CSF progesterone and spread of subarachnoid analgesia in pregnancy

Sir,—Hirabayashi and colleagues [1] suggested that a sustained (at least 3–4 months) increase in cerebrospinal fluid (CSF) progesterone concentration may be necessary to produce enhanced spread of spinal anaesthesia in pregnant women. We believe that these conclusions are misleading and unsupported by the results.

Maximum cephalad spread of analgesia was quoted as being higher in the second trimester compared with the first, but there were no results of statistical tests that directly compared these two trimesters. Median maximum cephalad spread of analgesia was the same (T4) in the first and second trimesters, and this makes it unlikely, although not impossible, that there was a significant difference between the two groups. The figures do not show all data points, perhaps because overlapping points are not separated, and it was impossible for us to confirm the results.

The CSF progesterone concentration data were also surprising. CSF progesterone concentrations were said to be increased similarly in the early and middle stages of pregnancy. This appeared to form the basis for Hirabayashi and colleagues suggesting that chronic exposure to progesterone increased spread of spinal anaesthesia (assuming that there really is increased spread in the second trimester compared with the first). However, the results stated that there was no significant increase in CSF progesterone concentration during early and middle pregnancy compared with the control group. The CSF progesterone concentration data were further complicated by the larger number of patients with undetectable progesterone, even at term gestation. Other studies have detected CSF progesterone concentrations in all patients [2, 3], with mean concentrations at term gestation approximately double those reported by Hirabayashi and colleagues.

Given the wide variation in both the CSF progesterone concentration and the spread of spinal anaesthesia, we are not convinced that a meaningful association can be made between chronic exposure to progesterone and increased spread of analgesia. The study design certainly does not permit one to conclude that progesterone may be a causative factor.

The suggestion that chronic exposure to progesterone may be necessary for increased sensitivity of nerves to local anaesthetics was derived from a series of in vitro studies using rabbit vagus nerves [4]. However, the same research group has recently reported that bupivacaine conduction block of B and C fibres in nerves [5]. The results may be caused by increased diffusion of bupivacaine through the nerve sheath rather than a direct action on the nerve itself. Therefore, the effect of progesterone on nerve block after intrathecal administration of local anaesthetics remains uncertain.

Hirabayashi and colleagues quickly dismissed mechanical factors as a possible cause for increased spread of spinal anaesthesia in the second trimester, but did not provide supporting evidence. Anatomically, the gravid uterus is first palpable above the pubic symphysis at 12 weeks’ gestation. By 16 weeks’ gestation, the uterus extends above the sacral promontory where the inferior vena cava usually bifurcates [6]. Cervical compression may occur in early pregnancy. When pregnant women of 13–16 weeks’ gestation were placed supine, direct femoral venous pressure measurements increased by 50% [7]. It is thus possible that a progressive increase in caval compression throughout pregnancy may contribute to a progressive increase in the spread of spinal anaesthesia.

Although not specifically stated in the article, we wonder if data from some of the patients in this study have been reported previously [8]. In that article, it was also concluded that maximum cephalad spread of analgesia was higher in the second trimester compared with the first trimester. Again, there were no statistics provided that directly compared the two trimesters.

By arguing that spread of sensory block in the second trimester increases that to the first trimester but similar to that at term, the authors have implied in both reports that there is a cut-off point in the second trimester where spread of sensory block increases. Given the progressive nature of pregnancy and artificial division of gestation into trimesters, it may be just as likely that there is a gradual increase in spread of sensory block from the non-pregnant state to term gestation, whatever the cause(s).

We also suggest that there may be bias in the conclusion that CSF progesterone concentrations were greater in twin pregnancies compared with singleton pregnancies in the third trimester. Figure 1 shows that in the third trimester group (25–36 weeks), at least four of the singleton pregnancies were between 25 and 27 weeks, while none of the twin pregnancies was less than 32 weeks. There is an inconsistency between table 1, which lists the smallest weight in the second trimester group as 50 kg, and table 2, where the corresponding minimum weight is 40 kg.

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SIR,—In our study, we found a small, non-significant increase in CSF progesterone concentration in the first trimester and second trimester groups. In addition, we found higher cephalad spread of analgesia in the second trimester group compared with the non-pregnant group. Cephalad spread of analgesia in the first trimester group was similar to that of the non-pregnant group. From this we concluded that not only a minimum concentration of progesterone in CSF but also a particular duration of exposure to elevated CSF progesterone concentrations may be necessary for enhancement of spread of spinal analgesia. I studied the report of Lambert and colleagues [1] and understood that the effect of pregnancy on neural block observed in their earlier studies [2, 3] may be caused by increased diffusion of bupivacaine through the nerve sheath and not a direct effect on the nerve itself. Both CSF progesterone concentration and spread of spinal analgesia show a wide variation in clinical practice. Consequently, I also understand that further studies are needed to draw final conclusions on the direct involvement of progesterone with pregnancy-induced enhancement of spinal analgesia.

Because unfortunately we did not measure plasma progesterone...
concentration simultaneously in our study, we cannot determine the reason why there are some disparities in CSF progesterone concentration between previously reported studies and ours. I suggest that racial differences might contribute to the disparities. By 20 weeks of pregnancy the uterus is spherical, and thereafter becomes more and more elongated as the conceptus is converted from spheroid of cylindrical form [4]. At 16 weeks, the fundus of the uterus rises to approximately half of the distance between the symphysis and the umbilicus, and it is at the umbilicus by 20 weeks [5]. The spherical uterus may occupy a considerably space in the pelvic cavity and may increase femoral venous pressure. However, it remains uncertain if this increase in femoral venous pressure is accompanied by engorgement of the extralud venous plexus. Many patients with gynaecological tumours have an increased femoral venous pressure comparable in magnitude with that seen in the latter months of pregnancy [6]. However, to our knowledge, there are no studies which demonstrate that such patients usually show higher spread of spinal anaesthesia compared with patients without gynaecological tumours. I suggest that the inferior vena cava, which is formed on the right side of the 5th lumbar vertebra by the junction of the two common iliac veins [7, 8], may not be compressed by the spheroidal uterus. Nevertheless, because there are no studies which have determined when the enlarged pregnant uterus begins to compress the inferior vena cava and engorge the extralud venous plexus [9], further studies focusing on this issue should be performed.

We reported previously on the spread of subarachnoid hyperbaric amethocaine in pregnant women [10]. In that report, we collected data on the spread of sensory block from 90 patients. We anaesthesitized these patients with amethocaine 8 mg, but did not collect any CSF. The patients in our previous study differed from the 134 patients in the present study in which 1 ml of CSF was withdrawn just before administration of amethocaine 8 mg. Both the methodology and patients examined in these two studies were different.

I agree with the suggestion that artificial division of pregnancy into trimesters is not possible for evaluation of pregnancy-induced enhancement of spread of spinal anaesthesia which may increase gradually. However, I believe that this division of pregnancy into trimesters, which is standard practice in prenatal care, provides useful information in clinical management of spinal anaesthesia. Pregnancy during the first trimester does not affect spread of spinal anaesthesia, while pregnancy during the second trimester until term enhances it. What is required is to determine when enhancement begins to develop, especially in the second trimester of pregnancy.

We had compared CSF progesterone concentrations in 40 twin pregnancies (median 36 (range 12–38) weeks of pregnancy) with those in 81 singleton pregnancies (37 (8–41) weeks of pregnancy), when we analysed the data in the present study. The results confirmed that CSF progesterone concentrations were greater in those in 81 singleton pregnancies (37 (8–41) weeks of pregnancy), further studies indicated that the data being described are accurate, and that all relevant financial interests and potential conflicts be addressed. As Dr Saidman stated “the overriding opinion is that the commonly used high fresh gas flows. The safety of sevoflurane in low-flow anaesthesia remains to be established.

In the discussion regarding the renal toxicity of compound A, the authors mentioned a conflict of interest in a previous study [5] and the effect this may have on objective validity [6]. The source of research funding, and the possible effect on bias and integrity, are important issues that should always be declared. In contrast, the authors failed to acknowledge their own previous involvement with Abbott Laboratories [7]. This clearly represents a similar conflict of interest to the one they highlighted. Omission of this fact from the article represents a considerable oversight that must be addressed. As Dr Saidman stated “the overriding opinion is that all relevant financial interests and potential conflicts be disclosed, which at a minimum allows the audience, be it the readership of a journal or those attending a lecture, to judge themselves whether the data being described are accurate, and that the conclusions and recommendations are fairly stated” [6].

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Sevoflurane

Sir,—I read with interest the recent review article on sevoflurane [1]. There are, however, two points that were inadequately considered.

The section on renal toxicity was largely limited to the effects of increased serum fluoride concentrations the potential for renal toxicity caused by renal tubular damage after production of compound A was questioned [1]. The authors failed to highlight that the clinical studies to date, although without reports of nephrotoxicity, have largely examined indices of glomerular function [2, 3]. The functional reserve of the kidney protects renal toxicity being detected, except in circumstances of severe injury. Studies that have attempted to assess tubular damage have used relatively high fresh gas flows, thereby limiting production of compound A [4]. This also reflects the difficulty in accepting the large clinical experience gained with sevoflurane in Japan, because of the commonly used high fresh gas flows. The safety of sevoflurane in low-flow anaesthesia remains to be established.

In the discussion regarding the renal toxicity of compound A, the authors mentioned a conflict of interest in a previous study [5] and the effect this may have on objective validity [6]. The source of research funding, and the possible effect on bias and integrity, are important issues that should always be declared. In contrast, the authors failed to acknowledge their own previous involvement with Abbott Laboratories [7]. This clearly represents a similar conflict of interest to the one they highlighted. Omission of this fact from the article represents a considerable oversight that must be addressed. As Dr Saidman stated “the overriding opinion is that all relevant financial interests and potential conflicts be disclosed, which at a minimum allows the audience, be it the readership of a journal or those attending a lecture, to judge themselves whether the data being described are accurate, and that the conclusions and recommendations are fairly stated” [6].

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Sir,—Thank you for allowing us to respond to Dr Daniel. Our section on renal toxicity was primarily directed towards elevated serum fluoride concentrations because human nephrotoxicity has occurred previously with methoxyflurane. Until relatively recently, toxicity was believed to be an inevitable consequence of exceeding a “threshold” serum fluoride concentration. As concentrations in excess of 50 μmol litre⁻¹ are not infrequently produced by exposure to clinically relevant concentrations of sevoflurane, it was necessary to examine the evidence for fluoride-related nephrotoxicity with sevoflurane. It was partly the lack of such toxicity which has led to an increased understanding of the relationship between fluoride-producing anesthetics and renal damage.

In contrast, it is not known if compound A is nephrotoxic to humans or, if it is, by what mechanism or at what concentrations. In the rat, compound A is nephrotoxic. The LD₅₀ is approximately 1000 ppm, although histological signs of tubular damage are seen in rats exposed to concentrations of 50 ppm or more of compound A. It is not yet clear what is the natural history of these lesions in rats. Of greater importance, it is by no means certain that compound A is as toxic to humans as it is to rats. Recent evidence from Kharasch’s group [1] suggests that compound A has to undergo further metabolism to produce nephrotoxicity. The pathway by which this occurs is approximately 10 times more active in rodents compared with humans, suggesting that compound A may indeed be substantially less harmful to humans [1]. This is supported by the absence to date of any signs of renal dysfunction (tubular or glomerular) in humans exposed to sevoflurane under a wide range of clinical conditions. A recent Japanese study showed no evidence of renal or hepatic toxicity after 13 MAC-h of anaesthesia in 50 patients exposed to sevoflurane at a total flow rate 1 litre min⁻¹ [2]. Rather than “limiting compound A production”, this regimen produced a mean level of 24.6 ppm (range 13.6–41.3 ppm). Nevertheless, “limiting compound A production”, this regimen produced a mean level of 24.6 ppm (range 13.6–41.3 ppm). Nevertheless, postoperative indices of hepatic and renal function did not differ from those of control patients in propofol and isoflurane groups [3]. Finally, the Committee on Safety of Medicines has reviewed published data on sevoflurane and data on file with the manufacturer, Pharmacia (the manufacturers and distributors of desflurane) for studies with products which could be considered commercial “rivals” to sevoflurane. For these reasons, we did not mention our studies with sevoflurane in low-flow anaesthesia.

Sir,—We read with interest the article by Morris and Marjot demonstrating that laryngeal mask airway (LMA) cuff pressures can be reduced to 22 mm Hg without significantly affecting tidal ventilation in spontaneously breathing anaesthetized patients [1]. While agreeing that reducing intracuff pressure may minimize pharyngeal morbidity, we suggest that perioperative cuff deflation to such low pressures may be potentially hazardous.

A major function of the LMA cuff during spontaneous breathing is to protect the larynx from oropharyngeal saliva. To perform this function an oropharyngeal leak pressure of up to 10 cm H₂O may be required (the approximate pressure of fluid at the larynx during swallowing is 10 cm H₂O). Cuff deflation below 10 cm H₂O would result in a significant increase in laryngeal morbidity. We also suggest that cuff deflation may result in significant respiratory depression. In patients with respiratory depression, cuff deflation below 10 cm H₂O would result in a significant increase in laryngeal morbidity. We also suggest that cuff deflation may result in significant respiratory depression.

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Removal of extradural catheters

Sir,—Two previous communications [1, 2] have commented upon removal of extradural catheters. My experience supports the view put forward by Morris [2]. In two cases of ankylosing spondylitis who had undergone total hip replacement the junior resident was unable to remove the extradural catheter on the fourth post-operative day; in both, the extradural catheter had been inserted in the left lateral position under general anaesthesia. The lumbar spine in both patients was partially fused and the extradural placement was technically difficult. I was also unable to remove the catheter in the flexed sitting position, but on turning the patient into the left lateral position with flexion, the catheters were removed without any problems.

In the postoperative period, extradural catheters are usually removed in the flexed sitting position because of patient comfort. I suggest that in patients with technically difficult extradural catheter placement the catheter should be removed in the same position as that used for insertion and undue force should not be applied. I further suggest that the nurses and residents should be made aware of this simple manoeuvre, and the position in which a catheter has been inserted should be written on the anaesthesia records.

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Optimal intracuff pressures with the laryngeal mask

Sir,—We disagree with the statement by Morris and Marjot demonstrating that laryngeal mask airway (LMA) cuff pressures can be reduced to 22 mm Hg without significantly affecting tidal ventilation in spontaneously breathing anaesthetized patients [1]. While agreeing that reducing intracuff pressure may minimize pharyngeal morbidity, we suggest that perioperative cuff deflation to such low pressures may be potentially hazardous. 

A major function of the LMA cuff during spontaneous breathing is to protect the larynx from oropharyngeal saliva. To perform this function an oropharyngeal leak pressure of up to 10 cm H₂O may be required (the approximate pressure of fluid at the larynx during swallowing is 10 cm H₂O). Cuff deflation below 10 cm H₂O would result in a significant increase in laryngeal morbidity. We also suggest that cuff deflation may result in significant respiratory depression. In patients with respiratory depression, cuff deflation below 10 cm H₂O would result in a significant increase in laryngeal morbidity. We also suggest that cuff deflation may result in significant respiratory depression.
the posterior pharyngeal wall if the oral cavity is flooded. An intracuff pressure of 22 mm Hg may or may not be sufficient to ensure an adequate seal to prevent contamination of the larynx with oropharyngeal secretions depending on the factors outlined above. We would therefore suggest that in patients undergoing spontaneous ventilation a leak pressure of greater than 10 cm H₂O is a more useful guide to airway safety than intracuff pressure alone. Other factors, such as avoidance of lignocaine gel for lubrication, choice of correct size of LMA and ensuring that tension in the pilot balloon does not increase during nitrous oxide anaesthesia may help minimize the risks of pharyngeal morbidity.

The authors infer that pharyngeal mucosal blood flow may be significantly impaired at commonly used cuff pressures. This concept was based on a study by Marjot where mucosal pressures were calculated, but not measured directly [2]. Hamakawa, Nakamura and Kawasaki directly measured the pressure on the middle part of the outside of the LMA and showed that extracuff pressure is approximately 25 mm Hg and does not increase during oxygen-nitrous oxide anaesthesia, despite increases in intracuff pressure [3]. Although there are obvious limitations to measuring pressure at one arbitrary point, this study may help to explain why pharyngeal morbidity is uncommon. It also confirms that the relationship between intracuff and pharyngeal mucosal pressure is non-linear making guidelines based on intracuff pressures alone less useful.

It is important to distinguish between pressure in the cuff, pressure exerted by the cuff on the mucosa and pressure in the airway at which leaks occur. Unfortunately because of the nature of the anatomy surrounding the mask and the low probability that the mask is exactly the right size for any given patient, there can be no fixed relationship between these three variables. It is therefore logical to determine an intracuff pressure which provides an effective seal empirically, a “just seal” pressure. This value is higher if the mask is small relative to the anatomical space available and lower if the mask is large relative to the available space. For this reason it is sensible to choose as large a size of mask as possible in order to ensure the “just seal” pressure is as low as possible. The smaller the mask relative to the patient, the weaker the relationship between intracuff pressure and average pressure on the mucosa, as the elastic material of the cuff is being stretched relatively more than the tissues surrounding it. On the other hand, because the cuff surface becomes more rigid with increasing intracuff pressure, local high pressure points may develop if excessive stretching of a small mask is resorted to as a means of achieving a seal in a large patient. The inventor suggests that to determine correct mask size a good rule of thumb is to use the largest size which is not displaced out of the pharynx after insertion when the cuff is inflated to a pressure of 60 cm H₂O.

Finally, a new recommendation is to appear in the forthcoming updated LMA instruction manual stating that smoothest recovery is likely to be obtained by reducing intracuff pressure to the minimum required to maintain an effective seal. This must be done with care to avoid accidental laryngeal contamination and should be carried out by the anaesthetist rather than delegated to the recovery staff. Cuff overinflation may cause premature rejection of the LMA or provocation of incomplete and therefore ineffective reflex responses. This may promote laryngeal spasm or regurgitation. Full deflation of the cuff should only occur synchronously with removal of the LMA to avoid secretions entering the larynx and provoking laryngeal spasm. Alternatively, the LMA may be removed with the cuff still moderately inflated to aid more complete removal of salivary secretions.


Sir,—Thank you for the opportunity to reply to Drs Brimacombe, Berry and Brain.

The excessively high intracuff pressures of the laryngeal mask in situ have been reported by various independent workers [1–3]. There are two crucial questions raised by this finding.

First, is a significant proportion of this pressure arising as a result of pressure on the adjacent pharyngeal mucosa? There is evidence to suggest that this is the case [2, 3], although no one as yet has implanted a pressure transducer into the pharyngeal mucosa. We were unable to trace the referenced work by Hamakawa, Nakamura and Kawasaki from the citation given. Our study was designed to determine if the manoeuvre of reducing intracuff volume and pressure during anaesthesia, which have been advocated by these authors and others [1, 4–6], was feasible in practice. To this end, we reduced intracuff pressure to the unequivocally “safe” pressure of 22 mm Hg (that of an estimated mucosal capillary perfusion pressure), and studied its effect on the primary function of the LMA, namely the unobstructed conveyancing of tidal ventilation from the anaesthetic breathing system to the patient’s lungs. Any secondary function of laryngeal protection from oropharyngeal secretions was not investigated (although there was no evidence of this manifesting as laryngospasm, coughing, etc). We agree that unless intracuff pressure is reduced to a safe level, then monitoring is meaningless, as it is impossible to distinguish that proportion resulting from pressure on the mucosa and that of stretching the cuff. Yet, intracuff pressure monitoring is still recommended by the manufacturers and others [1, 7, 8]. The advice to deflate the cuff to a 10 cm H₂O “leak pressure” and the feeling of the “tension of the pilot balloon” would seem to be crude and unsubstantiated gauges of intracuff and therefore mucosal pressures. However, these may be the simplest methods of ensuring cuff volumes are kept to a minimum in practice.

The second question is whether pressure on the pharyngeal mucosa by the LMA cuff causes problems. Are we looking for a cure to a problem that does not exist? The LMA has rightly been embraced into anaesthetic practice throughout the world. The paucity in the international literature of morbidity resulting from the LMA cuff would indicate that the risks are very small. Perhaps it is now time to acknowledge this and dispense with the recommendation of intracuff monitoring, then the LMA could rest (or wedge) in peace.

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Prevention of cardiovascular response to tracheal intubation

Sir,—We were interested to read the recently published article on the effects of nicardipine, diltiazem and verapamil in controlling the cardiovascular responses to tracheal intubation by Mikawa and colleagues [1]. We would like to offer some comments.


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The authors stated that anaesthesia was induced in a rapid-sequence manner by administering thiopentone and vecuronium, and ventilating the lungs with 1 % isoflurane and 50 % nitrous oxide in oxygen, and laryngoscopy was carried out 2 min after administration of thiopentone–vecuronium. This is not the correct use of an accepted terminology. The accepted meaning of rapid-sequence induction of anaesthesia is a sequence which allows rapid intubation of the trachea without manual ventilation of the lungs and with cricoid pressure applied to prevent passive regurgitation and aspiration of gastric contents.

Verapamil is effective in attenuating the pressor response but does not control the tachycardia after laryngoscopy and intubation [2, 3]. In this study, heart rate was increased from a mean of 80 to 100 bpm by 25 for more after administration of verapamil before laryngoscopy and intubation. With these values, it is difficult to conclude, as they did, that verapamil successfully attenuated the increase in heart rate after intubation. In their previous study using a similar anaesthetic technique, they could not demonstrate the role of verapamil in preventing the tachycardic response [2]. In this study, it may have been possible to demonstrate attenuation of tachycardia if they had omitted atropine as premedication.

With regard to measurements of plasma concentrations of adrenaline and noradrenaline, it has been shown that N-type calcium channels are responsible for release of neurotransmitters, and so-called classical calcium channel antagonists such as nicardipine, verapamil, diltiazem and others do not have much interaction with these channels [4]. On theoretical grounds it would be expected that these calcium channel blockers would have no effect on plasma concentrations of catecholamines after laryngoscopy and intubation.

Among the different methods used for attenuating undesirable cardiovascular responses to tracheal intubation, short-acting opioids appear to have a reliable and constant effect but they may contribute to postoperative respiratory depression. Lignocaine is the drug used most often, but its efficacy has been questioned in recent studies [5, 6]. Nebulized bupivacaine is only partially effective in blunting the haemodynamic response to tracheal intubation [7]. Beta blockers prevent tachycardia more than the pressor response [8] and because of their depressant effect on the myocardium, their role still remains to be defined, especially in patients with cardiac disease. A combination of esmolol and alfentanil has been shown to reliably suppress the response to laryngoscopy and intubation [9]. Clonidine and calcium channel blockers seem to be less effective in preventing haemodynamic alterations [10]. The risk of hypotension from calcium channel blockers such as nicardipine and verapamil when used with inhalation agents for maintenance of anaesthesia should be constantly borne in mind. Therefore, in clinical practice it is more appropriate to use a sufficient dose of an ultra-short-acting drug as mentioned above. The accepted meaning of rapid-sequence induction of anaesthesia is a sequence which allows rapid intubation of the trachea without manual ventilation of the lungs and with cricoid pressure applied to prevent passive regurgitation and aspiration of gastric contents.

3. Wig J, Sharma M, Baichoo N, Agarwal A. Nicardipine and verapamil attenuate the pressor response to laryngoscopy and intubation. 
7. Victory RA, Gajrai NM, Pace NA, Ostman LP, White PF. Nebulized bupivacaine attenuates the heart rate response following tracheal intubation. 

Tea-total
Sir,—Is the British Journal of Anaesthesia introducing a neologism or is the spelling of teetotal (tea-total [1]) different east of the Pennines? Dick Turner is stirring uneasily beneath his Preston (Lancashire) tombstone which bears the inscription: "Beneath this stone are deposited the remains of Richard Turner, author of the word Teetotal as applied to abstinence from all intoxicating liquors, who departed this life on the 27th day of October, 1846, aged 56 years" [2].

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Analgesia: dose-effect or pre-emptive effect?
Sir,—We were interested to read the recently published double-blind study on the influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements by Mansfield, James and Kinsella [1] and would like to offer some comments.

In this study patients undergoing abdominal hysterec- tomy were allocated randomly to receive one of three different analgesic regimens: morphine 0.3 mg kg

before the start of surgery (pre-high), morphine 0.15 mg kg

before surgery (pre-low) and morphine 0.15 mg kg

at the start of abdominal closure (post-low).

The dose of i.v. morphine given in the recovery room, total 24-h morphine PCAS requirements and total dose of morphine in the perioperative period, including that given in theatre, were recorded. Statistical analysis revealed reduced 24 h use of morphine in the pre-high group compared with the pre-low and post-low groups. When total perioperative morphine consumption was analysed, there was a significant difference between the pre-high and post-low groups only. On the basis of these analyses the study reported evidence of pre-emptive analgesia.

We are concerned that patients given morphine 0.15 mg kg

on abdominal closure apparently received no intraoperative analgesic supplements other than 66 % nitrous oxide. Could the authors comment as to how adequate analgesia was ensured in the perioperative period in order to satisfy ethical considerations in the post-low-dose group?

Is it possible the results of this study indicated that a large dose of morphine provided better analgesia than a small dose of morphine, rather than providing evidence of pre-emptive analgesia? It is unclear if the analysis of 24-h postoperative morphine dose included total PCAS requirements in the first 24 h in addition to recovery room analgesic requirements, as no specific information was given on the dose of morphine administered immediately after operation in the recovery room. If 24-h morphine requirements included both recovery room morphine supplements and 24-h PCAS requirements, it is possible that administration of morphine in the recovery room was solely responsible for the significant

that patients in the post group (morphine 0.15 mg kg⁻¹ on peritoneal closure) received no analgesia other than nitrous oxide until near the end of operation. All patients did, however, receive morphine either before or during surgery, well before awakening after general anaesthesia. In addition, the pattern of analgesic consumption and pain scores do not support the hypothesis that the post group suffered significantly more pain than the two other groups. As this method has been used by other workers, including Richmond and colleagues (reference [4] quoted by Mallick and Dearden), we do not believe there is any ethical dilemma relating to our methodology.

Drs Mallick and Dearden ask if it is possible that our study “indicated that a large dose of morphine provided better analgesia than a small dose, rather than evidence of pre-emptive analgesia”. First, we did not demonstrate better analgesia in the pre-high group (although pain scores were consistently lower in this group, the difference between groups was not statistically significant). Second, we were careful not to conclude a pre-emptive analgesic effect from our results. We did conclude that “a large dose of morphine administered on induction of anaesthesia significantly reduced postoperative morphine requirements from a PCA machine compared with a smaller dose given on induction of anaesthesia or at the time of abdominal closure”. While it is possible that this is indeed a pre-emptive analgesic effect of a large dose of morphine, we have not tested this hypothesis in our study. Table 1 shows the amount of morphine administered by us in the recovery ward and PCA morphine use by the patient, from the end of surgery until 24 h after operation.

Table 1  Morphine consumption in the recovery room and PCA morphine use, from the end of surgery until 24 h after operation (median (interquartile range))

<table>
<thead>
<tr>
<th>Group</th>
<th>Morphine in recovery (mg)</th>
<th>24-h PCA morphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post</td>
<td>3.5</td>
<td>61</td>
</tr>
<tr>
<td>Pre-low</td>
<td>3.0</td>
<td>54</td>
</tr>
<tr>
<td>Pre-high</td>
<td>0.0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>(0–17.5)</td>
<td>(51–79)</td>
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<tr>
<td></td>
<td>(0–7.5)</td>
<td>(45–65)</td>
</tr>
<tr>
<td></td>
<td>(0–5.0)</td>
<td>(30–49)</td>
</tr>
</tbody>
</table>

While there appears to have been less morphine administered in recovery in the pre-high group compared with the post group, this was not statistically significant ($P = 0.45$, Kruskal–Wallis). As found in the original data analysis, there was a significant difference in the amount of morphine used by patients (PCA) in the pre-high group compared with the post group ($P = 0.0002$) and the pre-low group ($P = 0.0015$, Kruskal–Wallis) but there was no difference between the pre-low and post groups. The suggestion by Mallick and Dearden that the difference in postoperative morphine consumption was caused primarily by an effect in the recovery room is not, therefore, supported.

Finally, we agree with the hypothesis that NMDA antagonists may have a useful role in postoperative pain relief, although this was not tested in our study. Whether they will prove to have a pre-emptive effect remains speculative. It seems unlikely that any single group of analgesic agents will ever be able to abolish pain completely, and that multimodal analgesic strategies are required to optimize postoperative pain relief.

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Convective warming after CABG

Sirs,—I read the article of Harrison and Ponte on convective warming [1] with great interest. Have the authors considered the effect of propofol on thermoregulation? It was administered to all patients at a rate of 50–200 mg h⁻¹. Propofol is a well-known vasodilator and may have caused vasodilation in addition to that caused by glyceryl trinitrate. Propofol is also known to attenuate adrenaline and noradrenaline release which would alter the rate of thermogenesis [2]. Was there any significant difference between the dose of propofol administered in each group?

The authors administered glyceryl trinitrate at a rate of at least 15 mg h⁻¹ to both control and study patients. As the effect of the Bair Hugger is to cause further vasodilatation, did the authors find that less glyceryl trinitrate was subsequently required in this group compared with the control group, and if so, could this have influenced their results? The authors dismissed the possibility that large doses of glyceryl trinitrate used in the study accelerated cutaneous heat loss from the control group because of rewarming “at a rate close to that usually observed in the absence of glyceryl trinitrate”. It would have been interesting to know how the rate of rewarming in the control group compared with “that usually observed”. It appears that peripheral temperatures in the control group were significantly colder during the first 2 h after operation compared with the Bair Hugger group. As heat from the peripheral compartment does not flow up a gradient to the core, it would appear that peripheral cooling could only be caused by loss of heat across the skin to the environment.

The peripheral temperature sites of toe and fingertip may be inaccurate in patients with severe peripheral vascular disease. Were these patients excluded from the study?

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1. Harrison SJ, Ponte J. Convective warming combined with oxi d e d u r i n g  p h a s e  1  o f  th e  f o r m a l i n  t e s t  d e m o n s t r a t e d  a different abilities to block sensitization. We found that rats that concentrations of commonly used volatile anaesthetics have sensitization. (3) if nitrous oxide interferes with the ability of spinal sensitization, (2) if nitrous oxide alone blocks spinal induction of spinal sensitization by anaesthetic agents [3]. In this 1995.


Sir,—Our purpose was not to study thermoregulation. For example, in the methods section we stated clearly that thermoregulatory shivering was deliberately abolished; similarly, the doses of glyceryl trinitrate used in both groups were aimed at overcoming physiological mechanisms (thermoregulatory or not) of cutaneous vasoconstriction. The aim of the study was merely to find out if forced warm air could increase the rate of rise of rectal and nasopharyngeal temperature having deliberately minimized thermoregulatory mechanisms, as stated in the discussion section.

The rate of rewarming “usually observed” refers to that observed in most other patients subjected to similar operations in our department, but not included in the study, which is similar to that quoted in references [6, 7 and 16] of our paper. No patient with diabetes or evidence of peripheral vascular disease was included in the study. Apart from the differences between groups described in the results section, there were no other differences in other variables, such as amount of glyceryl trinitrate or propofol infused.

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Adequate general anaesthesia—what are we trying to achieve?

Sir,—Further to the article by Sun, Shyu and Shieh [1] and the accompanying editorial [2], we wish to bring your attention to some relevant findings of studies which were carried out by us in 1995.

We refer in particular to an article on inhibition of nociception-induced spinal sensitization by anaesthetic agents [3]. In this study we sought to determine: (1) if volatile agents reliably block spinal sensitization, (2) if nitrous oxide alone blocks spinal sensitization, (3) if nitrous oxide interferes with the ability of volatile anaesthetics to block sensitization, and (4) if equipotent concentrations of commonly used volatile anaesthetics have different abilities to block sensitization. We found that rats that received halothane, enflurane, isoflurane, desflurane or nitrous oxide during phase 1 of the formalin test demonstrated a significant decrease in phase 2 activity compared with controls, that is suppressed spinal sensitization to pain, with desflurane causing the most suppression. Those rats that received a combination of nitrous oxide and halothane exhibited no difference, that is no suppression was demonstrated.

There is now increasing evidence that volatile anaesthetic agents exert their effect at the spinal cord level [4–7] and this may explain their possible role in pre-emptive suppression of spinal sensitization. There are also many studies which suggest that inhalation anaesthetic agents may suppress nociception in the spinal cord by modifying the activity of NMDA receptors in dorsal horn neurones [8, 9]. While the mechanism by which inhibition of transmission of noxious stimulation by inhalation anaesthetic agents is achieved is still speculative, it has been well documented that they enhance GABA mediated sensory in hibition [10–13] and it has been suggested that inhalation anaesthetics may produce suppression of spinal cord sensitization through GABAA mediated agonism [14]. Some of the analgesic action of nitrous oxide has also been attributed to depressant action on dorsal horn neurones in the spinal cord, perhaps via activation of a supraspinal descending inhibition system. Interestingly, nitrous oxide has been shown to reverse EEG burst suppression provided by isoflurane [15, 16] and desflurane [17], suggesting that it opposes the effect of volatile anaesthetics on the central nervous system. It has also been demonstrated that nitrous oxide has antagonistic effects on the MAC of volatile agents [18]. Taken together, these studies indicate that nitrous oxide may antagonize the depressant effects of volatile agents on the central nervous system and this may explain its apparent antagonism of suppression of spinal sensitization by volatile agents in the rat formalin test.

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suppression of nociceptor induced spinal sensitization. Regional Anaesthesia 1994; 19: 5.

Sir,—We thank Drs O’Connor and Abram for their interest in our article [1].

In their letter they highlight the results of their study in which they tested the efficacy of various anaesthetic agents given around the time of formalin administration in inhibiting the subse- quent pain-related behaviour, known as the phase 2 formalin response [2]. The phase 2 formalin response consists of complex pain-related behaviour, including licking of and flinching with the affected paw, which occurs 10–60 min after administration of formalin. This latter phase of pain behaviour can be distinguished pharmacologically from the first phase that immediately follows formalin injection into the paw, in that activation of spinal cord NMDA receptor is critical to the second phase, but not first phase of flinching. In contrast, the first phase occurs within the first 5 min of administration of formalin and has been shown to be sensitive to AMPA antagonists. Activation of the NMDA receptor has, in order studies, also been shown to mediate sensitization of individual spinal cord neurones (including “windup”) and also to mediate enhancement of spinal cord reflexes [3].

In their study, O’Connor and Abram gave 1 MAC of a volatile anaesthetic agent or 70% nitrous oxide, or propofol (initially 10 mg kg\(^{-1}\) and then another 3 mg kg\(^{-1}\), 1 min after formalin) before and during the period of expected phase 1 flinching. They showed that there was suppression of phase 2 flinching with this pre-emptive treatment and so they inferred that spinal cord sensitization had been suppressed (the only exception was that pre-emptive halothane and nitrous oxide given together did not prevent phase 2 flinching). The implications are that conventional anaesthesia does protect the spinal cord during surgery. However, when one looks for other evidence for inhibition of spinal cord sensitization by conventional anaesthetics, the results are conflicting and often depend on the end-point being used. For example, in other studies of formalin-evoked flinching, Abram and Yaksh have shown that even 2.5% isoflurane only reduced phase 2 flinching by 35% when given pre-emptively (and, incidentally, in this study the addition of nitrous oxide to isoflurane abolished this benefit) while intrathecal morphine reduced flinching by 80% [4]. However, in another study, Abram and Olsen found that pre-emptive high-dose systemic opioids did not reduce phase 2 flinching [5]. As for propofol, other studies have not reproduced the findings of O’Connor and Abram [2] in that pre-emptive propofol 10–20 mg kg\(^{-1}\) did not reduce phase 2 flinching [6, 7]. Barbiturates similarly show variable efficacy in inhibiting spinal cord sensitization [6–8]. Abram and Yaksh [4] also point out that many of the studies that examined C-fibre induced spinal sensitization were carried out under surgical plane of anaesthesia [9].

Clinical studies have shown that a simple nocuous stimuli-evoked reflex in volunteers was inhibited by 0.25–0.5% end-tidal isoflurane. However, repetition (five times at 2 Hz)of the same noxious stimulus caused facilitation of the nociceptive reflex and required 1–1.5% isoflurane to suppress it (and the authors pointed out that this dose is similar to the MAC of isoflurane). The authors then suggested that even this higher dose of isoflurane alone would not be adequate for inhibiting surgically evoked excitability in actual operations [10].

Those agents that are generally accepted to produce that state we call anaesthesia were never chosen for their analgesic potential. Several end-points have been used to define an adequate dose of anaesthetic, including loss of consciousness, inhibition of memory formation, lack of intraoperative movement, etc. However, when the results of studies examining more analgesic end-points for conventional anaesthetics are analysed, we find confusing and seemingly contradictory examples, as discussed above. This is because clinically accepted doses of anaesthetics have only moderate ability, at best, to inhibit (i) primary afferent input, (ii) the development of spinal cord sensitization and (iii) short- and long-term pain perception. Fortunately, perhaps conventional anaesthetics do show some analgesic effects, including NMDA receptor blocking activity, but this is unlikely to be contributing to their anaesthetic effect [11].

The purpose of the articles to which O’Connor and Abram refer, is to show that by using immediate early gene end-points, noxious stimulation still enters the spinal cord during seemingly adequate anaesthesia (see references in [1]). It is not surprising that clinical studies of pre-emptive analgesia show little effect when the agents we use are not particularly good at doing what we ask of them, that is protecting the spinal cord against incoming afferent stimulation. For example it has been demon- strated previously that radically different outcomes in terms of long-term pain behaviour can be produced experimentally with different adjuncts to isoflurane anaesthesia (α2 agonists, NMDA antagonists, peripheral blocks with local anaesthetic but interestingly, not μ agonists) despite similar lack of responsiveness during anaesthesia [12, 13]. Furthermore, as discussed previously, the ability to suppress fos expression by these adjuncts parallels these behavioural outcomes (see references in [1] and also Munglani, Fleming and Hunt, data submitted for publication).

As Abram and Olsen have previously written: “there is a dichotomy between behavioural response to a noxious stimulus and the development of enhanced responsiveness”. Furthermore, Abram and Yaksh concluded “that the anaesthetised state, as defined by loss of consciousness, or lack of motor response, may be dissociated from the processes leading to post injury facilitation” [4] an observation recently re-emphasised by Goto, Marota and Crosby [14].

As anaesthetists we pride ourselves on producing a state of anaesthesia which includes loss of consciousness, lack of memory formation and minimal autonomic activity. However, the evidence is that conventional anaesthetics (including μ agonists) do not adequately inhibit the longer term consequences of painful stimulation for the patient. Electrophysiological and immediate early gene studies suggest that we need to radically re-think what are our goals for anaesthesia and how we are to achieve them.

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Spinal anaesthesia for Caesarean section

Sir,—We read with interest the letter from Stoneham and Souter on spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia [1]. We congratulate them on their excellent results in 12 such patients, none of whom developed a sensory block above T3. Whether the results in this small series of patients implies that this is a safe technique is still dubious, especially in the face of the frequency of case reports of unexpectedly high spinal block associated with pre-existing extradural block (references [2–7] in Stoneham and Souter’s communication).

We take issue with one aspect of their methods. In the list of indications for performing spinal anaesthesia in the presence of a pre-existing extradural block, they included patient(s) in whom the urgency of the situation was considered not to allow time for extension of the extradural block. They then described their technique which involves not preparing the patient for surgery until 20 min after the spinal injection. Therefore, the time taken to have the patient ready for surgery is 20 min in addition to the time taken to transfer the patient to theatre, position the patient and perform the spinal anaesthetic. Our technique of choice in this group of patients is to extend the extradural block using an alkalined mixture similar to that described by Fernando and Jones [2], namely 0.5 % bupivacaine 10 ml, 2% lignocaine 10 ml, 1 ml of adrenaline 1 in 10 000 (resulting in a final concentration of slightly less than 1 in 200 000) and 2 ml of preservative-free 8.4 % sodium bicarbonate. Although we have no audit of our own patients on the time taken for extension of the block to an acceptable height, this time is certainly less than 20 min. Using a similar mixture, Fernando and Jones found that the mean time to achieve sensory block T4–S5 in a group of 10 patients was 12.7 min (range 10–14 min) [2]. These patients were undergoing elective Caesarean section and thus had no pre-existing extradural block.

We would advocate the above technique for emergency Caesarean section as it provides suitable surgical anaesthesia without the patient undergoing an additional invasive procedure, that is performance of a spinal anaesthetic and the attendant risks thereof, and achieves this more rapidly than the technique described by Stoneham and Souter.

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Sir,—We agree with Drs Foster and Rogers that the technique described by Fernando and Jones of extending an extradural block may be more appropriate than subjecting the patient to the additional risks of a spinal anaesthetic if there is no evidence that the extradural is inadequate. There were two patients in our group of 12 who had unilateral extradural blocks in whom it was felt that there was insufficient time to manufacture a reliable extradural block.

In our limited study, we set out to investigate the unusual situation of women with inadequate extradural blocks who require a regional anaesthetic technique for Caesarean section. Since writing our letter to the British Journal of Anaesthesiology, there has been further anaesthetic correspondence on this matter [1, 2] recommending that spinal anaesthesia should be avoided under these circumstances until further work has been done. We intended


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Sir,—We agree with the letter from Stoneham and Souter [1]. There is a lack of data on the safety and dose requirements of subarachnoid anaesthesia in women undergoing emergency Caesarean section after extradural analgesia for labour. Therefore, we have recently conducted an audit in order to produce a regimen for the management of these patients on our unit. During the 5-yr period 1990–1994, 30 such patients were identified. There were a variety of reasons for subarachnoid block; 21 cases had inadequate quality of extradural block, the extradural catheter had recently become displaced in eight patients and in the remaining patient there was inadequate time for extension of the extradural. The dose varied between 2 and 3.5 ml of heavy 0.5 % bupivacaine, with 17 patients receiving 2.75 ml or more. Four patients also received subarachnoid fentanyl. In 12 cases the injection was given with the patient in the lateral position. We believe the variation in dose and position reflects individual anaesthetist’s usual practice. The upper level of the block was recorded in only 16 patients. This varied from T1 to T5, with no correlation with either dose of bupivacaine or position of the patient during injection. In those patients where no block height was recorded, there was no evidence of an abnormally high block. Two of the four patients who received less than 2.5 ml of 0.5 % heavy bupivacaine required supplementary analgesia (one general anaesthesia and one alfentanil and nitrous oxide–oxygen). This compared with only two patients requiring supplementation (both alfentanil alone) of the other 26 patients who had received bupivacaine 2.5 ml or more. Three of the four patients requiring additional analgesia had an adequate block height documented before surgery; there was no documented block height recorded for the remaining patient.

As a result of our findings, we have recommended in our unit that patients requiring subarachnoid anaesthesia for Caesarean section after extradural analgesia should have subarachnoid block performed in the anaesthetist’s preferred position, using 2.5 ml of heavy 0.5 % bupivacaine. Careful attention to positioning, as recommended by Stoneham and Souter, should occur whenever subarachnoid block is given, regardless of whether or not the patient has previously received extradural analgesia. Neither we nor Stoneham and Souter have conclusively demonstrated the safety of the technique and we do not know the incidence of high block, which may be no greater than for subarachnoid block in the absence of pre-existing extradural blocks. We believe, however, unlike the recommendation by Kick and Bohrer [2], that reducing the dose of bupivacaine below our recommendation carries a significant risk of inadequate block.

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to show that it is possible to perform spinal anaesthesia in patients who have had previous, recent extradural analgesia provided that rigorous care is paid to the positioning of the patient, although of course we are not attempting to suggest that it is safe from the results of studying such small numbers of patients.

The 30 patients described by Drs Vickers and Wilkey are further evidence that it is possible to administer spinal anaesthesia safely in these circumstances, although information on the dose of local anaesthetic, or opioid agents, or both, administered into the extradural space, or how recently they had been given in these 30 patients would have been useful. In addition, we believe that the position of the patient during the siting of the spinal may be less important in determining the outcome than the position of the patient while the spinal anaesthetic develops. Nine of the 10 case reports of unexpectedly high spinal block after failed extradural analgesia were placed in the wedged supine position immediately after spinal injection [3–9]. It is known that the supine hypotensive syndrome is not completely abolished in the wedged supine position [10]. The intriguing possibility arises that partial maternal aortocaval compression in the wedged supine position, leading to extradural venous engorgement, may result in unpredictably high blocks after spinal anaesthesia, particularly where there is already exogenous fluid in the extradural space as in all of these case reports. We are investigating the possibility that positioning patients in the wedged supine position while a spinal anaesthetic is developing may produce a more unpredictable final block height than the lateral position and this may be exacerbated if there is already fluid in the extradural space.

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