Second, alcohol,⁵ diazepam⁵ (via a Gaba-ergic-opioid link)⁶ and nitrous oxide (at analgesic concentration) may well have strong functional links to the opioid system. Nitrous oxide particularly has been shown both in vitro^{7,8} and in many animal⁹⁻¹¹ and human¹²⁻¹⁴ studies to have opioid activity at analgesic concentrations. The work^{4,15-17} cited to bolster their argument particularly in the case of N₂O is also unfortunate, since all these "so called" contradictory papers measured the effect of Nx on anaesthetic and not analgesic concentrations.

In a study where analgesia caused by N₂O was not reversed by Nx,¹⁸ the experimental design had not made sufficient allowance for the pharmacokinetic differences exhibited by these agents.¹⁹

Although Nx may well have a non-specific analeptic effect,¹ it would be incorrect to assume that none of the effects associated with anaesthesia, such as analgesia are mediated via naloxone-sensitive opioid mechanisms.

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REPLY

We welcome the comments of Dr. Gillman as they stimulate the exchange of ideas in a fast-moving field such as opioid activity. We would like to respond to his comments by stressing the following points.

His statement that we did not refer to a possible endogenous release through non-opioid compounds is not correct. We stated: "Antagonism of endogenous opioids (enkephalins or endorphins) at opiate binding

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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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: