sites in the CNS is proposed as the mechanism of action of naloxone."¹

We fully agree with his statement that there is a distinct difference between anaesthesia and analgesia, both of which may be mediated by different central mechanisms. Because of this difference it was our aim to evaluate the effect of naloxone (Nx) on the hypnotic and depressed baroreceptor reflex activity during halothane anaesthesia. The known weak analgesic effect of halothane was not evaluated.

With regards to the analeptic effect of naloxone and not to the antagonism of analgesia during halothane administration, Kraynack *et al.* have demonstrated a central cholinergic mechanism. Atropine, in rats, abolished the antagonistic properties of naloxone. The physiologic antagonism of Nx is of interest as naltrexone, a close relative to Nx, did not effect halothane-induced sleeping time and righting reflex. The analeptic effect therefore seems to be related only to Nx, suggesting a compound-specific reversal.^{2,3}

Such non-specific antagonism is underlined by the findings of Badawy *et al.*⁴ In their studies Nx reduced blood-ethanol levels by 31 per cent in rats while at the same time reversing the depressed redox state of the hepatic nicotinamid-adenine-dinucleotide system. Such peripheral biochemical activity was also applicable to the brain tryptophan metabolism.⁵

Naloxone on the other hand has low affinity for a subpopulation of opioid receptor sites. Rosenbaum and Sadee⁶ demonstrated in vivo different labelling of ³H-naloxone when compared to ³H-diprenorphine, another pure opioid antagonist of the oripavine series.

This concept of different receptor sites, originally brought forward by Martin *et al.*,⁷ may be of importance as a close relative to diazepam, i.e., tipluadom, has analgesic properties which are only reversible by high doses of Nx and low doses of opioid kappa-specific antagonists such as Mr 2266 and Win 44, 441-3.⁸⁻¹⁰

Modulation of nociception is not only mediated through the opioid receptor system; high doses of Nx produce similar effects (changes of cerebellar c-GMP) as GABA-antagonists.¹¹

In short, our paper has questioned the assumption of a halothane-induced endogenous release of opioids. However, when testing the analgesic properties of N₂O or halothane, different doses of a selective opioid antagonist and different selective antagonists should be used.

To our knowledge, an increase in the endogenous enkephalin and/or endorphin level during general anaesthesia has never been demonstrated.

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REFERENCES

- 1 Freye E, Hartung E, Schenk GK. Naloxone reverses the hypnotic effect and the depressed baroreceptor reflex of halothane anaesthesia in the dog. *Can Anaesth Soc J* 1983; 30: 235-41.
- 2 Kraynack BJ, Gintautas J, Kraynack LL. Analeptic action of naloxone abolished by atropine pretreatment. *Anesthesiology* 1982; 57: A 307.
- 3 Kraynack BJ, Gintautas JG. Naloxone: Analeptic action unrelated to opiate receptor mechanism? *Anesthesiology* 1982; 56: 251-3.
- 4 Badawy AAB, Evans M. The mechanism of the antagonism by naloxone of acute alcohol intoxication. *Br J Pharmacol* 1981; 74: 514-6.
- 5 Badawy AAB, Evans M, Pnjani NF. Reversal by naloxone of the effects of chronic administration of drugs of dependence on rat liver and brain tryptophan metabolism. *Br J Pharmacol* 1981b; 74: 489-94.
- 6 Rosenbaum JS, Sadee W. Demonstration of opiate receptor sub-types in vivo. *Life Sci* 1982; 31: 1299-1301.
- 7 Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* 1976; 197: 517-32.
- 8 Römer D, Büscher HH, Hill RC, Maurer R, Petzsch TJ, Zeugner H, Benson W, Pinner E, Milkowski W, Thies PW. Unexpected opioid activity in a known class of drugs. *Life Sci* 1983; 31: 1217-20.
- 9 Römer D, Büscher HH, Hill RC *et al.* An opioid benzodiazepine. *Nature* 1982; 298: 759-60.
- 10 Freye E, Hartung E, Schenk GK. Tipluadon induces suppression and latency changes on somatosensory evoked potentials which are reversed by opioid antagonists. *Life Sci* (In press).
- 11 Gumulka SW, Dinnendahl V, Schonhofer PS. The effect of naloxone in cerebellar cGMP content. A possible GABA-antagonistic action? *Naunyn-Schmiedeberg Arch Pharmacol* 1979; 30b: 169-72.

Nitrous oxide uptake in man

To the Editor:

We would like to comment on the views of Dr. Swanson *et al.* and Dr. Lin recently published.^{1,2}

Like Swanson *et al.* we wished to re-examine nitrous oxide uptake in man, using better instrumental methods, in this case a completely closed circuit.³ Using this circuit the rate of nitrous oxide uptake and nitrogen excretion were measured simultaneously in patients undergoing routine abdominal surgery.⁴ Our results may be summarised as follows:

1 Both nitrogen excretion and nitrous oxide uptake fitted well to the form $\dot{V}_{N_2O} = A \cdot t^k$ up to 100 mins into anaesthesia although a large range of values of the constants (A and k) between individual patients was found.

2 After 70 mins the results from a conventional compartmentalised model failed to produce an adequate fit to the data. Discrepancies between the predictions of the model and our data could be accounted for by hypothesising that measurable quantities of gas were lost or gained at the surgical incision. Comparison of the predictions of the model and our results with those of other authors including Virtue *et al.* indicated that the departure was not present for results obtained with intact volunteers.

3 The good agreement between our data and the model obtained from 4 to 70 mins into anaesthesia lead us to conclude that after wash out of the FRC uptake by the body as measured by a closed circuit is a true reflection of alveolar uptake. No "blood/gas" barrier need be hypothesised to account for the results.

We feel that the method we have employed updates the closed circuit method of Severinghaus⁵ in much the same way as the breath-by-breath methods of Swanson *et al.* update those of previous authors. Additionally we find that our results are in agreement with their conclusions. We would go further than Swanson *et al.*, however, in maintaining that Lin's continued insistence on the idea of a steady state of nitrous oxide uptake irrespective of washin to lung is both confusing and potentially hazardous. In some patients if it was used as a strategy for control of a closed circuit an unacceptable dilution of nitrous oxide by excreted nitrogen could result. The methods he has used to "establish" this idea do not bear close examination and his assumptions are questionable.

It would seem from our study that the power law relationship, $\dot{V}_{N_2O} = 1000 t^{-1/2}$, is a safe starting point for flow of gas in to a closed circuit. However, the wide variation in the constants between patients and the unpredictability of leaks in circuits in normal clinical use make oxygen monitoring essential when attempting a minimal flow technique in a closed circuit.

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REFERENCES

- 1 Virtue R, Sherrill DL, Swanson GD. Uptake of nitrous oxide by man. *Can Anaesth Soc J* 1982; 29: 424-7.
- 2 Lin CY, Swanson GD, Virtue RW, Sherrill D. Uptake of nitrous oxide by man. *Can Anaesth Soc J* 1983; 30: 447-50.
- 3 Beatty PCW, Wheeler MFS, Kay B, Greer W, Cohen AT, Parkhouse J. A versatile closed circuit. *Br J Anaesth* 1982; 54: 689.
- 4 Beatty PCW, Kay B, Healy TEJ. Measurement of nitrous oxide uptake and nitrogen excretion in man. In press. *Br J Anaesth*. Submitted March 1983.
- 5 Severinghaus J. The rate of nitrous oxide uptake in man. *J Clin Invest* 1954; 33: 1183.

Patient-controlled analgesia

To the Editor:

The paper by Sprigge and Otton on patient-controlled nalbuphine administration for postoperative analgesia¹ raises two interesting issues. Despite the demonstration that nalbuphine has a ceiling respiratory depressant effect² the authors consider the "possible risk of respiratory depression due to overdose" and suggest that the method be confined to a high dependency unit thereby negating the advantage of nalbuphine.

Our study of nalbuphine given on-demand³ allowed the patient to administer very much larger doses than those available to Sprigge and Otton's patients; a 20 mg bolus to start, 5 mg each demand, with a compulsory delay of three minutes between demands. Despite the fact that some patients re-