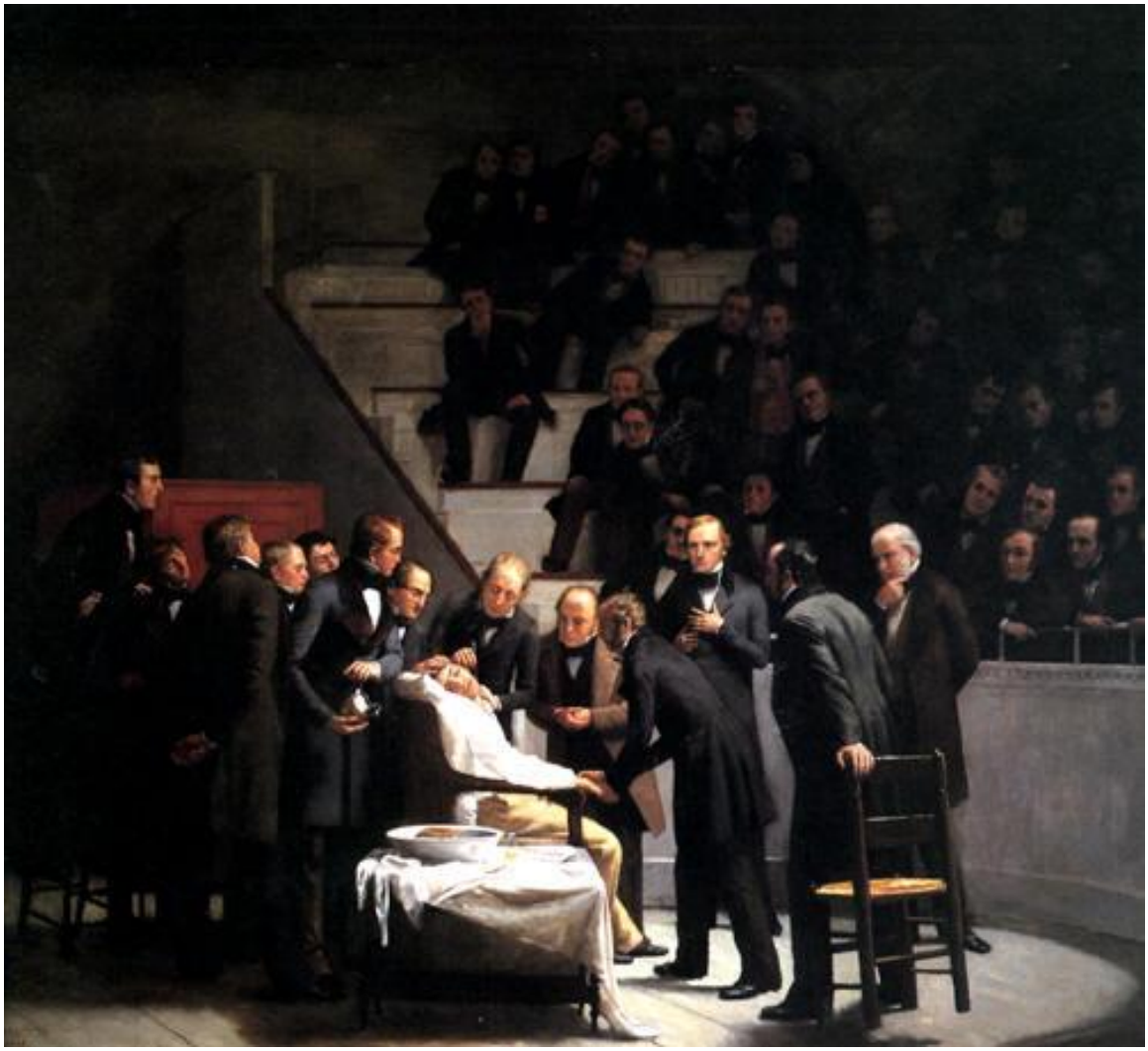
THE NORTHERN HOSPITAL

NITROUS OXIDE



"The First Successful General Anaesthetic October 16th 1846", Robert Hinckley, oil on canvas 1882

"…Yet when the dreadful steel was plunged into my breast, cutting through skin, vein, flesh and nerves, I needed no injunction not to restrain my cries. I began to scream which lasted unremittingly throughout the whole operation - and I almost marvel that it rings not in my ear still! - so excruciating was the agony. When the wound was made and the instrument withdrawn, the pain seemed undiminished, for the air that suddenly rushed into those delicate parts felt like a mass of minute but sharp poignards that were tearing the edges of the wound- but when again I felt the instrument, describing a curve, cutting against the grain, while the flesh resisted in a manner so forcible as opposed and tire the hand, then, indeed I thought I must have expired…The instrument withdrawn this second time I thought the operation was over- but no! Presently the terrible cutting was renewed - and worse then ever, to separate the bottom, the foundation of this dreadful gland from the parts to which it was anchored…Again, all description would be baffled - yet all was not over. Dr Larrey rested but his own hand: then I felt the knife rackling against the breast bone, scraping it. This performed, while I remained in utterly speechless torture, I heard the voice of M. Larrey, asking if anything more needed to be done. The general voice said

"rien"; but the finger of M. Dubois, which I literally felt elevated over the wound though I saw nothing, pointed to some further requisition and again started the scraping, atom after atom.

...Not for days, not for weeks or months could I speak of these terrible minutes without nearly again going through it and being violently sick…"

The Journal of Fanny Burney, 1810.

"...I invited a dozen or fifteen gentlemen to come upon the stage who would like to inhale it. Among those who came forward was Dr Horace Wells, a dentist, and a young man by the mane of Cooley. Cooley inhaled the gas and, while under the influence ran into some wooden settees and badly bruised his leg. Taking his seat next to Dr Wells, the doctor said to him, "You must have hurt yourself". "Not at all". Then he began to feel some pain and was astonished to note that his leg was covered in blood.

At the close of the exhibition Dr Wells came to me and said, "Why cannot a man have a tooth extracted under the gas and not feel it?" I replied that I did not know. Dr Wells then said that it could be done and would try it on himself...The next day I went to his office carrying a bag of the gas..."

Gardiner Colton, December 1844.

Fanny Burney's journal describes in chilling detail the ordeal of surgery in the pre-anaesthetic era. Though dosed up on large amounts of alcohol and at times life-threatening doses of "laudanum", it nevertheless took many stout hands to hold down a patient who had to undergo surgery. The pain despite the alcohol and narcotic would still be horrific and death from stress and shock was not uncommon. One of the greatest skills of the surgeon in the pre-anaesthetic era was considered to be the speed at which he could perform his procedure. The decision to undergo surgery was not to be taken lightly and those who did so would often suffer the psychological scars it would induce for the rest of their lives. One of the most momentous ideas in medical history took place one afternoon in December of 1844 at one of the popular demonstrations of the day of the "recreational" or "entertainment" effects of "laughing" gas. A little noticed observation during one of these shows, by a certain dentist by the name of Horace Wells was that the "laughing gas" appeared to have significant analgesic properties. But would this be enough to alleviate the horror of the surgeon's knife. Wells after trials on himself was convinced that it was, however in 1845 in a public demonstration of a tooth extraction he was discredited and severely ostracised when the patient cried out in pain. Wells became very bitter and disillusioned with the medical establishment's scathing dismissal of his idea of anaesthesia. He sadly finished his life a broken man, suffering from mental illness; he would eventually kill himself in 1848. It was not till the subsequent stunning demonstration of the use of ether as an anaesthetic agent by William T. Morton in October 1846 that the surgical establishment recognized that their art of surgery had been changed forever.

Although William Morton is remembered by posterity as the "inventor" of anaesthesia it was the insight and the courageous attempt, by putting his reputation on the line, at a public demonstration of the feasibility of anaesthesia by Horace Wells that gave Morton his idea to try things again, though with a different agent. Morton would forever claim for himself the credit for having discovered anaesthesia.

However it was Horace Wells who delivered humanity from the horror of the surgeon's knife forever and opened the way for the miraculous progress of surgery by "quantum leaps" over the subsequent centuries.

Horace Wells would have had some satisfaction to know that his "laughing gas" did ultimately have a more lasting place in medicine and that the ether of his great rival William T Morton would become obsolete by the middle of the twentieth century.

NITROUS OXIDE

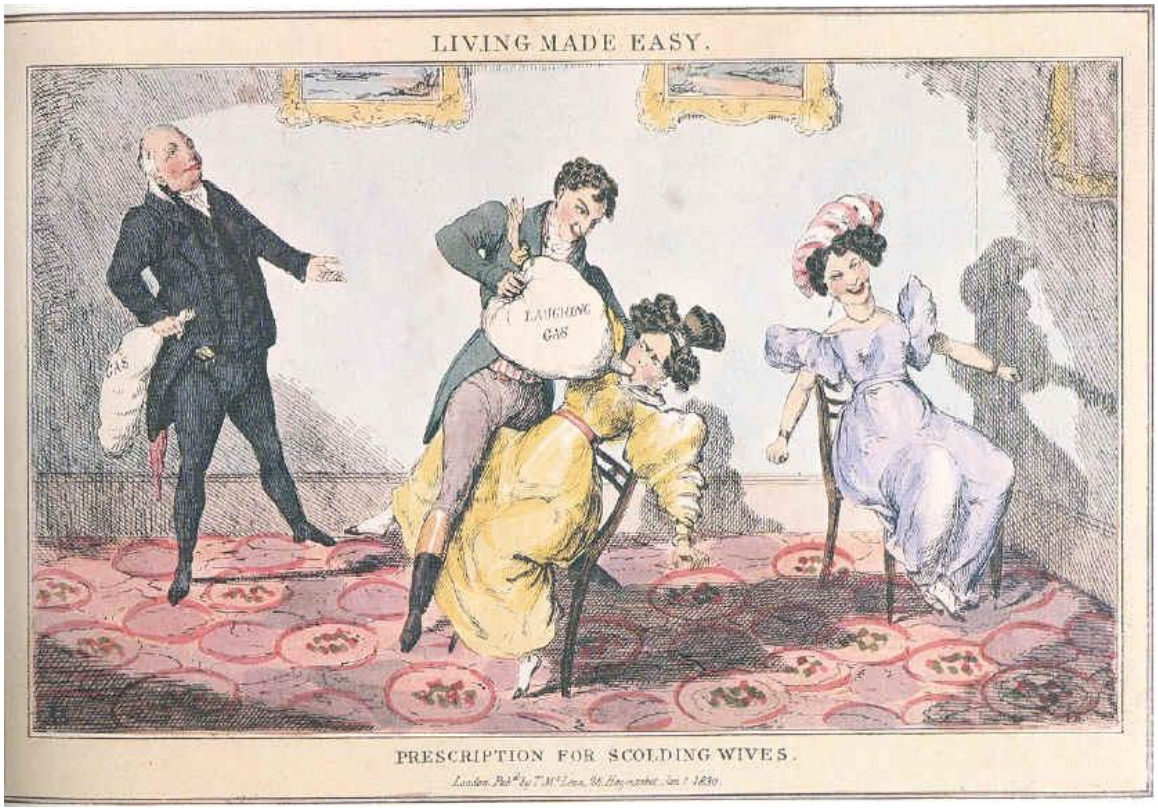
Introduction

- Nitrous oxide is a useful and safe agent for obtaining analgesia for moderate pain in a wide variety of applications in the Emergency Department, operating theater, pediatrics and obstetrics.

Historical

- Nitrous oxide was first synthesized by the English chemist and natural philosopher Joseph Priestley in 1772, who called it, *phlogisticated nitrous air*.

- In 1799 the great English chemist, Humphrey Davy noted its analgesic and anesthetic properties, however inexplicably never made the connection with its possible use in surgery that Wells did. It was used mostly as a "recreational" drug because of its well know dysphoric effects. These effects were the basis of the historical designation "laughing gas". Apparently Victorian doctors found the agent useful for subduing "scolding" wives.



"Living Made Easy, prescription for scolding wives", lithographic print, 1830

- Nitrous oxide was the world's first anesthetic agent, but its use was rapidly replaced by ether and chloroform as the standard agents of anesthesia in the mid Nineteenth century.

  The American dentist Horace Wells was the first to use it as an anaesthetic agent in patients he performed dental extractions on in 1845. Whilst this first demonstration was not a great success it did mark the historical birth of anesthesia, one of the greatest advances in medical history.

Preparation

- **Nitrous oxide is N_2O** (as opposed to *nitric oxide* which is NO and *nitrogen dioxide* which is NO_2)

- It can be prepared by the controlled heating ammonium nitrate at 170-240 degrees Celsius, (at much higher temperatures than this a runaway exothermic reaction can result in detonation. Major explosions have occurred in the commercial production of nitrous oxide!)

  $NH_3NO_3 \longrightarrow N_2O + 2H_2O$

- Medical nitrous oxide is stored in blue steel cylinders under pressure in equilibrium with the gaseous phase.

Environmental Note:

- Nitrous oxide is 230 times more potent as a "greenhouse" gas than carbon dioxide and takes around 120 years to naturally break down. Nitrous oxide currently contributes around 5% of the total greenhouse gases and the contribution of medical nitrous oxide contributes around 0.35% of the total.

Physical Properties

- It is a colourless gas (at 1 atmosphere and room temperature)
- It is said to have a slightly sweetish smell.
- It is non-flammable.
- It is non-irritant.
- Melting point: - 90.85 degrees Celsius
- Boiling point -88.48 degrees Celsius

Pharmacokinetic Principles

The significance of the alveolar concentration of anesthetic agent:

The alveolar concentration of an anesthetic agent is directly proportional to the depth of anesthesia.

The forward movement of an inhalational agent is determined by a series of partial pressure gradients, beginning at the vaporizer of the anesthetic machine, continuing in the breathing circuit, then to the alveolus, the blood, and finally the tissue. The driving force of this movement is the partial pressure gradients at each step. When the partial pressures have equilibrated gas flow ceases.

Ultimately it is the alveolar partial pressure that governs the partial pressure of the anesthetic in all the other body tissues; (**alveolar concentration is proportional to arterial concentration is proportional to tissue concentration**), they all will *ultimately* equal the alveolar partial pressure of the gas.

Factors that affect the alveolar concentration:

It is therefore important to understand the factors that affect the alveolar concentration of an anesthetic agent. It will be affected by factors which are related to input and factors which are related to the output away from the alveolus, (ie input – output, will determine the final value).

These factors include:

Input:

- The concentration of anesthetic agent delivered.
- The level of the alveolar ventilation.

Output

- The partial pressure difference between alveolus and pulmonary venous blood.
- The **solubility** of the anesthetic agent.
- The cardiac output.

The concentration of anesthetic agent delivered:

The actual concentration of nitrous oxide that is delivered to the alveolus has two important effects:

The concentration effect:

The rate at which alveolar tension, or partial pressure of an anesthetic agent rises, will be directly proportional to the concentration of the inspired anesthetic agent and the rate of alveolar ventilation.

Additionally **nitrous oxide is relatively insoluble in blood, yet even so it is around 30 times *more* soluble than nitrogen.** During anesthetic induction N_2O from the alveolus is exchanged for N_2 from the blood. During induction the *volume* of N_2O leaving the alveolus and entering the pulmonary capillaries is *greater* than the volume of N_2 leaving the pulmonary capillaries and entering the alveolus, because of the differential solubility values.

In other words nitrous oxide diffuses into the alveoli, along its concentration gradient at a much faster rate than nitrogen diffuses out of the blood back into the alveolus, and hence the gases left behind are concentrated into a smaller space and so become more concentrated. This is called the **concentration effect** of nitrous oxide.

Additionally this process can literally "draw in" further gas (O_2 and N_2O) from the trachea and bronchial tree in response to the diminished alveolar pressures, thus resulting in an increased availability of the anesthetic (N_2O), without an actual increase in the alveolar ventilation rate.

The second gas effect:

The gases left behind in the concentration effect may include a second inhalational anesthetic agent. When this *second agent's* concentration is increased by the disproportionate exchange of nitrous oxide and nitrogen the phenomenon is known as **the second gas effect.** Thus large volumes of nitrous oxide can enhance the potency (reduce the MAC) of a second volatile anesthetic agent.

Note that the concentration effect and the second gas effect are really just terms describing different aspects of the same phenomenon.

Diffusion hypoxia

The differential rates of N_2O and N_2 exchange described above also has important implications in the recovery phase of patients who have undergone anesthesia. At the end of anesthesia the elimination of N_2O from the blood into the alveolus is much quicker than the reuptake of N_2 back into the blood, when the patient is breathing atmospheric air (21% O_2 and 79% N_2) which results in the dilution of the inspired oxygen. Hypoxia can occur, especially if the patient's ventilation is inadequate and the patient has received N_2O for a prolonged period.

This problem is overcome by providing the patient with pure oxygen (ie 100%) for at least 2 minutes after cessation of the anesthetic.

Solubility of anesthetic gases in biological tissues:

Gases move from areas of high concentration to areas of low concentration by the process of simple diffusion. In the body the speed at which this occurs will depend upon the various solubility partition coefficients (also known as Ostwald solubility coefficients) that occur at the interfaces of different media (gas/ blood and blood/ tissue).

The solubility of an anesthetic agent in blood is defined as:

- Concentration of anesthetic in blood / Concentration of anesthetic in gas at equilibrium.

The solubility of an anesthetic agent in tissue is defined as

- Concentration of anesthetic in tissue/ Concentration of anesthetic in blood at equilibrium.

Note that "at equilibrium" means that there is the same **partial pressure** in blood and alveolar gas, it does *not* mean that the actual concentrations are equal in the two phases.

The solubility of nitrous oxide is in blood low (0.47 mls/ml of blood, cf nitrogen which is 0.014 mls/ml of blood)

The solubility of volatile anesthetic agents in blood is high.

The solubility of an anesthetic agent in blood will determine 3 important clinical effects. These are:

1. **The speed of anesthetic induction, (**the less soluble the agent, the quicker will be the anesthetic induction).

2. **The ease with which maintenance concentrations can be changed**

3. **The speed of recovery from anesthesia,** (the less soluble the agent, the quicker will be the speed of recovery from anesthesia).

In other words if **a highly soluble anesthetic vapor**, (such as methoxyflourane), is inhaled, as soon as it arrives in the alveoli it rapidly dissolves off into the bloodstream and then into muscle, fat, bone and other tissues, consequently it takes some time for the alveolar tension to rise and some time for the agent to arrive at the brain. Conceptually therefore it takes "all day" to go to sleep (and conversely to wake up). It takes longer until the equilibrium with the brain partial pressure of the gas is reached. In practice this drawback is overcome by initially increasing the inspired anesthetic concentration of highly soluble agents to levels well above those required for the maintenance of anesthesia, (see below).

Note further that all volatile inhalational anesthetics have very high fat/blood partition coefficients. This means that most of the gas will bind to fatty tissue as times goes by. The partial pressure of the gas in fatty tissue will rise very slowly, thus inhalational anesthetics stored in such tissue in obese patients may delay awakening at the end of anesthesia.

Nitrous oxide on the other hand, is **extremely insoluble**; it stays in the alveoli and only a small amount of agent passes, into the blood; the tension thus becomes high in the alveolus very quickly and hence the brain very quickly (remember that the tension in the alveolus is directly proportional to that of the arterial blood and in turn the brain). Consequently the patient goes asleep and wakes up very quickly.

The level of the alveolar ventilation:

The alveolar partial pressure of anesthetic agent can be raised by:

- Increasing minute ventilation
- Increasing the flow rates at the level of the vaporizer
- Using a non-rebreathing circuit.

Note that by increasing the rate of alveolar ventilation the rate of rise of the anesthetic agent will increase and the greater will be onset of action. Because nitrous oxide is

relatively insoluble, however its alveolar concentration rises very quickly and raising the alveolar ventilation rate does not add much to its rapidity of onset.

For a very soluble anesthetic agent however the rate of rise of the alveolar concentration is relatively slow, hence increasing the rate of alveolar ventilation will have a significant effect on increasing the speed of these types of agent's action.

The effect of the cardiac output:

With increased cardiac outputs a greater amount of anesthetic agent is taken away from the alveolus, hence the rate of rise of the alveolar partial pressure will be slower, hence so will that of the brain and hence induction of anesthesia will take longer.

Conversely a reduced cardiac output will result in a more rapid rise in alveolar partial pressures and consequently a quicker time of anesthetic induction.

Metabolism

- Nitrous oxide is not metabolized by the body.
- It is eliminated unchanged from the lungs.

Clinical Effects

1. **Analgesia**

    - It is a moderate analgesic agent

2. **Anaesthesia**

    It is a weak agent only when used for anaesthesia, having a MAC value of **104 %,** (ie hyperbaric conditions would be required to achieve surgical anaesthesia in 50 % of patients

    MAC (minimum alveolar concentration)

    This is a variable assigned to volatile anaesthetic agents to describe their anaesthetic **potency.**

    One drug is more potent than another if it takes a smaller amount of that drug than the other to achieve the same effect. Note that it is not the same thing as efficacy, which refers to the maximal clinical effect that can be achieved by an agent.

    MAC is defined as:

    - The minimum alveolar concentration of the agent (at one atmosphere pressure) is defined as the end tidal (expired not inspired) concentration of anaesthetic agent at which 50% of the population will not move in response to a surgical stimulus (skin incision)

3. **Euphoria/ Dysphoria.**

- These effects can be unpredictable.

4. Mild sedation

5. Amnesia.

   - There may some amnesic effects for the immediate period of light anesthesia, however there is no effect on a patient's long term memory.

6. Mild sympathomimetic effects

   - Mild tachycardia, elevation of blood pressure.

7. It has minimal cardiac effects or respiratory effects.

8. Raised intracranial pressure

   - May cause mild elevations in intra-cranial pressure, due to increased cerebral blood flow.

9. It is safe to use in patients with malignant hyperpyrexia.

Advantages

- Rapid onset of action and rapid recovery.
- Short duration of action.
- Simple to administer.
- Relatively inexpensive agent
- Does not greatly depress conscious state or airway reflexes in usual therapeutic dosing.
- Does not cause significant cardiovascular depression.
- A fasting state of 2-4 hours is desirable, though this is not strictly nessesary in emergency or urgent situations.

Disadvantages

- May be used as an adjunct to other analgesia, but of itself, is often not adequate in cases of severe pain
- Nitrous oxide compressed into steel cylinders (when full contains 4/5 liquid and 1/5 gas under 51 atmospheres of pressure). This makes the agent cumbersome and difficult to deliver in remote areas or areas outside an ED or operating theater in general.
- Requires specialized circuits to deliver a safe anesthetic mixture (nitrous oxide and oxygen) and optimal delivery of this.

Indications

1. For quick provision of moderate analgesia, especially in the setting of:
    - Emergency departments
    - Obstetrics, (delivery)
    - Pediatrics, (avoids the need for a needle)
2. For moderate analgesia required for short painful procedures, (eg major joint reductions, splinting of fractures, IV insertion in children, abscess drainage)
3. For patients undergoing general anaesthesia:
    - Nitrous oxide can reduce the MAC value, (ie increase he *potency*) of concurrently used volatile anaesthetic agents.

Contraindications

- Abdominal distension / bowel obstruction.
- Decompression sickness or air embolism.
- Intrathoracic injuries / pneumothorax.

Adverse Reactions

1. Nausea/ vomiting
2. Closed gas filled cavity expansion
    - Any gas closed gas filled cavity within the body may expand (or increase in pressure, or both) during nitrous oxide anesthesia, due to the relatively rapid entry into the cavity of the nitrous oxide in exchange for the relatively slower exit of nitrogen from the cavity into the blood stream.
    - Nitrous oxide therefore should be avoided in patients with bowel obstruction, middle ear or sinus disease and especially pneumothorax, (70% nitrous oxide may double the size of a pneumothorax in as little as ten minutes)
3. Diffusional hypoxia at the end of anaesthesia, (see above)
4. Hypoxia in cases where concurrent oxygen delivery is less than 21% oxygen
    - This cannot happen when proper circuits are used for delivery. These circuits do not allow for the delivery of less than 50% (entenox) or 30% (quantiflex) oxygen. Occasionally lay “recreational” users who do not appreciate the need for concurrent oxygen delivery may suffer hypoxia if they inhale 100% nitrous oxide for prolonged periods or within small

enclosed areas, (lethal cases have occurred with "recreational use" in cars with closed windows) [2]

5. Inactivation of vitamin B12

- A property unique to N_2O is its ability to oxidise and inactivate the vitamin B12 components of certain enzymes in both animals and man. One such enzyme, methionine synthetase is essential for normal DNA production. Because of this fact concerns have been raised about effects on the haematological, immune, neurological and reproductive systems via this mechanism. [3] The clinical significance of these effects however is uncertain. The main danger being in those with repeated and/or prolonged exposure.

Dosing/ Administration

Nitrous oxide may be delivered in two ways:

1. Via an anaesthetic, (or Boyle's machine) within the operating theatre.

2. Via specialized cylinders and circuits for use in the Emergency department. Two main types of circuits are available:

The Entenox system

- This system delivers a *fixed* proportion of 50% nitrous oxide and 50% oxygen to the patient.

- It does *not* have a scavenging system

The Quantiflex system

- This system can deliver a *variable* proportion of nitrous oxide and oxygen to the patient. Nitrous oxides concentrations that can be given range from 30% to 70%.

- It *does* have a scavenging system.

- **See also "Use of the Quantiflex Circuit for Nitrous Oxide", in these guidelines for the operation of this circuit.**

  Only staff that have been specifically trained in the use of this circuit should use it.

Note that concentrations of nitrous oxide of up to 70% will not provide reliable *surgical* anaesthesia and it should be used merely as a moderate analgesic agent.

Unconsciousness may be induced in concentrations above 80%, how the attendant hypoxia that this entails make contra-indicate these concentrations.

References

1. N.M Cass, Pharmacology notes, 1980, Nitrous Oxide.

2. "Local pulled laughing gas victims from car", Sydney Morning Herald, Jano Gibson, Les Kennedy, AAP, September 19, 2005

3. Brodsky JB. Adverse effects of nitrous oxide. Med Toxicol 1986 Sep-Oct; 1(5):362-74.

Dr J. Hayes
Dr D. Pescod, Staff Anaesthetist Northern Hospital.
Dr Julie Considine CNE, Northern Emergency Department

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