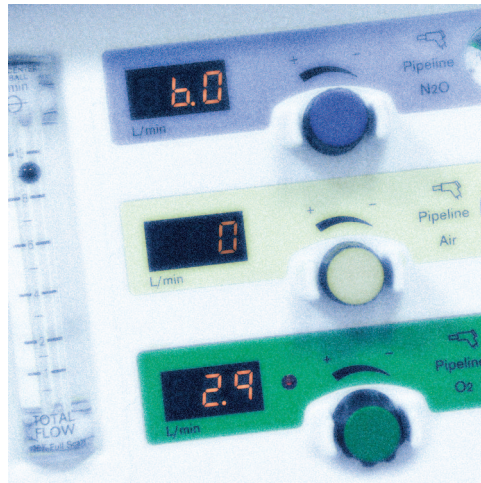


Notorious Oxide

NITROUS oxide has an unusual pharmacologic side effect that is unrelated to its anesthetic action: it inactivates vitamin B₁₂. The inactivation of vitamin B₁₂ is irreversible and causes a subsequent accumulation of homocysteine in the cell, because methionine synthase, an important enzyme that converts homocysteine to methionine, depends on the active form of vitamin B₁₂ and is therefore also inactivated by N₂O. The accumulation of homocysteine can be measured clinically by an increase in plasma total homocysteine (bound and unbound homocysteine), the magnitude of which is tightly correlated with the duration and dose of N₂O exposure. This effect of N₂O has long been known and repeatedly shown in animals and adult humans, but not in young children – until now. Together with a recent report in adolescents,¹ the study by Pichardo *et al.* in this issue of ANESTHESIOLOGY² provides the first evidence regarding the effects of N₂O on homocysteine in young children, for which the authors should be congratulated. Not surprisingly, the authors found a 25% increase in plasma total homocysteine after N₂O anesthesia in their cohort of 32 children age 3–126 months. The absolute increase was small (+1.3 μmol/l) and substantially lower than found in a previous report (+9.4 μmol/l),¹ but this discrepancy may be explained by the substantially longer N₂O exposure times in the latter study. Furthermore, Pichardo *et al.* obtained only a single homocysteine measurement 24 h after N₂O exposure, which may have missed the plasma homocysteine peak that typically occurs immediately after the cessation of N₂O administration.

The study by Pichardo *et al.* thus confirms – not unexpectedly – that N₂O causes a dose-dependent increase in plasma homocysteine in children. But what is the clinical



“Isn’t it quite remarkable how little definitive evidence we have regarding [nitrous oxide], the oldest . . . drug in our armamentarium?”

there a general association, perhaps even a causal one, between plasma homocysteine elevation, atherosclerosis and cardiovascular risk. Was homocysteine a cardiovascular risk factor?

To answer this scientific question, several well-conducted observational studies with thousands of patients were performed in the 1990s that unanimously showed that a chronic elevation of plasma homocysteine is a strong predictor of cardiovascular mortality in adult patients.^{4,5} The studies showed a strong, graded risk increase with plasma homocysteine concentrations less than 9 μmol/l conferring the lowest and concentrations more than 20 μmol/l the highest cardiovascular risk. By then it was long known that increased homocysteine can be fairly easily lowered by diet supplementation with B vitamins (vitamin B₂, B₆, B₁₂, and folic acid [= vitamin B₉]), so several research groups instituted large homocysteine-lowering clinical trials with the goal to ameliorate the cardiovascular risk associated with increased plasma homocysteine concentrations. The expectation was clear: lowering plasma homocys-

relevance of this finding? What is the clinical relevance of an acute increase in plasma homocysteine? What is homocysteine?

Homocysteine is a nonessential amino acid whose main role is in the remethylation pathway of methionine. Homocysteine rose to prominence as a potential causative risk factor for early-onset atherosclerosis and cardiovascular disease after McCully published his seminal report in 1969³ on two children who died of premature atherosclerosis due to homocysteinuria with massively increased plasma homocysteine concentrations. Normal plasma total homocysteine concentrations in children range between 4–8 μmol/l (adults 8–12 μmol/l); children with homocysteinuria, if untreated, have 10-fold higher concentrations. The question then became are these homocysteine elevations confined to rare diseases such as homocystinuria, or was

Photo: J. P. Rathmell.

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◆ This Editorial View accompanies the following article: Pichardo D, Luginbuehl IA, Shakur Y, Wales P, El-Sohemy A, O’Connor DL: Effect of nitrous oxide exposure during surgery on the homocysteine concentrations of children. ANESTHESIOLOGY 2012; 117:15–21.

teine to “normal” concentrations would decrease cardiovascular morbidity and mortality. Unfortunately, everyone was wrong. Eight randomized controlled trials with more than 37,485 patients and a follow-up period of more than 5 yr showed absolutely no benefit of B vitamin supplementation on a reduction in cardiovascular morbidity and mortality (relative risk 1.01; 95% CI 0.97–1.05), despite a strong homocysteine-lowering effect.⁶ The homocysteine hypothesis has become a homocysteine controversy; in fact, most researchers now believe that homocysteine is a (bio-)marker rather than a mediator of atherosclerosis and cardiovascular disease.⁷

Now back to the question of N₂O and the acute increase in plasma homocysteine. It is an irrefutable fact that N₂O anesthesia will cause a dose- and duration-dependent increase in plasma homocysteine in all patients. However, is there evidence that acute hyperhomocysteinemia is of clinical consequence for patients? The answer to this question is actually more difficult and complicated than it may seem. Currently, a few studies in human volunteers found that experimentally induced acute hyperhomocysteinemia by way of methionine loading causes endothelial dysfunction.^{8,9} This finding was replicated by Myles *et al.* who investigated N₂O-induced hyperhomocysteinemia,¹⁰ but the clinical relevance of the observed endothelial dysfunction is unknown.

Before we all rush to the conclusion that N₂O-induced hyperhomocysteinemia is potentially harmful, a word of caution. Thus far, not a single study has conclusively proven that it is actually homocysteine that causes endothelial dysfunction. It may well be that homocysteine is nothing but an innocent bystander, a biomarker, for the reduced activity of the folate and methionine pathway and for the temporary vitamin B₁₂ inactivation caused by N₂O. It is telling that the first publication linking N₂O and homocysteine was in 1998,¹¹ right at the peak of the “homocysteine hype”; all studies in the three decades before that investigated N₂O's effects on vitamin B₁₂ – and there were many! – focused exclusively on the decrease in methionine.^{12,13} Currently, even the evidence regarding N₂O and potential adverse cardiovascular outcomes is weak and ambiguous. In adults, two clinical trials are currently investigating the risk of perioperative myocardial infarction related to N₂O (ENIGMA-2 and Vitamins in Nitrous Oxide [VINO]-trial), and it appears prudent to wait until definitive evidence from these trials is available before evaluating the risk associated with N₂O in adults. In children, perioperative myocardial infarction is of no concern and the only potential adverse cardiovascular outcome related to acute hyperhomocysteinemia is venous thrombosis. However, there is currently zero evidence to support this notion.

So, how should we therefore interpret the findings of Pichardo *et al.* in this issue of ANESTHESIOLOGY when serious cardiovascular outcomes related to N₂O are unlikely to be expected in children? The small increase in plasma homocysteine observed in the study is probably of little clinical relevance and we should not attempt to change our clinical prac-

tice based on that finding. What we should be doing, however, is to look at outcomes beyond the operating room. For instance, does the temporary vitamin B₁₂ inactivation caused by N₂O and indicated by an acute increase in plasma homocysteine result in adverse outcomes typically seen in vitamin B₁₂ deficiency such as neuropathy or megaloblastic anemia in children? This question has never been investigated and is unanswered.

Isn't it quite remarkable how little definitive evidence we have regarding N₂O, the oldest anesthetic drug in our armamentarium? Many questions are still unanswered. Is the use of N₂O safe in vulnerable patient populations such as patients with coronary artery disease or children? Or may N₂O actually confer significant benefits to patients as a very interesting recent study suggests, indicating a significantly lower risk of chronic pain after surgery?¹⁴ Is an acute increase in plasma homocysteine of any clinical relevance, recognizing that just because we can easily measure a metabolite in the blood such as homocysteine does not necessarily mean it is important and/or related to observed clinical effects? Answers to these questions and definitive evidence are crucial before we can fully assess the benefit/harm ratio of N₂O in children and adults.

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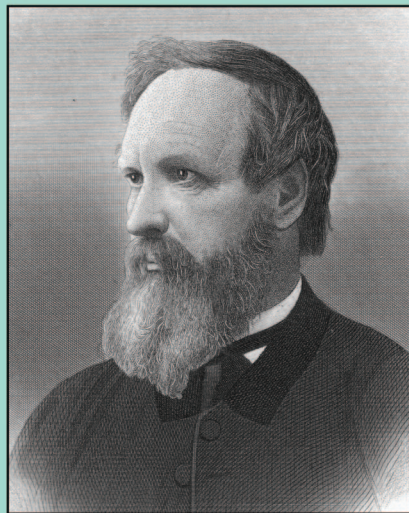
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Edmund Andrews' Portrait by Galaxy Publishing Company

*Edmund
Andrews*



About 5 years after G. Q. Colton had begun repopularizing dental anesthesia with near-asphyxial "laughing gas," another Vermont native, a Chicago surgeon named Edmund Andrews (1824–1904), became famous in 1868 for supplementing clinical use of nitrous oxide with oxygen. Decades later, supplemental oxygen would also help Andrews rally briefly in 1904 before dying postoperatively just days after surgery to remove a bladder stone. As previously released by Philadelphia's Galaxy Publishing Company, Andrews' portrait (*above*) captured his likeness not only for the grieving medical community but also for the Chicago Academy of Sciences, which he not only founded but also served as president for many years. (Copyright © the American Society of Anesthesiologists, Inc.)

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