used extensively and evaluated over the past 17 yr”) which provided a reference [7] which discussed eight published studies in postoperative pain. Several other studies are discussed in a subsequent review [8] and a further large study has been published recently [4]. We therefore consider that there is an extensive database showing the benefits of tramadol in acute postoperative pain.

G. C. FENN
Medical Department
Searle
High Wycombe, Bucks
S. RATCLIFFE
International Medical Department
Grunenthal

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Post traumatic stress disorders
Sir,—I wish to report three cases of post traumatic stress disorders (PTSD) associated with anaesthesia which I have collected, where in two cases the patient was not paralysed and in the third not anaesthetized.

Patient No. 1, a 54-yr-old Caucasian male, was anaesthetized for plastic surgery to both hands with fentanyl 1 μg kg⁻¹, followed by propofol 2 mg kg⁻¹. Enflurane up to 2% and nitrous oxide in oxygen was given using a laryngeal mask which may have been inserted incorrectly. The masks are incompatible with ventilation, resulting in the return of consciousness. He felt pain more severe than he had ever experienced and could not attract attention, being unable to speak. Eventually a nurse noticed his open eyes and he was re-anaesthetized. He cannot time the event because of its horrendous nature. The stress of the awareness and pain resulted in the development of an extremely severe PTSD, diagnosed by a consultant psychiatrist and lasting for 5 yr.

The second patient was a 45-yr-old Caucasian woman who awoke during a vaginal repair operation. She was “anaesthetized” with fentanyl 200 μg, propofol 200 μg and enflurane, and had a laryngeal mask inserted, breathing enflurane from a circle system. When she awoke she tried to speak to stop the surgeon. She developed a severe stress disorder, diagnosed by a consultant psychiatrist, lasting for 4 yr.

The third patient, a 40-yr-old Caucasian woman, received lignocaine anaesthetic infiltration for avulsion of small varicose veins. When the surgeon started she felt severe pain and was unable to speak. When she was able to tell the surgeon that she
we emphasize that when a block is complete, patients do not need sedatives or analgesics.

Sir,—While agreeing with much in the comparative study of vigilance and time keeping reported in a recent issue [1], we should state that the authors’ generally negative conclusions towards the Arkive automated anaesthesia record keeping system (AARK) neither reflect our experience nor their own experiment. Their study does not test the state-of-the-art of these systems, which have continued to evolve far beyond the early production version they examined, and they present no data to support the assertion of “inadequate design” in the Arkive Organizer (Arkive Information Systems Inc., San Diego, CA, USA). Perhaps our difference in enthusiasm can be explained by our department’s more committed approach and by the use of advanced features in the Arkive system not available when the study was performed more than 3 yr ago.

In 1992 we switched overnight to exclusive implementation of the Arkive AARK in a 30-room operating suite. Of the 70 000 cases performed since then, only a handful have been recorded manually. Several features in our system differ from those of the authors and probably contribute to its enhanced usefulness. Our system is fully networked from a central fileserver which allows patient data to be downloaded every day from the hospital information system. Combined with the use of case templates, in which standard text notes for anaesthesia events are pre-written, these two modifications reduce the need for users to type, saving record keeping time considerably. We also defend the use of the touch screen, soft keyboard interface, awkward as it is. These units have performed reliably in the hostile operating room environment and are far less vulnerable than a loose keyboard. Our 57 units have amassed 195 “screen-years” of continuous use, with only seven replacements. Few of our users are expert touch typists and, as any computer user knows, a keyboard physically searated from its screen can be an ergonomic nightmare.

Last year we surveyed all 105 users of our system [2] and 87% of responders would not return to a manual record. This value included CRNAs and faculty, with many years of experience with manual records, which are still kept routinely at remote sites in the hospital. Interestingly, CRNAs and residents indicated a higher acceptance of the system than faculty, who tend to have a lower level of expertise. We agree with the authors’ observation that vigilance does not differ significantly from a manual record, but our survey revealed a definite preference for automated recording for difficult cases and in emergency situations.

Finally, all opinions on the interactive efficacy of these systems disregard their most valuable feature, compilation of a database. Under pressure to reduce anaesthetic cost, we have combined database analysis and departmental practice guidelines to reduce our drug cost per case from $78 to $34 over the past year, yielding projected savings of about $1.1 m. Utilizing a series of custom tools, we are optimizing the use of our system for clinical research, gaining time and cost-savings in the process. Studies which would take months of combine through hospital records can now be completed in a matter of days.

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Sir,—Although I agree with Pälve and colleagues’ suggestion that the maximum recommended doses of lignocaine and hence other local anaesthetics should be re-evaluated [1], I wish to make the following points.

The commonest cause of local anaesthetic toxicity is inadvertent i.v. injection of the agent, where maximum recommended doses are irrelevant. It is also worth nothing that the site of vascular entry is important, for example 100 mg of lignocaine injected into the vertebral artery is equivalent to 3 g injected into a peripheral vein, in terms of amount of drug reaching the brain [2]. However, although toxicity resulting from overdose of local anaesthetic is less common, it can still occur. The authors suggest that maximum doses should be revised to incorporate route of administration, which affects plasma concentrations. In addition, it should be remembered that although adrenaline reduces peak concentrations of the agent in blood, the degree of reduction depends not only on the specific local anaesthetic, but also on the site of injection.

Adrenaline 1 : 200 000 decreases the peak plasma concentration by 20–30% after intercostal, extradural or brachial plexus blocks, but by 50% after s.c. infiltration [3]. Therefore, recommended maximum doses of local anaesthetic should be revised to incorporate route of injection and addition of adrenaline.

However, clearly there are ethical problems in performing studies to obtain these types of data.

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Sir,—Dr Grange shares our view that the maximum recommended doses should be revised to incorporate both site of injection and addition of adrenaline. However, we do not find these further studies necessarily unethical. We have to bear in mind that there are a large number of incomplete blocks where additional blocks are required and it is unethical to perform surgery when there is pain or discomfort. These studies will inevitably benefit both patients and anaesthetists. Furthermore, we have seen 10 patients with PTSD resulting from severe pain where local and conduction anaesthesia have failed. These patients suffered intense pain before their plight was recognized.

The association of laryngeal masks with the two cases of general anaesthesia indicates that speech may be impossible when the laryngeal mask is used. All patients who are severely stressed in relation to anaesthesia, whether local or general, should be seen by an anaesthetist with experience of stress disorders and will usually require counselling and psychiatric assessment [1].

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Maximum doses of local anaesthetics


Sir,—We thank Drs Sanderson, Coleman, Lubarsky and Reves for their letter regarding our recent publication on automatic intraoperative anaesthesia record keeping [1]. Apparently, this group thinks that we are opposed to new technology. On the contrary, we are supportive of new and useful patient monitoring technology. This fact is evidenced throughout our three intraoperative time studies [1–3] and in our commitment to install a first-generation automatic anaesthesia record keeper (AARK) (Arkive Organizer, Diateck Corp., San Diego, CA, USA) at the Ohio State University Hospitals in 1987 and make it the standard record keeping modality for the anaesthetist in the operating room. We were one of the first groups to recognize the importance of, this technology as a way to improve anaesthetist vigilance. In the late 1970s and early 1980s, we developed and tested our own AARK at a time when only a handful of institutions were investing resources in this direction.

The purpose of our study was to establish the strengths and weaknesses of automatic anaesthesia record keeping technology as implemented in our AARK. We expect that a manufacturer would take information from studies such as this into account when they are designing the next generation of machines. Anaesthetist vigilance and patient safety are likely to improve in the process. Our comments in the article were based on data extracted painstakingly from some 180 h of videotape and from frank discussions with enthusiastic AARK users. It appears that our observations about our AARK are, for the most part, in concordance with those of the Duke group. The small touch screen keyboard of the AARK was found to be awkward, as we both pointed out, and this added a substantial ergonomic overhead to record keeping time. We agree that networking the AARK with the hospital’s information system and using pre-configured case templates could potentially reduce intraoperative record keeping time for the anaesthetist. This time would ideally be reallocated to direct or indirect patient monitoring. These observations and comments are clearly stated in our discussion.

We are encouraged to learn of the success that Duke University has had with their newer Arkive AARK and look forward to reading their report. We hope that Duke University presents quantitative data in their report that will allow readers to objectively compare our original Arkive AARK model with their state-of-the-art machine.

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Use of the lighted stylet for tracheal intubation via the laryngeal mask airway

Sir,—Tracheal intubation via the laryngeal mask airway has been used successfully in patients with difficult airways [1, 2], and several methods have been reported [1–4]. Passing a fiberoptic bronchoscope through the laryngeal mask under direct vision is the most reliable method for tracheal intubation through the mask [1, 3]. The fibrescope, however, is not always readily available.

Alternatively, a gum elastic bougie can be inserted through the laryngeal mask into the trachea [2]. Entry of the bougie into the trachea can be confirmed both by a “clicking” sensation during advance of the top of the bougie over the tracheal cartilages and by “hold up” of the bougie at the carina [5]. However, it may be difficult to locate the laryngeal inlet with a bougie. The success rate of insertion of a Cook exchanger through the laryngeal mask into the trachea was very low (30%) [4].

There have been no reports of the use of a lighted stylet for tracheal intubation through the laryngeal mask. In theory this could have some advantages over a gum elastic bougie. The position of the tip of the lighted stylet can be detected by observing the transillumination of the neck when only a handful of institutions were investing resources in this direction. It should therefore be possible to detect deviation of the tip of the stylet and also inadvertent entry of the stylet into the oesophagus. Furthermore, entry of the stylet into the trachea can be confirmed reliably by transillumination of tissues over the larynx and trachea [6] and disappearance of the light under the sternum. It should therefore be easier and faster to locate the laryngeal inlet with a lighted stylet than with a bougie.

We have found that the Trachlight (Laedal Medical Corporation, NY, USA) is suitable for tracheal intubation through the laryngeal mask (fig. 1). The Trachlight has a long wand (about 35 cm in length) and the inner malleable metal stylet can be withdrawn. The inner stylet is partially withdrawn and the wand is curved (below).

Figure 1 The Trachlight (Laedal Medical Corporation) has a long wand and an inner malleable metal stylet can be withdrawn. The inner stylet is partially withdrawn and the wand is curved (below).

Correspondence
place correctly in this case. In no patient did arterial haemoglobin oxygen saturation decrease to less than 97%.

The Trachlight was passed easily into the larynx with minimal difficulty in most patients. However, the position of the wand was not confirmed with a bronchoscope. No attempt was made to pass a tube over the Trachlight into the trachea. We have shown that tracheal intubation through the laryngeal mask over a fibreoptic bronchoscope is usually very easy [7, 8]. Thus we feel that tracheal intubation through the laryngeal mask over the Trachlight into the trachea should also be easy.

One of the advantages of the use of the lighted stylet over other styles is that it is easier to assess the position of the tip of the stylet during insertion by observing the transillumination in the neck. Thus any lateral or posterior deviation of the stylet from the laryngeal inlet can be detected and the position of the stylet adjusted. We believe that when a fibreoptic bronchoscope is not readily available, the use of a lighted stylet may be a better option than the use of a gum elastic bougie.

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**Convective warming after hypothermic cardiopulmonary bypass**

Sir,—Despite results which showed that convective warming blankets resulted in significantly improved warming of peripheral tissues after hypothermic cardiopulmonary bypass (CPB), Moors and colleagues [1] concluded that they “failed to demonstrate the effectiveness of convective warming blankets” in this situation. This conclusion is based on the observation that, in those patients allocated randomly to receive postoperative convective warming, there was no reduction in the time taken to reach core normothermia. We can only assume that they consider peripheral warming, and therefore augmentation of peripheral perfusion, to be a relatively unimportant goal in the early postoperative management after hypothermic CPB as this factor was improved significantly by the use of convective blankets. Such a belief would be at variance with the widely held view that restoration of peripheral temperature is an important aspect of patient care after hypothermic CPB [2]. Many of the potential benefits of warm tissues in such patients, including lower systemic vascular resistance, less accumulation of metabolic products, improved drug redistribution and improved platelet function, apply as much to peripheral tissues as they do to body core.

In emphasizing the importance of restoration of core temperature after hypothermic CPB, Moors and colleagues mentioned the effect of “the legacy of heat transfer” on “core temperature... and the time to extubation”. The implication is that they believe that more effective methods of warming would be likely to allow earlier extubation. This contradicts the results of their study where the mean times to extubation were almost twice as long as those to reach core normothermia, suggesting that any improvement in the rate of rewarming would be unlikely to affect the time taken to extubation. This, coupled with the ambivalence of the authors towards restoration of peripheral temperature after hypothermic CPB, leaves us wondering why they were interested in assessing the effectiveness of convective warming as it would appear that improved methods of rewarming would be unlikely to affect their practice.

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**Red blood cell substitutes**

Sir,—In her review article on red blood cell substitutes [1], Dr Jones illustrated the theoretical “optimal” oxygen delivery that can be obtained by haemodilution, substantiated by reference to the work of Messmer and colleagues [2], which considers the reduction in viscosity to be important. Recent direct measurement of oxygen uptake in skeletal muscle, during maximal oxygen uptake, suggests that haemodilution can impair oxygen uptake by the tissues [3]. Isovolaemic haemodilution from 15.9 to 13.8 g dl⁻¹ reduced maximum oxygen uptake by 17.7%. About two-thirds of the decrease was because of a reduction in oxygen delivery and one-third was caused by impairment of diffusion of oxygen. This impairment of diffusion may be caused by altered oxygen release from haemoglobin or altered red cell spacing in the capillary. There was no evidence that blood flow was increased by haemodilution.

Although mildly to moderate haemodilution is often clinically convenient and frequently has no discernible effect on outcome, the repeated citation of the simple and perhaps simplistic “delivery-viscosity” argument may be merely justification for these clinical exigencies rather than firm evidence of clinical value. I cannot help thinking that the entire process of oxygen transfer, from air to cell, is perhaps best done with a haemoglobin concentration found naturally, even in the unnatural conditions we often impose in our patients. Although patients may “tolerate” haemodilution without apparent harm, is it wise to expect them to do so? Studies of maximally exercising volunteers can only provide surrogate measures of these clinical events, but as clinical outcome depends on so many other factors, studies such as these may be the best index we may have of the influence of changes such as haemodilution.

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Sir,—Dr Drummond is correct in his first point that the scientific basis for the practice of haemodilution is the work of Messmer and colleagues [1]. It is also true that there is now a large body of clinical evidence that correctly selected patient may be subjected to haemoglobin (Hb) concentrations of 7–10 g dl⁻¹ during surgery without coming to any harm [2].

Dr Drummond’s second point is that until more experimental evidence is forthcoming, it might be safer to keep our patients’ Hb concentrations within the normal range. If Dr Drummond’s suggestion were universally followed, the demand for allogenic
blood for transfusion would increase and, assuming that the
demand could be met easily, exposure of patients to the hazards of
allogenic blood transfusion would increase also.

The article Dr Drummond quotes in support of his view [3] is
an interesting study of maximum oxygen uptake by leg
muscles in conditions of maximal exercise in volunteers. The
subjects had just returned to sea level after an 8-week stay at high
altitude, during which their Hb concentration increased from 13.8
to 15.9 g dl \(^{-1}\). The measurements were made during bouts of
exercise when the subjects breathed 21 % or 12 % oxygen in
random order, and were repeated after the subjects' Hb
concentrations were lowered to pre-altitude values by normovolemic
haemodilution with 5 % albumin. As Dr Drummond says, oxygen
uptake and delivery in the subjects' legs decreased when their Hb
concentrations were returned to normal. These experiments
perhaps provide evidence in support of the successful, but illegal,
practice of "blood doping" in racehorses and long-distance
runners. I do not think they throw any light on oxygen supply to,
or uptake by, vital centres in anaesthetized subjects who are at rest
and breathing oxygen-rich gases. I conclude that the study is
therefore not relevant to the question of the safety of haemoco-
dilution in anaesthetic practice.

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Incidents and critical incidents

Sir,—Dr Jayasuriya suggested omitting the term "critical" when
describing anaesthetic incidents [1]. He suggests that the im-

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Cutaneous heat loss during anaesthesia

Sir,—Anttonen and colleagues [1] quoted our value for the
combined heat exchange coefficient for radiation and convection,
heat [2]. This coefficient implies that the temperature gradient and
the resulting heat exchange are linearly related. However, Anttonen and colleagues claimed that the relationship is not linear but “exponential”. To prevent any confusion, which we feel sure the authors did not intend, this apparent contradiction requires clarification.

The basic equation for any heat exchange mechanism is \( Q = \Delta T \) by that \( h \) = heat exchange coefficient (W m\(^{-2}\)°C\(^{-1}\)) particular to that mechanism; and \( \Delta T = \) temperature gradient appropriate for that mechanism. The combined heat exchange coefficient for radiation and convection \( (h_{RC}) \) contains the first-order heat exchange coefficient for radiation, \( h_{R} \) and the heat exchange coefficient for convection, \( h_{C} \). The appropriate temperature gradient for radiation is skin \( (T_{SK}) \) to radiant temperature \( (T_{R}) \), and for convection, skin to air \( (T_{A}) \).

The convective coefficient, \( h_{C} \) (W m\(^{-2}\)°C\(^{-1}\)), is dependent on the square root of air velocity (8.7 v\(^{0.5} \)), but is independent of its temperature gradient [2]. Therefore, convective heat exchange, \( Q_{C}/A \) (W m\(^{-2}\)) is a linear function of that temperature gradient.

The first-order coefficient for radiation, \( h_{R} \), is dependent on its temperature gradient: \( h_{R} = 5.67E-8 \) (K m\(^{-1}\)°C\(^{-4}\)) (\( T_{SK} - T_{R} \)); where \( K = \) absolute temperature in Kelvin and \( ^{°}T = \) actual temperature (°C) [2]. Despite this, for all practical purposes the heat exchange by radiation, \( Q_{C}/A \), can be considered a linear function of its temperature gradient because the gradients encountered clinically are small.

When there is no radiant heat source, \( T_{A} \) can be considered equal to \( T_{S} \). The total heat exchange \( (Q_{TOT}/A) \) measured by heat flux transducers (HFT) is the sum of the radiative (\( Q_{R}/A \)) and convective \( (Q_{C}/A) \) heat exchanges. Therefore, a plot of \( (T_{SK} - T_{A}) \) against \( Q_{TOT}/A \) gives a relationship with a slope of \( h_{C} \). In our experience, the slope of \( h_{C} \) is linear over \( (T_{SK} - T_{A}) \) gradients of \(+20^\circ C \) to \(-15^\circ C \), and approximates 10 W m\(^{-2}\) °C\(^{-1}\), whether measured in volunteers or models, or from convective air warmer covers or hot water mattresses.

The thermal conditions when collecting data for figure 5, which shows a non-linear relationship between \( (T_{SK} - T_{A}) \) and \( Q_{TOT}/A \), are not given. Clearly, there was a radiant heat load from the OR lights. As the lights were focused on different locations during surgery, it was impossible to define the area which was affected mostly by the lights and we have omitted that part from the article. It is possible that they produced heat gain in some skin areas. Because of the small number of cases, the curve in figure 5 is descriptive and the exponential appearance is not based on statistical calculations.

Pharmacokinetics of ketamine enantiomers

Sir,—In 1993 we reported no statistically significant differences between S-ketamine after administration of the S-form, and S-ketamine after administration of the racemate with respect to pharmacokinetic variables using non-compartmental analysis [1]. However, after racemate administration we observed a smaller clearance and volume of distribution for R-ketamine compared with S-ketamine. As ketamine is a drug that exhibits multi-compartmental pharmacokinetics after i.v. administration, it has been suggested that the differences seen clinically between S-ketamine and the racemate (e.g. prolongation of recovery after racemate administration) might be explained partly by stereoselective differences in redistribution half-lives. We report here the compartmental pharmacokinetics of ketamine based on re-analysis of the previously published data. For detailed “materials and methods” we refer to the original article [1]. Blood was collected before and after 1, 3, 5, 7, 10, 15, 30 and 45 min and at 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 10.0 h after administration of the ketamine bolus (S-ketamine 1 mg kg\(^{-1}\) vs racemate 2 mg kg\(^{-1}\)). Pharmacokinetic variables were calculated using the TOFPIT program [2] with a three-compartment model given by the equation:

\[ C(t) = A e^{-\alpha t} + B e^{-\beta t} + C e^{-\gamma t}\]

where \( t \) = time after administration, \( C(t) \) is the measured plasma concentration at time \( t \), \( A \), \( B \), and \( C \) = coefficients of the exponential term, \( \alpha = \) apparent distribution rate constants, and \( \gamma = \) apparent terminal rate constant. In addition, micro-constant \( (h_{k1a}, h_{k1b}, h_{k2}, h_{k3}) \) were calculated. The goodness of the fitting procedure was evaluated by visual inspection of the fitted curve vs the data and by statistical methods offered by the TOFPIT program package [2]. Mean (SD) values were calculated to express the central tendency of the data. Data were submitted to analysis of variance (ANOVA). Variables of ketamine enantiomers within the racemate group were compared using the paired t-test. The level of significance was set at \( P < 0.05 \).

Statistically significant differences were observed between enantiomers within the racemate group S-ketamine exhibited a larger volume of distribution \( (V_{S}, V_{A}, V_{F}) \) and greater values for the microconstants \( k_{1a} \) and \( k_{2} \). In addition, total clearance was significantly higher for S-ketamine compared with R-ketamine.
There were no statistically significant differences for variables of S-ketamine between the two groups with the exception of the volumes of distribution for the tissues ($V_2$) and deep tissue compartment ($V_3$). The distribution and terminal half-lives, $T_{1/2}$, $T_{21}$, $T_{13}$ did not differ. Detailed pharmacokinetic data are given in table 1.

We conclude that the differences seen clinically between S-ketamine and the racemic compound are not apparently caused by different pharmacokinetic behaviour, for example differences in redistribution half-lives. Thus phenomena such as prolongation of recovery observed after racemic ketamine might be explained by pharmacodynamic interactions of the enantiomers, as previously discussed in detailed by White and colleagues [3].

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Gastric tonometry

Sir,—We write to provide some balance to Fiddian-Green’s extensive review of gastric tonometry [1].

First, to our knowledge there are no published data demonstrating an association between “leaky” gut and gastric intramucosal pH. Only one [2] of the five references quoted examined intestinal permeability. Fink and colleagues showed that in endotoxic pigs, increased intestinal permeability is associated with decreased ileal intramucosal pH determined tonometrically [2].

Second, only one study [3] has demonstrated that “timely therapeutic measures that restore the intramucosal pH to normality and ‘gut-directed’ and ‘pH-directed’ therapies…are associated with improved outcome”. (The other references quoted do not refer to outcome studies.) The investigators demonstrated that in patients with an admission APACHE II score of 15–25 and a normal gastric intramucosal pH (pHi), treatment aimed at restoring pHi to normal, should it fall, was associated with improved hospital survival. However, they provided no data to show that their treatment altered pHi. We have tried to replicate this study in severely ill patients (mean APACHE II score 23) admitted as an emergency to our intensive care unit and have recently analysed preliminary results. These indicate that intervention aimed at correcting pHi was associated with a significantly higher hospital survival than standard therapy but did not alter pHi, compared with standard therapy, suggesting that the improvement in outcome was unrelated to pHi. Indeed, it may not be possible to resuscitate severely ill patients against pHi. In patients with severe sepsis, pHi does not distinguish between survivors and non-survivors in the acute phase (<24 h) [4] and experimental evidence suggests the reliability of gastric tonometers (Tonometrics Inc., Worcester, MA, USA) both in vitro [5] and in vivo (95 % confidence limits at pHi of 7.3 ± 0.12 [unpublished data]) is too low to allow valid decision making.

Third, although we agree that the countercurrent mechanism in the intestinal villi renders the most superficial layer of the mucosa relatively hypoxic, making it “especially sensitive to alterations in the adequacy of tissue oxygenation” we note that there are no villi in the stomach and, to our knowledge, no countercurrent mechanism has been demonstrated in the stomach.

Fourth, we note that Fiddian-Green repeatedly quoted three letters [6–8] to support his contention that pHi is a superior monitor to arterial blood-gas measurement but failed to mention, in this context, the study [9] to which these letters were a response. The authors of this article concluded that the information obtained from gastric tonometry can be obtained more simply from arterial blood-gas analysis.

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intramucosal acidosis, is clearly an unrecognized and major
arterial bicarbonate was less and base deficit and lactate con-
deficit and blood lactate in the two groups. But the final mean
a significant reduction in arterial bicarbonate and increase in base
surface area within or between the two groups studied. There was
eliminated postoperative complications (20 % to 0 %), reduced
outcome [4]. In this study, plasma volume expansion that
incomplete resuscitation, defined as gastric intramucosal acidosis,
Moreover, resuscitative efforts that eliminate the presence of
The study of Maynard and colleagues [2] confirmed these findings.
study addressed the two other explanations for their observations. First, it may take many hours
and even days for the improvement in tissue oxygenation accomplished by successful therapeutic intervention to be ac-
accompanied by a return of gastric intramucosal pH to normality in
patients whose microcirculation is severely damaged. In the case
illustrated in figure 10 of the review, for example, it took some
50 h for gastric intramucosal pH to return to normal after a severely septic patient had been treated successfully by removal of
an infected cadaveric renal transplant. Second, judging from the
95 % confidence limits they report, Gomersall and colleagues have
not established the systems necessary to ensure reliable and
reproducible measurements of gastric intramucosal pH in their
clinical setting. The establishment of such systems may enable them to detect changes in pH within 24 h.
The review referred to “damaged” and “leaky” gut in the same
sentence and that may have been confusing. A gastric intramucosal acidosis is predictive of the presence of gastric mucosal injury
(reference [40] in the review) and a sigmoid intramucosal acidosis of sigmoid mucosal injury in patients (references [36, 89] in
the review). Changes in gastric intramucosal pH occur in parallel with changes in the small and large bowel in shock and resuscitation
(reference [79] in the review) and sigmoid intramucosal pH in patients having abdominal aortic surgery [5]. Changes in en-
dotoxin and cytokine concentrations have been correlated with changes in both locations but, as Gomersall and colleagues point
out, most of the evidence relating to the “leaky gut hypothesis” has been obtained from measurements made in the small intestine
in animal studies. The evidence for the “leaky gut hypothesis” is summarized by Fink in reference [45] cited in the review.
While the countercurrent mechanism in the gut has been demonstrated in the villi of the small intestine, the vascular
anatomy of the stomach is consistent with the presence of a countercurrent exchange mechanism in the stomach. The relative
hypoxia has been reported in the villi of the small intestine (reference [71] in the review) but not in the stomach.
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routine blood-gas analysis and from gastric tonometry for

 Sir,—It would seem that Gomersall and colleagues believe the
case for gastric tonometry was overstated in my review [1]. They appear to base their opinion, in part, on the claim that the information obtained from gastric tonometry can be obtained more simply from arterial blood-gas analysis. Their opinion appears to be based on the article published in the Lancet by Boyd and colleagues (reference [10] in the review). The deficiencies in this misleading article were addressed in the three letters cited in the review, particularly that in the Lancet published by Mythen, Salmon and Webb (reference [84] in the review). It has subsequently been addressed more definitively by Maynard and colleagues [2] and Gutierrez and colleagues [3]. In the article by Maynard and colleagues, receiver operator curves show gastric intramucosal pH being clearly superior at predicting an adverse outcome relative to all systemic indices of the adequacy of tissue oxygenation, including arterial pH, base excess and blood lactate.
In the article by Gutierrez and co-workers, increases in global oxygen delivery induced by dobutamine that caused a dose-related increase in gastric intramucosal pH in patients with gastric intramucosal acidosis, and decrease in blood lactate concentrations in patients with an elevated blood lactate did not change the blood-gas tensions. As illustrated in figure 10 and stated in the review, changes in the systemic metabolic indices of the adequacy of tissue oxygenation reflect the washout of tissue metabolites during resuscitation and in these circumstances are dissociated from the changes in the adequacy of tissue oxygenation determined with the actual and especially the standard gastric intramucosal pH.
Gomersall and colleagues are correct in pointing out that there
was only one prospective randomized study cited (reference [56] in
the review) demonstrating that pH-guided therapy improves outcome. The second outcome study addressed the effect of “gut-directed therapy” as a longitudinal audit (reference [6] in the review). There were other studies cited that have demonstrated the association between the return of a low gastric intramucosal pH to normality and a favourable outcome relative to patients in whom the gastric intramucosal pH either decreased to abnormally low values or could not be returned to normality. The study of Maynard and colleagues [2] confirmed these findings. Moreover, resuscitative efforts that eliminate the presence of incomplete resuscitation, defined as gastric intramucosal acidosis, were shown in a recently published prospective randomized study of patients undergoing elective cardiac surgery to improve outcome [4]. In this study, plasma volume expansion that increased stroke volume to a maximum reduced the incidence of gastric intramucosal acidosis after surgery from 56 % to 7 %, eliminated postoperative complications (20 % to 0 %), reduced ICU stay by 41 % and hospital stay by 37 %. There was no difference in oxygen delivery or oxygen delivery indexed to body surface area within or between the two groups studied. There was a significant reduction in arterial carbamate and increase in base deficit and blood lactate in the two groups. But the final mean arterial bicarbonate was less and base deficit and lactate concentration greater in the control group than in the study group.
Incomplete resuscitation, defined as the presence of gastric intramucosal acidosis, is clearly an unrecognized and major problem in patients undergoing major surgery, and resuscitative measures that eliminate gastric intramucosal acidosis by the end of surgery improve outcome and, by inference from ICU and hospital stay, reduce the costs of care.
Patients undergoing elective major surgery have an intact microcirculation pH and measures that prevent or restore promptly the cause of inadequacy of tissue oxygenation, usually hypo-
volaeemia, can be expected to be accompanied by a prompt return of gastric intramucosal pH to normality. Patients admitted to an ICU are different. Many have been critically ill for an extended period, are splanchnogically and presumably have a severely damaged microcirculation. As mentioned in the review, measures that increase global oxygen delivery have an unpredictable effect on gastric intramucosal pH in these circumstances when assessed in the short term. Gomersall and colleagues confirmed that survival in ICU patients may be improved by resuscitation that arresting gastric intramucosal pH to normality but observed that the improvement in survival was not accompanied by improve-
ment in gastric intramucosal pH at 24 h. There are two other explanations for their observations. First, it may take many hours
and even days for the improvement in tissue oxygenation accomplished by successful therapeutic intervention to be ac-
accompanied by a return of gastric intramucosal pH to normality in
patients whose microcirculation is severely damaged. In the case
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Effect of i.v. diamorphine on regression of spinal block

Sir,—I read with interest the recent article by Henderson and Jones [1] and agree that the effect of i.v. diamorphine on regression of spinal block may find clinical use. However, their logic in using cold sensation rather than pinprick in an attempt to differentiate between sensory level and analgesic level of block may be flawed. Although discrete receptors for the sensations of cold and pinprick exist, the afferent transmission of impulses from both receptors is via Aδ fibres. As the mechanism of spinal anaesthesia is a direct action of local anaesthetic on axons as they pass through the cerebrospinal fluid to enter the spinal cord, one would expect both sensations to be blocked equally. If, as postulated, diamorphine decreases spinal blood flow thus prolonging the duration of block, this would be represented by both sensory and analgesic prolongation in parallel.

Furthermore, as the stimulating temperature decreases, the frequency of afferent impulses from cold receptors decreases and the frequency of afferent impulses from pain receptors increases. At temperatures below 7 °C, all afferent impulses arise from pain receptors and no stimulation of cold receptors occurs [2]. Ethyl chloride spray therefore stimulates the same receptors as pinprick sensation thus negating this as a test for sensory rather than analgesic level of block. Stimulation of opioid receptors at a spinal level modulating onward transmission of afferent impulses from these Aδ fibres must therefore represent a fourth possibility as a mechanism of action for the prolongation of block produced by i.v. diamorphine.

In summary, I believe that it is not possible to differentiate between sensory and analgesic level by the method described.

These considerations do not however detract from the clinical value of the study.

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Sir,—We thank Dr Findlay for his comments. Our study has shown a useful interaction between i.v. diamorphine and regression of spinal block, but we agree that no comment can be made on any effect on sensory rather than analgesic level of block. Certainly it was more pleasant for the patients to be tested with ethyl chloride rather than pinprick. We also note the suggestion of a fourth possibility for the mechanism of interaction.

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