The benefits attributed to the use of nitrous oxide have long been recognized. 
More recently we have learned that this agent has both side effects (untoward actions that disappear with the elimination of nitrous oxide) and toxic effects (adverse changes that remain after elimination). The purpose of this review is to summarize both the advantages and disadvantages that result from the clinical application of nitrous oxide.

Until recently, it appeared that nitrous oxide would continue to enjoy universal acceptance and use by the anesthesia community. A long history of seemingly safe application in the healthy and ill patient recommended its use. However, the apparent safety of nitrous oxide is now being questioned. The purpose of this report is to provide the anesthetist with the information needed to assess the relative benefits and risks associated with this oldest of all inhaled anesthetics. (All primary and secondary references for this article may be found in the book edited by Eger.1)

Desirable properties of nitrous oxide

Several properties of nitrous oxide recommend its use. Its nonflammability is a prerequisite for any modern anesthetic. The absence of any odor except a slightly sweet smell, makes it pleasant to breathe. It is the least soluble of all presently used inhaled anesthetics. These physical characteristics result in a rapid equilibration between the inspired partial pressure of nitrous oxide and that in the brain. The speed of induction is further increased by the concentration effect and the accelerated rise in alveolar concentration of any potent inhalation anesthetic given concurrently (second gas effect).

It is thought that nitrous oxide produces little or no depression of respiration or circulation. In healthy volunteers, PaCO₂ is not increased at 1.1 and 1.55 atmospheres of nitrous oxide, nor do such partial pressures decrease cardiac output, myocardial contractility, or systemic arterial blood pres-
sure. The substitution of nitrous oxide for an
equivalent MAC fraction of a potent inhaled an-
esthetic decreases PaCO2 in the spontaneously ven-
tilating patient. The perception that nitrous oxide
has little or no effect on the circulation is sug-
gested by its use for the measurement of cerebral
blood flow in humans.

Analgesia is produced by nitrous oxide, an
effect that may involve the release of endogenous opioids or enhancement of the nervous pathways
stimulated by these opioids. Enhancement may be
by a direct action or by an indirect action on the
sensitivity of the opioid receptors. The latter may
result from the sympathomimetic effects of nitrous
oxide; increased sympathetic activity potentiates the
effect of narcotics. Although part of the anal-
gesia produced by nitrous oxide may result from
an action on opioid receptors, it is clear that a
greater degree of analgesia results from an action
independent of such receptors: administration of
large doses of naloxone does not affect a major
portion of the analgesia produced by nitrous oxide.

Paul Bert used nitrous oxide in a pressure
chamber to produce anesthesia without hypoxia.
His investigations suggested that nitrous oxide
could produce excellent surgical conditions. Others
also advocated the use of nitrous oxide in pressure
chambers, but the logistic considerations of such
an application precluded its widespread accept-
ance.

Nitrous oxide has enjoyed a reputation for
safety that is unmatched by any other inhaled an-
esthetic. Its 140-year history and current wide-
spread use in general anesthesia (and occasionally
as a supplement to regional anesthesia) reflect the
continuing favorable perception of its properties.
We know that no other currently used anesthetic
undergoes less biodegradation, and we tend to
equate less biodegradation with less organ toxicity.

**Is our perception of the safety of nitrous oxide incorrect?**

One of the strongest arguments for the con-
tinued, unrestricted use of nitrous oxide is its re-
cord of safety. However, the evidence supporting
this record may be questioned. Our perception of
nitrous oxide as a safe anesthetic may blind us to
some of the adverse effects that it might also pos-
sess: we are unlikely to look for effects that are not
thought to exist. Furthermore, the current nearly
universal use of nitrous oxide almost precludes a
comparison of its effects with an alternative anes-
thetic agent. Without such a comparison it is diffi-
cult to assign any given adverse effect to nitrous
oxide.

Finally, certain adverse effects may be subtle
—not apparent during the course of anesthesia, but
delayed for hours or days. A delayed effect may not
be readily connected to its cause. In the next sev-
eral sections, we will present evidence to support
the argument that nitrous oxide may not be as
beneficial or safe as it was once thought to be.

**Unwanted side effects of nitrous oxide**

Probably the greatest immediate risk to the
use of nitrous oxide results from its limited po-
tency. The MAC of nitrous oxide is 104% of 1
atmosphere. One cannot administer 100% (or
nearly 100%) oxygen and simultaneously admin-
ister nitrous oxide. Hypoxia from the deliberate
or the accidental administration of high concen-
trations of nitrous oxide has caused severe brain
damage, cardiac arrest, and death. Recognition of
this danger led to the development of anesthetic
machines that prevent the delivery of hypoxic gas
mixtures and warn the anesthetist when the oxygen
concentration falls below a predetermined level.

Even a “normal” concentration of oxygen may
be inadequate in some patients. The patient who
requires inspiration of 100% oxygen to sustain the
saturation of hemoglobin is not a candidate for
anesthesia with nitrous oxide. Less obvious is the
effect of higher concentrations of nitrous oxide on
the fetus: 75% nitrous oxide is thought to decrease
fetal oxygenation, and consequently Apgar scores
and neurobehavioral scores.

Some of the desirable attributes of nitrous
oxide may be viewed negatively. Although nitrous
oxide is not flammable, it will support combustion.
Intestinal bacteria produce several flammable gases
including methane and hydrogen. If electrolysis
occurs during a transurethral resection of a pros-
tatic or bladder tumor, hydrogen may be pro-
duced. The partial pressure of oxygen in the bowel
or bladder is normally too low to support combus-
tion. The low partial pressure of oxygen results
from the consumption of oxygen by the adjacent
tissues. Administration of nitrous oxide via the
lungs will result in the development of a nitrous
oxide partial pressure in bowel and bladder that
is sufficient to support combustion.

The desirable pharmacokinetic properties
of nitrous oxide (low blood and tissue solubility,
rapid induction of and recovery from anesthesia)
must be weighed against some undesirable phar-
macokinetic properties. Although the solubility is
less than that of any other currently used inhaled
anesthetic, it is far greater than that of several
other gases often present in the body. The blood/
gas partition coefficient for nitrous oxide (0.46) is 30 times greater than that for nitrogen (0.015). Blood passing a nitrogen-filled gas space within the body can deliver a greater volume of nitrous oxide to the space than the volume of nitrogen it removes from the space. As a result, either the volume of the space or the pressure within the space will increase when nitrous oxide is administered.

Nitrous oxide will therefore expand the volume of gas within the bowel. A doubling or tripling of volume can occur. Usually this expansion is of little significance because the normal volume of intestinal gas is less than 200 ml. However, the expansion becomes important when bowel obstruction is present and the bowel contains large volumes (in excess of a liter) of gas. Closure of the abdomen becomes difficult, and the pressure of the abdominal contents upon the diaphragm may compromise ventilation. Nitrous oxide is contraindicated in the presence of an unrelieved tension pneumothorax or an air embolus where the rapid expansion of the gas space may cause cardiovascular collapse.

Nitrous oxide administration will increase the pressure within gas spaces surrounded by walls with limited compliance. Pressure increases can occur in the middle ear or facial sinuses, the eye injected with air or sulfur hexafluoride, the ventricles of the brain when air is injected for pneumoencephalography, or the inflated endotracheal tube cuff or balloon of a pulmonary-artery catheter. Each of these increases may produce undesirable results, such as rupture of the eardrum or herniation of the brain.

At the end of anesthesia, the elimination of nitrous oxide decreases the partial pressure of oxygen in the lungs, an effect known as diffusion hypoxia. The outpouring of nitrous oxide dilutes alveolar oxygen and carbon dioxide. The dilution of oxygen directly decreases oxygenation, whereas the dilution of carbon dioxide indirectly decreases oxygenation by decreasing respiratory drive. Diffusion hypoxia is of little importance in the patient with normal lungs who breathes normally, but may be important in the patient with depressed ventilation or emphysema.

Nitrous oxide does not appear to depress the circulation of a normal patient; indeed, it may stimulate the circulation in some patients. Blood pressure and pulse rate may increase. An underlying depressant effect of nitrous oxide (perhaps common to all inhaled anesthetics) may be balanced by stimulation of the sympathetic nervous system. Depression of the circulatory system may become evident in patients with limited sympathetic reserve or when the sympathetic response has been blocked. Thus the hypovolemic patient or the patient given a narcotic may be more susceptible to the depressant effects of nitrous oxide. Nitrous oxide is often used with such patients because of the perception that depression will be avoided.

In dogs subjected to a critical stenosis of the left anterior descending coronary artery, nitrous oxide may produce myocardial ischemia. In one study in humans undergoing coronary artery bypass surgery, nitrous oxide decreased myocardial perfusion and markedly elevated coronary sinus lactate concentrations. However, nitrous oxide may not have directly produced myocardial ischemia: the addition of nitrous oxide also produced a substantial decrease in systemic arterial pressure.

Nitrous oxide increases pulmonary-artery pressure. The change is usually modest, and is greatest in patients who have pre-existing pulmonary hypertension.

Regional blood flows are affected by nitrous oxide. Studies in animals and humans indicate a decrease in portal venous and hepatic arterial blood flow without a simultaneous decrease in hepatic oxygen consumption. The results indicate a tendency to decrease hepatic oxygenation and thus predispose the patient to hepatic injury. As do other inhaled anesthetics, nitrous oxide has a modest inhibitory effect on hypoxic pulmonary vasoconstriction. The effect may be limited by the potency of nitrous oxide.

Like other inhaled anesthetics, nitrous oxide increases cerebral blood flow and intracranial pressure. At a given MAC multiple, the increase in flow and pressure appears to equal or exceed that produced by other inhaled anesthetics. The increase may be greater with nitrous oxide because it has little effect on cerebral oxygen consumption, while potent inhaled anesthetics may produce depression. Sustained oxygen consumption exaggerates (relative to anesthetics that depress consumption) any tendency to increase cerebral blood flow, and hence intracranial pressure. In patients with decreased intracranial compliance, the increase in pressure may equal 40 mm Hg.

Like other inhaled anesthetics, nitrous oxide depresses electroencephalographic (EEG) activity. The result at anesthetic levels is a slowing of the frequency and increase in voltage of the EEG. An anecdote suggests that, in a rare individual, nitrous oxide may produce convulsive activity on induction of anesthesia. Such an effect is not well-docu-
mented. However, it is clear that mice convulse if stimulated soon after anesthesia with nitrous oxide. Similarly, humans given 30% nitrous oxide have abnormal EEG traces after they stop breathing nitrous oxide. Mice given even subanesthetic concentrations of nitrous oxide are predisposed to convulsions after exposure to nitrous oxide. The potent inhaled anesthetics do not produce this effect after either anesthetic or subanesthetic exposure.

It is not known whether the delirium, or nausea and vomiting that follow anesthesia with nitrous oxide is related to this central nervous system effect. The nausea and vomiting may be related to the ability of nitrous oxide to increase the pressure in the middle ear or to stimulate the sympathetic nervous system. Other anesthetics that produce sympathetic stimulation (such as cyclopropane, diethyl ether, and fluroxene) also predispose the patient to nausea and vomiting. Diethyl ether and fluroxene can produce convulsive EEG activity.

The limited potency of nitrous oxide may predispose the patient to one other problem, particularly when anesthesia is managed solely or primarily with muscle relaxants, narcotics, and nitrous oxide. Occasional patients given this regimen may be aware of intraoperative events: MAC awake is estimated to be approximately 70% of 1.0 atmosphere of nitrous oxide. Fortunately, almost all of these patients are analgesic and feel no pain. However, the awareness can be unpleasant, particularly if it extends to the realization that paralysis is present.

Although 1.1 to 1.5 atmospheres of nitrous oxide do not increase PaCO₂ in spontaneously ventilating healthy volunteers, other indices of respiration do reveal depression. Nitrous oxide depresses the ventilatory response to imposed increases in PaCO₂ (that is, the CO₂ response curve) roughly as much as do inhaled anesthetics such as halothane or isoflurane. Similarly, the administration of 0.1 and 0.4 MAC of nitrous oxide depresses the ventilatory response to hypoxia by 40% to 70%. Despite this depression, when given at 1.55 atmospheres nitrous oxide does not decrease oxygen consumption. The greater density of nitrous oxide increases airway resistance. A 26% increase (above that found during respiration of air) results from respiration of 50% nitrous oxide/50% oxygen.

Nitrous oxide predisposes the patient to atelectasis in isolated alveoli because it is more readily absorbed than other gases, including oxygen. Although there may be alternative explanations, two studies have produced data consistent with the thought that anesthesia with nitrous oxide predisposes the patient to postoperative atelectasis and hypoxemia. The substitution of nitrogen for nitrous oxide decreases the incidence of postoperative atelectasis in patients having correction of a hiatus hernia. Such substitution may lower the postoperative closing capacity (which should, thereby, decrease atelectasis).

Although narcotics can cause a "tight chest," their effect is less than that produced by nitrous oxide. Nitrous oxide, alone or in combination with narcotics, decreases total pulmonary compliance and functional residual capacity.

The "tight chest" caused by nitrous oxide results from an increase in muscle tone in the abdomen and larynx. Volunteers anesthetized with 1.55 atmospheres of nitrous oxide have a generalized increase in muscle tone, some becoming opisthotonic. This effect usually mandates the use of muscle relaxants when nitrous oxide is given alone or in combination with narcotics. The addition of a potent inhaled anesthetic to nitrous oxide appears to counteract the tendency to increase muscle tone. Unlike the potent inhaled anesthetics, nitrous oxide does not potentiate the action of injected muscle relaxants, and the addition of nitrous oxide to a constant level of a potent inhaled anesthetic does not alter the effect of an injected muscle relaxant.

Possible toxic effects of nitrous oxide

The preceding section indicates that nitrous oxide is not the ideal anesthetic (except for potency) that it once was thought to be. But then, no currently available anesthetic is perfect. Indeed, as noted in the preceding section, many of the imperfections possessed by nitrous oxide are shared by other inhaled anesthetics. When the side effects of nitrous oxide are weighed against the benefits accruing to its use, it would appear that nitrous oxide demonstrates a cost/benefit ratio that is competitive with that of other inhaled anesthetics.

However, evaluation of nitrous oxide on this basis fails to take into account one other factor. Nitrous oxide may be toxic, and this toxicity may be unique to nitrous oxide. Epidemiologic, clinical and/or experimental evidence indicates that nitrous oxide can injure the hematopoietic system, fetus, brain, lung, liver, and kidneys. Although some of the evidence for a toxic effect has existed for several decades, most has been accumulated in the past few years.
Hematologic effects. The first substantial evidence of a toxic effect of nitrous oxide was published in the 1950s.* Patients having tetanus were given nitrous oxide for prolonged periods to secure sedation and analgesia. They developed bone marrow depression and granulocytopenia. Two patients died from aplastic anemia. This effect in humans was confirmed in rats. Nitrous oxide produced a depression of the white blood count that was directly related to the concentration and duration of exposure to nitrous oxide.

In both these studies, nitrous oxide was administered for prolonged periods (that is, for days). Most recent work indicates that the acute exposures experienced by patients produce similar, albeit more subtle, changes. Changes develop more readily and appear to last longer in critically ill patients.

Another aspect of the effect of nitrous oxide on the hematopoietic system is its influence on the function of white blood cells. Results from in vitro studies suggest that nitrous oxide impairs neutrophil and monocyte chemotaxis. This inhibition equals (methoxyflurane) or exceeds (enflurane, halothane) that produced by other inhaled anesthetics. Isoflurane had little or no effect on either neutrophil or monocyte chemotaxis in this study.

The in vivo impact of nitrous oxide on chemotaxis is less clear. Inhibition of diapedesis has been suggested as a mechanism for the peripheral leukopenia present after 24 hours of exposure to nitrous oxide. Such an exposure should not appreciably and acutely alter the stores of white blood cells. In humans anesthetized with nitrous oxide, leukocyte mobilization still occurs in response to the stress of surgery. The stress of surgery may be more important than the action of nitrous oxide.

Effects on the fetus; congenital anomalies. Results from several studies in animals (primarily rodents) demonstrate that exposure to nitrous oxide can cause congenital anomalies. The classic study of Lane and coworkers was particularly important because it indicated that the effect of nitrous oxide was not necessarily the result of anesthesia per se. Lane and colleagues gave 70% nitrous oxide to rats for 24 hours during their ninth day of pregnancy. Anomalies in the offspring of this group were several times more frequent than in similar groups given 70%, nitrogen (control) or 70% xenon. The offspring of the rats given xenon did not differ from the offspring of control rats. Because xenon is more potent (MAC is 71% of an atmosphere), this suggests that the effect of nitrous oxide may result from a property peculiar to that agent.

However, the production of teratogenic changes by nitrous oxide requires prolonged application of high concentrations at particular times during pregnancy. Teratogenic changes are not produced by shorter intervals of exposure, lower concentrations, or exposure during times other than the middle trimester. That is, at worst nitrous oxide is a weak teratogen.

Epidemiologic studies of occupational exposure provide conflicting evidence for a possible teratogenic effect of nitrous oxide in humans. Most of the results of such studies are confounded by the concurrent exposure of subjects to other inhaled anesthetics. This confounding effect was avoided in a study of dentists (males) and dental assistants (females). These subjects could be separated into personnel who used nitrous oxide in their practice and such personnel could be compared to personnel who used no inhaled anesthetics. Data from dentists and assistants who used inhaled anesthetics other than nitrous oxide were excluded from comparison.

The offspring of chairside assistants exposed to nitrous oxide had a 50% higher incidence of congenital anomalies than the offspring of unexposed assistants. However, the significance of this finding is questionable because the incidence was not related to the extent of exposure to nitrous oxide, and because the incidence in the children of exposed assistants was no greater than that in children of wives of exposed and unexposed dentists. There also was no trend toward a dose-response relationship in the children of wives of dentists. Finally, it should be noted that the usual concentrations of nitrous oxide in dental offices are more than 10 times greater than levels found in surgical operating rooms. This higher concentration results from the use of nonrebreathing systems without scavenging.

Effects on the fetus: Spontaneous abortions. The evidence for an abortifacient effect of nitrous oxide is far stronger than the evidence for a teratogenic effect. Exposure of pregnant rats to nitrous oxide increases the incidence of resorption of developing fetuses. Most, but not all, (10 of 12) epidemiologic surveys show a correlation between occupational exposure to nitrous oxide and the incidence of spontaneous abortions. The incidence of abortions is increased in dental assistants and

*In 1800, Davy reported symptoms that might have indicated a toxic effect on the brain resulting from the recreational use of nitrous oxide.

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the wives of dentists exposed to nitrous oxide. Furthermore, this increase is related to the level of occupational exposure, doubling at the highest level.

Central nervous system toxicity. Humphry Davy was the first to report that nitrous oxide adversely affects the nervous system. In his book, published in 1800, he noted that his chronic recreational use of nitrous oxide led to "increased sensitivity of touch: my fingers were pained by anything rough, and the tooth edge produced from slighter causes than usual. I was certainly more irritable, and felt more acutely from trifling circumstances. My bodily strength was rather diminished than increased."

It is now clear that abuse of nitrous oxide and even occupational exposure can cause injury to the nervous system. Initial symptoms include numbness, paresthesias, difficulty in thinking, and impairment of equilibrium or gait. Lhermitte's sign appears and the patient becomes impotent, incontinent, and unable to walk without assistance. Neurologic signs included a positive Romberg's sign or ataxic gait, muscle weakness, impaired sensation, diminished knee or ankle jerks, and extensor plantar reflexes. In many patients, symptoms and signs regress after exposure to nitrous oxide is discontinued. Residual symptoms and deficits remain in some patients. An increased incidence of both specific (pernicious anemia) and nonspecific (numbness and tingling) signs of neurologic injury were found in dentists and chairside assistants exposed to nitrous oxide.

Experimental evidence is consistent with the above epidemiologic and anecdotal data. Monkeys given 15% nitrous oxide develop ataxia after 2 days of exposure. This sign regresses if the exposure to nitrous oxide is discontinued. However, if exposure continues for more than 2 weeks, neurologic injury becomes permanent and histologic examination of the spinal cord and peripheral nerve reveals degeneration. Injury can be prevented or ameliorated if the monkey is fed methionine during the exposure to nitrous oxide. It is of interest that the injury produced by nitrous oxide in humans or other primates is not produced in rodents, even when the exposure concentration is increased to 50% nitrous oxide.

Injury to the liver. Rats have hepatic injury after pretreatment with phenobarbital and then exposure to hypoxia and 0.3 MAC nitrous oxide. A similar effect can be produced with other anesthetics and may be caused by the effect of these agents on hepatic blood flow and oxygen consumption. Recall that nitrous oxide decreases hepatic blood flow but does not decrease hepatic oxygen consumption. Mice exposed to 20% nitrous oxide for 35 days have a higher incidence of focal inflammatory lesions (but not hepatic necrosis) than unexposed mice. Similarly treated rats or guinea pigs do not develop focal inflammatory lesions. In the study by Cohen et al., both dentists and their chairside assistants were more likely to have liver disease if nitrous oxide was used in their work environment. The incidence of liver disease was related to the level of occupational exposure. Studies in patients have not shown a definite connection between administration of nitrous oxide and hepatic injury.

Injury to the kidney. Animals exposed to 20% nitrous oxide for 35 days are more likely to have calcification of distal renal tubules. Similarly, renal lithiasis increases in dentists occupationally exposed to nitrous oxide; however, the increase in the incidence is small. Chairside assistants also have a higher incidence of renal disease (but not lithiasis) if exposed to nitrous oxide.

Injury to the lung. Administration of nitrous oxide may predispose the patient to postoperative hypoxemia and respiratory complications. The intent of a recent study was to examine the effect of humidification of respired gas during anesthesia on postoperative hypoxemia and respiratory complications. However, patients given humidified gas did not breathe nitrous oxide, whereas those given dry gas did breathe nitrous oxide. A greater incidence of complications resulted in the second group and may be interpreted as a consequence of nitrous oxide administration. This group had a lower PaO₂ for 3 to 5 days after anesthesia.

Injury to the critically ill patient. Both the normal patient and the critically ill patient have megaloblastic changes in their bone marrow after anesthesia with nitrous oxide. The changes appear to persist for a longer period of time (roughly 3 to 6 days versus 1 to 3 days) in the critically ill patient. More important, the critically ill patient who has megaloblastic changes is more likely to die than the critically ill patient who does not have such changes.

An explanation for the toxicity of nitrous oxide: Inactivation of methionine synthetase

A relationship between the administration of nitrous oxide and the diverse toxic effects noted in the preceding sections is made more credible by the recent finding of an explanation for these effects. Nitrous oxide inactivates methionine syn-
thetase, an enzyme that catalyzes the conversion of homocysteine and methyltetrahydrofolate to methionine and tetrahydrofolate. This conversion is of vital importance because methionine is an essential amino acid and tetrahydrofolate is essential for the synthesis of DNA. Recall that administration of methionine ameliorated the development of central nervous system injury by nitrous oxide.

It should be emphasized that nitrous oxide inactivates rather than inhibits methionine synthetase. Were the effect of nitrous oxide to simply inhibit, then the enzyme would recover with the elimination of the nitrous oxide. Inactivation results from oxidation of the cobalamin (vitamin B₁₂) cofactor of methionine synthetase. Cob(I)alamin is converted to cob(II)alamin. The oxidation is irreversible and thus the oxidized enzyme must be replaced. Administration of vitamin B₁₂ will not restore the activity of the enzyme.

Nitrous oxide is known to inactivate methionine synthetase in the liver, brain, and placenta. The extent of inactivation depends on the duration of nitrous oxide administration, the concentration used, and the species. Humans given 50% nitrous oxide for 2 hours have a 50% inactivation of the enzyme in the liver; mice and rats have an 80% to 95% inactivation. In rats, inactivation persists for several days; in mice, activation is restored in 1 to 2 days. The rate of restoration of activity has not been measured directly in humans, but DNA synthesis may be impaired for 1 to 6 days. No other anesthetic (enflurane, halothane, isoflurane, and xenon) produces inactivation of methionine synthetase.

The impairment of DNA and methionine synthesis may explain many of the toxic effects of nitrous oxide (such as effects on hematopoiesis and on fetal development). The impairment also suggests that nitrous oxide may diminish immune defenses against infection or cancer, but to date no evidence indicates that nitrous oxide enhances the likelihood of infection or cancer. Although DNA synthesis is required for the repair of tissues, nitrous oxide does not limit wound-healing in rodents.

How should we continue to use nitrous oxide?

For some anesthetists the question is “Should we continue to use nitrous oxide?” They would argue that the advantages of nitrous oxide do not outweigh its disadvantages when compared to the benefits and drawbacks inherent in other approaches to the delivery of anesthesia. They may be particularly concerned with the possible toxicity of nitrous oxide. The anesthetists who would continue to use nitrous oxide argue that it is better than the alternatives. They would argue that the evidence for toxicity in patients is far from convincing, and that all anesthetics may have toxic effects. “Nitrous oxide has been used for a longer period and has been given to more patients than any other inhaled anesthetic. No other anesthetic has better stood the test of time. Nitrous oxide has persisted because it reliably produces a light level of anesthesia and rarely produces important untoward effects. Laboratory evidence of ill effects in animals does not have a recognizable counterpart in clinical practice. Its record of efficacy and safety speaks for itself.”

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<th>Table I</th>
<th>A review of the properties of N₂O</th>
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<td><strong>Where N₂O might be used</strong></td>
<td><strong>Where alternatives to N₂O might be selected</strong></td>
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<tr>
<td>1. For induction of anesthesia (especially in children)</td>
<td>1. In patients with severe lung disease</td>
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<td>2. For short procedures</td>
<td>2. In patients at risk from expansion of gas spaces (as in air emboli or pneumothorax)</td>
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<td>3. To eliminate more soluble anesthetics at the end of anesthesia</td>
<td>3. When nausea and vomiting must be avoided</td>
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<td>4. For long anesthesias or for short anesthesias repeated at close intervals</td>
<td>5. In the pregnant patient</td>
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<td>6. In patients where healing, infection, or immune defenses are a particular concern. (Evidence for this point is equivocal.)</td>
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The proponents of the continued use of nitrous oxide agree that there are some circumstances in which its use is not warranted. Similarly, those who would abandon nitrous oxide acknowledge that some patients would benefit from its continued use (Table I). For example, the pharmacokinetic properties of nitrous oxide and the absence of an unpleasant odor recommend its application where anesthesia is induced by inhalation, especially for children. If the toxic effects of nitrous oxide exist, and if these effects result from inactivation of methionine synthetase, then anesthesia with nitrous oxide for less than an hour should be acceptable since only a minor fraction of methionine synthetase will be inactivated in that time. Longer periods of anesthesia may also be acceptable if an antidote to the toxic effects of nitrous oxide can be found. Folinic acid may be such an antidote.

Proponents of the widespread continued use of nitrous oxide agree that in some patients the risk of anesthesia with this agent outweighs the advantage. These patients include the respiratory cripple who requires 100% oxygen to sustain oxygen saturation, the patient who has an unrelieved tension pneumothorax or an air embolism, and a patient in the first or second trimester of pregnancy (indeed, we would try to avoid the use of any inhaled anesthetic in such a patient).

We recognize that no anesthetic is ideal. If we avoid the use of nitrous oxide, what shall we substitute? A totally intravenous anesthetic is a possibility (for patients having cardiac surgery, such an approach is widely applied). Similarly, anesthesia can be safely provided with any potent inhaled agent except methoxyflurane. Many anesthetists would prefer an approach combining intravenous agents and potent inhaled anesthetics.

The anesthesia best for most patients is still a matter for debate. The era when we considered nitrous oxide to be an ideal anesthetic is past. Whether we continue to use nitrous oxide widely or selectively is the present issue. We should choose nitrous oxide because of perceived advantages for each patient for whom it is selected. As should be the case for all drugs used in anesthesia, it should not be given automatically or by rote.

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AUTHORS

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At the 52nd AANA Annual Meeting held in Anaheim during August, 1985, Dr. Eger presented a lecture on the topic “Should we not continue to use nitrous oxide?”

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