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NITROUS OXIDE

Who will have the last laugh?

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CONTENTS

Index

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HISTORY

Nitrous oxide is the venerable old gentleman of the anaesthetic world. Its long, eventful and often controversial "life" began in 1772. It was in this year that it was first synthesised by Joseph Priestley, clergyman and discoverer of many "airs" or gases, including oxygen. In 1799, while conducting research into the role of "airs" in spreading disease, Humphrey Davey inhaled nitrous oxide and made an observation that if heeded could have prevented half a century of needless surgical suffering… surgeons! Noticing that it eased the pain of his erupting wisdom tooth he wrote, "As nitrous oxide…appears capable of destroying physical pain, it may probably be used with advantage during surgical operations."

After such a promising childhood nitrous oxide experienced a rebellious adolescence. Its chief use was in nitrous frolics and public demonstrations. Here it gained the moniker "laughing gas" for the amusement it generated in those watching the intoxicated volunteers. Nitrous oxide also dabbled in the arms trade during this period…at least indirectly. Samuel Colt used the money he earned as a nitrous oxide peddler to finance the development of his Colt six-shooter, perhaps the best known weapon of all time. This misspent youth was not entirely wasted, however. It was at one of these public displays, in 1844, that Horace Wells, a dental surgeon, had an epiphany. As he watched, a volunteer accidentally cut his leg while under the influence of nitrous oxide. The man appeared to feel no pain and Wells wondered if the gas would allow painless dental extractions. The following day Wells had one of his own teeth extracted without pain or adverse effect. Filled with enthusiasm he managed to arrange a demonstration at Harvard Medical School in January 1845. The subject groaned and moved while undergoing a dental extraction and the demonstration was viewed as a failure, although the patient later claimed to have felt very little. Discredited Wells withdrew from the development of nitrous oxide and committed suicide three years later.

After another long period in the shadows nitrous oxide reappeared in 1863. In this year, Gardner Q Colton, who had given the demonstration attended by Wells in 1844, resumed his laughing gas shows and successfully administered a dental anaesthetic with nitrous oxide. Soon afterwards the Colton Dental Association was established and achieved great popularity. All of this early activity had occurred in America. The worldwide spread of nitrous oxide anaesthesia began in 1867 when Colton successfully demonstrated its use at the First National Congress of Medicine in Paris. It

subsequently became incorporated into obstetric practice, for labour analgesia and, as predicted by Wells, found a valuable role in the operating room.

It has however had a most eventful adult life, with great triumphs being interspersed with dark controversy. Our knowledge of its physics and pharmacology has grown enormously from the belief that hypoxia was central to its mechanism of action and that cyanosis, lividity and clonic movements of the limbs, secondary to severe hypoxia, were a regular accompaniment to its use. We have witnessed it being lauded as an essential component of almost every general anaesthetic. We have also, increasingly, seen wave after wave of scandals: hypoxic events, neurological complications, foetal loss…especially now as new, more glamorous pretenders to the throne try to unseat it.

What is the truth (or the nearest we have to it: hard science) and what is a fairy tale?

BASIC SCIENCE

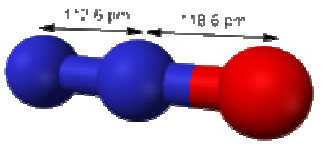
In order to fully appreciate the issues surrounding nitrous oxide a sound understanding of its physicochemical properties and pharmacological actions is required.

Physicochemical Properties

Nitrous oxide is a colourless, non-irritant, odourless, inorganic gas with a molecular weight of 44. It has a boiling point of -88.5ºC and a critical temperature of 36.5ºC. It is thus a gas at room temperature and pressure but can be stored as a liquid under pressure. Although non-flammable and non-explosive it supports combustion well.

Its MAC is 104%, and is thus not suitable as a sole anaesthetic agent,

except theoretically, under hyperbaric conditions. It is inexpensive.



Nitrous oxide is relatively insoluble when compared to the volatile anaesthetic agents. This leads to one of the key characteristics of nitrous oxide-its very rapid onset and offset. As can be seen from the table below only desflurane has a lower blood/gas partition coefficient, however, even its fat/blood partition coefficient is 10 times that of nitrous oxide.

Agent	Blood/Gas	Brain/Blood	Muscle/Blood	Fat/Blood
Nitrous Oxide	0.47	1.1	1.2	2.3
Halothane	2.4	2.9	3.5	60
Isoflurane	1.4	2.6	4.0	45
Sevoflurane	0.65	1.7	3.1	48
Desflurane	0.42	1.3	2.0	27
Nitrogen	0.013			

Table 1: Partition coefficients of inhalational anaesthetics at 37ºC[83].

Nitrous oxide is however far more soluble than nitrogen and as a result nitrous oxide diffuses into air-filled spaces far more rapidly than nitrogen can diffuse out (clinically relevant because of high concentrations used cf. volatiles). This leads to the expansion of the space, if compliant, or, if poorly compliant, to a rise in pressure. Thus nitrous oxide may lead to expansion of pneumothoraces, air emboli, or bowel. It may also increase intracranial pressure in the presence of a pneumocephalus, intraocular pressure when intraocular gas injections have been performed, middle ear pressure, and cuff pressures in endotracheal tubes and supraglottic airways devices.

A similar process leads to the phenomenon of diffusion hypoxia, which may be seen at the end of a nitrous oxide-containing anaesthetic. This problem is however overstated and is easily prevented by a short period of supplemental oxygen during emergence/recovery.

Two other phenomena related to nitrous oxide's physicochemical properties are the concentration effect and the second gas effect. The concentration effect refers to the increase in the rate of rise of the alveolar concentration of nitrous oxide with increasing inspired concentration, i.e. increasing the inspired concentration of nitrous oxide will disproportionately augment its own uptake. This is as a result of two processes: the concentrating effect and the augmented inflow effect, which are discussed in most standard texts. The concentration effect of nitrous oxide will also augment the uptake of concomitantly administered volatile agents: this is known as the second gas effect. It is one explanation for more rapid gas induction when

used in conjunction with a volatile agent. It is, however, probably not clinically very important, the supplementary anaesthetic effects of nitrous oxide being more relevant.

These phenomena are traditionally viewed as being short-lived and only relevant to nitrous oxide and the volatile agents. However, Peyton et al described the persisting concentrating and second gas effects of nitrous oxide on oxygenation[31]. They found that after a mean of 47.5 minutes of anaesthesia with 70% N_2O/30% O_2, PaO_2 rose by 1.8 kPa, compared to 70% N_2/30% O_2. This was only noted when there was significant ventilation/perfusion (V/Q) inhomogeneity: as occurs commonly during anaesthesia. The authors concluded that the perfusion-driven uptake of soluble gases (in relation to nitrogen and oxygen), for example N_2O, occurs in lung units with a relatively low V/Q ratio.

So, even after the phase of rapid uptake of nitrous oxide is completed, there is ongoing uptake from these low V/Q units, and thus, ongoing concentrating and second gas effects on alveolar PO_2. As these lung segments receive a large proportion of pulmonary blood flow the effect on arterial PO_2 is significant and is greater than the competing effect of absorption atelectasis, which is also significant with nitrous oxide.

Mechanisms of Action

Although some controversies remain, we have come a long way from the days when hypoxia was thought to be the key to the mechanism of action of nitrous oxide. As can be seen from the table below, nitrous oxide exhibits many similarities to ketamine and xenon, with regards to its mechanism of action and clinical features, and in this regard differs substantially from both the intravenous anaesthetic agents and the volatile anaesthetics[64].

	Group 1	Group 2	Group 3
General anaesthetics	Etomidate, propofol, pentobarbital	Nitrous oxide, ketamine, xenon, cyclopropane	Halogenated ethers (e.g. isoflurane, sevoflurane, desflurane) and alkanes (e.g. halothane, chloroform)
Clinical features	Strong hypnotics Strong amnestics Weak immobilizers Slow cortical EEG	Weak hypnotics Weak immobilizers Potent analgesics No EEG slowing	Strong hypnotics Strong amnestics Strong immobilizers Slow cortical EEG
Ratio of MAC-immob. to MAC-awake	4 (propofol)	1.5 (N_2O)-2 (Xe)	2 (halothane)-3 (halogenated ethers)
Molecular targets	$GABA_A$ receptors (β_3 and β_2 subunits)	NMDA receptors AMPA receptors Neuronal nAChRs 2-pore K^+ channels	$GABA_A$ receptors Glycine receptors Glutamate receptors (NMDA and AMPA) Neuronal nAChRs 2-pore K^+ channels

EEG, electroencephalogram; NMDA, *N*-methyl-D-aspartate; $GABA_A$, gamma-aminobutyric acid subtypeA; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

Figure 1: General anaesthetic classification based on clinical features and molecular targets[64].

The sedative and immobilising effects of nitrous oxide appear to be mediated separately to its analgesics effects and will thus be discussed individually[7, 11, 47, 64, 72]. This is not only important conceptually but may have practical implications, as discussed later.

Sedative/Amnestic/Immobilising Mechanisms

Central to the mechanism of nitrous oxide's anaesthetic action appears to be the noncompetitive inhibition of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Glutamate is the major excitatory neurotransmitter in the brain. N_2O thus markedly inhibits glutamate-mediated excitatory neurotransmission. Whether this effect is partially mediated by other glutamate receptors i.e. AMPA and kainite, is currently not known.

Inhibition of these receptors alone is, however, insufficient to fully explain nitrous oxide's anaesthetic actions. Also important appears to be the two-pore domain potassium channels, in particular TREK-1. This is a background leak potassium channel that regulates the resting membrane potential in neurons of the brain and spinal cord. When activated these channels open, resulting in increased potassium conductance/efflux, hyperpolarisation and decreased excitability of the neurons.

Inhibition of the $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptor may contribute to the amnestic action of nitrous oxide.

What is important to note is that unlike the IV and volatile agents, $GABA_A$ receptor enhancement does not occur as part of nitrous oxide-induced anaesthesia.

Analgesic Mechanism of Action

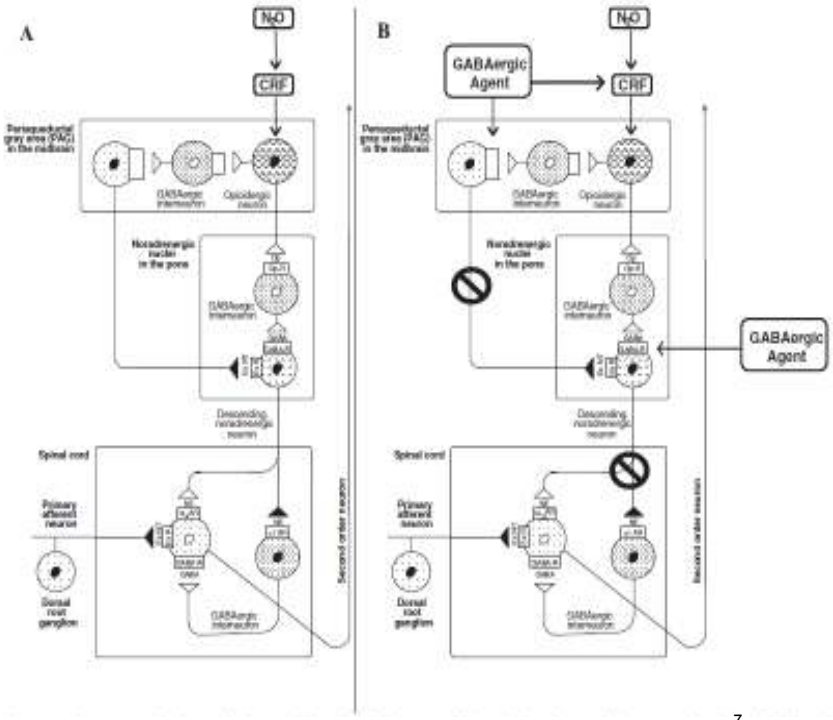


Figure 2: Neuronal pathways for nitrous oxide-mediated analgesia[7].

Nitrous oxide-induced analgesia is initiated supraspinally. A key initiating event appears to be the release of corticotrophin-releasing factor (CRF) from the hypothalamus, as a result of NMDA receptor antagonism. Activation of opioidergic neurons in the periaqueductal grey matter (PAG) and noradrenergic neurons in the locus ceruleus, A5 and A7 areas in the brainstem then follows. Specifically, CRF causes release of opioid peptides in the PAG. These activate opioid receptors on GABAergic interneurons, inhibiting these inhibitory interneurons. Recent evidence also points to a role for the nociceptin receptor ("opioid-like") and its endogenous

ligand, nociceptin[47]. This system works via either direct dopamine antagonism or indirectly via GABA inhibition. The end result of the above mechanisms is the removal of the GABA-mediated inhibition of the excitatory interneurons of the descending inhibitory noradrenergic neurons of the pons/medulla. Simply put, one now has activation of the descending noradrenergic pathways, which release noradrenaline (NA) at their nerve terminals in the dorsal horn of the spinal cord. NA then activates α_1 receptors on GABAergic interneurons, increasing GABA release, which in turn activates inhibitory $GABA_A$ receptors on second order afferent neurons. In addition, there is activation of postsynaptic α_{2B}-receptors on the second order neurons. The nett effect is inhibition of the second order neurons and a reduction in the ascending transmission of pain impulses to the brain.

It is interesting to note, as shown in B) of figure 2, that addition of a GABAergic agent can attenuate the nitrous oxide-induced activation of the noradrenergic descending inhibitory interneurons. In addition, animal studies have shown that GABAergic agents, e.g. volatiles and propofol, reduce nitrous oxide's analgesic effect. The clinical evidence to back this up is poor but it has led some authorities to state that its analgesic effect, when coadministered with a volatile, is minimal and is not critical to its anaesthetic action.

The clinical correlate of this view is that nitrous oxide is a potent analgesic when administered alone, e.g. for procedural sedation, but when administered as part of a balanced anaesthetic the analgesic effect is reduced and may in fact be minimal. This view is not in accordance with an overwhelming number of publications that attest to its analgesic efficacy, even when used as part of a balanced anaesthetic technique. As an example, Mathews et al in Anaesthesia and Analgesia of 2008, equate a remifentanil whole blood concentration of 2ng/ml with 66% N_2O - hardly insignificant[62].

Also of interest, and a topic of some controversy, is the interaction between N2O and opioids. The review by Sanders noted two studies that suggest that if sufficient fentanyl is given, the addition of nitrous oxide does not have any further MAC-reducing effect[7]. In contrast to this the same review refers to a study that noted a 60% MAC reduction in sevoflurane when nitrous oxide was added to a sevoflurane-remifentanil anaesthetic.

The authors felt that this may be because nitrous oxide's NMDA receptor antagonism counteracts the potentiation of NMDA receptors by remifentanil (not seen with fentanyl) and thus continues to be MAC sparing when used with remifentanil but not with fentanyl. It is also thought that this

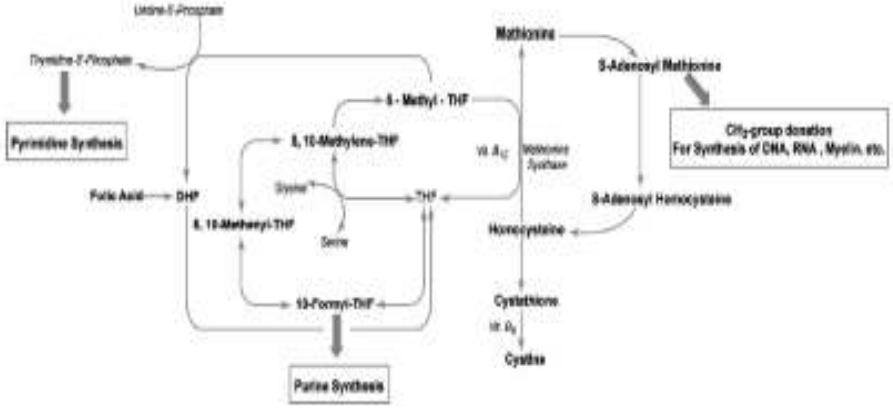
mechanism may allow nitrous oxide to block remifentanil-induced postoperative hyperalgesia. So, is the role of nitrous oxide interchangeable with that of the short-acting opioids, or are there important differences? Many questions remain. It is clear, however, that the interaction between nitrous oxide and the volatiles and opioids is more complex than frequently realised. We can safely say that we don't know all the old dog's tricks, let alone what new ones it can still be taught.

Pathophysiological Mechanisms

Inhibition of methionine synthase by nitrous oxide is central to the pathophysiology of many of its claimed adverse effects and will thus be discussed in some detail[7,13,14,57,60,61]. The pathophysiology of the adverse effects resulting from its physicochemical profile, e.g. expansion of air-filled spaces, has been alluded to previously and will not be discussed further here.

Figure 3: Pathophysiology related to methionine synthase inhibition[7].

Nitrous oxide irreversibly oxides the cobalt I (Co+) form of cobalamin (vitamin B12) to the cobalt III (Co3+) and cobalt II (Co2+) forms. Oxidised



cobalamin is no longer biologically active and can thus no longer act as the cofactor for methionine synthase, leading to its inhibition. As can be seen from the figure, methionine synthase is central to the generation of methionine, and hence S-adenosyl methionine, from homocysteine. S-adenosyl methionine is the methyl donor in over 100 metabolic steps including the methylation of DNA, RNA, proteins, phospholipids, myelin,

polysaccharides, cathecholamines and neurotransmitters. Inhibition of methionine synthase will thus result in a reduced concentration of methionine and an elevated concentration of its precursor homocysteine.

Methionine synthase also requires 5-methylenetetrahydrofolate (5-methylene-THF) as a cofactor. Tetrahydrofolate (THF) is methylated, via methyl groups donated from the interconversion of serine and glycine, to 5,10-methylene-THF. The enzyme 5,10-methylene-THF reductase (MTHFR) then reduces 5,10-methylene-THF to 5-methylene-THF, which in turn donates a methyl group to cobalamin, forming methylcobalamin and regenerating THF. This process is central to the broader folate cycle which, in turn, is crucial for purine and pyrimidine synthesis. Methylcobalamin is the final methyl donor for methionine synthase.

Folate-cobalamin cycle inactivation has been proposed to be responsible for adverse effects of nitrous oxide as diverse as megaloblastic anaemia, neurotoxicity (including subacute combined degeneration of the spinal cord), immunosuppression, impaired wound healing, and teratogenicity. The elevated homocysteine has been linked to endothelial dysfunction and hypercoagulability and the consequences thereof e.g. perioperative adverse cardiac events and venous thromboembolism.

In addition, hyperhomocysteinaemia has been associated with the development of atherosclerosis and its consequences, neurodegenerative diseases/dementia, and potentiation of excitotoxicity.

What is the clinical relevance of these changes though?

There are a number of factors to consider.

Firstly, what level of exposure is required to significantly inhibit the above pathways? Human data suggest that 70% nitrous oxide results in a 50% reduction in methionine synthase activity within 46-90 minutes, with almost no activity being detectable after 200 minutes. Recovery appears to occur within 3-4 days.

Second, are all patients equally susceptible? It appears not. Most patients have adequate stores of S-adenosylmethionine to see them through the perioperative period. At risk patients include those who are at risk of vitamin B12 or folate deficiency and those with certain genetic profiles.

Risk factors for B12/Folate deficiency	
Nutritional	Elderly
	Vegans
	Alcoholics
Malabsorption	Pernicious anaemia
	Atrophic gastritis
	Gastrectomy
	Whipple's
	Ileal resection
	Crohn's disease
	Prolonged antacid use
Infection	Intestinal bacterial overgrowth
	Intestinal parasites

Table 2: Risk factors for vitamin B12 or folate deficiency. Modified from Sanders et al[7].

Certain rare genetic disorders have been associated with adverse outcomes following nitrous oxide anaesthesia, e.g. autosomal recessive MTHFR deficiency/ Type III homocystinuria. These are exceedingly rare, and arguably not really relevant in routine clinical practice. What could be far more relevant, however, are certain fairly recently described, relatively common, single nucleotide polymorphisms (SNP's) of the MTHFR gene. The 677 cytosine-thymidine (677C>T) and 1298 adenosine-cytosine (1298A>C) SNP's result in reduced MTHFR activity. Homozygosity for these mutations results in higher baseline plasma homocysteine levels and greater postoperative increases after nitrous oxide exposure compared to both wild-type and heterozygous patients. The clinical correlates of this difference are as yet unknown. These reports are of interest, however, as these mutations are common, with approximately 20% of the Western European population being homozygous for one of the mutations. It must also be pointed out, though, that many non-genetic factors influence homocysteine levels, including drugs (antibiotics, isoniazid, antiepileptics) and medical conditions (hypothyroidism).

Thirdly, are any adverse effects time-dependent? The answer is yes in some circumstances: subacute combined degeneration of the cord, for example, is almost exclusively described in long-term nitrous oxide use/abuse. It is not, however, as clear in other situations. Elevated homocysteine levels appear to result in endothelial dysfunction and hypercoagulability in the acute setting. Chronic hyperhomocysteinaemia is associated with atherosclerosis and chronic neurological disease e.g. dementia. The exact time scale and range of effects, if any, of elevated homocysteine in the perioperative setting is not currently known. It is not even known if the elevated homocysteine is causative or if it is merely an "innocent bystander".

Fourth, can these potentially adverse biological effects be prevented? It appears that they can. A study by Badner et al showed that preoperative supplementation with folate, B6 and B12, for a week prior to orthopaedic surgery, prevented the nitrous oxide-induced postoperative increase in plasma homocysteine[61]. This obviously needs further study, for example to optimise the timing and duration of supplementation, but is an interesting prospect.

From the above it is clear that much remains to be learnt regarding the nitrous oxide's pathophysiological mechanisms and the relevance of these to routine clinical practice. Some interesting points are raised though. Perhaps we should be moving to a point where as part of our preoperative assessment we evaluate a patient's risk of B12/Folate deficiency clinically and with guided laboratory testing. Surely the preoperative assessment of the future has to include genetic profiling, with MTHFR SNP's being an appropriate example. It also raises the question of whether vitamin supplementation should be part of our premed, or postoperative therapy, if we are considering nitrous oxide as part of our anaesthetic regime.

A CRITICAL APPRAISAL OF THE RISKS AND BENEFITS OF NITROUS OXIDE

As has been alluded to above, nitrous oxide is not the known quantity many of us thought it was. We are learning more and more about this agent and finding more unanswered questions with modern anaesthetic research. It has become scientific fashion, at least amongst many of us in this department, and probably country, to view nitrous oxide as an anaesthetic Untouchable or at best a second-rate citizen. I wish to re-examine conventional wisdom and see how much of it still holds true and hopefully come to a unified conclusion of sorts regarding its place in anaesthetic practice in 2010.

ENIGMA

Before examining the individual claimed risks and benefits I wish to briefly discuss the "ENIGMA" trial which was published in 2007[26]. Entitled "Avoidance of Nitrous Oxide for Patients Undergoing Major Surgery", this trial was taken by many to be the death knell for nitrous oxide: a view endorsed by the accompanying editorial[27]. This trial recruited 2050 patients, randomly assigning them to either a nitrous oxide-free (80% oxygen, 20% nitrogen) group or a nitrous oxide-based (70% nitrous oxide, 30% oxygen) group. All patients were scheduled to undergo major surgery of at least 2 hours duration. It was presented as a pragmatic study, with no attempt to control for possible confounding variables and the anaesthetist

had the option to cross over from one group to the other. The primary endpoint was duration of hospital stay. Secondary endpoints included duration of ICU stay, severe PONV, pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, awareness, and death within 30 days.

The results showed that there was no difference between the two groups with regard to the primary endpoint, duration of hospital stay. Analysis of the secondary endpoints, however, appeared to show a lower rate of major complications (wound infection, atelectasis, and pneumonia) and severe PONV. No significant difference in major adverse cardiac events or death was reported. The validity of these results, particularly with regard to the secondary endpoints, has generated a flurry of controversy. The opponents of nitrous oxide use have enthusiastically endorsed these results as definitive evidence to abandon its use. This view is inappropriate for a number of reasons. The chief reason is that the primary endpoint of the study showed no difference between the two groups. Presumably this endpoint was chosen as a composite endpoint to reflect any significant adverse postoperative events, and was adequately powered to detect any significant differences. The fact that it showed no difference can thus be taken, as one correspondent to Anesthesiology put it, "as additional evidence of the remarkable safety of nitrous oxide over the past 150 yr"[23]. In addition, results of the secondary endpoints must be viewed with suspicion. As even the authors of ENIGMA noted "We undertook multiple comparisons, which increases the chance of a type I error; the secondary, exploratory, and subgroup analyses should be treated cautiously."

Other criticisms of ENIGMA include the choice of 80% O_2/20% N_2 as a control group. The question which has been raised frequently is thus, is any difference between the groups due to a nitrous oxide effect or an oxygen effect? Although academically interesting, I don't think it discredits the study. It simply means that if we believe there is a difference between the groups, it could be due to avoidance of N_2O or use of a high inspired concentration of oxygen. It is useful to know which of these it is, but, as a high FiO_2 would be impossible to achieve with the use of nitrous oxide, for our purposes, it makes little practical difference.

A more important factor is that the depth of anaesthesia between the two groups was not equivalent. The median end-tidal agent concentration in the nitrous oxide-free group was 0.87 MAC while in the nitrous oxide group the total was 1.31 MAC. Monk, et al showed that cumulative deep hypnotic time was an independent predictor of postoperative mortality[79]. The

difference in depth of anaesthesia between the two groups casts significant doubt on the validity of the findings of the study.

In addition, due to the pragmatic nature of the study other confounding variables may not have been adequately accounted/controlled for. As an example, the nitrous oxide-free group received significantly more propofol. It's not possible to say whether this affected the PONV results, or any other outcomes.

The authors of ENIGMA have also been accused of bias against N_2O. They appear to have highlighted the adverse secondary outcomes over the neutral primary outcome. In addition, the study was not blinded.

It should also be highlighted that ENIGMA included only patients undergoing major surgery predicted to last longer than 2 hours. This represents only a proportion of surgical procedures, and a group of patients at particular risk of adverse perioperative outcomes.

As a final word on ENIGMA, clinical practice should generally not be altered on the basis of a single study. This is especially true when based on secondary outcomes of doubtful validity.

In response to these concerns regarding ENIGMA, ENIGMA II commenced enrolment in 2007[4]. This study aims to recruit 7000 patients at risk of coronary artery disease, undergoing non-cardiac surgery, to test the hypothesis that omitting N_2O will reduce the incidence of death and major adverse cardiac events. A key difference (vs. ENIGMA) is that the control group will now use a 70% N_2/ 30% O_2 mix to avoid the possible confounding effect of the high FiO_2 in ENIGMA. Thus far 2367 patients have been randomised and we eagerly await the results of this study.

It is now time to analyse the claimed risk and benefits of nitrous oxide individually.

Claimed Risks		Claimed Benefits	
Haematological	Bone marrow suppression/ Megaloblastic anaemia		
Immunological	Immunosuppression		
	Increased infectious complications		
Neurological	Neurotoxicity	**Neurological**	Neuroprotection
	Myelinopathies		Improved CBF
	Intracranial dynamics		
	Neurodevelopmental		
	POCD		
CVS	Endothelial dysfunction	**CVS**	Haemodynamic stability
	Thromboembolism		Improved vasoreactivity
	Myocardial Ischaemia		
	Sympathetic stimulation		
	Myocardial depression		
	Pulmonary vasoconstriction		
Respiratory	Hypoxia	**Respiratory**	Reduced respiratory depression
	Atelectasis		Improved oxygenation
PONV			
Expansion of air-filled spaces	Bowel		
	Pneumothorax		
	Pulmonary bullae		
	Pneumocephalus		
	Venous air embolism		
	Middle ear		
	Intraocular		
	Cuff		
Teratogenicity/ Foetotoxicity			
Occupational	Reproductive		
	Genotoxicity		
	Neurological		
	Haematological		
Environmental			
		Awareness	
		Anaesthetic sparing	Volatiles
			Opioids
			Muscle relaxants
		Cost-effective	
		Induction	Faster
			Smoother
			Fewer adverse events
		Emergence	Rapid
		Miscellaneous	Versatile
			Simple to use
			Extensive experience
			Familiarity
			Established safety profile

Table 3: Claimed risks and benefits of nitrous oxide use.

Haematological
On any list of nitrous oxide-related adverse effects, haematological complications feature prominently. These are secondary to methionine synthase inhibition and include bone marrow depression, megaloblastic changes, megaloblastic anaemia, leukopaenia, thrombocytopaenia, and agranulocytosis. What is the clinical relevance though?

It appears that prolonged exposure of at least 12-24 hours is required to cause significant megaloblastic bone marrow changes in healthy patients. Of more concern are studies pointing to the development of these changes after relatively short periods in certain vulnerable groups. Amos et al described the presence of megaloblastic bone marrow changes in critically ill patients. Eighteen of 22 patients with megaloblastic changes had received a nitrous oxide-based anaesthetic lasting 2-6 hours. Of note though, 4 patients with megaloblastic changes had therefore not received nitrous oxide. Deleu et al examined the effect of nitrous oxide exposure in 69 elderly patients undergoing eye surgery. They noted that patients exposed to nitrous oxide exhibited a decreased serum folate and increased mean red cell volume.

No significant differences in red cell folate, haematocrit and haemoglobin levels were found between the nitrous oxide and nitrous oxide-free groups. Three patients exposed to nitrous oxide developed symptoms suggestive of folate deficiency, which responded to folate therapy. It appears that these megaloblastic changes may resolve as early as 12 hours after cessation of the exposure and can be avoided by preoperative folate or B12 supplementation. The clinical implications of these haematological changes, when they do occur, are not clear but I have found little evidence to suggest that they contribute directly to adverse outcomes[7, 45, 48, 51, 52].

In conclusion, it appears that the haematological effects of nitrous oxide exposure have been overstated. Healthy patients should safely tolerate exposures of 12 hours or longer. It does seem prudent, however, to exercise more caution with patients at risk of B12 or folate deficiency if lengthy procedures (> 2 hours) are planned. These risk groups include the elderly, critically ill, or malnourished. Ideally these patients should be tested to identify those truly deficient in B12 or folate, but if this is impractical or too costly, empiric perioperative B12 and folate supplementation is simple, safe and cost effective.

Immunological
Immunosuppression is another oft-stated adverse effect of nitrous oxide[7, 45, 48, 51, 52]. In addition to the theoretical risk of leukopaenia/granulocytopaenia

from bone marrow suppression, a number of laboratory studies have fuelled these immunological concerns. Studies have variously reported reduced neutrophil chemotaxis, reduced mononuclear proliferation, impaired cell-mediated cytotoxicity, and reduced alveolar macrophage activity. In contrast, unaltered or increased neutrophil chemotaxis has also been reported. In addition, impaired methionine production may impair protein synthesis and thus wound healing.

Again, the clinical impact of the laboratory data is not clear. The results of ENIGMA have been discussed in some detail already. Although the apparent increased incidence of wound sepsis and pneumonia in the nitrous oxide group is of concern, as previously mentioned, these results must be viewed with circumspection. In contrast to ENIGMA, Fleishmann et al reported on the effect of nitrous oxide on wound infection in colonic surgery patients[35]. 418 patients were randomised to either 65% N_2O or 65% N_2. The rate of wound infection in the N_2O group (15%) did not differ significantly from that in the N_2 group (20%). Other studies have pointed to a possible reduction in wound infection with the use of high inspired oxygen concentrations. The validity of these results and required inspired concentration is still the topic of debate.

In summary, surgery/anaesthesia impairs immune function irrespective of the anaesthetic agents used with no real evidence to support one agent over the other. It is likely that attention to detail with regard to temperature control, prophylactic antibiotics, glycaemic control, and respiratory hygiene is more likely to influence the risk of perioperative infectious complications than the choice of anaesthetic agent.

Neurological
The effects of nitrous oxide on the nervous system have generated more controversy and comment than probably any other aspect of this agent. Many of the debates are still ongoing but islands of clarity appear to be emerging from the confusion.

Myelinopathies
Nitrous oxide has been well documented as a cause of myelinopathies. The presentation may range from the classic subacute combined degeneration of the cord to any combination of mental state abnormalities, seizures, paraesthesias/ dysaesthesias, weakness, or spasticity. This form of toxicity appears to be directly related to inhibition of methionine synthase. These effects are classically described in nitrous oxide abusers or patients who received long-term N_2O sedation in the ICU. Case reports do exist of neuropathies following routine nitrous oxide exposure in patients with

vitamin B_{12} or folate deficiency. These cases appear to respond to well appropriate supplementation. Therefore, a high index of suspicion for B_{12} or folate deficiency and a low threshold for B_{12} and folate pre-treatment or therapy should essentially abolish this small risk. Folate supplementation should never be given in isolation as it may worsen neurological injury in patients with an unrecognised B_{12} deficiency.

A few case reports exist of severe adverse neurological outcomes in patients with rare congenital abnormalities of B_{12} or folate metabolism, for example MTHFR deficiency. These disorders are extremely rare and unlikely to be more common than the possibility of an idiosyncratic reaction to any other drug or an adverse effect such as malignant hyperthermia with the volatiles. This should not affect the use of nitrous oxide in the paediatric population. Again, though, common sense, a high index of suspicion in any child with unexplained neurological symptoms, and a low threshold for investigation and treatment of any unexplained postoperative neurological symptoms, should allow for appropriate management of these rare cases.

Neurotoxicity/Neuroprotection

An area of great controversy is whether nitrous oxide is neurotoxic or, in fact, neuroprotective. The waters here are extremely muddy but I have tried to tease out the salient points from the available literature.

Focusing first on hypoxic-ischaemic or excitotoxic injury, selective NMDA receptor antagonists have been shown experimentally to exacerbate neuronal injury. N_2O itself has been shown to impair electrophysiological recovery from hypoxic injury in the rat brain[48]. In addition, Miura et al found that cerebral injury in a model of near-complete ischaemia was worse in nitrous oxide/fentanyl-exposed rats and ketamine-exposed rats, versus those anaesthetised with isoflurane. No difference was found with incomplete ischaemia, however[49]. Other studies have shown morphological changes consistent with neurotoxicity in rat cortices after N_2O exposure. However, these changes only occurred with hyperbaric exposure to nitrous oxide and resolved within 3 hours[7]. In addition, further studies have shown that coadministration of a GABAergic agent, for example a volatile or propofol, as occurs in clinical practice, can prevent these changes[7, 48].

To further complicate matters, it is well known that excessive stimulation of the NMDA receptor by glutamate leads to an excessive neuronal calcium load. This may lead to neuronal injury or death, especially if cellular energy stores are depleted, as with ischaemia. Thus NMDA receptor inhibition may actually be neuroprotective. Haelewyn et al showed that

nitrous oxide reduced the injury associated with intracerebral NMDA injection and reduced infarct volume after middle cerebral artery occlusion in rats[10].

The effect of nitrous oxide on dopamine release may also play a role in its neurotoxic/neuroprotective effect. Some studies show nitrous oxide increases dopamine release, with haloperidol, a dopamine antagonist, protecting from the subsequent neurotoxicity[7]. In contrast, Haelwyn showed that nitrous oxide resulted in less dopamine release after oxygen-glucose deprivation in a rat-brain model.

The neurobiological and animal data is thus inconsistent and often contradictory. The best available clinical data in humans come from a study by Pasternak et al, published in Anesthesiolgy in 2009[5]. This study was a post hoc analysis of a subset of data from the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST). A previous report had shown no adverse effects of nitrous oxide on outcome in the full set of IHAST patients; in fact there was a trend to improved 3-month neurological outcome and more patients were discharged home (vs. a long-term care centre) in the nitrous oxide group[5, 16, 17]. As a result of vocal opposition to the use of nitrous oxide in patients with, or at risk of, ischaemic brain injury, the authors decided to perform a further analysis on the IHAST patients at greatest risk of ischaemic cerebral injury: those who underwent temporary cerebral artery clipping. It was felt that if nitrous oxide did adversely influence outcome, it would be apparent in this group. In fact, the study showed that nitrous oxide had no detrimental effect on long-term gross neurologic or neuropsychological function. Although there was an initial increase in delayed ischaemic neurological deficits in the nitrous oxide group, there was a significantly decreased risk of impairment in one or more neuropsychological tests at 3 months.

This study has the flaws inherent in a post hoc analysis, however, its large size and the quality of the IHAST database make this the best available evidence on the use of nitrous oxide in neurosurgery, and in particular in patients at risk of cerebral ischaemia. It is unlikely that a larger study will be undertaken in this population any time soon. Thus, the conclusion from the original analysis that, “nitrous oxide is unlikely to lead to adverse neurological…outcomes in neurosurgical patients at risk of cerebral ischaemia”, remains the final word for the foreseeable future.

Neurodevelopment

Concerns over possible adverse neurodevelopmental effects of nitrous oxide have also been raised and this has created much alarm amongst paediatric anaesthetists. NMDA receptor antagonists were initially shown to cause widespread neuronal apoptosis in neonatal rats. Subsequently it was shown that nitrous oxide, on its own, up to a concentration of 75%, does not have this effect. It does however appear to worsen isoflurane-induced neurodegenerative changes, with the combination of nitrous oxide, midazolam and isoflurane resulting in widespread apoptosis and learning impairment after 6-hours exposure in 7-day old rats[7, 60]. In contrast, Slikker et al showed that a 3-hour exposure to ketamine (an NMDA antagonist like N_2O) did not result in any neuronal death in 5-day old rhesus monkeys[60]. For those enamoured with animal studies, this should provide some comfort as it mimics normal clinical paediatric anaesthesia better than the studies mentioned above.

These findings need to be put into perspective. Whether NMDA antagonists or GABAergic, practically every anaesthetic agent has been shown to cause neurodegenerative changes in some animal model. The extrapolation of animal studies to humans is fraught with difficulty. As an example, synaptogenesis lasts from two days before birth to two weeks of age in rats. In humans, however, the equivalent period spans from the last trimester to the first few years of life. A 6-hour anaesthetic in a 7-day old rat equates more to a few days anaesthesia in a human infant. Other sources suggest that the vulnerable periods for rats and monkeys, actually, more closely correlates with the 22-26th weeks of human gestation[69]. In addition, it is not known if the apoptosis shown in these studies is pathological, or is merely an acceleration of the apoptosis that is essential for normal brain development.

Furthermore, there is no clinical evidence linking N_2O, specifically, to any adverse neurodevelopmental outcomes in humans. There is a potential link to anaesthesia in general but these studies are heavily flawed. If anything, they suggest that only a very small number of individuals who have an anaesthetic exposure early in life may be susceptible to anaesthesia-induced neurodevelopmental problems[69]. It must be emphasised that these studies focus on anaesthesia in general and not nitrous oxide specifically.

In summary, there is no current evidence to suggest any adverse neurodevelopmental effects from nitrous oxide in routine clinical practice.

POCD

Nitrous oxide has also been linked to postoperative cognitive dysfunction (POCD) in a rat model. Clinical trials have found no such link. The available evidence suggests that POCD results from a neuroinflammatory response to surgery and that the choice of anaesthetic plays little role in its development.

Intracranial dynamics

With regards to intracranial dynamics, N_2O is widely stated to increase cerebral metabolic rate ($CMRO_2$); cerebral blood flow (CBF) and thus cerebral blood volume (CBV) and intracranial pressure (ICP); and impair autoregulation. The increase in CBF appears to be a result of an indirect vasodilatory effect secondary to the increased $CMRO_2$. Some sources, however, state that the increased CBF is independent of cerebral metabolic rate[48]. The specifics and clinical implications are, however, more complex.

Nitrous oxide has been shown to increase CBF, or its surrogate, cerebral blood flow velocity (CBFV), when added to isoflurane and propofol; to decrease CBF when added to 1 MAC sevoflurane; and to have no effect with 1 MAC desflurane[49, 77].

It impairs autoregulation when used on its own, and when added to 1 MAC sevoflurane, but not when added to propofol or 1.5 MAC sevoflurane[44].

Carbon dioxide reactivity appears to be preserved when used with both volatiles and propofol[44].

These studies raise a number of issues worth considering:
Is there a dose response relationship for the effects of nitrous oxide on cerebral dynamics? A variety of inhaled concentrations of N_2O were used in these studies but none have addressed this question.
Are some combinations (e.g. N_2O and propofol) superior to others? It appears that the effects of nitrous oxide differ according to the agents with which it is coadministered. However, we simply do not know for certain with the current research.

In addition, it appears that the effects on CBF, CBV, and ICP are in fact mild, and as CO_2 reactivity is preserved, any increase in these parameters can be readily offset with mild hypocapnia[44, 49]. It should be noted though, that the effect of hypocapnia is abolished if N_2O is added after the induction of hypocapnia[44].

It is also worth considering the fact that a number of these studies added N_2O to 1 MAC and above of a volatile. I don't believe that this reflects best clinical practice, and probably defeats the purpose of using N_2O. In any case, when one administers greater than 1 MAC of a volatile, the adverse effects of the volatiles on intracranial dynamics begin to predominate. To tie in with this, it has been reported that if a patient is lightly anaesthetised, addition of N_2O may actually depress cerebral metabolism and reduce CBF. Again, this suggests that, if used appropriately, N_2O does not have the adverse effects commonly stated[44].

With regard to relevant clinical studies, Ostapkovich reported that two N_2O-based anaesthetic techniques resulted in good surgical conditions in patients undergoing supratentorial brain tumour surgery. This was despite many of the patients having significant midline shift[49].

To further complicate matters, Hancock et al reported on the effects of nitrous oxide on zero flow pressure (ZFP) and cerebral perfusion pressure (CPP) [38]. CPP, the driving pressure in the cerebral circulation, is essentially upstream pressure less downstream pressure. Traditionally CPP has been viewed as being equal to mean arterial pressure (MAP) – ICP or central venous pressure (CVP), whichever is higher. Vascular tone is, however, a potentially significant, previously ignored, determinant of the downstream pressure. The ZFP is the arterial pressure at which cerebral blood flow would cease, and reflects the interaction between ICP, CVP, and vascular tone; with vascular tone actually being the primary determinant. It thus, represents a more accurate means of describing the downstream pressure. Hancock found that 50% N_2O reduced ZFP and increased CPP during normocapnia. The implication is that although nitrous oxide-induced cerebral vasodilation increased CBV, the effect on ZFP dominated and resulted in a nett increase in CPP. This study is limited by the fact that it only included subjects with normal intracranial compliance. Although the results, as they stand, cannot be extrapolated to routine clinical practice and patients with reduced intracranial compliance, it is an interesting alternative perspective to traditional views on intracranial dynamics.

Thus, although complex and incompletely elucidated, it appears that the effects of N_2O on intracranial dynamics are at most mild and are easily managed, if required, with mild hypocapnia. To err on the side of caution, it is probably best to avoid N_2O in patients with severe, acute elevations of ICP, for example severe TBI. This is purely in the absence of definitive proof of its safety in this population, and with misgivings about the volatiles and IV agents as well. Attention to systemic haemodynamics and avoiding

secondary insults is probably more important than the choice of anaesthetic agent.

Although not a direct neurological effect of nitrous oxide, its haemodynamic stability deserves a mention in this context. Episodes of hypotension have been shown to correlate with adverse neurological outcomes in head-injured patients. Nitrous oxide is less likely to cause hypotension than other anaesthetic agents, for example propofol, isoflurane and remifentanil, and allows a dose reduction of these agents. It is unlikely to be tested, but this may theoretically contribute to improved neurological outcomes with the use of nitrous oxide in vulnerable neurosurgical patients.

The easy titratability and rapid offset of nitrous oxide are also useful for neurosurgical procedures; where one wants to cover stimulating intraoperative periods but also wishes to have rapid postoperative awakening to assess neurological function.

So, it must be emphasised that used appropriately N_2O is unlikely to cause any adverse effects in the neurosurgical population, and is a useful weapon in the neuroanaesthetist's arsenal.

Cardiovascular

The cardiovascular effects of nitrous oxide are an exciting area of debate and research, with much controversy and conflicting results regarding the actual balance between the purported risk and claimed benefits.

Nitrous oxide is often stated to have little overall effect on cardiovascular physiology. This applies to both healthy adults and children[52]. Constant et al reported that 50% N_2O in children had no effect on mean arterial pressure, systolic pressure variation, and baroreceptor sensitivity. It did decrease heart rate variability, with a shift to parasympathetic dominance, but there was a rapid return to baseline after stopping the agent[66].

Although the direct effect on the heart is mild negative inotropy, this is generally offset by increased sympathetic activity[48]. Kawamura et al reported that 60% N_2O increases cardiac output during the first hour of administration, with the cardiac output returning towards baseline during the second hour[68]. This suggests that the cardiovascular stimulation may be transient.

Sympathetic activation also results in vasoconstriction, most likely via α-adrenergic stimulation. This has a greater effect on the pulmonary vasculature, resulting in elevated pulmonary vascular resistance and an

increase in pulmonary artery pressure[52]. Preexisting pulmonary hypertension is thus a relative contraindication to nitrous oxide, as it may aggravate the pulmonary hypertension and cause right ventricular afterload. This effect is at least partially counteracted by the increased right ventricular function secondary to sympathetic activation[45].

The stimulatory effects of nitrous of nitrous oxide may be obtunded by high-dose opioids, unmasking the direct depressant effects[45, 48]. This may also occur in patients with severe left ventricular dysfunction or pre-existing marked sympathetic activation[52]. This has led some authors to recommend great caution when using nitrous oxide in patients with cardiovascular risk factors, or severe underlying cardiovascular disease with increased peripheral vascular resistance or impaired cardiac function[52].

It has also been reported that the sympathetic activation may sensitise the myocardium to the arrhythmogenic effects of catecholamines.

These haemodynamic criticisms are probably overstated and represent a narrow view of the effects of nitrous oxide in isolation, because, in comparison to other anaesthetic agents, nitrous oxide appears to actually promote haemodynamic stability.

Cardiovascular depression is seen especially with > 1 MAC of the volatiles, and throughout the concentration range with propofol infusions[51]. Inada et al, however, reported that 65% nitrous oxide, with either isoflurane or sevoflurane, produced less hypotension than equi-MAC concentrations of the volatiles alone[51]. McKinney et al also reported that in elderly patients, a 50% N_2O/Isoflurane mix produced less cardiovascular depression than 1 MAC isoflurane alone[48, 59]. Shiga et al showed that adding 70% nitrous oxide to increasing target concentrations of propofol did not cause any effect on the blood pressure until the target concentration was over 5ug/ml[51]. Hopkins is of the opinion that these haemodynamic benefits are especially important if cardiovascular reserve is reduced, whether from age, pathology or medication[51]. As an example, the hypotensive effects of the volatiles and propofol are potentiated by calcium channel blockers, as they all inhibit myocardial and smooth muscle calcium channels. Nitrous oxide does not affect these channels and therefore causes no additional cardiovascular depression in patients on calcium channel blockers.

The significance of the improved intraoperative haemodynamic stability is not known. Kheterpal et al found that high risk patients with sustained (≥ 10 minutes) intraoperative hypotension (MAP < 50mmHg or a decrease in MAP by ≥ 40%) were significantly more likely to experience adverse cardiac

events[55]. As nitrous oxide may allow improved intraoperative stability, while still allowing adequate depth of anaesthesia, its use could theoretically improve postoperative outcomes. This is purely conjecture at this point as we still don't know if "improving the numbers" actually improves outcome. It is, however, an exciting potential benefit that needs to be investigated further, especially in high risk patients[2].

Also of interest is a study by Samarska et al that found that nitrous oxide use attenuated shock-induced changes in vascular reactivity[56]. They examined mice anaesthetised with either 1.4% isoflurane alone, or 1.4% isoflurane and 66% nitrous oxide. Haemorrhagic shock was induced by venesecting the mice, with subsequent fluid resuscitation. It was found that administration of nitrous oxide during the shock phase prevented vasomotor dysfunction during the post-shock period. It is thought that post-shock vascular hyporeactivity may lead to organ hypoperfusion and multiple organ dysfunction syndrome. The volatiles also interfere with vasoresponsiveness and, thus, may lead to, or aggravate, organ hypoperfusion. Samarska suggested that nitrous oxide offsets the haemodynamic effects of the volatiles and prevents shock-induced vascular hyporeactivity by preventing shock-induced decreases in vascular COX-1 expression. COX-1 appears to be important in endothelial production of contractile prostaglandins.

This study raises the interesting prospect that our choice of anaesthetic, in particular the use of nitrous oxide, may improve postoperative outcomes, especially in trauma surgery and other major procedures, by influencing post-surgical vascular reactivity.

This is of course only an animal study and did not look at clinical outcomes, but it is an exciting finding that should be explored further in human clinical trials.

Against these largely positive cardiovascular effects must be balanced nitrous oxide's effect on homocysteine, and a possible increased incidence of perioperative myocardial ischaemia.

Badner and Drader et al, Badner and Beattie et al, Ermens et al, and Myles et al have reported postoperative increases in plasma homocysteine in patients exposed to nitrous oxide[8, 45, 57]. These elevated levels appear to persist for at least a week[45]. As mentioned previously, acute elevations in homocysteine may lead to endothelial dysfunction, and hypercoagulability (via activation of factor V, inhibition of protein C and increased platelet aggregation) [8]. The extent of the endothelial dysfunction seems to correlate with the duration of nitrous oxide exposure[8]. Chronic

hyperhomocysteinaemia appears to be a risk factor for coronary artery and cerebrovascular disease, but the acute effects in this regard are not known.

Concerns have consequently been raised in the literature that nitrous oxide use may be a risk factor for perioperative myocardial ischaemia. Let us examine this in more detail.
Badner and Beattie et al reported on 90 patients undergoing carotid endarterectomy, randomly assigned to receive either isoflurane alone or isoflurane and > 50% N_2O[57]. The patients in the nitrous oxide group were found to have a significantly higher incidence of postoperative myocardial ischaemia, more ischaemic events, and more ischaemic events of ≥ 30 minutes. There was no difference in patients with ≥ 2 hours cumulative postoperative ischaemia and no difference in intraoperative ischaemia. Intraoperative haemodynamics did not differ between the groups but the isoflurane-only group received significantly more phenylephrine. The end-tidal isoflurane concentrations differed by only 0.19% between the groups, suggesting that the depth of anaesthesia was not equivalent between the groups. Another interesting finding is that although N_2O has a relative risk for postoperative myocardial ischaemia of 2.0, the relative risk for isoflurane concentrations of > 0.7% is also 1.4.

This suggests that the difference in outcomes may be related to depth of anaesthesia and not necessarily anaesthetic agent. Even if the results are taken at face value, there are a number of questions regarding their actual significance. While Flesicher found that episodes of ischaemia ≥ 30 minutes correlated with adverse outcomes, Landesberg found a correlation with cumulative ischaemia of 2 hours or more. Where does this study leave us then, with more episodes of ischaemia of ≥ 30 minutes but no significant difference in those ≥ 2 hours? We simply do not know. Another factor to consider is that myocardial ischaemia is only a surrogate marker and we have no idea, from this study, of the effect of nitrous oxide on any clinical cardiac outcomes.

It is often quoted that ENIGMA found an incidence of myocardial infarction of 0.7% in the N_2O-free group, versus 1.3% in the nitrous oxide group. This was not statistically significant and should not be used to guide us either way.

Hohner et al found that although nitrous oxide increased the risk of intraoperative ischaemia, there was no difference in postoperative ischaemia[57].

In contrast to the above results, Mitchell et al and Cahalan et al found that nitrous oxide does not induce myocardial ischaemia in patients with ischaemic heart disease, with or without left ventricular dysfunction[57].

Of particular interest is the study by Kozmary et al[75]. They randomised 70 patients undergoing carotid artery surgery to receive either isoflurane alone or isoflurane and 60% nitrous oxide. Although they found no significant difference in intraoperative and postoperative myocardial ischaemia/infarction, there was a trend to a lower incidence of intraoperative ischaemia and postoperative infarction in the nitrous oxide group.

Another factor to consider is the finding by Badner, Freeman, and Spence that postoperative increases in homocysteine can be prevented by vitamin B_{12} supplementation prior to surgery. This implies that if nitrous oxide does increase the risk of perioperative myocardial ischaemia as a result of elevated homocysteine; this can be easily prevented by perioperative B_{12} supplementation[51].

We are thus left with a rather interesting dilemma. On the one hand we have the improved haemodynamic stability and preservation of vascular reactivity seen with nitrous oxide. Against this must be balanced the possible increased risk of perioperative myocardial ischaemia. Identifying which side of the risk-benefit ratio the scales are tipped is of particular importance in those at high cardiac risk. At the moment we simple do not know. ENIGMA II may help us, but results are some way off. However, based on available evidence, I am of the opinion that nitrous oxide use is of cardiovascular benefit if used optimally and with a low threshold for B vitamin supplementation. This applies particularly to the patient with cardiovascular risk factors undergoing major non-cardiac surgery. In future our decision making may be refined by the use of biomarkers and genetic profiling. As with any intervention we are most likely to see positive results if we tailor care to the individual patient.

Respiratory
The respiratory effects of nitrous oxide are complex. Purported negative effects include diffusion hypoxia. As mentioned earlier this is overemphasised as an adverse effect of nitrous oxide, and is easily preventable. In patients without significant cardiorespiratory disease, routine use of supplemental oxygen is not required in the recovery room, even if N_2O has been used. Also on the negative side, nitrous oxide has been reported to blunt the hypoxic respiratory drive, even at low concentrations. All anaesthetic agents exhibit this effect to some degree

though. Due to its rapid removal following cessation of delivery, this is unlikely to be clinically significant with nitrous oxide postoperatively. Nitrous oxide may lead to absorption atelectasis as readily as high inspired oxygen concentrations. The evidence that this leads to significant postoperative atelectasis/ postoperative pulmonary complication is not convincing (cf. ENIGMA).

In favour of nitrous oxide is the improvement in arterial oxygenation due to its persisting concentrating and second gas effects. Peyton et al showed that this effect improves oxygenation despite the competing effect of absorption atelectasis[31]. This may not be too important clinically but does show that absorption atelectasis is probably not a significant concern with nitrous oxide.

Also on the positive side, nitrous oxide causes less respiratory depression than the volatile agents. Nitrous oxide/volatile mixtures have been shown to reduce the ventilatory depression associated with the administration of equipotent concentrations of a volatile alone. This has been shown with halothane, isoflurane and sevoflurane. Einarsson et al[63] demonstrated the practical advantages of this effect. They randomised patients undergoing abdominal hysterectomy to receive either 1.3 MAC sevoflurane or an equi-MAC sevoflurane/65% N_2O mix. The sevoflurane/N_2O group resumed spontaneous breathing 8 minutes earlier than the sevoflurane-only group and was extubated 13 minutes earlier; both statistically significant differences. These findings were obtained in the context of a rigid trial protocol and quicker times to spontaneous breathing and extubation can be obtained in the "real-world" setting. The study does, however, demonstrate quite elegantly one of the benefits of nitrous oxide that can be exploited clinically.

In overview, the respiratory benefits of nitrous oxide outweigh the disadvantages.

PONV

Nitrous oxide is a risk factor for postoperative nausea and vomiting. This is often used in a binary fashion by it detractors as evidence against its use. Once again the full story is far more complex. Firstly, there is a dose-dependent, and not all-or-nothing, effect on PONV[9]. Secondly, the effect of N_2O on PONV has probably been overemphasised. Apfel et al showed that while the antiemetics ondansetron, dexamethasone and droperidol each reduced the risk of PONV by 26%, and propofol versus a volatile reduced the risk by 19%, omitting nitrous oxide only reduced the risk by 12%[43]. Tong et al made the point that while nitrous oxide, the volatiles and

opioids are all risk factors for PONV, the only anaesthesia-related risk factors included in current scoring systems are the volatiles (isoflurane) and postoperative opioids[29].

Tramer et al reported that the omission of nitrous oxide had no significant effect on the complete control of PONV, with only a reduction in postoperative vomiting, in high-risk patients thought to be significant. They also noted that because of the increased risk of awareness, the potential risk for harm from omitting N_2O negated any possible benefit on PONV[59]. In an elegant review, Apfel et al put the role of N_2O in PONV in perspective[67]. Since propofol TIVA (avoiding N_2O and volatiles) only reduces PONV by 20-25%, inhaled agents are clearly not the most important risk factors for PONV. In addition, while volatiles increase the risk of PONV 2-3 times in the first 24 hours, N_2O has a relative risk of only 1.3. The PONV-reducing effect of omitting nitrous oxide is thus limited. Perioperative opioids are probably the main factor. Since omitting both volatiles and N_2O is only as effective as using a single prophylactic antiemetic, omitting N_2O (and volatiles) is unlikely to have any additional effect when appropriate prophylactic antiemetics are used[58, 67]. It appears that another adverse effect has been overstated.

Expansion of Gas-filled Spaces

Nitrous oxide causes expansion of gas-filled spaces, or an increase in intracavitary pressure if the space is nonexpansile. This is a direct result of its physicochemical properties. Its low potency results in the use of high inspired concentrations, while the low blood/gas partition coefficient leads to a high propensity to partition into the gas phase. The fact that it is 40 times more soluble than N_2 means this diffusion into gas spaces occurs faster than nitrogen can diffuse out.

What are the clinical implications? I will briefly discuss this with regard to a number of clinical scenarios.

It has been reported that 70% nitrous oxide can double the size of a pneumothorax in 10 minutes and triple it in 45 minutes[45].

Nitrous oxide use in patients with intraocular gas bubbles may result in a 3-fold increase in the volume of the bubbles after an hour's exposure, possibly leading to increased intraocular pressure and complications such as central retinal artery occlusion. A number of case reports have documented adverse visual effects in patients with intraocular gas bubbles after N_2O exposure during nonopthalmic surgery. The risk period is 7-10 days for sulphurhexaflouride (SF_6) and 4-6 weeks for perfluoropropane, but

may extend to 10 weeks for the latter agent. It is thus probably prudent to avoid N_2O for 70 days after intraocular gas injection. In contrast, the use of nitrous oxide during ophthalmic surgery that involves injection of intraocular gas is probably insignificant[81].

Nitrous oxide has also been shown to increase middle ear pressure and cases of tympanic membrane rupture have been reported[48]. It is thus best to avoid its use in middle ear procedures such as tympanic membrane grafting.

It is often stated that patients at risk of venous air embolism (VAE) should not receive N_2O. Some animal evidence points to a worsening of outcome from ongoing VAE with the use of a volatile/N_2O anaesthetic. Interestingly, there was no such adverse effect with a barbiturate/N_2O anaesthetic[82]. This study was, however, probably not representative of the real-world clinical situation. I would argue that the rapidity of occurrence of a clinically significant VAE would mean that effective treatment, or patient demise, would have occurred before N_2O diffusion has had time to have any significant effect. This is not evidence-based but it does seem unreasonable to omit nitrous oxide solely because a patient is at risk of a VAE. The situation with patients undergoing cardiopulmonary bypass (CPB) is pathophysiologically different from that of a patient, undergoing a craniotomy for example, who has a sudden large VAE. It may thus be appropriate to avoid nitrous oxide in patients undergoing CPB.

Intestinal gas volumes have been reported to increase by 75-100% with 2-hours' exposure to nitrous oxide, and 100-200% with 4-hours' exposure. In addition, delayed recovery of bowel function, delayed hospital discharge, and impaired intraabdominal operating conditions have been claimed to result from N_2O exposure[48]. A metanalysis by Orhan-Sungur et al found that although N_2O resulted in a time-dependent increase in intraoperative bowel distension, this did not affect operating conditions, time to bowel movement, or hospital stay[74]. In a randomised trial of patients undergoing laparoscopic cholecystectomy, Taylor et al found identical intraoperative condition regardless of whether or not nitrous oxide was used[59].

In summary, nitrous oxide should be avoided in patients with gas-filled spaces where expansion or increased pressure could cause significant adverse effects, for example: pneumothorax, pulmonary bullae, intraocular gas bubbles (when already in situ), tympanic surgery, or pneumocephalus. It is probably safe to use it in intraocular surgery, even if gas bubble injection is planned, and in patients undergoing surgery with a theoretically

risk of VAE. In addition, despite previous concerns, nitrous oxide appears safe in intraabdominal surgery.

As a final point, N_2O diffuses into the cuffs of airway devices. Ong et al reported a consistent increase in endotracheal tube and laryngeal mask cuff pressure when nitrous oxide was used[12]. Of note, however, significant cuff hyperinflation occurred whether or not nitrous oxide was used. It thus appears that whether or not nitrous oxide is used, cuff pressures should be monitored with a cuff manometer. The only disadvantage with nitrous oxide is the slight inconvenience of more frequent cuff pressure assessment. It is also worth noting that PVC cuffs are less susceptible to this effect[37].

Awareness

Nitrous oxide is claimed to reduce awareness. This claim has reasonable pharmacokinetic and pharmacodynamic underpinnings[51].

From a pharmacokinetic perspective, the ability to accurately estimate the blood concentration of nitrous oxide from the end-tidal concentration offers a significant advantage over propofol TIVA, for example. This advantage of N_2O may even extend to the volatiles. To illustrate this, with propofol TCI the blood concentration of propofol may be 20% above or below the target concentration; the blood concentration of isoflurane, after 15 minutes stable end-tidal concentrations, may be 35% below the end-tidal concentration; with nitrous oxide, however, after 15 minutes the blood concentration is only 10% less than the inspired concentration[51].

Pharmacodynamically, the fact that nitrous oxide has an analgesic effect with a similar dose-response profile to its amnestic effect should make recall of a noxious surgical stimulus less likely. To this end, nitrous oxide has been shown to have a more potent amnestic effect for a noxious stimulus, than the volatile anaesthetics[51].

Where does this leave us clinically? A number of studies point to a reduced risk of awareness with the use of nitrous oxide[1, 6, 51]. Most startling is the metanalysis by Tramer et al, which reported that the number needed to treat (NNT) to prevent a case of awareness with nitrous oxide was 46. There are a number of criticisms of the awareness component of this study, but to put it into perspective, the NNT to prevent awareness with BIS monitoring may be close to 1250. So, even if Tramer is incorrect by a factor of 10, nitrous oxide would still be more effective than BIS in preventing awareness.

Environmental
Nitrous oxide acts as a greenhouse gas in the troposphere and, via photochemical conversion to nitrogen oxides, contributes to destruction of the ozone layer in the stratosphere[51, 52, 59]. It is the third most climatologically significant greenhouse gas, and has 300 times the global warming potential of CO_2 over 100 years[3]. Medical sources, however, only contribute 1% of nitrous oxide emissions[52]. So, even if we, as green anaesthetists, were to completely cease using N_2O, the effect would be negligible[59].

Teratogenicity/Foetotoxicity
Prolonged exposure to nitrous oxide has been shown to teratogenic/foetotoxic in animal studies[7, 48]. These included exposures of up to 24 hours on the first day of gestation and are unlikely to be applicable to clinical practice. Clinical studies in human pregnancy are obviously limited but do not show any increase in foetal loss or abnormalities with nitrous oxide exposure[48]. In fact, there appears to be no significant association between anaesthesia in general and foetotoxicity/teratogenicity[7].

Occupational Exposure
The possible adverse effects of occupational exposure to nitrous oxide have created much heated and often emotional debate. Sanders et al have compiled an excellent overview of this topic[7]. They noted that claimed effects include reproductive effects: impaired fertility, increased abortion, and increased risk of low birth weight and small for gestational age babies; neurological effects: neuropathies and neurocognitive dysfunction; genotoxicity; and haematological effects.

They make the key point that many of these claims have arisen from animal studies which have used high exposures that are inconsistent with workplace exposures, or from studies published prior to adequate workplace scavenging. With modern scavenging that adheres to current occupational health guidelines, occupational exposure to anaesthetic gases is low. Occupational exposure limits (OEL), represent the maximum allowable 8-hour time-weighted average (TWA) exposure to N_20. These range from 25 TWA/ppm in the USA and Australia, to 100 TWA/ppm in South Africa and the UK. Prior to modern scavenging, exposures were routinely 1000-2000 ppm.

They also note that the studies are tainted by reporter bias, poor response rates, inadequate controls, and inconsistent results. In addition, there are

a number of confounders: shift-work, physical strain, age and exposure to toxins.

The conclusions drawn from this review are reassuring. The available studies do not substantiate concerns about reproductive toxicity in a scavenged environment. There is no evidence that nitrous oxide alone cause genotoxicity, although some evidence suggests that exposure to mixed gases may increase markers of genotoxicity. The clinical effects of this are not known. There is no reliable evidence to suggest an increased risk of neuropathies with routine occupational exposure. Exposure to levels approximately a 1000 times above occupational limits is required to impair neurocognitive performance. Haematological toxicity does not occur at occupational exposure limits.

This is comforting, but it remains our responsibility to safeguard our wellbeing by ensuring that sound occupational health guidelines are adhered to.

Anaesthetic-sparing and Cost-saving Effects
It is often claimed that nitrous oxide has a significant anaesthetic-sparing effect and consequently results in a reduction in the cost of anaesthesia. As these two effects are so closely linked they will be explored together.

As a general rule the MACs' of nitrous oxide and the volatiles are additive, with the MAC-reducing effect of 60-70% N_2O approximately 0.55-0.65[62]. This is substantiated by Jakobsson et al, who reported a 60% reduction in sevoflurane consumption with 66% nitrous oxide[65]. Muzi et al reported that 66% nitrous oxide reduced sevoflurane consumption during gas induction[73].

Nitrous oxide also reduces propofol consumption. The administration of 66% nitrous oxide prior to propofol induction reduced the induction dose by 44%[59]. More importantly, nitrous oxide 65-67% has been found to reduce propofol infusion requirements by 25-50%[48, 51, 59].

It is, in addition, opioid sparing. This effect is well documented intraoperatively, but the influence on postoperative opioid consumption is not well established[45]. Nitrous oxide 70% has been found to be equivalent to 0.17 ug/kg/min of remifentanil, with 66% N_2O equivalent to a whole blood remifentanil concentration of 2ng/ml[39, 62].

It has also been reported that 70% nitrous oxide reduces the EC_{50} of rocuronium by 20%[36]. This is probably of minimal impact economically but may theoretically alter the dosing of muscle relaxants.

What are the implications of the above?
There is a reduction in the exposure to other anaesthetic agents, each with their own potential toxicities, and the risk of drug interactions is, theoretically, reduced. In addition, there are cost implications, which are of particular interest in this era of spiralling medical costs.

This is an extremely complex area, with little in the way of studies that take into account all the potential cost implications. In addition, it is very difficult to generalise cost results from one centre to another, especially if in different countries.

Muzi et al reported a 15% cost reduction in gas inductions in adults, with sevoflurane/66% N_2O instead of sevoflurane alone[73]. Jakobsson et al reported an almost 60% reduction in the cost of sevoflurane anaesthesia with 60% N_2O[59, 65]. A study by Jakobson et al put a slightly different perspective on this. They reported that the cost of a sevoflurane/N_2O anaesthetic, at a fresh gas flow of 3 l/min, was equivalent to the cost of sevoflurane, as a sole agent, at 1 l/min. Thus, for the same cost, one can benefit from the faster, easier titration afforded by a higher fresh gas flow[59].

The reduction in propofol consumption with concurrent nitrous oxide administration is also likely to result in cost savings versus pure propofol TIVA. Hopkins reports that trials by Arellano et al and Visser et al demonstrated substantial cost savings, without additional costs from increased side effects, when anaesthetic techniques incorporating nitrous oxide were compared with propofol TIVA. It must be noted, though, that only the study by Arellano compared propofol TIVA with propofol/N_2O, while Visser compared propofol TIVA with isoflurane/N_2O[51].

Nitrous oxide may also result in cost savings by reducing intraoperative opioid use. This is particularly so if it results in the reduction or elimination of remifentanil usage.

All is not so clear-cut, however. Baum reported that if nitrous oxide is omitted from low-flow anaesthesia, the cost of increased volatile and opioid consumption may be offset by the saving from the complete removal of nitrous oxide from the institution[52]. It is also claimed that eliminating nitrous oxide use makes closed-circuit anaesthesia possible, which could result in significant savings. Whether closed-circuit anaesthesia offers much financial advantage over minimal-flow or low-flow anaesthesia is debatable. The increased cost of sodalime and the practical difficulties of closed-circuit anaesthesia also need to be taken into account.

On the balance of all the evidence, nitrous oxide definitely reduces the consumption of other anaesthetic agents and probably results in a reduction in anaesthetic costs. It appears that only the complete elimination of nitrous oxide from a hospital could counterbalance the cost savings from reduced agent consumption. This is because it would eliminate the costs of not only nitrous oxide, but also, theoretically, of maintaining the nitrous oxide infrastructure, such as N_2O pipelines. A further factor to consider, however, is the cost of the disposables and infusion pumps necessary to run TIVA or remifentanil infusions. Ultimately each hospital should perform its own detailed anaesthesia-related cost-analysis to determine the financial implications of various anaesthetic agents. In the interim, I would suggest that nitrous oxide is most likely to result in significant cost reductions when used with the more expensive agents, such as sevoflurane, desflurane, propofol, and remifentanil.

Effects on Induction
Many practitioners claim that nitrous oxide offers advantages during gas induction in children. Its use prior to the addition of sevoflurane provides some sedation and better tolerance of the latter agent's odour. It is also claimed to provide a smoother, quicker induction. These benefits also extend to gas inductions in adult patients. Muzi et al reported a 27% reduction in the time to acceptable intubating conditions in adults undergoing gas inductions with sevoflurane/66% N_2O versus sevoflurane alone[73]. The also reported a 50% reduction in breath holding and a 38% reduction in expiratory stridor in the N_2O group. Hall et al similarly reported a 14% reduction in induction time, a smoother induction with fewer adverse events, and a greater first time success rate for LMA insertion when 66% N_2O was added to sevoflurane during a vital capacity induction technique in adults[59]. Ng et al showed a 41% reduction in induction time with the addition of nitrous oxide prior to propofol induction[59]. Nitrous oxide also reduces the pain from propofol injections; another useful characteristic during induction.

Effects on Emergence
Nitrous oxide undergoes rapid elimination and thus, theoretically, results in faster recovery than when high concentrations of the primary agent are used alone. This is supported by a number of studies. Servin et al and Sukhani et al reported a 16-24% reduction in the time to orientation with N_2O/propofol vs. propofol TIVA. Jakobson et al found a 40% reduction in time to orientation with sevoflurane/N_2O vs. sevoflurane alone[59]. Einarsson et al showed that isoflurane/N_2O resulted in an earlier return to spontaneous breathing and earlier extubation than MAC-equivalent

isoflurane alone[48]. Although the recovery time with desflurane is unlikely to be improved by concomitant use of nitrous oxide, the potential for significant cost containment still makes this an attractive combination.

It should be noted that recovery from a nitrous oxide-based anaesthetic may appear delayed if BIS monitoring is used to titrate depth of anaesthesia. This is because BIS monitoring is insensitive to nitrous oxide; and if not taken into account while using BIS with nitrous oxide, it will result in a greater depth of anaesthesia than expected[59]. As noted before, Brodsky et al found that the risk of diffusion hypoxia is overrated and of minimal clinical significance. Therefore, it appears that nitrous oxide offers potential benefits during emergence without significant adverse effects.

Miscellaneous

There are a number of miscellaneous benefits associated with nitrous oxide.

It is an extremely versatile agent. Aside from its use as an anaesthetic adjunct, nitrous oxide has been used extensively as a labour analgesic. It is also safe and effective when used for procedural sedation/analgesia, in adults and in childen[24, 34]. It may also be used an as effective alternative to EMLA for venous cannulation in children[53].

Its simplicity of use, the extensive clinical experience with this agent, and the familiarity of anaesthetists with its use, are further points in its favour. Despite the many criticisms of nitrous oxide, its 165 years of use attest to its remarkable safety. It is noteworthy that it undergoes no metabolism, has no significant drug interactions, does not cause hepatotoxicity or nephrotoxicity, has no adverse reactions with soda lime, and is not a trigger for malignant hyperthermia.

Alternatives

If we were to abandon the use of nitrous oxide on the advice of the naysayers, what would the alternatives be? One would want an agent that has analgesic and amnestic effects, acts rapidly, and is of short duration. The closest current matches are xenon and remifentanil.

Xenon, with a MAC of 70%, offers the advantage that it can be used as a sole anaesthetic agent. It demonstrates cardiovascular stability, is neuroprotective and has no direct adverse environmental effects. It is however extremely rare and exorbitantly costly[59]. In addition, its manufacture is energy intensive and thus it has indirect adverse

environmental effects. Xenon is thus not a practical alternative to nitrous oxide.

Remifentanil is the closest contender for nitrous oxide's crown. As with all opioids, it is a potent analgesic but a poor amnestic agent[51]. It has been reported that 66-70% nitrous oxide is equivalent to 2ng/ml or 0.17ug/kg/min of remifentanil[39, 65]. A combination of remifentanil and midazolam has been suggested as a more appropriate alternative to remifentanil alone[51]. There are, however, a number of potential problems with remifentanil. It is expensive. As with all intravenous agents, there is greater pharmacokinetic variability compared to nitrous oxide. It is more complex to administer. It causes significant respiratory depression and is thus not suitable for use in spontaneously breathing patients. It causes cardiovascular depression, with a dose-dependent decrease in mean arterial pressure and cerebral perfusion pressure, and may cause significant bradycardia. It has also been associated with acute opioid tolerance and an increased risk of postoperative pain, hypertension and agitation[44, 51, 59].

From the above, it is clear that nitrous oxide is a unique agent, with no readily available replacement.

CONCLUSION

Nitrous oxide is a unique drug with many positive attributes and deserves an important place in anaesthetic practice in 2010 and beyond. Although modern anaesthesia would not collapse with the removal of nitrous oxide, or any other anaesthetic agent, it would be much poorer for its absence.

As can be seen from this review, most of the commonly quoted adverse effects of nitrous oxide are grossly overstated, are of little clinical impact, or are outweighed by its benefits. Table 4 shows the evidence-based risks and benefits; a very different picture from the conventional wisdom shown in Table 3. The risk-benefit ratio for the use of nitrous oxide in patients at high cardiac risk is, for me, an exciting area of future research; the results of ENIGMA II are eagerly awaited.

Benefits		**Risks**	
CVS	Haemodynamic stability	**Expansion of air-filled spaces**	Pneumothorax
Respiratory	Reduced respiratory depression		Pulmonary bullae
	Improved oxygenation		Pneumocephalus
Awareness	Reduced		Middle ear
Anaesthetic sparing	Volatiles		Intraocular +/-
	Opioids	**PONV**	Limited effect
Cost-effective		**Pulmonary hypertension**	Mild exacerbation
Induction	Faster		
	Smoother		
	Fewer adverse events		
Emergence	Rapid		
Miscellaneous	Versatile		
	Simple to use		
	Extensive experience		
	Familiarity		
	Established safety profile		

Table 4: Evidence-based risks and benefits of nitrous oxide in routine clinical practice.

As with any agent, attention to its indications and contraindications is a prerequisite for its safe use. After examining the available evidence, the

contraindications no longer comprise the traditional daunting list. In fact, even when taking a conservative view of the current evidence, the contraindications should only consist of the four categories noted below:

Contraindications to Nitrous Oxide	
Absolute	Potential significant adverse effects from expansion of gas-filled spaces (as noted above)
	Known deficiency of enzyme or substrate in methionine synthase pathway
Relative	Pulmonary hypertension
	Severe acutely raised intracranial pressure?

Table 5: Contraindications to nitrous oxide use. Modified from Sanders et al[7].

Hopefully this review has also shown us that we need to look beyond the often formulaic approach to preoperative assessment, and the traditional approach to premedication. We need to look to a future where our perioperative management is tailored to the patient's phenotype and genotype.

So, let's suspend our general bias against nitrous oxide and grant it the place it deserves in anaesthetic practice in 2010. We might even find that this faithful old anaesthetic dog has some exciting new tricks to show us.

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