Nitrous oxide. The good, the bad (and the ugly)

L0002835 © Wellcome Library, London. Administering nitrous oxide gas. From: The discovery of modern anaesthesia. By: Nevius, L. W. Published: Nevius New York 1894

Nitrous oxide is ubiquitous in our delivery rooms, our theatres, our kitchens and in the atmosphere. Non-medical use of nitrous oxide even outside of the food industry, where it is known as the additive E492, is also surprisingly widespread. The power output of the internal combustion engine can be greatly enhanced by modification to allow the injection and ignition, in short bursts, of nitrous oxide in the manifold – NOS modified cars, as they are known, are technically legal for street use in the UK. Nitrous oxide gas can act as the oxidiser in amateur and commercial rocket engines, although it is thankfully considered too unstable for military use.

Nitrous oxide is an important contributor to climate change. However, unlike chlorofluorocarbons, it has always been present in the atmosphere, since 70% of its production is unrelated to human activity being from bacteria in the soil and oceans. Among greenhouse gases it ranks fourth in order of importance. Weight for weight it is 300 times more harmful than carbon dioxide over a 100 year time interval but its concentration in the atmosphere is much lower. It is also a potent cause of ozone depletion. Non-agricultural human-based emission of nitrous oxide has diminished but agricultural production of nitrous oxide represents about 65% of the total and remains almost unchanged in quantity since 1970. Obviously a discussion of the causes of climate change is beyond the scope of this article, but it will be apparent that medical release of nitrous oxide in to the atmosphere while not insignificant is just a small fraction of total emissions.

Until 1772 nitrous oxide was quite unknown, for that was the year that Joseph Priestley first isolated it at Lord Shelbourne's private laboratory in Calne, Wiltshire. This was three years earlier than Priestley's still more famous discovery of oxygen, a distinction he shares with Antoine Lavoisier and Carl Scheele. No-one claimed co-discovery of nitrous oxide. That was his feat alone when Priestley heated moistened iron filings with sulphur (brimstone) and nitric oxide (nitrous air). But what are we to make of his naming it 'diminished nitrous air' or 'dephlogisticated nitrous air'? Priestley, a natural philosopher and dissenting preacher, was not quite a pure scientist in the mould of Lavoisier, and adhered unswervingly to the soon to be disproved phlogiston theory, but at least in his seminal publication *Observations of Different Kinds of Airs* he finally laid to rest the principle of Four Elements.

It was not until a further 25 years had elapsed that nitrous oxide was harnessed in any way to take advantage of its properties. A certain Dr Mitchell had not advanced it much when he stated that it was the primary cause of contagion and fatally harmful even in tiny quantities. Keen to disprove such nonsense, the physician Thomas Beddoes, in his Pneumatic Institute at Bristol, had the idea of investigating the possible medical uses of nitrous oxide, particularly as a treatment for tuberculosis. Beddoes is perhaps less well known now than his son, the poet Thomas Lovell Beddoes. However Beddoes Senior was certainly more than a country quack, and his ideas for pneumatic medicine, though misguided, showed evidence of his willingness to challenge the status quo.

Beddoes employed a young Humphry Davy, his fame and a baronetcy some distance in the future but fresh from an apprenticeship in his native Cornwall, to be his assistant. Much is made of the book which Davy published in 1800 entitled *Researches, Chemical and Philosophical*. Deep inside the closely printed pages of that tome, Davy refers to the analgesic effects of nitrous oxide and later to the possibility that it might be used for surgical operations. Davy did not pursue this any further and left for the Royal Institution shortly thereafter to follow different avenues of investigation. Some historians regard this as a missed opportunity to herald the discovery of anaesthesia. But just how unsafe an anaesthetic might it have been given its extremely weak ability as an induction agent unless given to the almost total exclusion of room air? Perhaps it was a blessing in disguise that it was not taken up at this time. It is worth remembering that after Horace Wells' failed demonstration of nitrous oxide anaesthesia in 1845, it was barely used even as a dental anaesthetic until championed by Gardner Colton in 1862 and subsequently in London in 1868 by an American dentist from Paris, Thomas Evans. Even though Andrews of Chicago had stated that same year it should be given in combination with at least 20% oxygen, in 1910, McKesson of Toledo, Ohio, was a firm proponent of its use as an anaesthetic with no more than 5% oxygen and designed a very popular anaesthetic machine for that purpose. Thus it earned the grim sobriquet of the 'black gas'.

Remarkably, Paul Bert, the French physiologist and protégé of Claude Bernard, devised the answer to all of this in 1880. He had the extraordinarily clever idea of building a hyperbaric chamber in which patient, surgeon and anaesthetist, and anyone else who happened to be inside it (for it was quite large), were subjected to a pressure of two atmospheres. He knew that as nitrous oxide is effective at a partial pressure of one atmosphere, it could at such an ambient pressure be given in a concentration of 50% with air. The surgical anaesthesia was said to be superb, skin colour excellent and patient recovery very swift. However, even though the chamber was mounted on wheels and could thus be moved around Paris from hospital to hospital, it was not a practical solution.

Humphry Davy's study of the effects of nitrous oxide owed a great deal to self-experimentation, even to the point where it has been suggested that he was briefly dependent on the drug. He risked his life and might well have paid a high price but for good fortune. There is little doubt that at times he experienced pronounced hypoxia and breathed harmful concentrations of carbon monoxide and of impure oxides of nitrogen. The effect of breathing nitrous oxide recreationally is the production of a state which some users describe as no more than dizzy and others as nothing less than a psychedelic experience. That was certainly the effect that Davy's friends from the world of the arts were hoping to experience and by all accounts did. Peter Roget, of Thesaurus fame, and poets Samuel Taylor Coleridge and Robert Southey were particularly effusive. The normally sober Southey, Lord Nelson's biographer, described it rapturously as 'the air in heaven, a wonder working gas of delight'. Coleridge had already written his extraordinary metaphysical poem *The Rime of the Ancient Mariner*, and would later become a habitual user of laudanum and opium, as was typical of this period. Their friend Thomas De Quincey, in his celebrated book *Confessions of an English Opium Eater*, laid bare this drug-addled artistic life. Of all the romantic poets only William Wordsworth is known to have abstained.

Inhaling nitrous oxide from balloons was a popular pursuit amongst hippies on America's West Coast in the 1970s and has gained popularity in Britain over the last 10 years. The key to this is the ease with which it may be obtained and administered. Nitrous oxide has a place in the food industry as a preservative and is also used by restaurants in the making of whipped cream, for which purpose it is ideally suited. For this application it is supplied in very small pressurised canisters which when broken open will readily fill a small balloon. The party goer breathes in and out of the receptacle until some desired effect is obtained. This is not by any means a particularly clever thing to do, but surprisingly is not against the law. For the time being it is classed as a legal high, an anomalous situation that may well change if proposed government legislation reaches the statute books. Most British outdoor festivals already have zero tolerance of nitrous balloons.

There is not a great deal of evidence that occasional inhalation of nitrous oxide as a leisure pastime is overly hazardous. Compared to the known harmful effects of alcohol and tobacco it is relatively safe. Without doubt a great deal more harm was wrought by its cavalier use as an anaesthetic in the first half of the 20th century. The problem lies in the paradox that the success of nitrous oxide as a sole anaesthetic is dependent on using as little oxygen as possible. That this was done without ill effect on thousands of occasions cannot be disputed. As for how many patients were rendered neurologically compromised or dead remains a matter for conjecture, but it is a stain on the history of anaesthesia. Why did this hazardous practice persist for so long? There are many reasons. The skill of the experienced anaesthetist was a factor but so was hubris. The need for fast surgery, especially in dentistry was also an issue. However the widespread use of nitrous oxide as a sole anaesthetic agent for laparotomies and other prolonged procedures was reprehensible given the safer alternatives available at the time. As late as 1959, that doyen of British dental anaesthesia Victor Goldman was writing at length on nitrous oxide and air anaesthesia in chapter 17 of *General Anaesthesia*. This two volume book edited by Frankis Evans and Cecil Gray was published by Butterworth to popular acclaim so it will have reached a wide audience. Dr Goldman, of the eponymous vaporiser fame, espoused the so-called '4th breath technique'. The patient inhales 100% nitrous oxide until asleep and deeply cyanotic, and then air is given every fourth breath for no more than 2–3 minutes. To avoid 'the damaging effects of cerebral hypoxia'

it is recommended that oxygen should be judiciously added for longer procedures or if there is an increase in respiratory rate indicating marked hypoxaemia. Even as recently as 1973, in the 7th edition of that wonderful book *Synopsis of Anaesthesia*, this technique is briefly mentioned but there is, the authors state, 'little justification for its use in modern anaesthesia'.

Harm from the use of nitrous oxide did not result just from its overzealous administration, but sometimes from its inadvertent delivery to patients. Deaths occurred all too frequently as a direct result of gas cylinder connection errors prior to the adoption of the pin index safety system, a continuing state of affairs which, in 1945, *The Lancet* considered deplorable and demanded action. Even more contemporarily, right up until the 1990s in fact, the use of obsolete Boyle's machines which did not prevent hypoxic mixtures being delivered has resulted in inadvertent prolonged administration of 100% nitrous oxide with catastrophic results.

In recent years a more insidious attack on nitrous oxide in anaesthesia has come from Australia and some parts of the USA, where loud voices have claimed poorer outcomes following use of the agent in anaesthesia for major surgery. Their case has been overstated and the evidence is contradictory. Medical use of nitrous oxide has survived all of this and it seems likely that it will continue to be available for many years to come. The black gas may yet have a bright future.

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Further reading

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