confirmed and cholecystectomy carried out. Operative cholangiography was normal and an explanation for the chronic pelvic pain was provided by the finding of bilateral hydropsalpinges.

On reviewing the limited literature concerned with opioid-induced biliary colic, it would appear that case reports relating to this problem all concern patients who have had or are about to have biliary surgery [1–3]. This raises the possibility that opioid-induced colic is not a pharmacological response, but rather biliary tract pathology is a pre-requisite for it to occur. Biliary pressure studies have demonstrated biliary hyper-tension and spasm of the sphincter of Oddi as a common consequence of opioid administration. The results of these studies may be misleading as, by necessity, the measurements are made during the course of cholecystectomy (i.e. there is proven biliary disease) and, furthermore, pressures are measured by cannulation of the cystic duct (after the gall bladder has been removed), which is not a particularly physiological situation [4–6]. This view point is endorsed by canine studies which revealed that biliary pressures did not change in healthy dogs following administration of opioids unless the gall bladder had previously been removed [7]. This raises the possibility that the gall bladder is functioning as a pressure valve and limiting opioid-induced effects. On the basis of these observations, we would suggest that it is perhaps only those patients with an absent or non-functioning gall bladder who are at risk of opioid-induced colic. It may be, therefore, prudent to investigate the biliary tract in such patients rather than to dismiss the problem as a pharmacological response.

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REFERENCES

SUXAMETHONIUM AND INTRAOCULAR PRESSURE

Sir,—After reading the paper on the changes in intraocular pressure during induction and intubation associated with the administration of thiopentone or propofol [1], I felt that an important result of the study was rather ignored.

The results in table II clearly show that the combination of induction and suxamethonium did not cause a significant increase in intraocular pressure in any group when compared with baseline values. However, the authors preferred to use the post-induction values of intraocular pressure, and to state—in the summary—that there was a significant increase in intraocular pressure following suxamethonium. Yet the authors used baseline intraocular pressure as their reference point to comment on the lack of a significant increase in intraocular pressure with the combination of a second dose of propofol and intubation. (The use of the “post second dose induction value” of intraocular pressure, a reference point similar to that used when stating the significant increase in intraocular pressure with suxamethonium, would of course have given the result from a significant increase in intraocular pressure.)

Surely, the authors should be consistent (with reference points) when using statistics to conclude the possible beneficial effect of certain therapeutic measures. If it is “true” that a second dose of propofol protected against the increase in intraocular pressure secondary to intubation, then it is also “true” that suxamethonium did not cause an increase in intraocular pressure.

When considering the problem of how to maintain a stable intraocular pressure during induction and intubation, surely both these facts are equally important.

L. EDMONDSON

ANTINEOPLASTIC SYNERGISM OF NITROUS OXIDE AND METHOTREXATE

Sir,—The review article by Nunn [1] mentioned a suggestion by Ueland and co-workers [2] that the side effects associated with methotrexate could be increased, and the efficacy of leucovorin rescue be decreased, by anaesthetic regimens in which nitrous oxide is used. They further suggested that, until these possibilities have been rejected “...nitrous oxide should be used with caution in patients receiving methotrexate”.

Nunn went on to suggest that this theoretical problem has not been investigated. However, there is some work which indicates that, far from causing problems in association with

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R. K. MIRAKHUR

SIR,—Thank you for giving me the opportunity to reply to Dr Edmondson’s letter. While Dr Edmondson is correct in pointing out that we used the post-induction value intraocular pressure (IOP) for comparing the increase in IOP after suxamethonium administration, it was clearly stated in the text that, even after suxamethonium administration, the IOP was never significantly greater than the baseline value. The use of post-induction values after suxamethonium was used purely to show the increase that occurs in IOP following suxamethonium. Yet the authors comment on the lack of a significant increase in intraocular pressure, and to state—in the summary—that there was a significant increase in intraocular pressure in any group when compared with baseline values. However, the authors preferred to use the post-induction values of intraocular pressure, and to state—in the summary—that there was a significant increase in intraocular pressure following suxamethonium. Yet the authors used baseline intraocular pressure as their reference point to comment on the lack of a significant increase in intraocular pressure with the combination of a second dose of propofol and intubation. (The use of the “post second dose induction value” of intraocular pressure, a reference point similar to that used when stating the significant increase in intraocular pressure with suxamethonium, would of course have given the result from a significant increase in intraocular pressure.)

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methotrexate, nitrous oxide may well have a positive syner-
gistic action. For instance, it has been shown in vitro that a
combination of nitrous oxide and methotrexate was more
effective in depleting functional folate than either agent alone,
indicating the possibility that these agents might act syner-
gistically as anti-neoplastic agents in vitro [3]. Furthermore,
whilst the rescue effect of 5-methyltetrahydrofolate is dimin-
ished following exposure to nitrous oxide, this was not the case
with 5-formyltetrahydrofolate (folic acid) [4].

Such a finding is not unexpected, since both nitrous oxide
[1, 3, 5] and methotrexate [3, 4, 6] appear to disrupt steps in
folate metabolism only before the formation of folic acid. It
is, therefore, not surprising that, according to Ueland and
colleagues [2] the "rescue therapy seems to work in children
exposed to nitrous oxide". Indeed, this rescue effect of
adequate doses of folic acid has been shown quite clearly to
prevent megaloblastic bone-marrow changes in most human
subjects following extended analgesic and anaesthetic expo-
sures to nitrous oxide [1, 7]. It would appear, therefore, that
the presence of nitrous oxide is unlikely to have an effect on the
rescue effect of leucovorin, whilst possibly having a positive
anti-tumour action through its synergism with methotrexate
[3].

Therefore, far from decrying the use of nitrous oxide in
conditions sensitive to folic acid antagonists (such as metho-
trexate), the possibility of using these agents in combination
with the gas should be further investigated. Such investi-
gations could lead to better disease control or reductions in the
doses of methotrexate used. Apart from its synergistic anti-
eoplastic effect in this context, nitrous oxide would have the
further advantage of being an excellent analgesic [8].

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REFERENCES
1. Nunn JF. Clinical aspects of the interaction between
nitrous oxide and vitamin B12. British Journal of Anaes-
2. Ueland PM, Refsum H, Wesenberg F, Kvinnisland S.
Methotrexate therapy and nitrous oxide anesthesia. New
3. Kano Y, Sakamoto S, Sakuraya K, Kubota T, Hida K,
Suda K, Taku F. Effect of nitrous oxide on human bone
marrow cells and its synergistic effect with methionine
and methotrexate on functional folate deficiency. Cancer
4. Dudman NPB, Slowiaczek P, Tattersall MHN. Metho-
trexate rescue by 5-methyltetrahydrofolate or 5-formyl-
tetrahydrofolate in lymphoblast cell lines. Cancer Research
5. O’ Sullivan H, Jennings MB, Ward K, McCann S, Scott
JM, Weir DG. Human bone marrow and megaloblastic
hematopoiesis after nitrous oxide anesthesia. Anesthesi-
Rodwell VW, Mayes PA eds. Review of Physiological
Chemistry. 16th edn. Los Altos, California: Lange, 1977;
156–181.
7. Gillman MA. Haematological changes caused by nitrous
oxide: Cause for concern? British Journal of Anaesthesia