

**THE HISTORY OF
ANAESTHESIA SOCIETY
PROCEEDINGS**



Volume 16

**Proceedings of the Joint Meeting with the
Section of Anaesthetics
Royal Society of Medicine
London, 10th December 1994**

The History of Anaesthesia Society

December 1994 Meeting

Acknowledgements

The History of Anaesthesia Society expresses its gratitude to the President and Council of the Section of Anaesthetics of the Royal Society of Medicine, and to Neclama Lewis and Glynis Squires of the Sections Office.

The Meeting was sponsored by BOC Medical Gases.

Proceedings of the History of Anaesthesia Society

Editor Dr A Marshall Barr
Norscot, Rosebery Road,
Tokers Green, READING RG4 9EL
Telephone: 01734 479646

Publication Coordinator Dr F E Bennetts

The contribution of **Abbott Laboratories** to the preparation and printing of these Proceedings is gratefully acknowledged.

The Society acknowledges with thanks the Meeting photographs from Dr Geoff Hall-Davies of Birmingham.

**THE HISTORY OF ANAESTHESIA SOCIETY
COUNCIL AND OFFICERS DECEMBER 1994**

President	Dr D Zuck
Honorary Secretary	Dr J A Bennett
Honorary Treasurer & Membership Secretary	Dr Jean Horton
Honorary Editor	Dr A M Barr
Council Members	Dr G W Hamlin
	Dr W G G Loyn
	Dr Anne Naylor
	Dr J Ruprecht
	Dr T M Young
	Dr C Woollam
	Dr A Macdonald (co-opted)

Honorary Members

Dr Aileen Adams CBE
Dr T B Boulton OBE TD
Dr P Dinnick
Dr Barbara Duncum
Dr T Keys
Dr Ruth Mansfield
Dr H Rex Marrett
Dr W D A Smith
Dr C S Ward

**JOINT MEETING OF THE HISTORY OF ANAESTHESIA SOCIETY &
THE SECTION OF ANAESTHETICS OF THE ROYAL SOCIETY OF MEDICINE
SATURDAY 10 DECEMBER 1994**

List of delegates

Dr Aileen K Adams CBE	Cambridge	Dr G Hall-Davies CBE	Redditch
Dr C N Adams	Suffolk	Dr Margaret Hamilton	London
Mr A K Adatia	Bristol	Dr G W Hamlin	Blackburn
Dr R S Ahearn	Liverpool	Dr A G Henderson	
Dr H D Astley-Hope	Berkshire	Mr P Henrys	BOC
Dr R S Atkinson	Leigh-on-Sea	Dr G R Hibbert	Birmingham
Dame Josephine Barnes	London	Dr J D Hill	Epping
Dr A M Barr	Reading	Dr Jean M Horton	Cambridge
Dr J A Bennett	Bristol	Dr D D Howat	London
Dr F E Bennetts	Dorset	Dr D M Jackson	Swindon
Dr R C Birt	Essex	Dr R L Jayaweera	London
Dr J W Blizzard	Chelmsford	Dr Mary Knowles	Hampshire
Dr T B Boulton OBE	Berkshire	Dr R S Laishley	London
Dr Doreen Browne	London	Dr E Landes	London
Dr G Burton	Bristol	Dr J R Lane	Jersey
Dr Jennifer Burton	Leicestershire	Dr D G Larard	
Dr Caroline Carr	St Albans	Dr B Lawrence	Somerset
Dr A J Carter	Stoke on Trent	Dr P Lee	
Dr F F Casale	Colchester	Dr W G Loyn	Aberyswyth
Mr A D Clover	Luxemburg	Dr Ruth E Mansfield MBE	Surrey
Dr F R Coffin	W Sussex	Dr J S Mather	Birmingham
Dr P V Cole	London	Dr E T Mathews	Birmingham
Dr I M Corall	London	Dr S McDonald	
Dr D G Davies	Buckinghamshire	Dr I McLellan	Leicester
Dr J A Davies	Birmingham	Dr Lorna M Mendonca	London
Dr B T Davis	Birmingham	Dr Susan Milroy	
Dr G R Dickson	Birmingham	Dr J T Mulvein	Bristol
Dr O P Dinnick	Hampshire	Dr D W Munro	Wakefield
Dr P M Drury	Liverpool	Dr N Newton	London
Dr A Duin	Amsterdam	Prof J Norman	Southampton
Dr B Duncum	London	Dr J F Nunn	Middlesex
Dr M Dzolgic	Amsterdam	Dr Barbara Oliver	London
Dr R H Ellis	London	Dr M Otero	
Dr C Fagan	Denmark	Dr Buddug Owen OBE	Clwyd
Dr Ann Ferguson	Kent	Dr Ruth Owen	London
Dr B W Fickling	Middlesex	Dr A Padfield	Sheffield
Dr Anne M Florence	Cheshire	Dr W K Pallister	London
Dr C A Fuge	Bath	Dr S M Parr	Birmingham
Dr E P Gibbs	Essex	Dr F S Plumpton	E Sussex
Dr M R Gilles	France	Prof. D Poswillo	Kent
Dr A Gilston	London	Dr J Powell	Bristol
Dr M Goerig	Hamburg	Dr J Pring	Cornwall
Dr Julianne Goodwin	York	Dr Shashi B Rawal	Cheshire
Dr N Gorbutt	Nottingham	Dr G A Rees	Penarth
Dr N H Gordon	Glasgow	Prof H Reinhold	Brussels
Dr B Gough	West Midlands	Brig J Restall	Surrey
Dr R Greenbaum	London	Dr Barbara C Roberts	Cardiff

**JOINT MEETING OF THE HISTORY OF ANAESTHESIA SOCIETY &
THE SECTION OF ANAESTHETICS OF THE ROYAL SOCIETY OF MEDICINE
SATURDAY 10 DECEMBER 1994**

List of delegates continued

Dr Bodil Robertson	Canterbury
Dr Jean Robson	Guildford
Dr N M Rose	Herefordshire
Dr Eryl Rouse	Clwyd
Dr Rachel Rouse	
Dr J Ruprecht	Rotterdam
Dr G B Rushman	Essex
Dr Margaret Sealey	Solihull
Dr H F Seeley	London
Dr M A Skivington	Bournemouth
Dr B H Smith	Birmingham
Dr T G C Smith	Reading
Dr W D A Smith OBE	Leeds
Dr Diana H Spears	Essex
Dr J R Spears	Essex
Dr M Spencer-Swaine	
Dr Pamela J Stow	Sevenoaks
Mr P Sykes	Amphill
Prof Sir Keith Sykes	Oxford
Dr T A Thomas	Bristol
Dr A J Trench	Perthshire
Dr W D Turner	Leicester
Dr Maureen Van Ryssen	W Sussex
Prof D Vermeulen-Cranch CBE	Amsterdam
Dr R I Verner	London
Dr Barbara M Weaver	Avon
Dr Carole-Ann Webb	Staffordshire
Dr R Westhorpe	Melbourne
Dr G M White	Cleveland
Dr G Whitfield	N Yorks
Dr B R Whittard	Devon
Prof J A Wildsmith	Edinburgh
Dr D Wilkinson	London
Dr Susan A Williams	London
Dr Andrea L Wraith	
Dr T M Young	Cheshire
Dr P M Youngman	Suffolk
Dr J S Zorab	Bristol
Dr D Zuck	London



The Presidents

Dr D Zuck
History of Anaesthesia
Society

Dr A Padfield
Section of Anaesthetics
Royal Society of Medicine



Dr P V Cole



Dr Barbara Duncum



Mr P Henrys



Dr D D C Howat



Dr M Goerig



Dr R Greenbaum



Dr J E Pring



Dr J Ruprecht



Prof Doreen Vermeulen-Cranch



Dr R Westhorpe



Dr J A W Wildsmith



Dr D Wilkinson

**HISTORY OF ANAESTHESIA SOCIETY
AND
SECTION OF ANAESTHETICS OF THE ROYAL SOCIETY OF MEDICINE
CELEBRATORY SYMPOSIUM PROGRAMME**

to mark

**150 YEARS OF NITROUS OXIDE ANAESTHESIA
(Introduced by Colton and Wells 1844)**

		Page
The oxides of nitrogen and their early history	Dr J E Pring	11
Dutch chemists of the late 18th century	Dr J Ruprecht	16
The Connecticut connection	Dr J A W Wildsmith	20
Cyanosis in the early history of anaesthesia	Dr D Zuck	25
Reintroduction of nitrous oxide in the 1860s	Dr B Duncum	34
Frederic Hewitt's contribution to nitrous oxide anaesthesia	Dr D D C Howat	42
The history of the manufacture of nitrous oxide	Mr P Henrys	49
Nitrous oxide in Australia and New Zealand	Dr R Westhorpe	54
'No' to nitrous oxide in the Netherlands	Pr D Vermeulen Cranch	62
Historical use of nitrous oxide in Germany	Dr M Goerig	68
Nitrous oxide in the 1920s and 30s	Dr D Wilkinson	81
Entonox and obstetric analgesia	Dr P V Cole	85
Higher oxides of nitrogen	Dr R Greenbaum	87
oooOooo		
Dr Ruth E Mansfield - an appreciation	Dr D D C Howat	90

THE OXIDES OF NITROGEN AND THEIR EARLY HISTORY

Dr J Pring

Consultant Anaesthetist, West Cornwall Hospital, Penzance

The period we are dealing with extends back to the mid-17th century, when alchemy was gradually changing into chemistry, largely under the influence of Robert Boyle, who altered chemical attitudes, and prepared the way for Priestley, Lavoisier and the Chemical Revolution. In the earlier period the nomenclature of substances was confused,¹ and tended to be determined by appearance or physical characteristics, such as colour or smell, or origins, such as ash, earth or urine. Little or no distinction was made between different gases, which were all called 'airs' and were thought to be a single elementary substance.

Only gradually, starting with Boyle, and slowly through the 18th century, spurred on by the work of Brownrigg on carbon dioxide, did the idea develop that there were elastic fluids other than ordinary air.² But the phlogiston theory created further confusion, especially for those reading about it today. Broadly speaking, the presence of phlogiston was equivalent to absence of oxygen, and dephlogistication equalled the addition of oxygen.

From the 1780s, under the influence of the French chemists, most notably Lavoisier and his colleagues, the idea of oxygen replaced dephlogistication, and a new nomenclature based on chemical structure brought order to chemistry. However, this was a gradual process.

There is also the problem that we are conventionally taught that this or that researcher was the first to prepare this or that substance or gas (compare the rival claims of Clark, Crawford, Long and Morton for the introduction of ether as an anaesthetic agent!) As we shall see, the books are not always correct.

Nitrogen is pentavalent, and has five oxides. Of these, we are concerned here only with nitrous oxide, nitric oxide and nitrogen dioxide. We celebrate Joseph Priestley: 'dissident theologian and experimental chemist' as described at our last joint meeting in March 1993, for being the first to prepare nitrous oxide and oxygen, and to distinguish them from each other, and from ordinary air.

Nitric oxide

Following in Priestley's footsteps, we start with nitric oxide. Nitric oxide was previously known by Priestley as nitrous air, by Davy as nitrous gas, and by Brande, Davy's successor at the Royal Institution, as deutoxide of nitrogen. It can be prepared in several ways - one is by heating a mixture of ferrous sulphate, and dilute nitric oxide and sulphuric acids. Priestley prepared his nitrous air by the method originally used by Stephen Hales, reacting dilute aqua fortis (nitric acid) with iron pyrites.³ On Cavendish's advice, Priestley substituted the ordinary metals for pyrites, which he could not obtain, and on 4 June 1772 he managed to prepare a

supply of the gas from a 'solution of brass' in spirit of nitre - to this gas he gave the name 'nitrous air'.⁴ However, Boyle had been the first to collect nitric oxide, which he prepared by a similar reaction, between iron nails and aqua fortis, but he did not describe the properties of the gas he collected.⁵

Although Priestley was not the first to prepare nitric oxide, he was the first to use it for two purposes. Firstly, he observed that mixed with air it formed deep red fumes of what we now call nitrogen dioxide, NO_2 . The reddish-orange gas known to Davy as aeriform nitrous acid, can be produced by the action of concentrated nitric acid on copper or bismuth and also, as Priestley did, by reacting nitric oxide with oxygen. Secondly, Priestley observed that when this reaction was performed over water the volume of gas diminished by an amount equal to the diminution that resulted from an enclosed animal breathing in air. Finding that it was the respirable part of the air that was being removed, this gave him the idea that the reaction would be a kinder way of indicating the 'fitness' or 'goodness' of air for respiration. From this came the invention of the nitric oxide eudiometer, a graduated glass vessel in which measured volumes of air and nitric oxide were reacted together in the presence of water. The resulting reduction in volume indicated the volume of 'good' air removed.³ In addition, from this nitrous air, or nitric oxide, Priestley produced nitrous oxide.

Who first produced nitrous oxide?

Denis Smith's book, *Under the Influence*,⁶ discusses in depth the question of who first produced and who first identified nitrous oxide. In 1772 Priestley left nitrous air (nitric oxide) standing over a paste of iron filings, sulphur and water, and observed the generation of heat and a diminution of the gas to a quarter of its volume. But at this stage he did not distinguish the resulting gas, or 'air' as he called it, from others. The actual chemical reaction is the reduction of moist nitric oxide by sulphur dioxide. However, in 1774, he inadvertently produced the gas by the exposure of a large surface of iron to nitrous air to see whether it would rust. Priestley first called nitrous oxide 'diminished' or 'modified' nitrous air, but soon changed it to 'dephlogisticated nitrous air' since he observed that a candle burned in it with an enlarged flame. (We remember that dephlogistication was equivalent to the addition of oxygen). This property of supporting combustion was removed when the gas was shaken up with water. Davy, in 1800, called the gas nitrous oxide, while Brande in 1863 called it protoxide of nitrogen.¹

Priestley first prepared what he called 'eminently respirable air', and what Lavoisier (and much later, Jean Michael Jarre) was to call 'oxygène', by his famous experiment on the red 'calx' (or oxide) of mercury on 1 August 1774, but there was a delay of some seven months to about 8 March 1775, before he realised that although it supported combustion, it was different from nitrous oxide. There has been much dispute as to whether Lavoisier was already experimenting with the red oxide of mercury when Priestley met Lavoisier in Paris in October 1774 and talked about the new 'air' he had prepared. Priestley had found three differences: nitrous oxide, but not oxygen, was soluble in water, did not react with air to produce the red gas, and did not support life. Between 1774 and 1786 Priestley published various volumes of

his book, *Experiments and Observations on different kinds of Air*, in which he described the preparation and properties of a whole range of gases.

Davy prepared nitrous oxide by heating ammonium nitrate, the method commonly used today, but he was not the first to do this. Ammonium nitrate had first been prepared by Glauber in about 1650 from ammonia and aqua fortis (nitric acid). Johann Rudolph Glauber (1604-1670), famous for the preparation of Glauber salt, which is sodium sulphate, or sal mirabile as he called it, and which he thought would be a panacea and would make his fortune, described ammonium nitrate as 'a most secret and fiery sal ammoniac' and it became known as nitrum flammans because of its rapid decomposition with a mild explosion when heated. It was also known as 'volatile nitre', volatile in the early nomenclature, indicating the ammonium radical.¹ Both Robert Boyle and John Mayow in the 17th century prepared ammonium nitrate by the action of nitric acid on ammonia or ammonium carbonate, and Boyle isolated the typical fine long crystals. Both also heated it, as did Glauber, so they all must unknowingly have prepared nitrous oxide.

At the very first meeting of this Society, in 1986, Dr Denis Smith asked what ammonium nitrate would have been used for in Davy's time. One use was undoubtedly in freezing mixtures, which were used in the chemical laboratory to condense liquids and, as used by Glauber, to strengthen wine by freezing out the water.⁴ Boyle used freezing mixtures in his physics experiments and showed, for example, that water expands on freezing. Ammonium nitrate may also have been used as a flux, and as a constituent of explosive mixtures. It was an amusing substance to have around, going snap, crackle and pop when heated. A modern explosive, amatol, which was widely used during the Great War, consisted of 80% ammonium nitrate and 20% TNT.

Robison, Joseph Black's old pupil, describes finding in a bundle of old notes dated 1766, an account of heating ammonium nitrate, and the production of a gas which made a lighted paper 'burn with prodigious violence', indicating that Black must have produced nitrous oxide. The French chemist Berthollet produced nitrous oxide from ammonium nitrate in about 1785, while trying to determine the composition of ammonia and, in 1789, William Austin, in Oxford, found that when 'nitrous ammoniac' (ammonium nitrate) was heated, Priestley's dephlogisticated nitrous air was produced in great abundance. This observation had also been made in 1775 by the well-known Irish chemist, Bryan Higgins, who described the air produced as supporting combustion.³

Davy, Faraday and Brande

Humphry Davy, as well as naming it 'laughing gas', brilliantly investigated the chemistry of nitrous oxide, its impurities, and the effect of breathing it, and published his 580 page volume *Researches Chemical and Philosophical, chiefly concerning Nitrous Oxide, and its Respiration* in 1800.⁷ This has been the basis of all work since. While we tend to concentrate on his researches into the effects of breathing nitrous oxide, and the suggestion that it be used as an anaesthetic, we should remember that two-thirds of the book concerns the

chemistry of the gas. The best analysis of Davy's researches, from the point of view of the anaesthetist, is by Cartwright.⁸

It has been said that Davy's most important discovery was Michael Faraday whose Christmas lectures, begun in 1826, are still continued, and who appears on the reverse of our £20 note. Faraday had an intuitive grasp of the way physical nature might work, combined with a genius for experimentation, and great energy. In 1823, whilst working at the Royal Institution, he liquefied nitrous oxide.⁹

Davy was succeeded as Professor of Chemistry at the Royal Institution by W T Brande, who taught there for some 40 years. In 1863, together with A S Taylor, Professor of Medical Jurisprudence at Guy's Hospital Medical School, he published a textbook '*Chemistry*'¹⁰ which, although containing some 900 pages, was written mainly for the use of medical students. It is interesting to look at what medical students were being taught about nitrous oxide in 1863, only a few years before its reintroduction into clinical anaesthesia:

'This gas is a narcotic poison, and when breathed rapidly destroys the life of an animal.. It may, however, be taken by a human being in limited quantity; and if the lungs be emptied before it is inhaled, it rapidly causes a peculiar species of intoxication, the laughing or paradise gas when breathed is rapidly absorbed into the blood, and produces a great change in that fluid - manifested by a dark purple colour of the lips it is not to be regarded as an anaesthetic, like chloroform or ether ...'

Nitric oxide and the future

Nitrous oxide is now recognised to be not just a physiologically inert gas as was previously thought - it is known to interfere with Vitamin B₁₂ and haemopoiesis (by inhibiting methionine synthetase), an effect which may go back to an early period of life on earth.

Nowadays we are also interested in nitric oxide which, to everyone's great surprise, has been shown to be an effector molecule, probably of very primitive origin, synthesised by various types of cell. It is a vasodilator, a potent inhibitor of platelet aggregation and endovascular adhesion, and a neuro-transmitter. The study of nitric oxide is one of the fastest growing areas of research in physiology.¹¹

I should like to finish with a quotation:

'The rapid progress true Science now makes occasions my regretting sometimes that I was born so soon. It is impossible to imagine the heights to which may be carried, in a thousand years, the power of man over matter.'

Very appropriate for today, but written in 1780 by Benjamin Franklin, in a letter to Joseph Priestley.

Bibliography

- 1 Crosland MP. *Historical Studies in the Language of Chemistry*. London: Heinemann, 1962.
- 2 Gibbs FW. *Joseph Priestley*. London: Nelson, 1965.
- 3 Partington JR. *A History of Chemistry*. Vol.3, London: Macmillan, 1962.
- 4 Cartwright FF. *The English Pioneers of Anaesthesia*. Bristol: Wright, 1952, 20.
- 5 Partington JR. *A History of Chemistry*. Vol.2, London: Macmillan, 1961.
- 6 Smith WDA. *Under the Influence - a History of Nitrous Oxide and Oxygen Anaesthesia*. London: Macmillan, 1982.
- 7 Davy H. *Researches, Chemical and Philosophical, Chiefly Concerning Nitrous Oxide*. London: J Johnson, 1800.
- 8 Cartwright FF. *The English Pioneers of Anaesthesia*. Bristol: Wright, 1952.
- 9 Faraday M. On the condensation of several gases into liquids. *Phil. Trans. Roy. Soc.* 1823; 113: 189-198.
- 10 Brande WT, Taylor AS. *Chemistry*. London: Davies, 1863.
- 11 Kam PCA, Govender G. Nitric oxide: basic science and clinical applications. *Anaesthesia* 1994; 49: 515-521.

DUTCH CHEMISTS OF THE LATE 18TH CENTURY

Dr J Ruprecht

Department of Anaesthesiology, Erasmus University, Rotterdam

Towards the end of the 18th century, chemistry was considered an ancillary subject to medicine and there was little chance for professional chemists in the French oriented Kingdom of Holland. Chemistry saw its growth only among the enlightened rich classes.

A number of scientific societies were established at this period, some on a national level. Chemistry required a good knowledge of physics and mathematics and it is not surprising that a strong interest developed only about 1790. The other reason for the late development of scientific chemistry in Holland was the lack of an industrial base. Chemical industry had not been a significant employer, the country had ceased to be a world power and lived mainly from commercial intermediation. In a land previously embarrassed with its riches there was little incentive to develop an industrial society backed by a scientific educational system.

Discovery of new gases at the end of the 18th century caused controversy among Dutch phlogistonists and their opponents who adopted the new chemical system proposed by Lavoisier.¹ Martinus van Marum (1750-1837) travelled to Paris to learn first hand about the 'new chemistry'. Later he published his defence of Lavoisier's insights in his 'Outline - the first succinct exposition of the new system in its entirety'² and thus became the most prominent promoter of modern chemical thinking in The Netherlands. The intellectual elite interested in chemistry were not connected to the universities of that time. Nevertheless, the Dutch chemists were well informed about scientific developments in chemistry abroad and corresponded with German, French and British scientific contemporaries.³ By 1781, Joseph Priestley's *Experiments and Observations on Different Kinds of Air* was translated into Dutch by Jacob Ploos van Amstel (1726-1798). Lavoisier's work was equally well known as can be seen from P Nieuwland's treatise on Lavoisier's chemical system, published in Amsterdam in 1791.⁴

The Dutch are not easily taken by new fancies or scientific ideas. This characteristic made the acceptance of the antiphlogistic chemistry in The Netherlands a very long process. In persuading scientists to accept Lavoisier's chemistry, The Society of Dutch Chemists (Het Gezelschap der Hollandsche Scheikundigen) played a most prominent role.⁵

The Society of Dutch Chemists

The original name was De Bataafasche Societeit (The Batavian Society) but it was soon generally referred to as The Society of Dutch Chemists. The physician Deiman co-operated closely with P van Troostwijk and they invited P Nieuwland to join, forming the Batavian Society in late 1790 or early 1791. Later, three other members joined the society which functioned as an informal circle of friends.

Member	Years of membership	Age at joining	Occupation
A Paets van Troostwijk (1752-1837)	1790/91-1814	38	Merchant
J R Deiman (1743-1808)	1790/91-1808	47	Physician
P Nieuwland (1764-1794)	1790/91-1793	26	Lecturer
N Bondt (1765-1796)	1791-1796	26	Physician; Professor of botany (1793)
A Lauwerenburg (1758-1820)	1793-1808	35	Pharmacist
G Vrolik (1775-1859)	1796-1814	21	Physician; Professor of botany

Table 1. The Society of Dutch Chemists

Adapted from Snelders (1), with permission.

The leading figure was the merchant Paets van Troostwijk who had no academic background, yet this small group of enlightened citizens of Amsterdam produced scientific treatises of the highest order, and performed many original experiments in support of Lavoisier's system of chemistry. Their first articles were published in *Recherches Physico-Chimiques*, later ones in many German and French journals. Private financial support was obtained for their new Dutch journal, *Natuurscheikundige verhandelingen*. As can be seen from Table 2, there appears to have been a plethora of Dutch chemical journals at the end of the 18th century.

Journal	No. of vols	Years	Place	Editors
Chemische Oefeningen	3	1785-1788	Amsterdam	PJ Kasteleyn
Chemische en Physische Oefeningen	3	1792-1797	Amsterdam	PJ Kasteleyn; Vol. 3: N Bondt & JR Delman
Nieuwe Chemische en Physische Oefeningen	2	1798-1802	Utrecht	P van Werkhoven
Recherches Physico-Chimiques	3	1792-1794	Amsterdam	Soc. Dutch Chemists
Natuur-scheikundige Verhandelingen	4	1799-1808	Amsterdam	Soc. Dutch Chemists
Scheikundige Bibliotheek	2	1792-1798	Delft	Unknown
Nieuwe Scheikundige Bibliotheek	3	1799-1802	Amsterdam	Unknown

Table 2. Dutch chemical journals at the end of the 18th century

Adapted from Snelders (1), with permission

The scientific work and writings of the Dutch chemists were internationally appraised. Regular scientific exchange with chemists abroad is now considered to have contributed significantly to the acceptance of modern chemistry at that time. In 1793 the Dutch chemists published their studies on oxides of nitrogen.⁶ Their description of findings about nitrous oxide remains of great interest to anaesthesiologists.

Experiments on the properties of 'oxide gazeux d'azote'

Deiman et al introduced their essay about Priestley's gaz nitreux déphlogistiqué with a note that the gas enhanced burning of a candle but that animals die when breathing it. The authors stated that enhanced burning of a candle did not indicate more oxygen as compared to gaz nitreux (NO), a finding based on their experimental evidence. They criticised Priestley's choice of name which implied that the gas contained more oxygen than gaz nitreux. They conformed to the new nomenclature and called the gas 'oxide gazeux d'azote'.

Inflammable nitrous air (Priestley)	NO + Fe
Oxide gazeux d'azote (Dutch chemists)	NO + alkaline sulphides
Dephlogisticated nitrous air (Priestley)	NO + ZnCl ₂
Gaz nitreux déphlogistiqué	Metal + H ₂ SO ₄
Di-oxyle d'azote	NH ₄ NO ₃ , heated in sand
Gaz nitreux oxigéné (Dutch chemists)	Fe + Zn + HNO ₃
(NO: gaz nitreux)	Other methods
Table 3. Names probably referring to N₂O, 18th century	Table 4. Production of N₂O in Amsterdam, 18th century

Production of oxide gazeux d'azote (N₂O) was described along two lines: transformation of NO into N₂O or modification of the methods of production of NO. Some methods yielded more or less pure N₂O but usually N₂O was contaminated with other gases. For studies on the properties of N₂O very pure gas was used, such as obtained from heated ammonium-nitrate or from interaction of zinc with nitric acid.

The Amsterdam chemists observed that N_2O preserved its composition and volume when mixed with atmospheric air or oxygen. When mixed with nitrogen it still supported burning of a candle but this action depended on the content of N_2O in the mixture. It was thought that N_2O was completely absorbed into water, leaving behind only a residue of nitrogen which must have contaminated the gas. Solubility of N_2O in water had been described earlier by Priestley who regained the gas by warming the water and found that properties of the gas remained the same (Priestley, *Exper sur Aircs*, traduct.franc. IV: 240). Mixtures of hydrogen and N_2O were found to be explosive. Results of several other experiments with burning substances were discussed in the understanding that N_2O supported combustion but would not yield its oxygen.

Effects of N_2O on animal respiration

The Amsterdam chemists understood that breathing served the 'animal machine' to get rid of superfluous carbon by binding it to the atmospheric oxygen, this process occurring in the lung. They found that N_2O would not lose its oxygen to carbon and concluded that it could not subserve respiration. The confirmation for this reasoning was obtained experimentally by placing birds in N_2O . One bird died instantaneously, another in a few seconds. There is no mention as to whether the bird was left in the gas or taken out. It was also observed that electrical discharge or great heat could change the composition of N_2O . Various calculations showed that 100 parts of N_2O consist of 37.5 parts oxygen and 62.5 parts nitrogen. Oxygen was supposedly bound to nitrogen much more powerfully than in other nitrogen oxides. One would wish that a bird had been taken out of 'oxide gazeux d'azote' and had recovered from asphyxia and the anaesthetic effect: the observation of suspended animation would have been made. But another half century had to pass before scientists tested every available gas for possible anaesthetic properties. The Amsterdam chemists lived in a time ripe for acceptance of scientific chemistry but long before the concepts of suspended animation or reversible insensibility.

References

1. Snelders, HAM (1988) The New Chemistry in the Netherlands. Osiris, 2nd series, 4: 121-45.
2. Van Marum, M. (1787) Schets der Leere van M Lavoisier, omtrent de zuivere lucht van den dampkring, en de vereeniging van derzelver grondbeginzel met verschillende zelftandigheden. Verhandel. Teyler's Tweede Genoot. 4:I-XX, 235-66.
3. Deiman (1795) Vom Hrn. Dr Deimann in Amsterdam. *Chemische Annalen* II, 507-8.
4. Nieuwland, P. (1791) Schets van het Scheikundige leerstelsel van Lavoisier. De Eerven en Warnars; Amsterdam.
5. Snelders, HAM. (1980) Het Gezelschap der Hollandsche Scheikundigen: Amsterdamse cheici uit het einde van de achttiende eeuw. Amsterdam: Rodopi.
6. Deiman JR et al. 1793.

THE CONNECTICUT CONNECTION

Dr J A W Wildsmith

Consultant Anaesthetist, Royal Infirmary, Edinburgh

The Connecticut connection in the 150 years of the history of nitrous oxide anaesthesia is, of course, the work of Horace Wells, adjudged by many to be the 'father of surgical anaesthesia', let alone the pioneer of nitrous oxide administration. Horace Wells made an original observation, recognised its clinical significance, performed an appropriate experiment (on himself!), refined his method and then tried to promote it freely for the benefit of others. Unfortunately, his public demonstration was not the success that he hoped, and later he was the victim of the greed and ingratitude of others.

Wells memorabilia

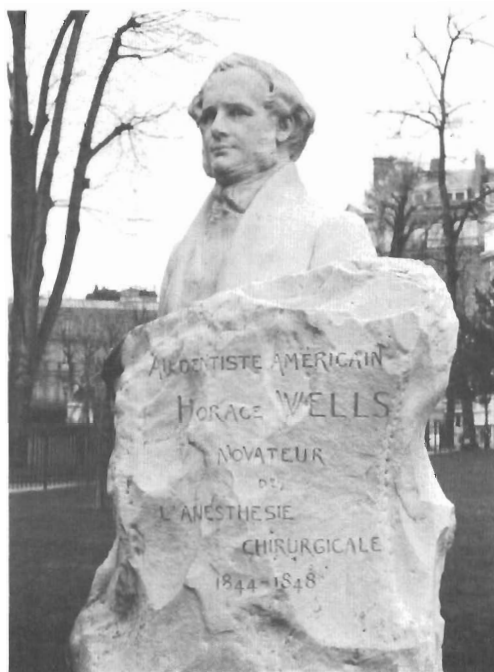
It is a measure of the youth of anaesthesia that the memorabilia of its pioneers are very often still accessible. New England, the birthplace of general anaesthesia, has the Connecticut River as its spine and Connecticut state as its most southern political component. Hartford, the state capital, was where Horace Wells spent most of his professional life, but his story actually began 160 miles north at Hartford, Vermont, where the house in which he was born still stands on School Street. In 1944, the American Society of Anesthesiologists placed a plaque there unambiguously crediting Wells with the discovery of anaesthesia.

Today, Hartford (Connecticut) is a relatively anonymous American city with its original centre almost lost under a maze of freeways, but you can still find the line of Main Street where Horace Wells had his office and where stood Union Hall, the site of the fateful public demonstration given by Gardner Quincy Colton on 10 December 1844. As a result of that demonstration Wells discussed with Colton, an associate called John Riggs and others, the ideas of 'pushing' the gas further than ever before. They convened the following morning in Wells' office. Wells breathed the gas until he lost consciousness and Riggs extracted a molar tooth. The site remains marked and Hartford contains many other places of interest. Still standing on Main Street is the First Church of Christ in which Wells met, and later married his wife and it contains a stained glass window depicting them. Nearby, Bushnell Park has a splendid memorial statue and just to the south of the city centre is Cedar Hill Cemetery where Wells and his family are buried. On the front of his tomb is the epitaph: 'There shall be no pain', while at one end is the inscription: 'I sleep to dream' and at the other: 'I awaken to glory'. The Chapel of Trinity College, which is on the road to Cedar Hill Cemetery, has a carved pew-end with a profile of Wells.

The other major site is the Historical Museum of the Hartford Medical and Dental Society. It has many treasures, but its heart, literally and metaphorically, is a room dedicated to Horace Wells and his memorabilia. It is impossible for anyone who has visited that room in the last decade or more not to have become acquainted with the museum's curator, Leonard Menczer, who gave much of his life to the collection. His knowledge, enthusiasm and personality made

Leonard himself worth a visit to Hartford. Sadly, he died recently, but the museum has been named after him in recognition of his work. The Wells Room has many personal possessions including his practice day book, which records receipt of tuition fees from William Thomas Green Morton and, later, loans of much larger sums to the same individual. Morton's subsequent resistance to giving any credit to Wells for the 'discovery' of anaesthesia was ingratitude indeed to one who was both teacher and banker. The motive was almost certainly Morton's attempt to patent, as well as ether, the principle of the process of anaesthesia by inhalation.

The Wells Room contains his passport, obtained for his trip to the French Academy in Paris to try and obtain recognition for his priority in the field of anaesthesia by inhalation. The French eventually found in his favour, but the news did not reach the USA before Wells' despair drove him to suicide. The French also erected a charming memorial statue in the Place des Etats Unis in Paris, the base bearing an inscription describing Wells as the discoverer of surgical anaesthesia. The Wells Room also contains a certificate of recognition from the UK which was produced when nitrous oxide anaesthesia was introduced there at the end of the 1860s.



Statue to Wells in Paris (photo by A Padfield, March 1995)

Irresolution or illness?

In spite of these tributes, subsequent historians have not been kind to Horace Wells. Consider what Stanley Sykes had to say in his *Essays*:

'We know that he [Wells] was irresolute, wayward and volatile for he kept abandoning his dental practice in order to make a living in strange and unusual ways, such as buying pictures in Paris to sell in the United States, and other queer ventures

'What really possessed Horace Wells that he had such an unhappy and unsuccessful life and such a tragic death? As I see it, he was a man who was easily depressed and discouraged, too easily led and influenced by others; for after one partial public failure, he completely abandoned his attempts to publicise nitrous oxide anaesthesia which had already been satisfactory in his hands in a number of cases.'

Leonard Menczer's wish was to correct what he considered to be such serious misinterpretations. On the day of the 150th anniversary the Hartford Museum published, in association with the Countway Medical Library in Boston, a volume of essays edited jointly by Leonard Menczer and Richard Woolfe which aims to set the record straight.*

Consider Wells' curriculum vitae. He studied dentistry in Boston for two years and then set up practice in Hartford in 1836. Within two years he was successful enough to get married and within four he had published his *Essay on Teeth*, as definitive an account of dentistry at the time as there is. In 1842 he devised a child's dental regulator, which makes him a pioneer of orthodontic practice as well as anaesthesia. In the same year he started to train others (not only Morton) and in 1843 the City of Hartford awarded him a prize of \$100 (then a significant sum of money) for best dentistry. He was also active as an inventor.

This is not an 'irresolute, wayward and volatile' individual. The death notice in the *Connecticut Courant* hardly confirms Sykes' view either, even allowing for the traditional kindness of the obituary writer:

'The death of this gentleman has caused a profound and melancholy sensation in this community. He was an upright and estimable man, and has the esteem of all who knew him. Of undoubted piety, simplicity and generosity of character, enthusiastic in the pursuits of science, and having just been acknowledged as the discoverer of etherisation in surgical operations, he was regarded with the highest respect in regard by all our citizens, and there was no-one who seemed less likely to meet the sad fate that has befallen him.'

- * *I Awaken to Glory: Essays Celebrating the Sesquicentennial of Horace Wells' Discovery of Anesthesia*. Hard-bound, 460pp, over 60 illustrations. Available from Science History Publications (USA), PO Box 493, Canton, Massachusetts 02021, USA. \$28.95 plus \$3 postage in the USA. Overseas purchasers may use Mastercard or Visa.

However, there was a darker side to Horace Wells. Advertisements in the press of the time reveal periods of suspension of his practice because of 'ill-health', and the sordid nature of his final offence - assaulting a prostitute - imply mental derangement. An obituary notice from further away from home (*Newhaven Journal*) was perhaps nearer to the mark:

'He was subject to great mental depression amounting almost to disease.'

Consider, also, some quotes from his suicide notes:

'I cannot proceed - my hand is too unsteady, and my whole frame is convulsed in agony. My brain is on fire.

'I feel that I am fast becoming a deranged man, or I would desist from this act. I cannot live and keep my reason, and on this account God will forgive the deed. I can say no more.'

Surely this poor man was a manic depressive. On the 150th anniversary of his fateful step into the unknown, he should be given a kind thought or two. We all owe him a great deal.

Visitors to New England with an interest in the history of anaesthesia might like to try and obtain a publication of the Trustees of the Section of the Wood Library-Museum of the American Society of Anesthesiologists, Inc: *An Historical Guide to New England Pertaining to the Discovery of Anesthesia*.

Addendum - The San Francisco Memorial

Dr Rod Calverley** of San Diego writes:

'In 1944 the Wells Centennial Committee planted a redwood tree in Golden Gate Park, San Francisco, to provide a living memorial to Wells. Sometime later the site was marked by an inscription carved upon a boulder, but the branches of the growing tree soon overshadowed it. In preparation for a proposed rededication, I visited San Francisco in January 1994 but hunted for it without success. I enlisted the assistance of John Severinghaus and Ralph Kellogg, who also failed to find the stone. Fortunately, Dr Kellogg returned and a lady, perplexed by his search, told him that she had seen the stone frequently, but that it had disappeared only a few weeks earlier. Dr Kellogg visited the park office and discovered that a deranged man had tried to remove the stone so the park gardeners had hidden it away for safety. The three of us then encouraged the park administration to return the stone to its original location and it has been secured in a concrete base.

'Visitors to San Francisco who wish to view the memorial redwood and its identifying stone should travel to the Steinhart Aquarium in Golden Gate Park. First face away from the Aquarium entrance and walk about 75 paces to the left along Middle Drive East until

you reach a meadow. The tallest tree on the meadow's edge (another 75 paces across the grass) is a solitary coast redwood about 70 feet in height. Below the lowest branches is a white marble boulder about 27 inches in length. It bears the inscription: 'Neither shall there be any more pain. This tree planted 1944 to the honour of Horace Wells, Dentist, discoverer of anæsthesia 1844'.

- ** Dr Calverley was tragically killed in a road accident some months after adding this note. An obituary will be published in the next volume of Proceedings.

CYANOSIS IN THE EARLY HISTORY OF ANAESTHESIA

Dr D Zuck

Hon. Consulting Anaesthetist to the Enfield Health District

President, History of Anaesthesia Society

On May 1st, 1847 Gideon Mantell of Lewes, surgeon and amateur geologist, discoverer of the iguanodon and other dinosaur fossils, recorded in his journal¹:

'Went to Bartholomew's Hospital, and witnessed two operations under the influence of ether: the first I have seen. The loss of sensibility in both instances was complete, no consciousness of the operation. But the effect on the system was appalling, though transient.'

What he meant can be gathered from a letter written by Dr Charles Locock of Hertford Street, London, to his friend James Young Simpson, some three months after the introduction of ether:

'Many thanks for your pamphlet on the ether inhalation, with which I have been much interested. People here and in Paris are getting frightened about it, as the arterial blood becomes black under its influence...'²

Disturbing reports had appeared almost from the outset. At Guy's Hospital a patient's face had been much congested³ and at St Thomas's there was so much coughing and turgidity of the face that the operation had been abandoned.⁴ At St Bartholomew's a patient's breathing was once or twice laborious, the abdomen heaving a great deal, the face, and even the whole surface of the skin, somewhat purple the greater part of the time.⁵ And as regards Mr Tomes's celebrated case of lithotomy at the Middlesex:

'...after breathing deeply and tranquilly for about two minutes, his countenance became livid....'⁶

Present-day anaesthetists will have no doubt that what was observed was cyanosis resulting from respiratory obstruction, yet such an explanation does not feature in any of the early accounts. Rather it appears that a chemical cause was being proposed. Dr James Pring of Weston-super-Mare wrote of the state of uncertainty among the profession about the propriety of using ether. French physiologists had described a dark, fluid state of blood in etherised animals, and a similar state had been seen repeatedly in this country by surgeons operating on patients under the influence of ether. The arterial blood exhibited the same change. The question was whether the change was due to a deficiency of oxygen, or whether it was an independent chemical change, in which case it would occur equally in blood removed from the body. To test this thesis he had collected two samples of arterial blood from a sheep, one of which had been mixed with a small quantity of washed ether. Within three minutes the etherised blood was almost black, and the coagulum was much softer than usual, while the unexposed blood remained florid, and coagulated normally. The experiment had been repeated with oxygen added to the ether bottle; the oxygen had neither prevented the colour

change, nor could the blackened blood be restored by oxygen. The conclusion was that the change was purely chemical. Whether to continue to use ether, in the face of this evidence, was for the surgeons to decide.⁷

Dr Pickford of Brighton, an early exponent of bashing the media, went even further.⁸ The public had been led by the daily press to expect perfect immunity from pain, without fear of any ill effects or consequences, but **he** wished to undeceive the public. What of the pulse, respiration, and countenance, during the state of insensibility? The circulation becomes first rapid then slow and feeble; the respiration laboured and stertorous, the countenance livid, the lips and tongue are blue, the pupils dilated the muscles universally relaxed, the functions of the brain and nervous system suspended and the patient, to all intents and purposes, was a senseless corpse. The condition had been compared by some to drunkenness, by others to asphyxia, or to apoplexy of the congestive form. But etherisation was more alarming and dangerous than any of these: there was a chemical and vital alteration in the constitution of the blood itself. Ether robs the blood of its oxygen, intensely blackens it by the solution of its corpuscles and their contained haematoglobulin, chemically deprives it of its powers of coagulation, and renders it unfit for the purposes of life. A black vitiated blood circulates through the system, analogous in many particulars to that in putrid and malignant fevers. This impaired condition of the blood is not even partially corrected until atmospheric air has been breathed for some time, and sufficient lymph corpuscles have found their way into the circulation to replace those destroyed by the ether.* The ether has dissolved the blood corpuscles, and permitted its contained haematogloblin to escape. Under the microscope numerous remains of the capsules of corpuscles could be seen.

Conflicting reports on cyanosis

In the face of all this, it is remarkable how little the bluish discoloration of the skin or the blood features in the early books on etherisation. Robinson, reporting on some 120 operations, mentions only one patient whose face was much congested, another who turned very red, or rather purple in the face, one with congestion of the face and head, the colour being somewhat livid, and one where the symptoms of congestion of the brain were so apparent that it was thought more prudent to delay the operation.⁹ Two of these cases appear to be identical with ones mentioned above. Robinson must have been aware that there was concern, because he quotes Boott reporting the observation of the surgeon, Mr Hale Thomson that, in his operations, under the full effect of ether, the arterial blood presented its usual appearance, nor was there any reason to suspect asphyxia.¹⁰

* Pickford supposed that red blood corpuscles were produced from the lymph corpuscles, an idea going back at least to Boerhaave, for whom one of the functions of the lungs was sanguification, the red cells being produced by the squeezing together of five or six lymph corpuscles as they passed through the lung capillaries. This shows how out of touch he was with contemporary physiology, which held that the red cells were produced in the spleen. The bone marrow was not recognised as the site of haemopoiesis until twenty years later.

John Snow, too, minimised its significance in his first treatises.^{11,12} Neither mention the word cyanosis, neither contain any indication of the recognition of respiratory obstruction. In fact, Snow was at pains to point out that in his patients:

'The blood that flows in operations is not much altered in colour ... the patient's lips remain unchanged in hue ... only when the patient has been holding his breath, or coughing, have I observed the arterial blood to be a dark colour; and I consider that those writers who have described it as being, usually or always, of a venous appearance, must have used inhalers that did not allow a proper supply of air. The blood always coagulates on the floor of the operating theatre, and the black blood which flows during an amputation when the tourniquet is applied, constantly becomes afterwards red on the surface from exposure to the air.'

Any problems with respiration were attributed only to the unsuitability of the apparatus. Snow repeatedly emphasised the importance of wide bore tubing and low resistance to breathing. Also, he was concerned to refute the suggestion, implicit in the comments quoted, that ether alters the blood chemically, and interferes with coagulation.

If one read only Snow's own writings, one would conclude that his patients were rarely if ever cyanosed. Only once does he refer, and in general terms, to one or two patients whose faces became purple, but should this occur: 'there need be no alarm'. The face-piece may be removed if thought proper, but breathing always becomes extremely regular when the next degree is attained.¹³ However, from early 1847, the *Lancet* published eye-witness accounts of the operating lists under general anaesthesia at the London teaching hospitals, and it is instructive to compare these descriptions of the same cases with those that Snow published later in his book. For example, on 28 January at St George's Hospital, Snow is described as having anaesthetised a little boy with a long sequestrum in the tibia. The account continues: '... inhaled - operation commenced after one and a half minutes - inhalation stopped a minute later just as his face was becoming rather purple, and the pulse feeble.'¹⁴ Snow's own account makes no mention of cyanosis.¹⁵ Then, on 11 February, he anaesthetised a woman with malignant disease of the breast. The account in the *Lancet* read as follows:

'The woman inhaled for four minutes, when it was ascertained by Dr Snow that the cap which admits air to the ether was not removed and, consequently, she got no ether, and but little air. This was remedied, and she had the disadvantage of beginning the inhalation of the ether rather out of breath. It excited some coughing, and in three or four minutes the face was becoming purple, and the pulse feeble and quick, and the features rather distorted. The inhalation was accordingly discontinued, and the operation commenced.'

She had inhaled sufficient ether to render her analgesic, so although she struggled, she afterwards denied having felt any pain. But in Snow's own account there is again no mention of the initial hypoxia, nor of cyanosis, only of coughing, which he attributed to existing bronchitis.¹⁶ It is disconcerting to find that one's hero at times made the same mistakes as the rest of us.

We read of cyanosis in other accounts also. In a case of bilateral amputation at the London Hospital after a train accident, described as 'the most formidable operation as yet performed ... under the influence of ether' it is said that: 'The blood in the small arteries was much darker than usual, so that it was really difficult to distinguish it from venous blood.'¹⁷ Of Mr Nunn's fatal case in Colchester, the account reads:

'After having inhaled the ether for eight minutes, the patient became fully under its influence, even to the extent of stertorous breathing, and the face and lips presented a livid hue'¹⁸

The disquiet continued. John Denham, in 1849, reporting on the use of chloroform in labour paints a:

'...fearful picture of the evils likely to arise from its use ... apoplectic stertor, convulsions, partial paralysis ... the blood blackened, the brain poisoned, and other still more formidable consequences, are among the number of dangers mentioned as liable to be induced by the state of anaesthesia.'¹⁹

Edward Murphy, in 1850, also remarked on the dark colour of the blood:

'It may be chloroform - it may be the imperfect oxydation of the blood - that produces the alteration; whichever is true, the question is well worthy of an attentive examination.'²⁰

Theories of cyanosis

Of the observers cited, only Murphy and Pring suggested that hypoxaemia might be a factor, and researchers into the history of medicine of the first half of the nineteenth century may come to share the view that there were two populations of doctors at large, the younger moderns, who knew what we would regard as the 'right' answers, and the older traditionalists, who clung to the 'elements of medicine' of the eighteenth century. The physiology textbooks of the early part of the nineteenth century reveal conflicting ideas about the process and functions of respiration, and the cause and significance of the colour difference between arterial and venous blood. This uncertainty includes the remnants of earlier beliefs, chemical, physical and mechanical, which ramify throughout the whole of the succession of systems of medicine.

Before Harvey, the difference in appearance of arterial and venous blood was attributed to the presence in the former of a bright red, thinner blood, together with the higher type of pneuma, the vital spirit.²¹ Harvey himself denied that there was any difference in colour between venous and arterial blood, and for this he was criticised as an inaccurate observer by Cohen.²²

Keilin more perceptively pointed out that it was in support of his revolutionary thesis that it was the same blood that circulated from the veins to the arteries and round again that he had to deny even a difference in colour.²³ **

Harvey's discovery, with its implicit erasure of those aspects of Galenic physiology that centred round the heart, raised questions about the lung function, the purpose of respiration, and the source of body heat, and these were addressed by the remarkable group of investigators who centred round Robert Boyle, and became the original members of the Royal Society.

The first recorded observations of the change of colour that blood undergoes when exposed to air was published by the anatomist Carlo Fracassati of Bologna in 1665. It was a classical observation that when blood was collected in a bowl it formed a clot with a red surface above, and darker parts below. This was seen as the sedimentation of its constituents, the light spiritous part uppermost, the humours below, with the heaviest, the black melancholy humour, at the bottom. but Fracassati showed that if the clot was turned over, its dark undersurface on exposure to air soon became a florid red. This observation upturned classical physiology. It was quickly picked up and confirmed by Robert Boyle (1627-1691) and by Robert Hooke (1635-1703), who noted also that when the red surface was progressively sliced off, the exposed dark beneath soon became florid.

The in vivo site of this colour change was demonstrated by Richard Lower (1631-1691) on the open thorax of a dog. Lower's suggestion that the change of colour was due to absorption of particles from the air was elaborated by John Mayow (1641-1679) who, in his *Tractatus Quinque* identified them as 'nitro-aerial' and attributed to them several of the properties that today are associated with oxygen.

However, this was only one of several explanations of the colour change, which can be classified as chemical, physical and mechanical. The chemical suggested that combination with certain aerial particles caused the change of colour; the physical and mechanical, that the churning and moulding that the cells underwent during their passage through the lungs caused a change in their shape that caused them to reflect light more brightly. So, while it might be thought that Mayow had put respiratory physiology on the right path, the mechanical physiology associated especially with Boerhaave delayed progress by the best part of a century. Haller, in the middle of the eighteenth century, actually denied that the blood changed colour at all during its passage through the lungs.

** For superb accounts of investigations and ideas regarding respiratory physiology from the mid-seventeenth century to the mid-nineteenth century see: Franks RG. *Harvey and the Oxford Physiologists*. Berkeley. University of California Press: 1980; Long Hall D. *Why do Animals Breathe?* New York. Arno Press. 1981; Hall Long D. "Bacon's mansion": the frustrations and rewards of respiratory physiology in the enlightenment. Bulletin of the History of Medicine. 1976; 50:151-173; Mendelsohn E. *Heat and Life: the Development of the Theory of Animal Heat*. Cambridge, Mass. Harvard University Press: 1964, and Goodfield GJ. *The Growth of Scientific Physiology*. London. Hutchinson: 1960.

So chemistry took a back seat until the elaboration of the lime-water test and the demonstration by Joseph Black in 1756 that fixed air, or carbon dioxide, is given out during exhalation. This was soon followed by the confirmation by the Italian anatomist, Giovanni Cigna, that blood did change colour, and that the change depended on contact with air. Lavoisier's experiments with the ice calorimeter established that oxygen is consumed, and related it to the amount of heat generated. Thus respiration became equated with combustion, in this case the combustion of waste carbon compounds, and the question then arose, where did this process take place? Two theories were proposed.

While some suggested that it took place throughout the body, ideas about the constitution of the organs and tissues were not far advanced, and the favoured site, supported by Lavoisier among others, was the lungs. This would account for the generation of body heat, but if waste carbon compounds were being combusted in the lungs, it followed that since all the oxygen being inhaled would be used up in the production of an equal volume of carbon dioxide that would be breathed out, neither gas should be found in the blood in the systemic circulation nor was it, until some fifty years later. So the darker colour of venous blood was explained by the accumulation in it of carbon which, as everyone knew, was black.

The second theory, associated with Lagrange and Hassenfratz, proposed that the reaction took place in the periphery. The demonstration of tissue respiration by Spallanzani at the beginning of the nineteenth century gave support to this, and by the 1820s the idea that the reaction took place in the peripheral capillaries was strongly gaining ground.

A change in nomenclature

Cyanosis is as old as haemoglobin, and much older than man. It is a state that we all pass through at each end of our lives. It used to be, and perhaps still is, one of the clinical signs that medical students are early on taught to look out for, so the absence of the word 'cyanosis' in any of Snow's writings was surprising. In the Oxford English Dictionary I was astonished to find that the first recorded use of the word was in 1834, in a book by John Mason Good, *The Study of Medicine*. Good, who based his work on the nosology of Cullen, itself inspired by the botanical classification of Linnaeus, listed Cyanea or Cyanosis, or Blue skin, as the third species of the Genus Exangia, of the Order Dysthetica, of the Class Haemata. His and other contemporary medical textbooks attributed cyanosis solely to congenital heart disease, and specifically to a patent foramen ovale. The first and second species of the genus were aneurysm and varix, and the connection between the three was that in all of them there is turbulent blood flow. Only slowly from the 1840s on, did the connection between cyanosis, other categories of heart disease, and pulmonary disease, become recognised.

Of course, the earlier word for blueness of the blood was lividity, but lividity appears to have carried a sinister connotation: it was associated with terminal conditions, and was hardly regarded as a readily reversible state, especially with no oxygen cylinder at the head of the bed. I think the question of why Davy's suggestion regarding the use of nitrous oxide as a pain relieving agent was not taken up may be answered, in part at least, by the contemporary view of lividity. In March 1800, in the company of Astley Cooper and others at a meeting of the Askesian Society, William Allen, lecturer in chemistry at Guy's Hospital (later of Allen and

Hanburys), inhaled what he called gaseous oxide of azote (nitrous oxide) and recorded in his diary that: 'The company said that my eyes were fixed, face purple, veins in the head very large, apoplectic stertor. They were all much alarmed, but I suffered no pain and in a short time came to myself.'²⁴ But a purple face, apoplectic stertor and dilated head veins were the signs of a stroke, and also current at that time and for the next thirty years, was the belief that blue or venous blood was poisonous to those tissues accustomed to being perfused with arterial blood. So, although Allen came to no harm, it is not surprising that the experiments were abandoned.

We know from his writings that John Snow kept himself fully aware of the latest developments in physiology. At the beginning of Part 17 of his series of publications *On Narcotism by the Inhalation of Vapours*,²⁵ he surveyed contemporary theories about the chemistry of respiration and its site in the body, and referred to the researches of W F Edwards, and of H G Magnus who, in 1837, demonstrated the presence of oxygen and carbon dioxide in the peripheral blood. Snow dismissed the lungs as the site of formation of carbon dioxide, and believed that the reaction took place in the capillaries of the systemic circulation. Also, the phenomena of asphyxia, previously attributed to an excess of carbon in the blood, were now known to be caused by want of oxygen in the arterial circulation. In the same series of essays Snow had clearly distinguished between anaesthesia and asphyxia, so he obviously felt no reason to be concerned by the fears raised by Drs Pring and Pickford. Also, as against his confessed disposition not to allow an occasional risk to stand in the way of ready applicability,²⁶ his experience with cyanosed patients who recovered and appeared none the worse for it, would soon have deprived the condition of its anxieties.

Would it have been easy to detect slight cyanosis in Snow's time? Artificial lighting was generally by candle or gas, both of which shift the colour temperature towards the red end of the spectrum, so it is reasonable to excuse failure to detect slight cyanosis, unless operating in daylight. However, we know that operations were usually performed about mid-day, and that operating theatres were lit by skylight. Also, of course, there was no shortage of accounts of cyanosis being observed.

Landmark publications after Snow's death were by Stokes,²⁷ who described the absorption spectra of oxygenated and reduced haemoglobin, and Pfluger,²⁸ who showed that the respiratory reactions take place not in the capillaries but in the tissues. In 1923, Lundsgaard and Van Slyke established that blood appears cyanosed when it contains 5g of reduced haemoglobin, and that this is an absolute figure.²⁹

For how long was cyanosis a feature of clinical anaesthesia? Those who have read Hewitt's *Anaesthetics and their Administration* have noted that he describes two types of anaesthesia, simple and complex.³⁰ Complex anaesthesia was what occurred in practice, and consisted of simple anaesthesia plus a varying degree of asphyxia, evidenced by cyanosis. Nitrous oxide anaesthesia was always expected to be accompanied by cyanosis until a general practitioner dental anaesthetist, Dr Tom, of Cheltenham, in an influential paper published in 1956, described his technique which was 'revolutionary' in that it postulated using a high percentage of oxygen (20%) with nitrous oxide.³¹

It is startling to realise that it is now perfectly possible for a well-taught and well-supervised trainee to spend a subsequent clinical lifetime without ever seeing a single instance of anaesthetic-induced cyanosis. With careful practice, the blue of cyanosis could be as archaic a condition as the green of chlorosis had become fifty years ago.

Summary

By a simple change of nomenclature in the 1830s, when Snow was a student, cyanosis as we understand it today, became a new concept. Its predecessor, lividity, was a fearsome condition, generally terminal. Growing understanding of the physiology of cyanosis, and experience of managing it in relation to anaesthesia, dispelled those fears. Putting it another way, familiarity bred contempt, so that when nitrous oxide was reintroduced in the 1860s, although there were further expressions of alarm about the cyanosis that inevitably came with it, notably from Clover and Benjamin Ward Richardson, these were not sufficient to prevent cyanosis from becoming, for many years, a tolerated concomitant of general anaesthesia.³²

References

- 1 Curwen EC. Ed. *The Journal of Gideon Mantell - Surgeon and Geologist - Covering the Years 1818-1852*. London: Oxford University Press, 1940; 215.
- 2 Duns J. *A Memoir of Sir James Young Simpson*. Edinburgh: Edmonston and Douglas, 1873; 208.
- 3-6 *Lancet* 1847; i: 78, 79, 105, 132.
- 7 Pring JM. Observations and experiments on the direct action of ether on the blood. *Lancet* 1847; i: 457-8.
- 8 Pickford JH. Injurious effects of the inhalation of ether. *Edinburgh Medical and Surgical Journal* 1847; 68: 256-8.
- 9 Robinson J. *A Treatise on the Inhalation of the Vapour of Ether*. London: Webster, 1847; 30, 32, 33, 34, 40.
- 10 *ibid* 12.
- 11 Snow J. *On the Inhalation of the Vapour of Ether*. London: Churchill, 1847.
- 12 Snow J. *On Chloroform and Other Anaesthetics*. London: Churchill, 1858; 44.
- 13 Snow J. *op. cit.* 1847; 37.
- 14 *Lancet* 1847; i: 158.
- 15-16 Snow J. *op. cit.* 1847; 56, 58.
- 17-18 *Lancet* 1847; i: 238, 343.
- 19 Denham J. *A Report Upon the Use of Chloroform in Fifty-Six Cases of Labour Occurring in the Dublin Lying-In Hospital*. Dublin: Hodges and Smith, 1849. (also published in the *Dublin Quarterly Journal of Medical Science* August 1849.)
- 20 Murphy EW. *Further Observations on Chloroform in the Practice of Midwifery*. London: Taylor and Walton, 1850; 39.
- 21 Singer C. *A Short History of Anatomy and Physiology from the Greeks to Harvey*. New York: Dover, 1957; 60. For more detail see Harris CRS. *The Heart and the Vascular System in Ancient Greek Medicine*. Oxford: Clarendon Press, 1973; 363-6 etc.
- 22 Cohen H. The philosophy of history. In Poynter FNL ed. *The Evolution of Medical Education in Britain*. London: Pitman Medical, 1966; 11-14.
- 23 Keilin D. *The History of Cell Respiration and Cytochrome*. Cambridge: Cambridge University Press, 1966; 11.
- 24 Quoted in Keys TE. *The History of Surgical Anesthesia*. New York: Dover Publications, 1963; 17-18, and discussed also by Smith WDA. *Under the Influence*. London: Macmillan, 1982; 29-30. (Originally published in the *British Journal of Anaesthesia* 1965; 37: 871-883.)
- 25 Snow J. *On Narcotism by the Inhalation of Vapours*. Ed. Ellis RH. London: Royal Society of Medicine Services, 1991 (Facsimile Edition); 91-95.
- 26 Snow J. *op. cit.* 1858; xxxv.
- 27 Stokes GG. On the reduction and oxidation of the colouring matter in the blood. *Proc. Roy. Soc. (London)* 1863-64; 13: 355-364.
- 28 Pflüger EFW. Zur Gasometrie des Blutes. *Zbl. med. Wiss.* 1866; 4: 305-308.
- 29 Lundsgaard C, Van Slyke DD. *Cyanosis* (Medical Monographs, Vol. 2). Baltimore: Williams and Wilkins, 1923; especially 27-8 and 71.
- 30 Hewitt F. *Anaesthetics and their Administration*. London: Macmillan, 1912; 3rd edn, 38-40.
- 31 Tom A. An innovation in technique for dental gas. *British Medical Journal* 1956; i: 1085, based on the 'amalgalgia' of Klock, (Klock JH. *Current Researches in Anesthesia and Analgesia* 1955; 34: 378).
- 32 Duncum B. *The Development of Inhalation Anaesthesia*. London: OUP, 1947, and the RSM Press for the History of Anaesthesia Society, 1994; 280-5.

REINTRODUCTION OF NITROUS OXIDE IN THE 1860s

Dr Barbara Duncum, Historian,
Honorary Member, History of Anaesthesia Society

Around the turn of the year 1846/47, when anaesthesia became an integral part of major surgery, there was no longer any need for surgeons to operate at top speed simply to curtail the ordeal for the patient. But when it was a matter of minor surgery for an able-bodied adult - tooth-drawing, for example - both parties to the operation still wanted it to be over as quickly as possible. For many years ether, which remained the anaesthetic of choice in the USA, and chloroform here and in most of the rest of Europe, were the only two anaesthetics readily obtainable, although neither was particularly well-suited for use in the bustle of a hospital outpatients' room or a GP's or dentist's surgery. Ether was considered safe and produced adequate muscular relaxation at an earlier stage than chloroform but induction and recovery were slowish and, as John Snow remarked, the smell of ether stayed on the breath for the rest of the day.¹

The drawbacks to chloroform were more serious. At home and abroad a growing number of doctors, dentists and lay people alerted by newspaper reports, noticed with alarm that patients only lightly anaesthetised and sitting upright on chairs sometimes collapsed and died quite unaccountably during induction or soon afterwards. Such fatalities led some authoritative persons to suspect an idiosyncratic reaction to chloroform itself, and many of them declared that chloroform ought not to be used in minor surgery - tooth-drawing in particular. Snow was not one of them. He did not always give an anaesthetic for a straightforward dental extraction unless the patient specially asked for it, but to the end of his days he believed that deaths were never caused by chloroform *per se* correctly administered, but always by an overdose having been given, usually by someone who did not fully understand what he was doing.² In one of a series of articles 'On narcotism by the inhalation of vapours' published in the *London Medical Gazette* between 1848 and 1851, Snow wrote:

'Chloroform is, I believe, not very generally employed in tooth-drawing in this metropolis. This is partly owing to the circumstance, that the pain occasioned by the operation, though severe, is usually but momentary; but another reason appears to be, that the majority of dentists are not sufficiently acquainted with the application of the medicine to be satisfied that they can use it with perfect safety, and it is not always convenient to the patient to have another medical man present. It is only in the cases of children and very nervous persons, who have not resolution to keep the mouth voluntarily open for the operation, that narcotism facilitates the work of the dentist; in other cases it adds to his trouble, and occupies more of his time.'³

An important cause of trouble was the nausea and vomiting which sometimes followed inhalation. This, Snow said, was felt to be more annoying in the dental surgery than after major surgery where the patient was necessarily regarded as an invalid. The chief benefit of chloroform anaesthesia to the dentist, in Snow's opinion, lay in bringing in more business. A

mouth could be painlessly cleared of teeth and stumps at one or possibly two sittings, in preparation for false teeth. Without anaesthesia for the patient such operations would never have been undertaken.⁴ In expressing this particular opinion, however, Snow appeared to have assumed that since gums could now be painlessly cleared for artificial teeth, dentists would clear them accordingly. In fact, most dentists in Britain continued to do what they had always done: they simply fitted the dentures over the stumps. In the United States where dentistry was more advanced, the gums were invariably cleared.⁵

As soon as J Y Simpson had introduced chloroform into practice, in November 1847, Snow made his own experiments and satisfied himself that a mixture of 4% chloroform vapour in air was a physiologically safe preparation. When he wished to make particularly accurate observations he sometimes filled a bag of known capacity with the mixture and attached the balloon (as he called it) to his valved and closely-fitting facepiece. In the course of his search for a more easily manageable dental anaesthetic than chloroform, Snow gave Dutch liquid (ethylene dichloride) from his inhaler for some extractions in the outpatients' room at St George's Hospital. And, on one occasion, for a nine year old boy, he successfully gave Dutch liquid from the balloon. But he finally concluded that, after all, chloroform was preferable. The liquid acted too slowly and a greater quantity was needed to produce an equivalent effect.⁶

Snow did not know that only a few years before, in Hartford, Connecticut, the dentist Horace Wells with no better equipment than the itinerant lecturer G C Colton's laughing-gas demonstration bag, with its clumsy wooden mouth-tube, had persuaded a number of dental patients to inhale nitrous oxide and then painlessly extracted teeth for them. If Snow, with his varied clinical experience, had had that information he might well have realised that his balloon and facepiece would be the very thing for administering nitrous oxide and tried it in the outpatients' room at St George's. By an odd turn of events, some twenty years later, J T Clover, having designed a chloroform inhaler directly based on the principal of Snow's balloon and facepiece, used it with considerable success in the early trials of nitrous oxide in London.

Professional status for dentists

Long before the dentist, W T G Morton, latched on to the idea that a fortune could be made by using inhaled ether to make tooth-pulling painless, dentistry had changed from a more or less skilled craft into a scientifically grounded profession, needing qualifications drawn from a range of complementary occupations. This change no doubt reflected a general trend in western medicine towards greater sophistication and specialisation. The wish for a thorough-going professional education seems to have started among dentists in the USA in the late 1830s. Dental colleges were established, each with its own curriculum based on four professorial departments: surgery, medicine, materia medica and mechanical dentistry. Each college was linked with a hospital to provide clinical experience. At the end of a course the student was examined by each of the four professors and successful candidates were awarded a diploma of fitness to practice and took the title Doctor of Dental Surgery (DDS for short).⁷

English dentists looked rather enviously at this system and later took it as a model.

The push by dentists in Britain to raise their professional status gained momentum during the long run-up to the passing of the Medical Reform Act of 1858. The Act established the Medical Register and restricted practice to persons jointly licensed by the College of Physicians (or, alternatively, the Society of Apothecaries) and the College of Surgeons. The dentists, of whom there were then some 1500, realising that they would not be eligible for registration, set about organising their own standards of fitness to practise, to be certificated by an approved examination system.

At a public meeting of dentists held in London in September 1856, a resolution was passed to establish a Society of Dentists which would sponsor a Dental College. A committee of 25, headed by the London dentist, Samuel Lee Rymer, was appointed to organise the Society and College in tandem order. The committee presented its first report of progress at another general meeting, in November 1856. The chairman was that eminent dentist and pioneer anaesthetist, James Robinson.⁸ By December, the sponsoring body and the College had been founded and named respectively, the Odontological Society of London and the College of Dentists. The Society's role amounted to little more than patronage. It was just another group of leading professional people who met once a month to discuss ideas and developments in their specialty. Their first meeting was on 5 January 1857. Soon they were recruiting 'corresponding members', distinguished dentists working abroad. Notable among them was Dr T W Evans. Evans, elected in May 1859, was an American who had built up a successful practice in Paris.⁹ His patients included not only friends and relations of Napoleon III, but the Emperor himself.

While members of the Odontological Society knew what they were doing, the College of Dentists had much to learn. Their first meeting was on 14 February 1857. At their headquarters, No.5 Cavendish Square, they at once organised lectures and, in due course, examined candidates for the Diploma of the College, and elected practising dentists of recognised ability. S L Rymer was appointed College Secretary, and their chief asset was their first President, James Robinson.

Robinson and the odontologists always intended the diploma of the College of Dentists to become recognised by the Royal College of Surgeons, to give it some authoritative standing. Early in 1858, when parliament was debating medical reform, Robinson asked his members to decide whether or not they should amalgamate with the Odontological Society to become the Institute of British Dentists with sufficient muscle to press the Royal College of Surgeons to establish a special Dental Diploma - as they had done with midwifery. At a general meeting on 8 January 1858, Robinson's proposal was rejected, on a show of hands. The majority of members did not wish to lose the name 'College of Dentists', nor did they want a diploma from the Royal College. They argued that as trained dentists they were better placed to assess fitness to practise than the surgeons of the Royal College, most of whom were not dentists. Robinson, disheartened, resigned as President and the odontologists withdrew.¹⁰

When the Medical Reform Act reached the Statute Book in August 1858, it was found that lobbying by influential persons - in particular John Tomes, surgeon dentist at the Middlesex

Hospital - had achieved an important concession for dentistry. The Royal College of Surgeons of England was empowered to institute examinations and licence anyone wishing and judged fit to practise dentistry. The licence carried the qualification LDS. The Royal College immediately set up a Dental Board, with Tomes as one of the examiners. It was left to individual dentists to decide whether or not to take the examination. The first licences were issued in 1860.¹¹

For a time the College of Dentists, with a new president, went on holding examinations and awarding its own diplomas. However, both exams and diplomas were frowned on by the Royal College of Surgeons, and also by the *Lancet* which had previously been friendly. In these chilly circumstances, dentists as a body saw that advancement lay in qualifying for the LDS, and the College of Dentists quietly gave up, merging with the Odontological Society of London in 1863 to become a new body, the Odontological Society of Great Britain.¹²

Although, in the late 1850s and early 1860s, the College of Dentists was still active, it was the Odontological Society of London, led by John Tomes, that established a dental hospital: the Dental Hospital of London opened in October 1859 at 32 Soho Square. A school of dentistry, the London School of Dental Surgery, was added to the hospital in 1860.

The College of Dentists had already in 1859 sponsored a dental school - the Metropolitan School of Dental Science - and housed it at 5 Cavendish Square. But the school was handicapped by not having its own clinical facilities. The lack was made good in 1860 when the National Dental Hospital was founded by subscription, under the auspices of the College of Dentists. Premises for the hospital were rented in Great Portland Street, and the Metropolitan School transferred there. Each of the two hospitals and their respective schools, attracted leading dentists and other experts as lecturers and demonstrators. But it was the odontologists at the Dental Hospital of London who first assisted Dr T W Evans when he brought nitrous oxide to London in 1868.

Influence of Colton

Between 1845, when Horace Wells so unluckily failed to convince surgeons at the Massachusetts General Hospital that laughing gas was indeed an effective dental anaesthetic, and the spring of the year 1862, nobody anywhere gave the matter much thought. Then, quite unexpectedly, the way was opened for Gardner Quincy Colton to introduce the gas into American dental practice for the second time.

Over the past eighteen years his peripatetic entertainments had included an account not of Wells's failure but of his successes. In the town of New Britain, Connecticut, a woman in Colton's audience, foreseeing the possibility of having some troublesome teeth extracted not only painlessly but safely, asked him to anaesthetise her so that a dentist, named Dunham, from a surgery nearby, could operate on her. This Dunham did, and also painlessly extracted teeth for other members of the audience. Dunham, just as Wells had done, then asked Colton to show him how to make and administer the gas.

When Colton returned to New Britain in the following year, he found that Dunham was regularly using laughing gas in his practice and doing very well. When Colton moved on for his next performance, in New Haven, Connecticut, in May 1863, he invited Dunham to go with him. There, they teamed up with a local dentist, Dr J H Smith, and at his surgery during the next three weeks Colton anaesthetised, and the other two painlessly extracted teeth for a large number of eager patients.¹³ The success of the New Haven venture convinced Colton that being an anaesthetist was altogether more rewarding than being an itinerant lecturer and off he went to New York, this time taking Smith with him as his dental partner. They recruited two other dentists and set up in business as the Colton Dental Association, undertaking only one kind of work: they received patients sent to them with instructions by New York dentists, painlessly cleared gums of teeth and stumps as directed, and sent them back ready to have false teeth fitted.

When Colton first started to work regularly as an anaesthetist he was still making nitrous oxide with the rough and ready generator he had invented for his laughing gas demonstrations twenty years earlier. It was not long before the enterprising Mr A W Sprague, in Boston, Massachusetts, saw that not only Colton in New York, but dentists all over the United States, were already in need of easily obtainable supplies of nitrous oxide. He designed and began marketing an efficient, simple to operate, apparatus. It comprised a coal-gas fired and regulated retort from which the nitrous oxide passed through four washing bottles to a counterpoised holder, to be drawn off into large reservoir bags.¹⁴ Soon, there was a widespread network of depots where nitrous oxide was on tap.

Colton bought a Sprague generator, and reorganised his inhaling equipment. He designed his own large reservoir bags into which nitrous oxide gas was decanted. During administration, the bag lay on the floor and the patient breathed the gas from it through a considerable length of rubber tubing and an ebonite mouth-tube half an inch in diameter. The tube was flattened in shape to be more easily held between the lips, and the patient's nostrils were closed by a clip.

In August 1863, shortly before the new system was introduced, a dentist named Latimer watched Colton anaesthetise two patients and he wrote it up for the American journal, *Dental Cosmos*. That December, S J Rymer in London read Latimer's article, and not realising that Colton had changed his methods, decided to use the information for a trial of his own. 'Dr Colton', Latimer said, 'administered the gas as for ordinary entertainment, save that the patient was sitting up, and the inhalation was continued for much longer.' In fact, Latimer noticed, it took two minutes to anaesthetise a calm young woman. Three minutes from the start of the operation - the extraction of five teeth - she was fully conscious again. The second case, that of a nervous middle-aged man, was not timed because induction was interrupted by some excitement.¹⁵

Rymer's first step was to enlist the help of a chemist named Tribe who taught metallurgy at the Great Portland Street School, and could use the facilities at the National Dental Hospital - meagre though they were - to make some nitrous oxide. Having provided himself with a galvanised rubber bag with a wide calibre, wooden mouth-tube, such as he thought Colton

might have used, and with a bladder as an alternative, Rymer asked each of three volunteers to inhale nitrous oxide for two minutes and then allow themselves to be severely pinched to test whether or not they had felt any pain. They duly breathed from and back into the bag, held in place by Tribe, while Rymer closed their nostrils with a finger and thumb and then did the pinching. They afterwards said that, uncomfortable though it had all been, they had not suffered any pain.

There was now only enough gas left for a single, and this time more positive test: a sixteen year old girl was fully anaesthetised by nitrous oxide and a decayed tooth was painlessly and uneventfully extracted by Mr William Perkins, surgeon to the National Dental Hospital.¹⁶ Rymer reported these happenings to the Odontological Society early in 1864, but his fellow members did not show any great interest in nitrous oxide (and neither did Rymer himself). Attention had already been engaged by the likelihood that, after all, chloroform **could** be safely used as a dental anaesthetic.

Was Evans' visit to London influenced by Clover's bag?

In 1862, J T Clover, not yet a dominant figure in anaesthesia, had launched his chloroform inhaler. It was well received by surgeons and in the medical press; and it attracted attention also because it looked so odd. A capacious impermeable sack was suspended from the collar of the anaesthetist's frock-coat and hung down his back, to be out of the way. From a top corner of the sack a 3 foot long rubber hose with a spiral of wire inside to prevent kinking, passed over the anaesthetist's right shoulder to a closely fitting facepiece. The thin ivory disc valves were also Clover's invention. The sack contained a pre-prepared mixture of 4½% chloroform vapour in a known quantity of air. This inhaler was, of course, a direct, though greatly improved, descendant of Snow's balloon.

Clover, justified by results in a number of cases, was able to claim that the unvarying 4½% of chloroform vapour in the inhaled air could not result in an overdose in any circumstances. By the mid 1860s, leading London dentists had no hesitation in inviting Clover to anaesthetise their private and hospital patients. That being so, it seems a little surprising to find Clover, on 2 March 1868, reading a paper on the use of his inhaler in dentistry, at a meeting of the Odontological Society. He described the apparatus in detail, spoke of its proven safety, and drew attention to the various dangers which could and did occur when other methods of administration were used - information which must long have been familiar to virtually everyone present.¹⁷ Perhaps the Society had expected Clover to take a different line.

Although Clover probably did not arouse much interest among the odontologists at the beginning of March, the Society's corresponding member in Paris, Dr T W Evans, undoubtedly caused a stir at the end of the month. On Monday, 30 March, apparently unheralded, he suddenly arrived in London with a Sprague apparatus and some Colton bags in his luggage. Having booked in at the new Langham Hotel in Portland Place, he set up the generator in a room where a source of coal-gas must have been available, made a supply of nitrous oxide, decanted into bags, and proceeded to give demonstrations over the next four days. On

Saturday, 4 April, he returned to France as abruptly as he had arrived. What was so strange about this visit was the timing and the lack of any surviving information to explain what had precipitated it.

Evans had been converted to the use of nitrous oxide some six months earlier by G Q Colton himself - in Paris to attend an international exhibition. During all those months, Evans had made no move to enlighten his confreres in London. What then had sent him racing across the Channel at the end of March, 1868. My guess is that he had just read the text of Clover's paper in the *Transactions* of the Odontological Society, circulated soon after the meeting of 2 March. The coincidence that Evans and Clover were independently using rather similar bags to hold an anaesthetic agent each of them believed to be safe, was striking. It was probably sufficient to convince Evans that he really must make plain the advantages of filling the English bag with nitrous oxide. Anyhow, that was the way things actually happened.

It is a little difficult to believe that Evans, burdened with the generator and a pack of Colton bags, would suddenly have turned up in London without warning. To guess again, I think he may have dropped a preparatory line to Thomas Underwood, the Odontological Society's secretary for corresponding members' affairs. All that Underwood himself later said, without a trace of surprise, was that Evans had called on him on the morning of Monday, 30 March, to talk about nitrous oxide and propose a series of demonstrations.¹⁸

The demonstrations started the next morning at the Dental Hospital of London, where Underwood was one of the surgeons. Everybody who was anybody in London dental circles came to watch. And, that evening, they met for more demonstrations, hospitably laid on for Evans by Mr Hepburn at his house in Portland Place. Hepburn, like Underwood, was a prominent member of the Odontological Society and on the staff of the Dental Hospital.

As Clover watched the demonstrations he saw that Evans frequently had trouble with the Colton bag: the inhaling tube kinked, air leaked in around the mouthpiece and the bag itself cluttered up the floor. He soon realised that his chloroform inhaler, with the sack filled with nitrous oxide, would be likely to function far more efficiently. A trial administration showed him and the rest of them that he was right.¹⁸

Clover's introduction of an appropriate type of inhaler was the turning point in the general acceptance of nitrous oxide as the dental anaesthetic of choice. Others, whose interest lay in developing anaesthetic technique rather than in promoting painless dentistry - notably Alfred Coleman - joined Clover in making further improvements. At last, nitrous oxide was recognised as a valuable anaesthetic agent in its own right.

References

- 1-4. Snow J. *On Narcotism by the Inhalation of Vapours*. Facsimile. Royal Society of Medicine Services 1991, pp 31-32, 52-53.
5. *Lancet* 1857; i:14. Letter to Editor.

6. Snow J. op.cit. pp 61-65.
7. *British Medical Journal* 1857: 182-183.
8. *Lancet* 1856; ii: 367 and 555.
9. *Transactions of the Odontological Society of Great Britain* 1857-60; 2: 159
10. *Transactions of the College of Dentists* 1857-61.
11. *Lancet* 1858; ii: 176.
12. Information from Dr P Narain. British Dental Association.
13. *Monthly Review of Dental Surgery* 1873-74; 2: 28-29.
14. *British Journal of Dental Science* 1868; 11: 254-256.
15. *Dental Cosmos* 1864; 5: 16-17.
16. *Dental Review* 1864; NS 1: 6-8.
17. *Transactions of the Odontological Society of Great Britain* 1867-68; 6: 99-122.
18. *British Journal of Dental Science* 1868; 11: 196-215, 237, 256.

FREDERIC HEWITT'S CONTRIBUTION TO NITROUS OXIDE ANAESTHESIA

Dr D D Howat

Immediate Past President, History of Anaesthesia Society

After John Snow and Joseph Clover, Frederic William Hewitt was perhaps the most important figure in anaesthesia in the last century. Not just because of his discoveries - he was the first to acknowledge the debt he owed to other workers - but because he showed by meticulously recorded experiments that it was not necessary to asphyxiate patients in order to anaesthetise them, and because of his concern that medical students and doctors should be properly trained in the administration of anaesthetics. These attributes are evident in his work on nitrous oxide anaesthesia.

Hewitt was born in 1857, the year before Snow died, and qualified from St George's Hospital, London in 1882, the year of Clover's death. He could not follow his chosen career as a physician owing to poor eyesight. What the defect was is not known, but it was probably some form of retinopathy. At that time it was common to forbid reading in such cases. Apparently, he never wore glasses and seldom read or wrote, members of his family doing it for him.¹ It seems remarkable that three of the greatest figures in the specialty, Snow, Clover and Hewitt, should have suffered from conditions which precluded them from practising surgery or internal medicine, but allowed them to practise anaesthesia with outstanding success.

Within three years of qualifying, Hewitt was appointed anaesthetist to Charing Cross Hospital and the Dental Hospital of London (later the Royal Dental Hospital); other appointments soon followed, to the National Orthopaedic, the London and, finally, to his alma mater, St George's.

A new method

In 1885, his first paper appeared in *The Lancet* - 'A new method of administering and economising nitrous oxide gas',² describing his experience with over 100 cases at the National Dental Hospital, to which he was attached for a short time. Briefly, the method consisted in permitting the patient to inspire half the contents of a 2 gallon (or 9 litre) bag filled with nitrous oxide (called a Cattlin bag after its inventor, a Brighton dentist), the expired gases escaping to the atmosphere, and then letting him breathe in and out of the bag until anaesthesia occurred. After removal of the facepiece, anaesthesia was adequate for short dental operations.

At this time 100% nitrous oxide was commonly administered until the patient showed signs of acute hypoxia - cyanosis, stertorous breathing, jactitations and muscle spasm. The gas was then withdrawn and the patient allowed to breathe air. During the subsequent 30 seconds or so, simple dental extractions or very minor operations could be performed before the patient recovered consciousness.

Hewitt's mask had an inspiratory and an expiratory valve incorporated in it, with a stopcock attached to it which allowed the admission of air. The patient breathed air until he was used to the apparatus; the air inlet on the stopcock was then closed by turning a tap and the patient inspired nitrous oxide from the reservoir bag, expiring through the expiratory valve, until the bag was half empty. A rod which shut off the two valves was then depressed, so that the patient breathed in and out of the bag.

Hewitt later modified it, so that the valves and stopcock were made in one piece, separate from the mask.³ Hewitt's 'economy' was directed at keeping a 'one-dose' anaesthetic in the bag which was portable and less expensive; not so important in private practice as in hospital, where the poorer patient had to pay a fee for an anaesthetic. However, he soon found it necessary to attach the bag to cylinders, so that more gas could be run in when needed.³ Hewitt felt that the low concentration of oxygen in the expired gases might reduce the chances of severe anoxaemia, even though the method might be considered unhygienic.

In 1869, Alfred Coleman, dental surgeon at St Bartholomew's Hospital and the Dental Hospital of London, had used carbon dioxide absorption by passing the gases over slaked lime; Hewitt tried passing them between sponges soaked in caustic potash, but was not impressed with the result.² He found that, without absorption, the carbon dioxide concentration of the gases in the reservoir bag was less than 2.5%, even after the patient had rebreathed them twenty times.⁴

In the following year, 1886, Hewitt published a paper in the *Journal of the British Dental Association* in which he developed this theme. He experimented with various different quantities of nitrous oxide in the reservoir bag, measuring the amounts in a gasometer. He found that an average of 3½ gallons (or 12 litres) of gas was required to produce anaesthesia, about half the amount used in the conventional method, although extra gas was needed in some cases.⁴

In 1876, Clover had described his apparatus for the administration of nitrous oxide, or nitrous oxide followed by ether.³ In 1887, Hewitt designed a portable apparatus on the same principle, but using Clover's portable regulating ether inhaler (to which Clover himself was never much attached).⁶ Later, he modified the inhaler to give it a wider bore and make it easier to handle.

In 1888, he published a textbook *Select Methods in the Administration of Nitrous Oxide and Ether* to illustrate these points and to stress the necessity for doctors and students to learn how to give anaesthetics.⁷

Importance of oxygen

In 1886, Hewitt noted that he was interested in the method of giving nitrous oxide and oxygen in a pressure chamber, introduced by Paul Bert, the Professor of Physiology at the Sorbonne. He gave 15% oxygen at 895 mm pressure (about 1.2 atmospheres). Claude Martin of Lyon found 12% oxygen at 1100 mm (or nearly 1½ atmospheres) more satisfactory. However, working under increased pressure was often unpleasant for the operating team.³

Hewitt realised that a simpler method of administering higher percentages of oxygen would be invaluable. He was well aware of the work done by others, first by Andrews of Chicago, who anaesthetised several female patients with 25% oxygen in nitrous oxide in 1869,⁸ but whose work was not followed up, and later by Klikowitsch of St Petersburg, who successfully relieved the pains of labour with a 20% oxygen mixture.⁹ Hillischer of Vienna devised a rather unwieldy apparatus consisting of two bellows-like bags, one for each gas, connected to a mask with a mixing valve attached, which Hewitt tried, but found inaccurate.¹⁰ These and other workers were using 20% oxygen at atmospheric pressure, but with very uncertain results. In the early days, air was not always excluded, because the patient had to close the mouth round a tube delivering the gases, while the nostrils were pinched by an assistant, and later because the mask did not always fit the face well, particularly in subjects with beards or sunken cheeks.

In a preliminary communication to *The Lancet* in 1889, Hewitt described his first experiments with nitrous oxide with oxygen.¹¹ He began by introducing various mixtures of the two gases into a metered gasometer. A tube with a stopcock at the outlet from the gasometer led to a reservoir bag and a suitable mask and stopcock. In this way he found that the most reliable results were achieved with a mixture containing 12.77% oxygen. Even then, a certain amount of positive pressure was needed to produce adequate anaesthesia, either by the weight of the gasometer bell, which had no counterpoise or, when he employed two bags, one for each gas, by getting an assistant to press on them.

However, the freedom from cyanosis and the other signs of anoxaemia convinced him that nitrous oxide, unlike nitrogen, did not act purely by causing a shortage of oxygen in the body. This had been a matter of discussion for many ears. He himself had anaesthetised patients at the Royal Dental Hospital for Sir George Johnson, a physician and Fellow of the Royal Society who believed, as a result of his own experiments, that nitrogen was as good an agent as nitrous oxide.¹² Hewitt used concentrations of between 3% and 7.5% oxygen to produce anaesthesia and the classical signs of cyanosis, jactitations, etc appeared in all but the frailest patients.¹³

In the years between 1889 and 1899, Hewitt performed many experiments with 100% nitrous oxide, nitrous oxide and air, and nitrous oxide and oxygen. His results were given in two papers, one to the Odontological Society of Great Britain in 1892,¹³ and the second in 1899 to the Royal Medical and Chirurgical Society, the precursor of the Royal Society of Medicine.¹¹

In his paper to the Odontological Society Hewitt cited 805 cases in which he had used nitrous oxide and oxygen. He first tried 20% oxygen at atmospheric pressure, making efforts to increase the pressure slightly by weighting the expiratory valve (in a sort of PEEP) or by using a wedge-shaped bag like Hillischer's on which the anaesthetist put his foot, but these had little effect. His apparatus now had two reservoir bags and a mixing valve, which had ten holes for the introduction of oxygen, and a separate stopcock.¹³ In a paper to the *British Dental Journal* two years later, he described a modification, consisting of a single bag, divided in two by a firm rubber septum.¹⁵ The tube leading from the oxygen cylinder was enclosed within that from the nitrous oxide cylinder, to make it more compact. The original mixing valve had proved too insensitive and the new one had ten smaller holes for the oxygen, by turning a tap,

very small changes in oxygen concentration could be made. The holes numbered from 1 to 10, but did not correspond to percentages of oxygen, although Hewitt stated that, when the first hole was opened, between 3½ and 6% oxygen was delivered, the opening of each additional hole adding a further 1-1½%.¹⁶ He had early realised that no two patients required the same concentration of nitrous oxide to achieve anaesthesia, and that the oxygen concentration had often to be varied from time to time in the same patient.

The cylinders were placed horizontally, one containing oxygen lying on two containing nitrous oxide. They were turned on and off by means of a foot control. Each half of the bag had to be kept about half full and at equal pressures and the oxygen concentration required very careful control. This needed considerable skill on the part of the anaesthetist. The whole apparatus was carried in a bag.

Textbooks and a classical paper

In 1893, the first edition of Hewitt's textbook *Anaesthetics and their Administration* was published.¹⁷ This was only the second comprehensive textbook of its kind, the first being Dudley Buxton's *Anaesthetics: their Uses and Administration*, which appeared in 1888. Hewitt's book was essentially a practical handbook for students and doctors. It was immediately popular and a second edition was published in 1901, containing additional chapters on the history, physiology and theory of anaesthesia. The fifth and last edition appeared in 1922, edited by Henry Robinson, six years after Hewitt's death. The late Sir Ivan Magill recorded in his Frederic Hewitt Lecture in 1965 that the 1912 edition was his most valuable guide when he took up full-time anaesthesia in 1919.

In 1897, Hewitt published a slim volume *The Administration of Nitrous Oxide and Oxygen for Dental Operations*, which reached its fifth edition in 1913.¹⁸ In it he gives a brief account of the gas since 1844 and describes his apparatus. The paper he read to the Royal Medical and Chirurgical Society in 1899 was of the greatest importance. He gave a detailed description of 231 anaesthetics he had administered at the Royal Dental Hospital between December 1894 and January 1897.¹⁴

He gave 20 patients 100% nitrous oxide, 106 had nitrous oxide with different percentages of air, varying from 3% to 33.1/3%, and 100 received 10 different percentages of oxygen, varying from 3% to 20%. Five patients were given two different anaesthetics on separate occasions, which allowed a comparison between two of the three methods.

He used a metered gasometer with a capacity of 18 gallons (nearly 82 litres), which permitted the preparation of accurate mixtures of the gases. He recorded the patients' age and sex, the number of teeth removed, and the times of inhalation and available anaesthesia. He noted change of colour, reflex movements, jactitations, unpleasant dreams and so on, giving points to each so that, added up, the lowest possible score of 0 meant perfect conditions and the highest 200, the worst.

These effects were shown in tables and on charts. The general results showed that the poorest rated at 95, were with 100% nitrous oxide, the next best with increasing percentages of air up

to 22%, and the best with nitrous oxide and oxygen, with a peak of 15 at 9% oxygen. None of these patients received any premedication, hence the poor results with the higher percentages of oxygen; they had only brief periods of anaesthesia available for dental extraction after the facemask was removed. After this paper, the physiologist, J S Haldane, opened the discussion saying:

'Although I am not an anaesthetist I have studied the subject from a physiological point of view - in respect, for example, of the symptoms produced by the want of oxygen. The paper contains the most valuable data on many points concerning which exact information is needed.'

He believed that this showed that nitrous oxide had a specific anaesthetic action, for which he said:

'Air containing only 10 per cent of oxygen can be breathed without any effect, whereas nitrous oxide containing 10 per cent of oxygen produces anaesthesia.'

He added that he was not convinced that there was no hypoxic effect with the lower concentrations of oxygen, as he had produced similar periods of anaesthesia with hydrogen or nitrogen and oxygen.¹⁹

Face mask or nasal mask

Many anaesthetists still preferred to use nitrous oxide and air, the difficulty being that air had to be introduced every few breaths either by removing the mask or by turning a stopcock. A fixed concentration necessitated the use of a reservoir, which was bulky and had to be refilled.

Both Joseph Clover and Alfred Coleman had described nasal masks in the 1860s and Coleman had recently reintroduced his. In 1899, Herbert Paterson of St Bartholomew's Hospital produced a nitrous oxide apparatus with a nasal mask for operations round the mouth, which Hewitt found interesting, but criticised, stating:

'The type of anaesthesia, however, can hardly be recognised as satisfactory in the modern sense; and in order that the best results may be obtained, a third person - that is to say, someone in addition to the surgeon and the anaesthetist - is needed to steady the patient, insert and adjust the Mason's gag, and sponge out the blood etc'

although he thought it might be improved in the future.³ Yet, as late as 1950, I and many others were still using nitrous oxide and air; occasionally replacing one of the nitrous oxide cylinders by an oxygen cylinder.

Hewitt always seems to have preferred a facemask, obtaining an average of 44 seconds' anaesthesia with nitrous oxide and oxygen, as opposed to only 30 seconds with 100% nitrous oxide. If the administration was prolonged for up to three minutes, a period of one to one and a half minutes' anaesthesia followed. Some years later, he wrote that the longest anaesthetic he had given with nitrous oxide and oxygen 'without allowing one breath of air' lasted 35

minutes; he had used it for operations such as Syme's amputation, lithotrity and mastectomy, where no muscular relaxation was required, but the oxygen percentage varied from 9% to 20%.²⁰

Abdominal operations were still performed under ether or chloroform anaesthesia for some years to come. The nitrous oxide-oxygen-ether or -chloroform sequence had to wait for another decade when, in the United States, Boothby in 1912 and Gwathmey in 1913 described the first sight-feed bubble flowmeters, which gave a visible sign of the proportion of gases being delivered. As so often, war gave the impetus to the next step. Hewitt did not live to see the next generation of anaesthetic apparatus developed by Geoffrey Marshall, Shipway, Boyle and Magill.

Hewitt's contribution was to show that nitrous oxide was a safe and a good anaesthetic agent in the presence of adequate oxygenation and to construct a practical and portable apparatus for its use. Others found that they had not Hewitt's expertise and it never became popular, but the work he did on nitrous oxide and the efforts he made by his writings and by his efforts to achieve proper instruction in anaesthesia for students and doctors, ensure his place in our history. He received the MVO for anaesthetising Edward VII in 1902 and was knighted in 1911, surely as much for his services to medicine as to his King.

Hewitt is on the list of founder members of the Society of Anaesthetists in 1893, but he never seems to have given a paper to the Society and does not appear on the list after that. However, he often took part in the discussions at the meetings of the Section of Anaesthetics after its formation in 1908. His last appearance was at the March meeting in 1915, when he stated that he had a high opinion of premedication. He died ten months later.

References

- 1 Howat DDC. Anaesthesia as a career. *Anaesthesia* 1977; **32**:979-995.
- 2 Hewitt F. A new method of administering and economising nitrous oxide gas. *Lancet* 1885; **1**:840-841.
- 3 Hewitt FW. *Anaesthetics and their Administration* 2nd edn. London: Macmillan, 1901.
- 4 Hewitt F. An enquiry into several methods of administering nitrous oxide gas. *Journal of the British Dental Association* 1886; **7**:208-216.
- 5 Clover JT. An apparatus for administering nitrous oxide gas and ether, singly or combined. *British Medical Journal* 1876; **2**:74-75.
- 6 Hewitt F. The administration of nitrous oxide and ether in combination or succession. *British Medical Journal* 1887; **2**:452-454.
- 7 Hewitt F. *Selected Methods in the Administration of Nitrous Oxide and Ether*. London: Baillière, Tindall & Cox, 1888.
- 8 Andrews E. Oxygen mixture: a new anaesthetic combination. *British Journal of Dental Science*. 1869; **12**:22-26.
- 9 Klinkowitsch S. Ueber das Stickstoffoxydul also Anaestheticum bei Geburten. *Archiv für Gynaekologie* 1881; **18**:81-108.
- 10 Thomas KB. *The Development of Anaesthetic Apparatus*. London: Blackwell, 1975.

- 11 Hewitt F. On the anaesthesia produced by the administration of mixtures of nitrous oxide and oxygen. *Lancet* 1889; **1**:832-835.
- 12 Johnson G. On the physiology of asphyxia and on the anaesthetic action of pure nitrogen. *Lancet* 1891; **1**:814-815.
- 13 Hewitt F. On the anaesthetic effects of nitrous oxide when administered with oxygen at ordinary atmospheric pressure. *Transactions of the Odontological Society of Great Britain* 1891-92; **24** (new series):194-239.
- 14 Hewitt FW. On the effects produced in the human subject by the administration of definite mixtures of nitrous oxide and air and of nitrous oxide and oxygen. *Medico-Chirurgical Transactions*. 1899; **82**:163-211.
- 15 Hewitt F. A new and portable apparatus for the administration of oxygen with nitrous oxide. *Journal of the British Dental Association*. 1892; **13**:661-668.
- 16 Hewitt F. Further observations on the use of oxygen and nitrous oxide. *Journal of the British Dental Association*. 1894; **5**:380-387.
- 17 Hewitt F. *Anaesthetics and their Administration*. London: Charles Griffin, 1893.
- 18 Hewitt FW. *The Administration of Nitrous Oxide and Oxygen for Dental Operations*. London: Claudius Ash, 1897.
- 19 Hewitt FW. On the effects produced in the human subject by the administration of definite mixtures of nitrous oxide and air and of nitrous oxide and oxygen. (Abstract) *Proceedings of the Royal Medical and Chirurgical Society of London*. 1898-9; (NS) **11**:56-68.
- 20 Hewitt FW. *Anaesthetics and their Administration*. 4th Edn. London: Macmillan, 1912.

THE HISTORY OF THE MANUFACTURE OF NITROUS OXIDE

Mr Peter Henrys

Manager, Operating Standards, BOC Gases

In contrast to the many developments in anaesthetic equipment for administering nitrous oxide, the production method remains as it was one hundred and fifty years ago. The main development has been in the scale of the operation. Today's methods are capable of producing the gas more efficiently and to a better quality, but the most fundamental changes have been to improve safety for both the plant and the operator.

Nitrous oxide was first identified by Joseph Priestley, who in 1772 exposed nitric oxide (he called it 'Nitrous Air') to a paste of iron filings and brimstone and noted the formation of a gas that he called 'Dephlogisticated Nitrous Air'. Some two years later, Joseph Black discovered a much simpler method of producing nitrous oxide by heating ammonium nitrate and allowing it to thermally decompose. When Humphry Davy at the Medical Pneumatic Institution was carrying out research involving nitrous oxide, he produced it using a plant designed and supplied by James Watt which thermally decomposed ammonium nitrate, in a manner not dissimilar to that in use today.

Over the 150 years that nitrous oxide has been produced as an anaesthetic gas, there have been other methods of manufacture. These have included direct oxidation of ammonia in the presence of a catalyst, and synthesis from nitric acid. These other methods have all had their problems with product quality and most have been abandoned. In 1994, the most common method of production around the world is that discovered by Joseph Black more than 200 years ago. Its popularity is based on the reliability of the plant, the simplicity of the operation and availability of the raw materials. Although the basic process has not changed significantly, there have been several developments to improve efficiency, product quality and operator (and equipment) safety.

Early manufacture

During the mid-nineteenth century, when nitrous oxide first became available commercially as an anaesthetic gas, initial supplies were in rubber bladders, filled from small plants producing the gas by heating ammonium nitrate. Some hospitals and clinics purchased their own plants, but as cylinders became available the benefits of this system faded. By 1870 the concept of liquefying the gas in the cylinder became established, and as the pressure rating of cylinders increased this became the preferred method of supply. At this time there were many suppliers throughout the UK, but gradually, as the gas business developed, the number of suppliers lessened.

By 1920, BOC was operating plants at Wembley in London and Worsley in Manchester, supplying cylinders of nitrous oxide throughout the country. With the introduction of Manufacturing and Product Licences by the Department of Health, there are currently only two suppliers of nitrous oxide in the UK today. BOC still produces on the Worsley site to supply the whole country.

Developments in the process

To look at the development of the ammonium nitrate process used today we need to review the basic requirements of the plant. The manufacturing process can be broken down into four stages:

Ammonium nitrate storage and feed system

One of the major advances in nitrous oxide production has been related to the supply of raw material. Ammonium nitrate is primarily produced for the fertilizer industry and for many years was only available in solid form, supplied in 25 kilogram bags. To thermally decompose the ammonium nitrate, you need to heat it above its melting point, so the initial stage in the production process was to load into a melter and apply heat so that it became liquid before being fed into the reactor. Today, with developments in the fertilizer industry, liquid ammonium nitrate is commercially available. This has the advantage of supply by tanker of 20 tonnes of feedstock, all of the same certified quality, into a liquid storage tank for feeding direct to the reactor. This has eliminated all handling, and enabled higher capacity plants to produce the nitrous oxide more efficiently. The storage tanks and transfer lines have to be heated to above the ammonium nitrate melting point to prevent it from solidifying prior to use.



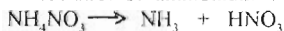
Figure 1

Heated reactor with primary scrubber

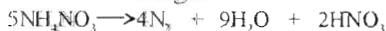
The basic design of the reactor has not significantly changed over the years. There have been many instances of reactors going out of control and exploding, and developments have been in the form of reaction control mechanisms and safety devices to protect the reactor. The thermal decomposition of ammonium nitrate ($\text{NH}_4\text{NO}_3 \rightarrow \text{N}_2\text{O} + 2\text{H}_2\text{O}$) takes place at temperatures above 250°C , and the reactor requires a heating source. However, the reaction is exothermic, so if the temperature is allowed to get out of control large volumes of gas can be produced very quickly, causing high pressures in the reactor and subsequent failure of the vessel. As recently as 1976 there are records of reactors exploding and these types of incident have given rise to the design used today. The temperature control systems are much more sophisticated, with internal electrical heaters to raise the temperature, and both internal and external water quenching systems to reduce temperatures quickly in the event of the reaction running away. In case all of these devices fail to control the reaction, the reactors are now fitted with large bore vents and bursting discs to relieve the pressure without loss of the vessel's integrity. Figure 1 shows a typical modern reactor with the large bore vent and quenching systems.

By controlling the temperature of the reactor to 250°C and using an ammonium dihydrogenphosphate catalyst, a compromise between yield and reduction of impurities is achieved, without jeopardising control of the reaction. There are, however, several side reactions at this temperature, which generate impurities that need to be removed for the gas to conform to the European Pharmacopoeia monograph. The main impurities are produced in the following three side reactions:

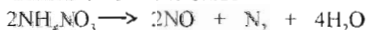
Dissociation of ammonium nitrate to ammonia and nitric acid



Formation of nitrogen



Generation of nitric oxide



The ammonia and nitric acid, along with any carryover of ammonium nitrate, are removed in the water scrubber on top of the reactor.

Gas purification system

Nitric oxide is the most important impurity to be removed as this can be lethal. In 1966, a batch of nitrous oxide cylinders with significant levels of nitric oxide resulted in the death of patients. This incident led to many changes in the control of the process and was a dominant factor in leading the UK to treat medical gases as pharmaceuticals twenty years before this became legislation within the EU. To remove the higher oxides of nitrogen, the gas is passed through a caustic scrubber and is continuously monitored for nitric oxide to ensure that it conforms with the specification. The requirement is levels below 2 vpm, but the purification system has been developed so that levels are maintained below 0.1 vpm. Figure 2 shows the purification system which includes an initial water scrubber, two caustic scrubbers to remove the nitric oxide, a

sulphuric acid scrubber to remove caustic carryover and a final water scrubber to ensure all impurities have been removed.

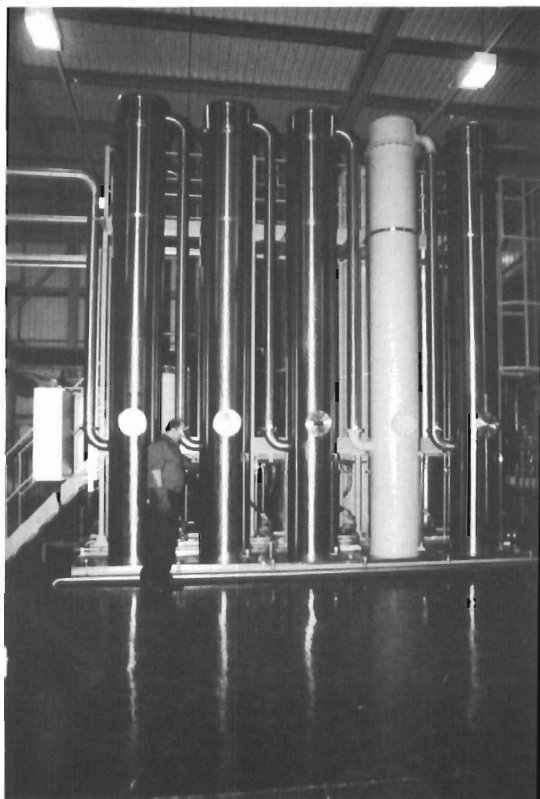


Figure 2

It is interesting to note the effort which has gone into producing a product free from the higher oxide of nitrogen while, in another area of medicine, development has been taking place to introduce a nitric oxide mixture for therapy.

After removing impurities, the major contaminant is nitrogen which is the most difficult to remove. Nitrogen is only partially soluble in nitrous oxide and so becomes concentrated in the gas phase above the liquid when nitrous oxide is compressed to liquefaction point. Nitrogen is removed at this stage using the principle of the difference in solubility of the two gases in water. It is because nitrogen is only partially soluble in nitrous oxide that, when using cylinders, the quality of the gas improves with use, reaching at least 99.95% by the time the cylinder is almost empty.

The specification for nitrous oxide is determined by the EP monograph, which is currently under review by the European Pharmacopoeia. Although there are minor changes to some of the impurity levels to bring the agent into line with other medical gas specifications, the major change in the monograph is away from traditional wet chemistry methods and toward modern analytical techniques. The assay now uses chromatography, and the higher oxides of nitrogen testing method utilises a chemiluminescence analyser. These changes have contributed to a better quality product with greater assurance that the gas is fit for its purpose.

Gas compression and storage

The gas from the purification system has to be compressed to liquefy it, for storage in batch vessels to permit it to be analysed and released. As nitrous oxide is an oxidant, great care has to be taken when compressing, as ignition in the compressor could have serious consequences. Conventional oil lubricated compressors cannot be used as nitrous oxide reacts with oil in a similar way to oxygen. Water-lubricated compressors have to be used. As there is little commercial requirement for this type of compressor, many of those in use today are over fifty years old. Only minor control systems modifications have been made to the original design. After analysis in the batch storage vessels, the nitrous oxide is transferred to a large storage tank, which holds the UK's entire requirement.

Trends

There has been little change to the way the gas has been supplied to hospitals over the past fifty years. As nitrous oxide is liquefiable, there is no benefit in using higher pressure cylinders. Consideration is currently being given to supplying nitrous oxide by tankers into bulk storage vessels to save handling of large numbers of cylinders, but with the decline in its use the benefits of this method are diminishing. The one major change in its supply has been the introduction of Entonox in the mid sixties. This was originally prepared by filling nitrous oxide into a cylinder and then topping up with oxygen. This obviously had the disadvantage that each cylinder was a unique batch and had the potential for danger if the oxygen was not added. To overcome this problem the process has been developed so that the gases are mixed at low pressure to the correct proportions and then filled into cylinders. This gives better control of the final mixture and permits the gas to be continuously monitored whilst being filled into a batch of cylinders.

When Joseph Black discovered that heating ammonium nitrate produced nitrous oxide he could have had no idea that two hundred years later we would be using the same method for producing the gas as an anaesthetic. Nor could he have foreseen the many improvements to produce the quantity and the high quality of the gas required today.

NITROUS OXIDE IN AUSTRALIA AND NEW ZEALAND

Dr R Westhorpe

Deputy Director of Anaesthesia, Royal Children's Hospital, Melbourne
Honorary Curator, Geoffrey Kaye Museum of Anaesthetic History

Looking back over the 150 years of nitrous oxide anaesthesia in Australia and New Zealand reveals the fear of all archivists - a lack of records. Regrettably, we can only piece together the snippets from newspapers, medical journals and company records.

1845-1870

The earliest known record is in the *Sydney Morning Herald* of Monday, 21 July 1845, where Mr J S Norrie advertised that his lecture on chemistry was to be delivered that evening, with the subject: '*The simple substances and the metals*. At the conclusion of the lecture the effect of the laughing gas will be exhibited.' Unfortunately, no report of the lecture was published.

Nitrous oxide must have been used for entertainment (if not anaesthesia) since the *Sydney Morning Herald* reports on 6 July 1847 that Dr Colin Buchanan had administered ether at the Australian Agricultural Company's Hospital at Stroud in New South Wales:

'.... and not being aware of the kind of apparatus used for the inhalation of ether, I tried the simple bladder with mouthpiece, similar to what is used in the inhalation of nitrous oxide, or laughing gas, which answered the purpose admirably'

A later reference to recreational use of nitrous oxide appears in an amusing contribution to the *New South Wales Medical Gazette* of 1870, by 'A Subscriber':

'Gentlemen, - as I understand that nitrous oxide gas, formerly called laughing gas, is used largely as an anaesthetic for dental purposes, and that excision of the mamma has been performed on a patient under its influence by Mr J R Begg, Surgeon to the Dundee Hospital, perhaps it would interest some of your readers to know the effects it produced upon me when taken on two different occasions, several years back. I inhaled it first in Sydney, at the residence of one of my friends.

'I had breathed about three quarts when the landlady of the house entered the room, and looked in an angry manner at me, to reprove me for being so ridiculous as to have the opening of a bullock's bladder in my mouth, like the figures in an old fashioned caricature; this look and the gas together caused me to have a violent fit of laughing; I laughed in the chair that I was sitting on, then I fell on the floor and rolled over and over on the ground still laughing, and this state lasted about five minutes. I then recovered perfectly without any unpleasant after-effects. I believe, however, I made an enemy of my friend's landlady ever afterwards as she never spoke to me again.

'The next time I took the gas was in the Square of one of the largest London hospitals, and in the presence of about 100 students, professors, tutors and others connected with the medical school there. I inhaled the gas as before, from two large bullock bladders, and after breathing about three quarts I looked around me, and felt indignant at having so many faces staring at me, so, without speaking, I walked up to the collected crowd and catching the eye of one of the students, when I was within three paces of him, I with a bound caught my friend by the throat and threw him on his back in the space of about two seconds. I then commenced pummelling him until I was taken away by the other students. Of course I apologised and was very sorry afterwards, and thus my second experience ended.

'This has had, no doubt, a great effect on the emotions, and if it produced only the excitement of laughter, there would be no reason why the profession should hesitate to administer it; but should the effect be that of exciting desires of a pugilistic nature, I should think most professional men would prefer using anaesthetics of a less stimulating character.

'I am, gentlemen, yours sincerely, *A Subscriber*. Sydney, August 20th, 1870.'

Tracing the medical use of nitrous oxide, we return to 1847 when the news of ether anaesthesia arrived in Australia. The first known surgical anaesthetic with ether was administered by Dr William Russ Pugh (although a recent study by Gwen Wilson casts doubt upon Pugh's medical credentials) in Launceston on 7 June 1847. On this same day, John Belisario, a dentist in Sydney, administered ether anaesthesia for dental surgery, although it is likely that this was not the first time he had done so.

Reports of ether anaesthesia appeared in newspapers and medical gazettes throughout the country, but without a single mention of nitrous oxide. Wilson reports that oxygen must have been available commercially when Benjamin Kent administered the first anaesthetic in South Australia on 30 September 1847.

The colony of South Australia was established specifically as an emigrant colony without any penal settlement. There was much political wrangling prior to the original charter in 1834 and it was not until 1836 that the colony became established. It remained isolated for many years, not only from England, but from neighbouring colonies until a rail link to Melbourne was completed in the late 1880s. Chapman, in his *History of Dentistry in South Australia* 1836-1936, describes how '.... supplies of instruments and appliances peculiar to dentistry had to be secured from England, and each man importing for himself alone, was subject to unavoidable delays and much anxiety'. He also writes that, in the 1850s: 'the introduction of laughing gas must have been greatly appreciated by those able to avail themselves of it'. This is an interesting observation and presumably refers to recreational use because the same author describes Lionel Newbolt Blackmore as probably the first to use nitrous oxide for dental anaesthesia in Adelaide. Blackmore did not arrive in Adelaide until 1870, by the end of which decade Chapman notes that: 'we find gold, platinum and vulcanite in use for artificial denture

bases, and nitrous oxide gas largely employed for extractions'. So it may be inferred that a lack of documentation does not mean that nitrous oxide was neglected. It was probably in common use, especially for dental procedures.

Further references to nitrous oxide do not appear until 1869, notably after Thomas Evans had introduced nitrous oxide to Britain the year before. In 1870, the *Australian Medical Gazette* reprinted a paper in the *Lancet* of 1869 by Dr Charles J Fox, Dental Surgeon to the Dental Hospital in London. He had learnt techniques from Colton and his paper extolled the virtues and safety of nitrous oxide anaesthesia, citing as an example the lack of ill effects, his experience of giving gas on two occasions to M Blondin for 'extremely severe dental operations' whereupon the patient 'performed all his most difficult feats on the high rope 430 feet long within three hours after I had given him the gas'. Soon after the cautionary letter by 'A Subscriber' in August 1870, the *Sydney Morning Herald* of 24 October reports that:

'Mr E Reading, Dentist, 128 Phillip Street, administers the nitrous oxide gas on 'Tuesday, Wednesday, Thursday and Friday. Patients wishing the gas applied must make appointments the day before.'

1870-1900

The *New South Wales Medical Gazette* of 1871 was the second medical journal to mention nitrous oxide, noting in the miscellanea section that nitrous oxide is likely to supersede chloroform for short operations.

The next publication appears in March 1873 in the *Australian Medical Journal* in the form of a review of Charles Kidd's prize essay entitled '*Chloroform, and substitutes for relief in pain*, Mr C Buxton, of London, having offered £3,000* as a prize for an essay on anaesthesia. The reviewer is critical of Kidd's style but quotes his strong advocacy of nitrous oxide as 'effectual, cheap and easy to apply, it is of much service by its safety in relief of pain. It is nearly tasteless, more agreeable than chloroform, curiously free from the depressing effects of other anaesthetics'. Another notable quotation from Kidd's essay relates to re-use of nitrous oxide: 'It has been found in practice that the nitrous oxide remains so much unchanged, that the same quantity of gas may be inhaled, exhaled and re-inhaled by a second and third patient without losing its anaesthetic properties'.

Kidd must have received a copy of the review in London for, in September 1873, his letter to the editor is published and makes amusing reading:

'Sir, - I feel obliged for your notice of my little book (March 1873). I think you will find where the style is involved, I am on purpose quoting the nebulous or involved oracular denunciation of the nitrous oxide gas, at first by Dr Richardson, or the unfair prominence

* The article says £3,000 - but this surely is a misprint! Ed.

given to ether in Dublin. That curious *fata morgana* of confusion, or mirage, conjured up of terrible deaths from chloroform, and the 'gas' has now cleared away. Let me say that this prize was offered under certain conditions, the idea taken for granted that pain is always an evil, and the prize offered for any 'substitute' for chloroform. In 1866, now seven years ago, the pure gas was unknown in London as an anaesthetic, and for suggesting it as then tried in America, I have had to undergo a seven year's persecution, like Dr Halford perhaps, at the hands of our European snake-bite theorists'

He goes on to denounce chloroform and complex inhalers and ends:

'I have chiefly met with violent opposition from those who denounced the nitrous oxide as the most deadly of all anaesthetics, or patentees of apparatus, or proprietary medicines or anodyne 'mixtures'. The young generation of medical men, like Mr Bryant of Guy's and Dr Poore, are breaking away from what the French style "*Regne Des Appareils*", reign of quackery and inhalers.'

Apart from an abstract of a German paper published in the *Melbourne Medical Record* of 1876, no further articles on nitrous oxide anaesthesia appeared in Australian medical journals before the turn of the century.

That nitrous oxide was in regular use, there is no doubt, as indicated by the existence of apparatus such as gasometers and photographs of dental anaesthesia using Cattlin's bag and Barth's stopcock. It is probable that the most prolific use of nitrous oxide was for dental anaesthesia and that it was so commonplace that no thought was given to documentation or discussion.

Nitrous oxide in New Zealand before 1900

The earliest known New Zealand reference appears in the local Napier newspaper in December 1878 and reads:

'Our Dentist, Mr H C Wilson, is about to commence the use of nitrous oxide (laughing) gas for producing insensibility to pain during dental operations we believe that Mr Wilson is the first dentist in the Colonies who has introduced the use of this anaesthetic into his practice: and we must add that we are glad to see Napier taking the initiative in this advance of science.'

In 1893, there was an interesting issue of stamps. The denominations ranged from one penny to one shilling and using varying coloured inks, each stamp in a sheet had a different advertisement on the back. These stamps were withdrawn soon after issue due to a rumour that the ink, when licked, was injurious to health! The one advertising S Myers and Company notes that painless extractions are available using nitrous oxide gas. Septimus Solomon Arthur Wellington Daniel Myers registered as a dentist in 1880 and is thought to have

introduced nitrous oxide in Invercargill. He then established a dental company in Dunedin, opening the Christchurch branch in 1888.

Faulding's Medical Journal

Further references are found in *Faulding's Medical Journal*, a company-sponsored quasi-scientific journal of news, advertisements and reviews of scientific papers. The *Journal* was published by the Adelaide based F H Faulding and Company, founded in 1845. A typical advertisement for dental anaesthesia appears in the May 1900 edition: 'New York Dental Institute of Grenfell Street, Adelaide offer teeth extracted painlessly with Cocaine, Eucaïne, Laughing Gas or Aether'.

In November 1901, comment appears regarding the Dental Bill which was then before the legislative council. Its purpose was to enable the establishment of a Board which would register dentists with appropriate qualifications and notably would prohibit all but those who held the diploma of one of the American or British dental colleges from administering nitrous oxide.

Faulding's Journal notes

'... it can hardly be claimed that this provision has been inserted for the benefit of the public, for it means that to less than one dozen dentists in South Australia is granted the sole right to administer this anaesthetic. The members of this privileged class are all with high class practices, who charge high fees. It is therefore obvious that the poorer classes will be practically denied the comfort and benefit of nitrous oxide when undergoing dental operations ...'

By the turn of the century Faulding's had become the major manufacturer and supplier of pharmaceuticals in the colony and the company exists today. Whether or not Fauldings manufactured nitrous oxide, we do not know, although they certainly supplied apparatus and pre-filled cylinders as indicated by advertisements in their journal.

Early manufacture of nitrous oxide

A clue regarding local manufacture appears in the *British Journal of Dental Science* in 1898, with the following entry.

'Australian Nitrous Oxide Gas - In addition to making their own dentists, Australia is beginning to make its own nitrous oxide, for an Australian Nitrous Oxide Gas Company has been formed and a complete plant for the manufacture of the gas has been imported. Operations have been commenced in South Australia, and distributing arrangements have been made for the colony of Victoria, but not as yet for the other colonies. The price will be lower than that of the imported gas, as the risk and expense of carriage as deck cargo is avoided, while the cylinders will be of uniform size. Advance Australia!'

No record can be found of an Australian Nitrous Oxide Gas Company. If it was Fauldings, they didn't mention it in their journal, so the mystery remains.

The twentieth century

The use of nitrous oxide in Australia and New Zealand in the early part of this century appears to have been confined to dental anaesthesia. As Geoffrey Kaye notes in a lecture of reminiscences given in 1962: 'Nitrous oxide was reserved in the main for single dose hypoxic smash and grab raids by dentists'. He believes that Leonard Lillies introduced nitrous oxide anaesthesia for surgery to Melbourne in 1924, however, it was not until the 1930s, under the influence of McKesson, Waters and Magill, that the use of nitrous oxide grew, together with absorption techniques. In 1931, in conjunction with John B Arnold Pty Ltd, Geoffrey Kaye developed the DM Austox machine, the DM standing for Dental Midwifery. This was a demand-flow nitrous oxide-oxygen apparatus which functioned on very similar principles to McKesson's apparatus.

Wars have a habit of influencing change in medical treatment and so it was that the 2nd World War had some influence on nitrous oxide anaesthesia in Australia.

Although ether and chloroform were the mainstays of anaesthesia early in the war, the Austox Field Service Apparatus was introduced for nitrous oxide oxygen anaesthesia. The apparatus was devised by Geoffrey Kaye with the Royal Australian Army Medical Corps in 1938-39 because of the approaching hostilities. It combined simplicity, sturdiness and low cost (about £35) and gave good service. It was advantageous to have the one type of relatively portable apparatus which could then be taken wherever gas supplies were available and used either in field units or base hospitals, all the nitrous oxide being imported from Australia.

The flowmeter was a water depression type and was ideal for continuous flow anaesthesia although soda lime absorption could be applied. The main fault with the apparatus was the absence of any reducing valves because they were in short supply at the time the device was manufactured. This was overcome by introducing fine control needle valves for setting up flows of gas. Geoffrey Kaye describes the problems as follows: 'These got scored in the frequent sand storms and then all your leisure time went in re-machining them until we got some stainless steel from Australia and could make more durable ones'.

At the end of the war these machines were sold off to anaesthetists returning to practice at a cost of £8-£10 complete with mask valve, bag and canister. The Austox Field Service apparatus was the forerunner of the CIG gas anaesthesia machine of 1948, eventually replaced by the first Boyle's machines in the early 1950s.

Manufacture and supply of nitrous oxide in Australia

We have mentioned the scant evidence of a manufacturing plant being established in 1898. Up to that time, the gas was either manufactured on the site or after 1870, imported in cylinders

from England. At the turn of the century, there were two major wholesale pharmaceutical suppliers in Australia, Fauldings in Adelaide, and Felton, Grimwade and Company, established in Melbourne in 1867. Felton, Grimwade had been producing small quantities of oxygen for some years before 1900, and this was used mainly by doctors for resuscitation and by theatre owners for lime-light projectors (using an oxygen and hydrogen flame to heat a lime block to incandescence). Russell Grimwade, one of the founder's sons, visited England in 1902 and developed an interest in oxygen manufacture and oxyacetylene welding and cutting. The Grimwades imported a German liquid air plant in 1909 and began production of oxygen in May 1910. In June, the Australian Oxygen Company was registered. The British Oxygen Company set up an oxygen plant with an agency in Sydney in 1912, trading as the Commonwealth Oxygen Company.

Just when these gas companies began producing nitrous oxide is not known, but the Australian Oxygen Company in Melbourne moved to a new plant in 1914 and within three years was producing nitrous oxide.

The next significant name is John B Arnold. Arnold was an engineer and an expert in acetylene welding who worked for Gardner Wear, a company responsible for supplying acetylene to most of the Australian market. He left that company in 1922 to start manufacturing welding equipment on his own. Grimwade encouraged Arnold to form John B Arnold Pty Ltd in 1924 with some investment by Australian Oxygen which was also to act as distributor, a partnership which eventually resulted in the giant CIG. It was John B Arnold who imported some early nitrous oxide/oxygen anaesthesia machines and who manufactured the first Australian anaesthetic machine.

Austox and Comox established a joint venture, creating Western Oxygen Company Ltd in Adelaide in 1923 and Western Oxygen (WA) in Perth in 1926. Several other gas supply companies were established, including Oxygen Supply, Oxygen Service, Allen-Liversidge (a subsidiary of the British firm of the same name) and Queensland Oxygen. British Oxygen Company and Allen-Liversidge amalgamated in Britain in 1930 and in January 1935, CIG, Commonwealth Industrial Gases, was incorporated in Australia, British Oxygen holding 60% of the shares. This brought together Commonwealth Oxygen and Accessories Ltd; Australian Oxygen and Industrial Gases Pty Ltd; Allen-Liversidge (Australia) Ltd; John B Arnold Pty Ltd; Oxygen Service and Manufacturing Company Pty Ltd; Queensland Oxygen Company Ltd; Western Oxygen Company Ltd (South Australia) and Western Oxygen Company Ltd (Western Australia).

In 1939 CIG acquired all the shares in EMF, a major supplier of welding equipment, and the Compressed Medical and Industrial Gases in Melbourne, thus establishing itself as the major supplier of medical and industrial gases and welding equipment in the Australian market. In recent years the medical arm of the company was established separately as CIG Healthcare which has now become part of the multi-national Ohmeda organisation.

Acknowledgments

I would like to acknowledge the invaluable help of Drs Gwen Wilson, Richard Bailey, Basil Hutchinson and Tony Newson

Bibliography

Chapman A. (Ed.) *History of Dentistry in South Australia 1836-1936*, Gillingham & Co Ltd Adelaide 1937.

Hutchinson B R. Early anaesthetics in New Zealand. *New Zealand Medical Journal* 1992; 105:343.

Newson A J. Nitrous oxide advertisements on New Zealand postage stamps. *NZSA Newsletter* 1972; 19:161.

Savage PC. *With Enthusiasm Burning*. Commonwealth Industrial Gases Ltd Sydney, 1974.

'NO' TO NITROUS OXIDE IN THE NETHERLANDS

Professor Doreen M E Vermeulen Cranch
Emeritus Professor of Anaesthesiology
University of Amsterdam

I could find no Dutch records on the early clinical use of Horace Wells' discovery that nitrous oxide could relieve surgical pain. If the discovery caused any interest, it was eclipsed by ether and chloroform, although neither roused the enthusiasm in the Netherlands with which they were greeted in Britain and America. Why was this? I believe it reflects the Dutch character. It also reflects the attitudes of Dutch surgeons, who influenced the law makers to impose limitations on the practice of dentistry and hindered the development of anaesthesia as a specialty.

A physician, Scholte, wrote in 1947:

'The Dutch resistance to the use of anaesthesia has existed from the time of its discovery and such an attitude was praised openly as being an indication of the prudence and wariness which typifies the Dutch character.'

The Dutch were by nature cautious, conservative stoics. The influence of Calvin was strong. Pain was inevitable and had to be accepted and borne. One would have thought that dentists and surgeons would have been overjoyed to relieve pain. But, true to the Dutch character, every innovation must first be observed and evaluated. *Primum non nocere* took precedence over enthusiastic acceptance of *Divinum sedare dolorum*, and the Dutch people accepted that.

The Dutch surgeon was responsible for the narcosis, but delegated it to the youngest surgical trainee or nurse. Anaesthesia was considered a lowly task. As long as the patient did not struggle against his tethered arms and legs, the surgeon was satisfied. If not, he displayed his authoritarian nature, often to the detriment of the young aspiring surgeon giving the anaesthetic. Because of deaths under ether and chloroform, anaesthetics were viewed with suspicion and fear. In 1904, Lans, a Professor of Surgery in Amsterdam said: 'The horror of general anaesthesia is the greatest evil which still cripples modern surgery'. Anaesthetics were often omitted when non-life-saving operations were carried out, particularly in children. The Sluder method of tonsillectomy and adenoidectomy which was performed without anaesthesia, continued until well after the Second World War. It was just not appreciated that a well-administered general anaesthetic could allow surgery to develop beyond hasty and crude techniques. No John Snow came forward to investigate anaesthetics and apply the knowledge to the care of patients. There was no Queen Victoria to praise 'Chloroform à la reine'.

In 1870 a Dutch pharmacologist, Prof Stokvis, claimed that anaesthesia with nitrous oxide was based on asphyxia and condemned its use. For 30 years, from 1870 to 1900, his teaching prevailed in the Netherlands. He did then change his opinion, but nitrous oxide remained under suspicion and never gained popularity until after the Second World War. The fear of asphyxia remained, in spite of the experiments of Paul Bert, who proved that nitrous oxide did

have anaesthetic properties and that, combined with oxygen, it was actually the safest anaesthetic. The developments in nitrous oxide anaesthesia at normal atmospheric pressure in Britain after 1868, also failed to change Dutch opinion.

Nitrous oxide in dentistry

How was dentistry practised in the Netherlands?¹ In the early 19th century, changes in Germany, France, Belgium and Britain were leading to the recognition of dentists. Unfortunately, Dutch dentists failed to give a work description of dentistry, claim dental procedures or plan training programmes. In contrast, the surgeons did, so they claimed the extractions, leaving the dentists the sale of tooth powders, the filling of teeth, the filing of roots before fitting artificial teeth, and orthodontics. In 1865 a law was passed whereby, in future, dentistry would require medical training, in order to deal with damaged gums, haemorrhage and, if necessary, to administer an anaesthetic.

The law was changed in 1876. Non-medical dentists were again allowed to practice, but were limited to the local treatment of teeth, gums and sockets, orthodontics and the fitting of artificial teeth. Prescribing or administering any drugs which could produce a generalised effect was forbidden. This robbed the dentist of any effective means of relieving pain or of giving any anaesthetic.

In 1895 a new dental clinic was opened in Utrecht by Theodore Dentz. He pointed out in his address that general anaesthesia with nitrous oxide was rarely used, first because its administration by dentists was forbidden by the law of 1876 and, secondly, because the doctors who were allowed to administer it knew nothing about how to use it.

There are, however, records of the use of nitrous oxide in private dental practice. A medically qualified dentist C L G Becht of The Hague, left records appertaining to 1870 and 1871. Becht prepared his own nitrous oxide, which he used 28 times. About 250 extractions were apparently without anaesthesia. A non-medical dentist, Stark, also had a luxury practice in The Hague. He had a Sprague's generating apparatus but would have required a physician to administer the nitrous oxide. An English dentist, Theodore Picnot (1820-1910) also had an elite practice in The Hague, where nitrous oxide could be used for extractions with an attending doctor.

A physician, Dr Hammes (1874-1951) of Amsterdam did take an interest in anaesthesia, including that for dentistry. In 1902 he visited the National Dental Hospital in London, where he gave 700 successful dental anaesthetics, using nitrous oxide and oxygen with the Hewitt's apparatus. He advocated the use of nitrous oxide for short surgical procedures and for dentistry. He devoted a chapter of his book on Narcose, published in 1906, to the safe use of nitrous oxide and oxygen. His efforts were largely ignored, because of the fear surgeons still had of asphyxia. Incidentally, Hammes strongly disapproved of any attempts by non-medical dentists to use nitrous oxide, even testifying against them in the courts of law.

Nitrous oxide for surgery

The first breakthrough came in 1923. The anoci-association teachings of Crile, who advocated local analgesia combined with nitrous oxide-oxygen anaesthesia in a premedicated patient, and Sauerbruch's positive pressure anaesthesia, which could prevent a patient dying if the thorax was opened, influenced Prof Zaaier of Leiden to produce an anaesthetic apparatus in the Netherlands.²

Nitrous oxide and oxygen from cylinders were led through ungraduated water bubble flowmeters and then mixed. The humidified mixture could be passed through an ether vaporiser, or bypass the vaporiser by means of a valve. The mixture then entered a breathing bag and on to a Y piece connected to a face mask, where inspiratory and expiratory gases mixed with each other. Expiratory gases passed through a long tube into a water bottle. The depth to which the tube reached in this water bottle determined the resistance to expiration. This was an attempt at positive pressure anaesthesia. Premedication was with morphine and scopolamine. Induction was with pure nitrous oxide. At the first sign of cyanosis, oxygen up to 10% was added and positive pressure increased to 15 cm. The surgeon then gave local analgesia subcutaneously at the site of the incision. Ether vapour was added to obtain better relaxation. There were problems: long induction times with breath holding, cyanosis, sometimes vomiting and poor relaxation.

Dr Van Wijhe of Leiden, who built a replica, confirmed in 1991 that CO₂ levels were too high, work of breathing was increased and oxygenation was low. It required considerable skill to anaesthetise a patient. Zaaier's machine was, of course, not the solution to the problems presented by an open thorax, with a spontaneously breathing patient. What is of interest is the system used to remove waste gases from the operating theatre with an expiratory tube disappearing into the floor. During the Second World War nitrous oxide was practically unobtainable. As a result, the object of the anti-pollution system was forgotten. Very few followed Zaaier's attempt to introduce nitrous oxide.

The next development came from Amsterdam, where local analgesia was largely used. In 1936 Van Gelderen,³ in training for surgery at the academic hospital under Prof Noordenbos, propagated the use of nitrous oxide, oxygen, using a German apparatus, the Dräger Stiefenhöfer. The reason was that operations like radical mastectomy and upper abdominal surgery required such large volumes of local analgesia that they approximated to the toxic dosage. If nitrous oxide and oxygen were given, sometimes with small amounts of ether, in the premedicated patient, it reduced the volume of local required. The oxygen concentration varied between 16 and 20% in men and 18 and 26% in women. The importance of patience before starting the operation and of a gentle operating technique by the surgeon were stressed. Emphasis was put on servicing the machine regularly to maintain the accuracy of the nitrous oxide and oxygen meters and the patented mixing chamber. The apparatus had a circle system with carbon dioxide absorption, but it was considered that the saving of gases did not outweigh the reduced accuracy of the gas mixture in the circle, which was therefore not used.

Hammes, Zaaier and Noordenbos all stressed the fact that the more complicated the machine, the more experience was required for the administration, but still no specialist anaesthetists were forthcoming.

Nitrous oxide analgesia

In the 1930s there were dentists in the Netherlands who were aware that in the US nitrous oxide was being used for conservative dentistry. They knew of Balter's and Langenbach's Analgesator and of Minnitt's gas and air machine. Novocaine was now being used by dentists for extractions.

In 1946, a Dutch dentist, Van de Kamer, dared to publish a paper¹ in which he extolled the use of nitrous oxide, not as an anaesthetic, but as an analgesic in dentistry, combined where necessary with local analgesia. He wrote that it calmed the nervous patient and alleviated pain if the local should be inadequate. He had used the method personally (probably in America) using a McKesson dental machine. It had a small rubber balloon, which the patient could squeeze if he required additional nitrous oxide and oxygen through the nasal mask. He also wrote that, provided they were trained to do so, dentists would be quite capable of administering the mixture to patients. This was the first record which I could find of the use of conscious sedation in dentistry in the Netherlands. Astonishingly enough, this dentist was not reprimanded or brought before the courts for flouting the still valid 1876 law. But neither did this important article have any impact on Dutch dental practice.

The start of modern anaesthesia

When I arrived from University College Hospital, London, at the University Clinic of Prof Noordenbos in Amsterdam, in June 1946, I found the Stiefenhöfer and also a simple Boyle's machine with two Coexter bobbin dry flowmeters for oxygen and nitrous oxide. The Magill expiratory valve near the face mask had been replaced by a long length of rubber tubing dipping into a water flask, to allow positive pressure breathing. They told me they liked the deep respiratory excursions which it produced! I soon changed it back to its original form and other changes followed. By September 1946 the first endotracheal anaesthesias with nitrous oxide, oxygen, ether, curare and assisted or controlled respiration, were being given in Amsterdam. In Utrecht, Prof Nuboer had told me that there were no anaesthetists in the Netherlands and that they were quite unnecessary. He, the surgeon, was responsible. Then, in August 1946, he appealed to me for help because three consecutive patients had died during anaesthesia. His McKesson nitrous oxide, oxygen and ether apparatus, I discovered, had been bereft of its unidirectional valves in the circle!

In Amsterdam, by October 1946, Prof Boerema had replaced Noordenbos. He asked me to stay on with him and, as a result, on 1 January 1947, the first School of Anaesthetics was set up for doctors to train as anaesthetists. The specialty was officially recognised in 1948.

By now nitrous oxide and oxygen cylinders were freely available but the colour coding was the exact opposite to that in the UK. Without pin index or ISO fittings, they required careful checking. By the autumn of 1947 Dutch surgeons, attending the first congress on thoracic surgery in Amsterdam, openly gave credit to anaesthesia. In 1948 closed cardiac surgery was started. In 1955 experimental work on hypothermia in dogs for cardiac surgery was published. Anaesthesia in a hyperbaric operating chamber for cardiac surgery at 3 atmospheres absolute,⁵ using nitrous oxide for oxygen in dogs was carried out, but we decided in 1960 to discard the nitrous oxide at high pressure in patients.

Revival of nitrous oxide analgesia and sedation

In 1947 the dentistry law of 1876 was changed. Dentistry became an academic study of six years, but there were no dentists in hospitals. They never used or asked for general anaesthesia, and were unaware of its advantages for certain patients.

Entonox, produced in 1961, was unknown in the Netherlands. In 1973 I organised, with Peter Baskett, a meeting on Entonox for dentists, anaesthetists, surgeons, cardiologists and obstetricians. The obstetricians just ignored the possibilities, but Entonox was fitted into ambulances and some surgeons used it for changing dressings. Slowly, dentists did become involved with nitrous oxide. Since about 1968 I had been giving regular lectures to dental students. It was important, I felt, to make them appreciate that many anxious and handicapped patients could be controlled with nitrous oxide-oxygen conscious sedation, if combined with local analgesia and behaviour management.

In 1979 a dentist at the Amsterdam Dental School asked me for help, because his standard of dentistry in anxious and handicapped patients was so low, due to their inability to co-operate, that the dentistry was not worth doing. That was the start of our working together for many years. An annual two weeks post-graduate course for dentists, on Inhalation Conscious Sedation with nitrous oxide, was started in 1981. It included resuscitation, an examination and a diploma.

Since 1984 anti-pollution systems combined with a meticulous technique have reduced the pollution of nitrous oxide sedation, to the officially required 50 ppm.⁶ In 1986 the Ministry of Health approved the Amsterdam post-graduate course⁷ and, since then, those dentists who have successfully completed the course can now legally administer nitrous oxide, oxygen for conscious sedation in dentistry. Thus was reached a true milestone in the history of Dutch dentistry - a late but fitting tribute to Horace Wells.

References

1. de Ranitz CJA. De ontwikkeling van de opleiding en de bevoegdheid van tandartsen in de Nederlandse wetgeving. *100 Jaar Tandheelkundig Onderwijs in Nederland 1877-1977*. Amsterdam, 't Koggeschip, 1977; 37.44.
2. Zaaier JH. Lachgas narcose. *Ned Tijdschr. voor Geneesk.* 1924; 68, 11:1449.

3. van Gelderen C. Over Narcose met Lachgas. *Geneeskd. Bladen* 33 Reeks. 1936; 213-245.
4. van de Kamer HJ. Honderd jaarlachgas als analgeticum. *Tijdschr voor Tandheelkd* 1946; 53:103-111.
5. Meijne NG, Vermeulen Cranch DME et al. Experimental cardiac surgery under high atmospheric pressure. *J Thor Cardiovasc Surgery* 1962; 44:749-758.
6. Schuijt HC, Vermeulen Cranch DME et al. Luchtverontreiniging door lachgas in de tandheelkundige praktijk. *Ned Tijdschr voor Tandheelkd* 1986; 93:431-436.
7. Gezondheidsraad. *Advies inzake Inhalatie Sedatie in de Tandheelkunde*. No.: 1986/12 's-Gravenhage.

HISTORICAL USE OF NITROUS OXIDE IN GERMANY

Dr M Goerig

Department of Anaesthesiology, University Hospital, Hamburg

It is impossible to describe all the contributions of German scientists to the development of nitrous oxide anaesthesia. This review therefore concentrates on the largely unknown men involved in the first attempts at its administration, which later led to its widespread use in Germany. As in the UK and France, the first to deal with the new agent were dentists, followed by the obstetricians, before the general surgeons realised its possibilities.

Origins of the spread of N₂O usage to German dentists

The reintroduction of N₂O anaesthesia in the German-speaking countries as elsewhere owed much to the energetic advocacy of Gardner Quincy Colton, who in the early 1860s had formed the Colton Dental Association in New York for the performance of dental operations under the influence of laughing gas. In 1864 the London dentist Samuel Lee Rymer (1833-1909) recorded successful cases, but it was a few years later, when Colton demonstrated the beneficial effects of N₂O in Europe, that it became the foremost anaesthetic in dentistry.



Fig.1
Jean Babbtiste Rottenstein

In 1867 Colton visited Paris to exhibit at the Paris Universal Exhibition. Here he met Thomas Evans (1823-1897), the American dentist practising in Paris, and taught him the use of N_2O . Soon after, the gas became available liquified in cylinders and therefore portable. At the same time, the pioneer of French dentistry Pierre-Apollonie Préterre (1820-1893) of Paris became familiar with the technique. He probably knew the American citizen Jean Baptiste Rottenstein (1832-1897), a dentist of some repute, originally from Frankfurt, Germany. I believe Rottenstein played an important role in the reintroduction of N_2O in Germany. Since he is relatively unknown, I present some biographical information not previously published.

From Frankfurt, where he lost his parents early, Rottenstein emigrated to friends in the US. He studied medicine and specialised at the Cincinnati College of Dental Surgery and the Starling Medical College, Columbus, Ohio. In 1855 he returned to Frankfurt and in a few years went to Paris. Like his colleague Evans, he was a specialist with vulcanite as a base for artificial dentures. It is said that Rottenstein was on good terms with the family of Napoleon III, who were also patients of Evans, and thus became a sought-after dentist in Paris high society. His relationship with the Emperor had probably developed through his friend Theodor Leber (1840-1917), an ophthalmologist with great experience in histology. He and Rottenstein had produced a textbook on caries, choosing a histological approach, which was published in Berlin in 1867 and a year later in Paris, London and New York. Leber had come to Paris at the suggestion of Richard Liebreich (1830-1917), a renowned eye specialist from Germany who had become the Emperor's family ophthalmologist. He, like Evans, assisted the Imperial family in their escape in 1870 from Paris to London. There, Liebreich became the leading ophthalmologist at St Thomas's Hospital.

When the war between France and Germany broke out, Leber had to leave France to serve in the Prussian army, while Rottenstein as an American citizen could stay. As a patriot he maintained close contacts with the German community in Paris. These circumstances and his fashionable clientele gave him considerable influence. He was made a member of the prestigious German Academy Leopoldina of Halle - an exceptional honour, dentists at that time being generally held in very low regard.

Through the Société Médicale Allemande de Paris, Rottenstein had maintained contact with his colleagues in Germany, and it is likely that the spread of the 'new narcotic', N_2O , in Germany directly followed from Rottenstein's recommendations.¹ In Berlin, men like the physiologist Luidimar Hermann (1838-1914), and dentists Carl Sauer (1835-1892) and Friedrich Busch (1844-1894) had been engaged in University studies on the effects of N_2O . This explains why the first articles on N_2O from Berlin were published in 1866/67 - the period when the use of the gas in dentistry was spreading from France.

Several years later, from 1878 to 1885, the French physiologist Paul Bert studied the effects of N_2O . He recommended its administration at pressures greater than 1 atmosphere, using the mobile 'car' or pressure tank designed by Fontaine. He proved its effectiveness by demonstrating its anaesthetic properties at 50% with O_2 in the pressure chamber. Rottenstein must surely have met Bert, since he frequently anaesthetised patients inside Fontaine's tank. According to an article by Bert in 1883, several of Fontaine's units were installed in Germany, but I could find no

confirmation in the German literature.² The pressure chamber vogue was short-lived because it was too cumbersome and too expensive; other techniques were needed.

Protagonists of N_2O /air/ O_2 anaesthesia in dentistry

The administration of N_2O in combination with air or O_2 was vigorously championed by Theodor Hillischer (1850-1924), a dentist in Vienna. He studied medicine at the University in Vienna and graduated in 1876. Two years later he founded the first dental clinical institution in Vienna. His interest in the pain problem of operative dentistry led him to become the first to use cocaine solutions in dentistry, soon after Koller's work was published in 1884. At the same time he began using N_2O in combination with air or O_2 . Hillischer was full of praise for the benefits and non-toxicity of N_2O used in this way, and warned of the cyanosis and asphyxia if N_2O alone was given. He developed a machine to give a mixture of N_2O with 10 - 15 % O_2 which he called Schlafgas, sleeping gas. An average dose of 60 litres from this device gave about 33 seconds of anaesthesia for the dental extractions.³ He obtained a patent in Germany in 1890 for this apparatus, featuring the capability of regulating the relative amounts of N_2O and O_2 .

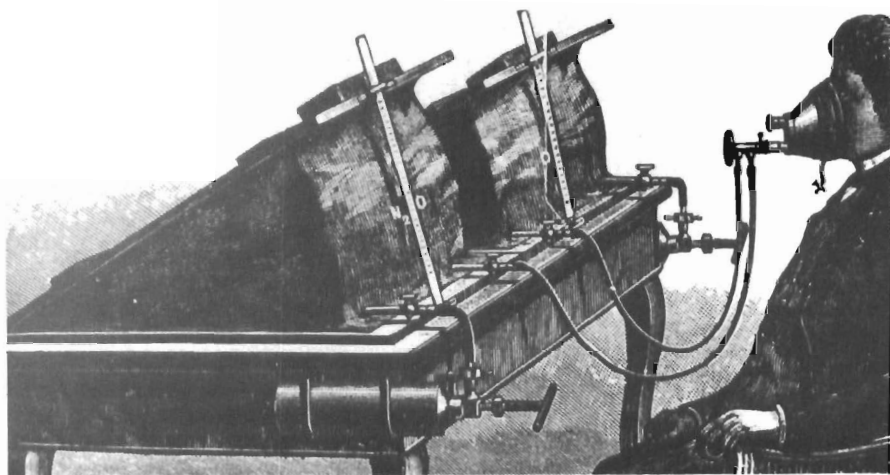


Fig.2

Theodor Hillischer's Schlafgas machine 1886

Nitrous oxide and oxygen could be administered separately from the two reservoir bags which were kept filled from the cylinders at the side of the table

Another protagonist was Adolph Witzel (1847-1906) of Bonn. He had studied medicine in Berlin and perhaps had contact with colleagues like Busch and Sauer, who were using N_2O . In 1889 Witzel published a monograph on N_2O in dental practice.⁴ He insisted that a minimum of 10% O_2 was required. He suggested storing both gases in a bag of india-rubber or a gasometer from which the patient inhaled via a mouthpiece held between the teeth.

One of the German proponents for the use of pure N_2O was a dentist called Watt. His arguments for the technique were vehemently rejected by Carl Sauer who later became the first specialist in prosthetic dentistry at a German university. Sauer in 1869 had suggested soda lime to remove CO_2 if a rebreathing technique was used. He recommended the intermittent administration of air or O_2 to prevent hypoxaemia.⁵ Another opponent of pure N_2O was the Berlin physiologist, Hermann. In 1866 he published one of the first articles on N_2O anaesthesia in a German non-dental journal.⁶ He condemned the common technique of applying the gas without air or O_2 . This kind of administration was nothing else than 'a life-threatening attack on all patients being operated upon'. Their condition was identical to that associated with the clinical signs of asphyxia. He also rejected the rebreathing technique used to rapidly deepen the anaesthesia, and recommended the use of air inlets in the mask. His views were confirmed by Ludwig Hollander (1833-1897), who later became a professor of dentistry in Halle. In 1868 Hollander identified the signs of cyanosis, bradycardia and cardiac collapse as due to direct intoxication with nitrous oxide and lack of oxygen. In the conclusion of his article, he questioned whether dentists were capable of dealing with such critical situations, and he asked for special training for those using nitrous oxide.⁷

N_2O in obstetrics and gynaecology

The introduction of N_2O to medicine in the German-speaking countries is closely connected with the name of the Russian military surgeon Stanislaw Klinkovitch (1853-1910). Before suggesting its use for pain relief during labour, he examined its therapeutic properties in the treatment of various internal diseases, a concept which was rather popular at that time in Europe. Between 1880 and 1883 he published several papers on the advantageous use of O_2/N_2O for therapeutic and anaesthetic purposes.⁸⁻¹⁰ He was the first to describe its obstetric use from a theoretical as well as practical point of view.⁹

Probably inspired by this last article, the Bavarian gynaecologist Franz Wilhelm von Winckel (1837-1911) and his Saxonian assistant Tittel began using N_2O for pain relief in labour. Von Winckel had started his career in Berlin under the outstanding obstetrician Eduard Arnold Martin (1809-1875) who, in 1848, had published a monograph on chloroform and its use in childbirth. Martin encouraged von Winckel to further anaesthetic researches. Acknowledging the stimulation of Klinkovitch's work, von Winckel studied the effects of N_2O in 50 women in childbirth. Shortly after Klinkovitch's publications, von Winckel and Tittel presented their first results at a meeting of the Gynaecological Society of Dresden. At the end of the meeting, Tittel anaesthetised a pregnant woman in front of the audience to demonstrate its beneficial effects. The short abstract and report of this meeting was probably the first publication in Germany on the use of N_2O in obstetrics and gynaecology.¹¹ Von Winckel and Tittel confirmed Klinkovitch's findings that there was no prolongation of labour noting, by abdominal palpation, the frequency, duration

and strength of uterine contractions before and after inhalation. They were convinced that in combination with 20% O_2 it was completely safe for mother and fetus, and was an effective analgesic in all stages of labour. As the patient inhaled only for short periods consciousness was never lost, and the ability to use accessory forces such as the abdominal muscles, was guaranteed. There was a reduced incidence, or the cessation of existing vomiting, and no side effects when the agent was repeatedly administered within short periods.

During the next decade, the spread of use of N_2O owed much to Paul Zweifel (1848-1922), one of the most renowned obstetricians of the period. He was born in Switzerland, and started his medical career at the University in Strasburg in 1872. In collaboration with the gynaecologist and physiologist Felix Hoppe Seyler (1825-1895), he demonstrated that drugs like chloroform and salicylic acid cross the placenta, an absolutely new concept at the time. Looking for alternatives, Zweifel became interested in N_2O . At the age of 28 he was appointed Chair of the Department of Gynaecology and Obstetrics at the University of Erlangen, where he was involved in the clinical use of the drug. Several years later, Zweifel changed to the University of Leipzig, where he had a long and distinguished career. He was one of the first to suggest an interaction between chloroform and gas lighting, and one of the first to use spinal anaesthesia during labour, after this was introduced in 1900 by the Swiss, Oskar Kreis (1872-1958). Zweifel held his appointment at Leipzig till his retirement in 1922. On his death at the age of 74 he was eulogised in many obituaries.

To understand the importance of Zweifel's position in Leipzig, it must be realised that the University of Leipzig was then a centre of scientific life in Germany. Surrounded by well-known colleagues like physiologist Carl Ludwig (1816-1895), pharmacist Rudolf Boehm (1844-1926) and surgeons Carl Thiersch (1822-1895) and Friedrich von Trendelenburg (1844-1924), Zweifel was able to establish a brilliant school of gynaecology, with intensive scientific exchanges between colleagues. Many of Zweifel's assistants later became famous obstetricians, having strong contacts with many institutions in Germany and abroad. Several of his assistants experimented with N_2O anaesthesia in obstetrics and operative gynaecology. Their numerous publications included indications, techniques, and side effects. I am sure the key to the spread of N_2O during these years was the scientific work of Zweifel's followers.

Albert Döderlein (1860-1942) was one of Zweifel's first assistants at Leipzig. In 1885 he reported his experience with N_2O/O_2 during labour.¹² He observed no delay in delivery, and he suggested using a transportable 200 litre balloon for home confinements. Döderlein also reported animal experiments with N_2O . The blood pressure did not change significantly, and there was no change in the O_2 content of the blood when a mixture of air/ O_2 and N_2O was used. For these experiments he probably used the sphygmomanometer described by Ludwig, and the spectrometric absorption technique of Hoppe Seyler of Strasburg.

Another of Zweifel's assistants was Bernhard Krönig (1863-1917) who became Head of the Department of Gynaecology and Obstetrics of the University of Jena in 1903. A year later he moved to the University of Freiburg, remaining as Director until his death in 1917. In 1903 he published an article on N_2O anaesthesia, reporting a new apparatus.¹³ This combined the Bennet inhaler with the system of Heinrich Braun's (1862-1934) apparatus, which could be used to give

chloroform or ether. His aim was smooth induction with N_2O , followed by the other narcotic to deepen the anaesthesia. It was one of the first devices in Germany which combined the use of N_2O , chloroform or ether, and air or O_2 . As late as 1924, it was described in a revised edition of the textbook '*Operative Gynaecology*'. Apart from his interest in N_2O , Kronig with his follower, Carl Friedrich Gauss (1875-1957), was involved in the introduction of twilight sleep, the analgesia/sedation concept using morphine and scopolamine, especially for women in labour. Gauss later introduced acetylene (Narcylene), which became a popular anaesthetic in Germany during the 1920s.

Carl Menge (1864-1945) had also attended Zweifel's department in Leipzig. He was offered the Headship of the Heidelberg Department and stayed there till his retirement in 1930. He was interested in furthering N_2O anaesthesia, and his most prominent assistant in this work was Maximillian Neu (1877-1940) whose name is closely associated with the introduction of flowmeter systems for better control of N_2O dosage.

The American Richard von Foregger (1872-1960) published two extensive reviews in 1946 and 1952 on the early use of anaesthetic flowmeter systems.^{14,15} He mentioned his inability to locate biographical data on Neu. Like Foregger, I found no obituary in the journals, which is explained by his Jewish origin.

Neu spent some months of 1902 in the Department of Internal Medicine at Badenweiler, near the Black Forest, headed by Albert Fraenkel (1848-1916) who introduced i.v. strophanthin. In 1903 he became Assistant in the Department of Gynaecology and Obstetrics at the University of Heidelberg, and in 1914 he was made Professor. He held this position until April 1933 when the National Socialists forced his dishonourable discharge from the University. He was made to sell his private Women's Clinic, and barred from private practice. Frustrated and overwhelmed by the inhumane circumstances under which they had to live, Neu and his wife committed suicide in October 1940.

From the beginning, Neu had close contacts at Heidelberg with the pharmacologist Prof Rudolf Gottlieb (1864-1924) and his assistant, W Madelung. They were studying the combination of morphine/scopolamine and N_2O/O_2 . Impressed by their results, Neu realized the potential value of N_2O in operative gynaecology. He first suggested filling cylinders with a mixture of N_2O with 20% O_2 , which had been discussed decades before by Hermann in Berlin. Neu, Gottlieb and Madelung discovered it was better to use separate cylinders, and Neu realized the importance of exact regulation of the mixture of gases.¹⁶

The Rotameter, a flow indicator with a tapered tube, was patented in Germany and the US in 1908 by Küppers of Aachen. The device was originally manufactured by the Deutsche Rotawerke, an Aachen-based company, so rotamesser (rotameter) became its common name. Rotawerke were the first ever to integrate flowmeters into an anaesthetic apparatus, which was the one used by Neu. Later, in the early '20s, the Dräger company in Lubeck installed a flowmeter system in a machine with Narcylene as an anaesthetic. After World War II, their model equipped with flowmeters became the Modell F of 1948.

It is said that Foregger visited the University Clinics of Heidelberg immediately after the war, to find the rotameter anaesthetic apparatus once used by Neu. According to the same source, he bought this and sent it home to the US. Several years later, the first American anaesthetic machine using flowmeters was produced by his company. One of those units now belongs to the Guedel Museum of San Francisco.

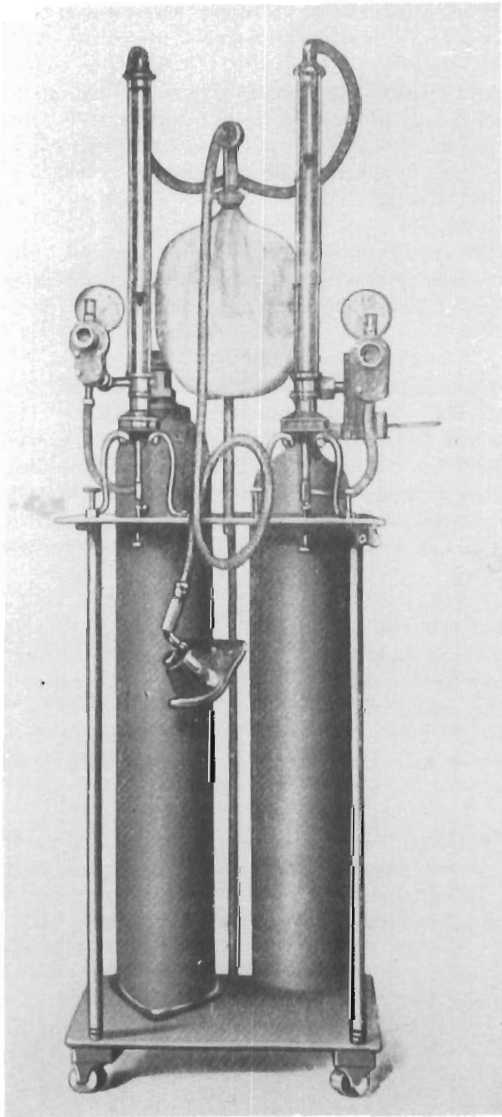


Fig.3
Neu's apparatus with integrated
flowmeters, made by Deutsche
Rotawerke of Aachen

Neu published several articles on the benefits of N_2O .¹⁶⁻¹⁹ He also displayed the new machine, notably at the annual meeting of the German Surgical and Gynaecological Society in 1911. Here he described it as 'the safest of all known anaesthesia methods'. Like others before him, he begged for the production of N_2O in Germany to lower its price.

Two other gynaecologists published studies on N_2O in 1911. It is no surprise that both had been assistants of protagonists of the gas. Hans Schlimpert (1882-1914) specialised under Krönig at Freiburg; Erwin Zweifel (1885-?), the son of Paul Zweifel, worked at the University of Munich where Döderlein had succeeded von Winckel in 1902. To overcome morphine/scopolamine-induced respiratory depression, Schlimpert suggested rebreathing from a reservoir bag.²⁰ Zweifel was convinced of the effectiveness of N_2O /air/ O_2 anaesthesia when used with preoperative medication, and additional vapours.²¹ Both were sure N_2O was the safest anaesthetic. According to their articles, Neu's rotameter apparatus was used in Heidelberg, Marburg and Munich. Zweifel mentioned a device developed by the American, Willis Gatch (1874-?), which allowed the patient to rebreathe until the first signs of cyanosis appeared, when O_2 could be given. To provide reliable muscle relaxation, ether could be added. Zweifel asked for comparable technical developments in Germany.

Early use of N_2O by surgeons

Neutek Nussbaum (1829-1890) of Munich was one of the first surgeons to use N_2O .²² He reported his adverse experiences in 1873 at the second annual meeting of the German Surgical Society. He had witnessed a lethal complication, and had often failed to achieve adequate anaesthesia with N_2O . It is likely, owing to his influential position that, for many, especially those who attended these meetings, N_2O became a topic not worth discussing. It was three decades before another paper on N_2O was presented - and this was Neu's laudatory report of 1911. The delayed acceptance of N_2O may be explained by the discovery in 1884 of the analgesic properties of locally administered cocaine, and the refinements of infiltration anaesthesia by the Berlin surgeon Carl Ludwig Schleich (1859-1922) and his Paris colleague, Paul Reclus (1847-1917). Results were so good that the surgeons could see little use for N_2O .

Thus up to 1910, N_2O was rarely mentioned in German surgical journals. The Austrian military surgeon, Ignaz Joseph Neudorfer (1825-1898), did describe it as safe if used correctly with added O_2 .²³ He urged further research, convinced of its excellent analgesic effect. Because only a few lethal accidents had occurred he labelled the agent 'harmless'.

Paul Sudeck and Helmut Schmidt of Hamburg

The negative attitude of the German surgeons to N_2O was finally overcome in the '20s and '30s. The two Hamburg surgeons Sudeck (1866-1945) and Schmidt (1895-1979) were particularly involved in its reintroduction to German-speaking countries. Schmidt's research in the early '20s had focused on anaesthesia related problems, and he became the first German surgeon to be appointed professor because of his contributions to anaesthesia. In 1928 he wrote a text '*Concerning the reintroduction of N_2O in Germany*'.²⁴ Due to his excellent relationships with the Hoechst-IG-Farben company, he persuaded them to start producing N_2O . His father Hans

Schmidt was senior chemical engineer at the company's laboratories in Eberfeld, and was probably in charge of the production which started in 1928.



Fig.4
Helmut Schmidt of Hamburg

It was with the two Hamburg surgeons that the Dräger company developed their N_2O/O_2 machine to be used with vapours like ether and Narcylene. Sudeck and Schmidt used this model in daily anaesthetic practice at the Hamburg University Hospital from early 1925. The Nitrous Oxide Anaesthetic Machine Modell A was the first to feature a circle system and CO_2 absorber. For

thoracotomies a positive pressure attachment was added. The anaesthetic was administered via a gas-tight mask, held to the face by a head harness. Premedication with morphine 10-20 mg and atropine 1 mg or scopolamine 0.5 mg was followed by induction with 100% N_2O for 5-10 breaths, then O_2 was added - 5%, then 10%, and after 20 minutes, 15-20%. A small amount of ether was added if necessary. The prime purpose of the machine was to reduce to a minimum the amount of N_2O and ether required. Often, when N_2O and O_2 alone were used, the anaesthetist switched to 100% N_2O for a few breaths to deepen anaesthesia, resulting in cyanosis.

At the annual Congress of North West German Surgeons in 1924, in Hamburg, the two surgeons reported their experiences.²⁵ This is noteworthy because the clinical introduction of CO_2 absorber systems is usually associated exclusively with the American, Ralph M Waters (1883-1979). Schmidt suggested the use of devices like the Dräger model to lower the cost of N_2O which still had to be imported. For the same reason, the circle system was integrated into another apparatus for Narcylene anaesthesia, primarily instigated by the Würzburg obstetrician Gauss. Both the devices performed flawlessly.

At the Hamburg University Hospital, a colleague in the Department of Internal Medicine, Hugo Wilhelm Knipping (1895-1984) developed a technique for even more economical administration.²⁶ His concept was to replace only the gases being metabolized by the organism. He used a circle system with CO_2 absorption and, to avoid hypoxaemic O_2 concentrations, he integrated an O_2 monitoring device, based on changes in electrical conductivity. The requirement of gases was reduced by 95%, and the risk of explosion from excess gases was lessened. Knipping's technique fell into oblivion, because he was only concerned with research on metabolic mechanisms rather than clinical anaesthesia. Nevertheless, a textbook of anaesthesia, by Hesse, Lendle and Schoen in 1934 found the device 'useful'.

Other machines similar to the Modell A were manufactured. The Hoechst Company, as producers of N_2O , developed their own apparatus, which was made and distributed by Stiefenhofer of Munich. The Georg Haertel Corporation of Berlin marketed a device of the Netherlands surgeon, J H Zaaijer (1876-1932). He had a great influence on the reintroduction of N_2O , since he was often visited by German doctors wanting to become familiar with the new technique.

At the same time as Sudeck and Schmidt's efforts to establish N_2O in surgery, a colleague in the Department of Dental Surgery Hans Pflüger (1884-1967) was researching its use in dentistry. He, with surgical colleagues in Eppendorf, and the Dräger Company, developed a Model B, especially for dental work. It became the best selling unit in this field, and was popular also with obstetricians for home or hospital delivery. The first prototype was used in the Department of Gynaecology and Obstetrics in Würzburg until it was destroyed during the war. The new model had a pneumatic automatic system, easy to use, and reliable in delivering the selected concentrations of N_2O and O_2 . The various devices for administering N_2O gained widespread favour. According to Joseph Haupt, an engineer with the Dräger Company, by 1950 it was not unusual to be selling 200 or 300 units per month. This development changed when new local anaesthetics became available in dental practice, and the inhalation methods were felt to be too time-consuming. In addition, widespread use by dentists had resulted in occasional fatal

accidents, and the German Anaesthesia Society, founded in 1953, was demanding standards which could not be maintained by dentists.

Why was N_2O so little used in Germany?

In the 19th century, it was simply too expensive. By 1910, N_2O was still being imported and the price of Neu's Rotameter Anaesthesia Apparatus was 600 Reichsmarks, falling to 450 RM a year later. At that time the cost of one hour of N_2O anaesthesia was about 10 RM - almost half the weekly wage of an average working man. Another reason was the effectiveness and relative safety of local anaesthesia. New agents like procaine and Stovaine with adrenaline, became very popular for various techniques including lumbar and sacral blocks. In the first decade of this century up to 80% of operations were conducted under some form of local anaesthesia.

The lack of physicians experienced and trained in general anaesthesia caused further delay in development. Skill was needed to deal with the short duration of action and poor relaxation of N_2O anaesthesia. Many surgeons favoured ether, which could be satisfactorily given by nurses. The reintroduction of N_2O in the '20s, with the occurrence of lethal complications, invoked discussions on its safety similar to the arguments of decades before, when the agent was first introduced. A consequence was increasing demand for anaesthetic specialists to improve patient safety.

N_2O anaesthesia in German textbooks

The state of the art of anaesthesia was well reflected in many texts and monographs. An early review of N_2O anaesthesia occupied only five pages of a book by Otto Kappeler (1841-1909).²⁷ In contrast, the Hamburg obstetrician Benno Wilhelm Muller (1873-1947) summarized the entire



Fig.5
Swiecicki's apparatus, 1888

knowledge of the subject available to him, in an 800 page monograph '*Narkologie*'²⁸. A few years later, in 1913, a textbook by Max von Brunn (1875-1922) gave an excellent review, including all important international references.²⁹ In the textbooks on surgery, gynaecology and obstetrics published between 1890 and 1920, the techniques were mentioned, but too poorly described to be satisfactory for practical guidance. In contrast, thorough descriptions were given in dental publications, usually written by experienced dentists.

The origins of N₂O apparatus in Germany

As with the agent itself, development of apparatus for the use of N₂O was largely influenced from abroad. The first devices were all imported, mostly from the UK. I think that the first attempts at development in Germany were made by the Polish obstetrician Heliodor Swieciecki (1854-1923). He began his specialisation under von Winckel in 1882, and later often visited Zweifel's hospitals in Erlangen and Leipzig, thus becoming familiar with the advantages of N₂O in labour. Later still, in 1919, he was appointed Chairman of the recently founded Medical University in Posnan. Highly honoured, Swieciecki died in 1922 being regarded as the father of modern Polish gynaecology.

In 1888, Swieciecki was the first to describe in a German journal a transportable nitrous-oxide-oxygen apparatus with an integrated reservoir bag. A mixture of 20% oxygen and 80% nitrous oxide was stored in a single iron bottle and could be transported in a wooden box. The narcotic was administered via a rubber tube leading the gas directly to a large reservoir bag from which it passed to the mask. He suggested inspiring as deeply as possible, and holding the lungs inflated as long as possible to obtain the best absorption by the lungs. This device was sold by the Berlin branch of the London firm of Ash & Sons.³⁰

In the following years, similar transportable devices were produced in Germany, gradually replacing the cumbersome gasometer systems. By the turn of the century, such apparatus was becoming more and more accepted, and it was only a matter of time before integrated flowmeters were added, leading to the modern anaesthetic machine.

References

- 1 Rottenstein JB. *Traité d'Anesthésie Chirurgicale*. Gernies-Ballière, Paris 1880.
- 2 Duncum B. *The Development of Inhalation Anaesthesia*. Wellcome Historical Medical Museum. Oxford University Press 1947.
- 3 Hillischer Th. *Ueber die allgemeine Verwendbarkeit der Lustgas-Sauerstoffnarkose in der Chirurgie*. W. Frick, Wien 1886.
- 4 Witzel A. *Ueber den Gebrauch des Schlafgases in der zahnärztlichen Praxis. Dtsch Zahnheilkunde in Vorträgen*. Verlag von Hermann Riesel & Comp., Hagen i.W. 124-200, 1889.

- 5 Sauer C. Vorläufige Mitteilung der weiteren Versuche mit Stickoxydul-Gemischen zu anästhesieren. *Bln Klin. Wschr.* 1869; **34**: 366-367.
- 6 Hermann L. Notiz über die Empfehlungen des Stickoxyduls als Anaestheticum. *Bln klin. Wschr.* 1866; **3**: 115-116.
- 7 Hollander L. Das Stickstoffoxydul als Anaestheticum. *Bln Klin. Wschr.* 1868; **22**: 234-235.
- 8 Klikowitsch S. Über die therapeutische Wirkung des Stickoxyduls in einigen Krankheiten. *St Petersburger Med. Wschr.* 1880; **30**: 117-118 and 249.
- 9 Klikowitsch S. Ueber das Stickoxydul als Anaestheticum bei Geburten. *Arch. f. Gyn.* 1881; **18**: 81-108.
- 10 Klikowitsch S. Das Stickoxydul und Versuch seiner Anwendung in der Therapie. *Virchow's Arch.* 1883; **94**: 184-185 and 227-278.
- 11 Tittel S. Sitzungsbericht der Gynäkologischen zu Dresden. *Cbl. f. Gyn.* 1882; **8**: 120.
- 12 Döderlein A. Über Stickoxydul-Sauerstoffanästhesie. *Wien. Med. Blätter* 1885; **40**: 1207-1211 and **41**: 1243-1246.
- 13 Krönig B. Über Lachgasmischnarkosen. *Münch. Med. Wschr.* 1903; **42**: 1817-1818.
- 14 Foregger R. The Rotameter in anesthesia. *Anesthesiology* 1946; **9**: 549-557
- 15 Foregger R. Early use of the Rotameter in anaesthesia. *British Journal of Anaesthesia* 1952; **24**: 187-195.
- 16 Neu M. Ein Verfahren zur Stickoxydul-Sauerstoffnarkose. *Münch. Med. Wschr.* 1910; **36**: 1873-1875.
- 18 Neu M. Demonstration zur Morphin-Skopolamin-Stickoxydul-Sauerstoff-Narkose beim Menschen. *Dtsch Med. Wschr.* 1910; **36**: 2367-2368.
- 19 Neu M. Die Stickoxydul-Sauerstoffnarkose. *Arch. f. klin. Chir.* 1911; **95**: 550-557.
- 20 Schlimpert H. Über Versuche mit neueren Narkose-Arten in der Gynäkologie. *Mschr. f. Geburtshilfe und Gyn.* 1912; **36**: 67-69 and 117-125.
- 21 Zweifel E. Klinisch-experimentelle Versuche mit Lachgas-Sauerstoff-Narkose. *Mschr. f. Geburtshilfe und Gyn.* 1913; **38**: 546-560.
- 22 Nussbaum N. Narkose mit Stickoxydulgas - 280 Experimente. *Verhandlungen der Dtsch Ges. f. Chir.* 1873; 93-95.
- 23 Neudörfer I. Ueber Aether und Stickoxydulnarkose. *Dtsch Zschr. f. Chir.* 1883; **18**: 461-483.
- 24 Schmidt H. Die Leistung der Stickoxydulnarkose in der Chirurgie. Eine vergleichende Narkosestudie zur Wiedereinführung und zum Ausbau der Lachgas-Sauerstoffnarkose in Deutschland. *Arch. f. klin. Chir.* Bd 151 1928; 121-175.
- 25 Schmidt H. Über Stickoxydulnarkose. *Bruns. Beitr. klin. Chir.* 1926; **137**: 506.
- 26 Knipping HW. Über die Möglichkeiten einer rationellen Stickoxydulnarkose. *Hoppe-Seyler's Zschr. f. Physiol. Chem.* 1924; **137**: 286-292.
- 27 Kappeler O. *Anaesthetica*. Verlag von Ferdinand Enke, Stuttgart 1880.
- 28 Müller WB. *Narkologie*. Trenkel, Leipzig 1908.
- 29 Brunn M von. *Narkose*. Enke, Stuttgart 1913.
- 30 Swiecicki H. Zur Stickoxydul-Sauerstoff-Narkose in der Geburtshilfe. *Cbl. f. Gyn.* 1888; **43**: 697-699.

NITROUS OXIDE IN THE 1920s AND 1930s

Dr D J Wilkinson

Consultant Anaesthetist, St Bartholomew's Hospital, London
Curator of Charles King Collection of Historical Anaesthetic Apparatus

The 20s and 30s were a time of considerable social and political change in the Western World. Nitrous oxide anaesthesia did not suddenly spring into prominence during these two decades; there had been a steady development in the art and science of its use since its inception some 80 years previously. However, it was in this era that some of the more important developments occurred.

Pre 1920s

Crile and Lower had published their work on Anoci-association in 1914¹ in which they described their technique of nitrous oxide anaesthesia following heavy pre-medication together with the liberal use of local anaesthetic infiltration. When Crile set up his Lakeside Hospital in France during the First World War these techniques proved very effective in shocked trauma cases. Also at this time Marshall, Boyle and Shipway were working with nitrous oxide anaesthesia in combination with ether. The military anaesthetists thus returned to civilian life with a new perspective on an old drug, but without the apparatus with which to administer it.

Apparatus in the 1920s

In operating theatres there were few nitrous oxide machines. There was usually an anaesthetic table with masks and dropper bottles together with bottles of ether, chloroform and ethyl chloride. Gradually the Boyle's machine began to be introduced; initially with a simple water sight flow meter and an ether vaporiser, then modified by the addition of a chloroform bottle. In outpatient and in dental practices there would be a simple nitrous oxide apparatus comprising a couple of cylinders of gas, without reducing valves. Control was by a foot key, the cylinders were connected to a Cattlin bag which was, in turn, connected to a stopcock and mask and the apparatus would then be used to provide a pure nitrous oxide anaesthetic for short dental extractions or minor operations.

Charles King, Francis de Caux and Elmer McKesson

Charles King opened his shop at 34 Devonshire Street to sell general medical instruments in the early 1920s.² Francis de Caux, an anaesthetist from the North Middlesex Hospital, had recently visited McKesson in Toledo, Ohio, when he came into King's shop with a McKesson machine. The mid-west of America was the birthplace of a wealth of nitrous oxide apparatus, from manufacturers such as Heidbrink, Teter, White, Gatch and McKesson. Examples of their equipment can be seen by those who visit the Wood Library-Museum of Anesthesiology in Park Ridge, Chicago.

At that time, de Caux was the 'doyen' of nitrous oxide anaesthetists in London and had written copiously on the subject.³ He had developed some special endotracheal tubes for nitrous oxide anaesthesia and these were introduced during the use of McKesson's technique of secondary saturation. This involved a pure nitrous oxide induction followed by the addition of about 10% oxygen; this was primary saturation. Once the patient was breathing satisfactorily with this mixture the oxygen was turned off and 100% nitrous oxide was given. When the patient was deeply cyanosed a 'burst' of oxygen was given, preferably 'under pressure' and the patient would then become apnoeic and totally relaxed, and intubation could take place. The patient who had undergone this 'secondary saturation' would then restart breathing 10% oxygen in nitrous oxide.

The best (if not the only) apparatus for this technique was the McKesson. The top of the range model of this line was the Indicating and Recording Nargraf. This was a truly sophisticated apparatus capable of continually recording the patient's respired volumes, blood pressure and inspired gas mixtures. de Caux persuaded King to import these machines and thus started him on his career related to anaesthetic apparatus. McKesson machines were soon to be found in almost all dental surgeries in the UK. McKesson continued to lecture and teach how to use his apparatus and published many books and monographs on the subject. de Caux modified the McKesson machine to his own specification and other practitioners developed a series of nasal and oral masks for dental anaesthesia. McKesson's influence on British anaesthesia can be seen in the preface to the 3rd edition of Boyle's *Practical Anaesthetics* (which was co-authored by Langton Hower) in which they pay recognition to McKesson's contribution of a complete chapter on monitoring during anaesthesia.⁴

Meanwhile, in Germany, Dräger had introduced their highly sophisticated Model A machine which incorporated a circle soda lime absorber. This was utilised because nitrous oxide was considered to be relatively expensive. At the same time, Ralph Waters was working on his 'to and fro' closed system and, with Lundy, produced a cuffed tracheal tube which was so elegantly demonstrated at the American Society of Anesthesiologists' Meeting when they performed their 'drowning dog' experiment. In this, they wheeled on to the stage a dog suspended underwater in a large tank. The dog, known as 'Airway' in their subsequent correspondence, was anaesthetised and breathing through a closed system via the cuffed tracheal tube. The dog was removed from the tank, the anaesthetic was stopped, the dog was extubated and made a complete recovery.

Other developments

This was the period when Ivan Magill and Stanley Rowbotham perfected their techniques of intubation. Magill, working with the engineering skills of King, produced a whole range of apparatus relating to nitrous oxide anaesthesia. There was a special reducing valve, and an endotracheal anaesthetic machine which incorporated Siebe-Gorman Rotameter-type flow meters, as well as the Magill tubes and laryngoscope. Magill also developed a special gas and oxygen apparatus at this time although this did not prove to be particularly popular.

In 1932 Robert Minnitt was asked to investigate the possibility of developing a nitrous oxide apparatus for use in obstetric analgesia by midwives. He, too, was a friend of Charles King and they developed the Minnitt's apparatus which was a bisected McKesson machine with some air entrainment holes added. A whole series evolved. Each was designed to give nitrous oxide analgesia using a mixture of 50% gas in air, i.e. about 10% oxygen. There was the added refinement of the CM attachment for the Hospital model which allowed the use of 100% nitrous oxide for about six breaths before reverting to 10% oxygen. Despite their shortcomings, obvious in this day and age, Minnitt's apparatus was used to great effect from the 30s to the mid 1960s.

In surgical practice, the Boyle's machine continued to evolve. The water sight flowmeter was replaced by the Coxeter dry bobbin flowmeter which, in turn, was replaced by the Rotameter. The Walton 1 machine was designed for use in dental surgeries as a replacement for the McKesson and, in Europe, a new form of anaesthesia was being developed with the introduction of the intravenous barbiturate induction agents like Evipan.

In 1932 Langton Hower produced the first edition of what would prove to be a long running series: *Recent Advances in Anaesthesia*. This edition referred to recent problems abroad with contamination of nitrous oxide cylinders with nitric oxide and noted the high purity of UK supplies. He also noted that secondary saturation techniques were regarded in the UK as causing considerable strain on the right side of the heart and not advisable for inexperienced anaesthetists.⁵ In the second edition, the presence of nitrogen in nitrous oxide was mentioned. This was more evident at the beginning of use of a cylinder when the inspired concentration might reach 8%. By 1939 Hower was writing about recent reports of destruction of the cerebral cortex in patients who had received pure nitrous oxide and oxygen anaesthetics in the USA. He believed that this was most likely to be due to hypoxia rather than a direct effect of the nitrous oxide.⁶

Clement's book on nitrous oxide anaesthesia was published at this time, with its dedication to his mentor McKesson, who had recently died. This book reviewed the full pharmacology and application of nitrous oxide anaesthesia from a US perspective.⁷ It is interesting that 'secondary saturation' was still recommended.

The decade thus ended with nitrous oxide anaesthesia firmly established. There were two basic forms of this use. Firstly, as a sole agent for rapid procedures such as dental extractions or as an induction agent; secondly, as an adjuvant or even a carrier gas with a Boyle's type machine. The use of 'secondary saturation' in the UK was rare and generally considered to be dangerous. The forthcoming world war would provide even greater impetus to the development and refinement of both techniques and apparatus for the use of nitrous oxide anaesthesia.

References

1. Crile GW, Lower WE. *Anoci-association*. WB Saunders Company. Philadelphia, 1914.

2. Wilkinson DJ. A. Charles King: a unique contribution to anaesthesia. *Journal of the Royal Society of Medicine* 1987; 80:510-514.
3. Wilkinson DJ. Francis Percival de Caux (1892-1965). An anaesthetist at odds with social convention and the law. *Anaesthesia* 1991; 46:300-305.
4. Boyle HEG, Hewer CL. *Practical Anaesthetics*. 3rd Edition. Henry Frowde and Hodder & Stoughton. London, 1923.
5. Hewer CL. *Recent Advances in Anaesthesia and Analgesia*. J & A Churchill. London, 1932.
6. Hewer CL. *Recent Advances in Anaesthesia and Analgesia*. 3rd Edition. J & A Churchill. London, 1939.
7. Clement FW. *Nitrous Oxide-oxygen Anesthesia*. Lea & Febiger. Philadelphia, 1939.

ENTONOX AND OBSTETRIC ANALGESIA

Dr P V Cole

Consultant Anaesthetist, St Bartholomew's Hospital, London 1965-1992

When I first became involved with Entonox my main problem was that I was working under Dr H G Epstein (Epp) of EMO (Epstein-Macintosh-Oxford vaporiser) fame - Professor Sir Robert Macintosh's (Mac's) right-hand man. Compared to most of us who have dabbled a bit in research Epp was a real scientist and when I showed him a cylinder of gas which supposedly went against the Gas Laws - in particular, Dalton's Law of Partial Pressures he was - not unnaturally, initially sceptical. I had to demonstrate its unchanging composition from beginning to end (with the aid of a Raleigh Refractometer) before I could investigate further. I didn't introduce Entonox - Mike Tunstall did. He had become unhappy whilst a registrar in Portsmouth at the low standard of pain relief in the mainly domiciliary labours, and wrote to the British Oxygen Company asking if they could supply N_2O and oxygen in a single cylinder. This, of course, had been done before in 1945 by Barach and Rovenstein, but only at a total pressure of 700 psi. BOC wrote back politely explaining the problems which we all thought occurred when one exceeded the critical pressure of N_2O but Mike persisted and after, I think the fourth letter, Arthur Bracken who was the Chief Chemist at BOC at the time, wrote back admitting that no one had actually tried mixing the gases at a higher pressure. Six months later they came up with not only 50:50 but also 60:40 and even 70:30 per cent cylinders of nitrous oxide and oxygen each at a total pressure of 2000 psi. To be honest, I think they were more surprised than anyone, and they only formally demonstrated the solvent effect of high pressure oxygen on liquid gases some four years later.

History of N_2O in obstetrics

Klikovitz, in St Petersburg in 1881, is credited with the first use of nitrous oxide in obstetrics, using the gas contained in 'guttapercha cushions' and there have since been many methods of administration of the gas to labouring women. By 1962, the standard method was 'gas/air' by means of Minnitt's apparatus. This was a demand analgesic machine which was supposed to deliver a 50% N_2O /air mixture (10.4% oxygen) over a range of minute volumes governed by the 'CMB' rules. When Dick Luxmoore and I checked the actual performance of 30 of these in maternity homes in the Oxford Region, over the range of minute volumes actually measured in labouring mothers, rather than those imagined by the Central Midwives Board (6-9 L/min), the machines usually delivered rather less oxygen than expected and some were downright dangerous. In addition, hospital models were often fitted with the 'CM' (Chassar Moir) attachment - up to six breaths of pure nitrous oxide before the mother began inhaling the hypoxic mixture (Chassar Moir was Professor of Obstetrics and Gynaecology at Oxford. He denied to me that the initials had anything to do with him!) You can easily see that an alternative method would be welcome.

The first move was to exchange air for oxygen. The first machine to do this was that of Andreas Warming of Copenhagen, introduced into the UK by Seward in 1949, but only two

were imported. The early home-produced machines were modified dental gas machines. The first was the Lucy Baldwin, a modified Walton V, suggested by John Elam and named after the then President of the National Birthday Trust. It was followed by the AE manufactured by Cyprane and suggested by me. Both were satisfactory. Both were also complicated and far from portable.

Entonox - low temperature experiments

Entonox was simple and easy to carry (the portable version weighed only six kilos). With hindsight it is amazing that it had taken so long to discover that liquid nitrous oxide would dissolve in high pressure oxygen. But it, too, had its snags. Under certain circumstances the gases would separate and thus become very unsafe!

In experiments designed to assess the effect of low temperatures, a piece of sewage pipe blocked off with concrete was used as a bath, and cold saline stirred with a stream of air used to cool the cylinders of premixed gas. Small samples were removed for analysis after holding the cylinders at a constant temperature for an hour. The delivered mixture increased its O_2 concentration at $-1^\circ C$ for the 60/40 cylinder and $-7^\circ C$ for the 50/50 one. We assumed that at these temperatures (not the 'pseudocritical' ones), the N_2O began to condense. Furthermore, if cylinders were allowed to rewarm to room temperature in the upright position the mixture 'layered' - the effect being to deliver an oxygen rich mixture at the beginning of their lives and an oxygen poor one at the end. We found that inverting the cylinders three times reformed the mixture. Alternatively, for very large cylinders, you could achieve the same thing by rolling them on the ground. Night temperatures are often lower than these, and to avoid the problem, as all examination candidates know, the cylinder must be stored indoors. But there is another safeguard - the demand valve used is a two stage one, the first stage being set at 200 psi. This means that when the cylinder pressure falls to this level gas flow ceases so there is no possibility of using the last bit of the mixture. This provides a useful additional safety device and useful extra profit for BOC.

Entonox today

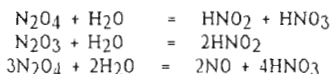
Today, everyone accepts Entonox and the initial problems we had with it are forgotten. It is used all over the world as a demand analgesic and nobody has produced a better one, although Mike Tunstall is looking at the effects of adding adjuvants to the mixture to increase its sedative properties. Entonox is even used in Canada with its very cold night temperatures. The USA was the only country where it was not accepted. The FDA, initially citing the cold winter night temperatures in the mid-west, has never passed Entonox. Of course, if it had been an American idea in the first place, I am sure there would have been no problem since they now, I believe, have their own version, 'Nitromox'. Perhaps it doesn't separate when cold! In conclusion, nitrous oxide/oxygen mixtures, however they are produced, have stood the test of time as the best, and quickest acting, safe demand analgesics available, and provided they are used for relatively short periods, have never been shown to have a detrimental effect on the patient or, indeed, on her attendants.

HIGHER OXIDES OF NITROGEN

Dr R Greenbaum

Consultant Anaesthetist, University College Hospital, London

The oxides of nitrogen other than nitrous oxide - the higher oxides, comprise a diverse range of reactive substances, free radicals, dimers and complexes. Examples include NO, NO₂, N₂O₄ and N₂O₃. These higher oxides react reversibly with each other and also react with water to produce hydrogen ions and nitrate and nitrite ions.



Nitric oxide (NO) is a free radical, boiling point 151.6°C. It is a widespread biological mediator and CNS messenger that is being intensely studied. The effects of nitric oxide are arterial vasodilation, pulmonary arterial vasodilation, reduced platelet adhesion and aggregation, smooth muscle relaxation and toxicity to pathogens.^{1,2}

The rate of oxidation of NO to NO₂ depends on the O₂ concentration and the NO concentration. This is illustrated in Table 1, which demonstrates that very dilute nitric oxide is very slowly oxidised.³

Table 1 OXIDATION RATE OF NO IN AIR AT 20°C

Concentration ppm	Oxidation time		
	25%	50%	90%
10,000 (1%)	8sec	24sec	3.6min
1,000 (0.1%)	1.4min	4min	36min
100	14min	40min	6hr
10	2.3hr	7hr	63hr
1	24hr	72hr	648hr

Nitrogen dioxide (NO₂) is a red brown pungent gas with boiling point 21°C. It exists mainly as the dimer dinitrogen tetroxide (N₂O₄).

2NO₂ = N₂O₄. At 25°C, 25% is monomer, and at 37°C 30% is monomer.

Dinitrogen trioxide (N₂O₃) is formed from the reaction of nitric oxide with nitrogen dioxide

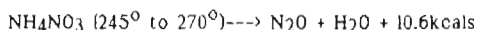
NO + N₂O → N₂O₃. At 25°C, 3% is N₂O₃.

Therapeutics and toxicity

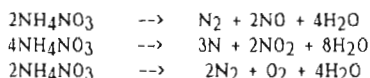
The higher oxides of nitrogen are relevant to medicine because of the use of nitric oxide as a therapeutic drug especially in neonatal persistent pulmonary hypertension and severe adult respiratory distress syndrome. They also comprise approximately 6% of air pollutant gas and are associated with worsening asthma even when the levels are as low as 2-3ppm. Larger concentrations damage alveolar cells, cause emphysema and interstitial fibrosis such as silo-fillers disease.

Toxic levels have been found in silo gas (0-150ppm nitric oxide and 0-360ppm nitrogen dioxide). Poisoning has also been caused in electroplating, arc-welding, photography and re-entry of an Apollo Space Shuttle.

The higher oxides of nitrogen have also occurred as an impurity in medical nitrous oxide which is produced by the controlled exothermic breakdown of ammonium nitrate.



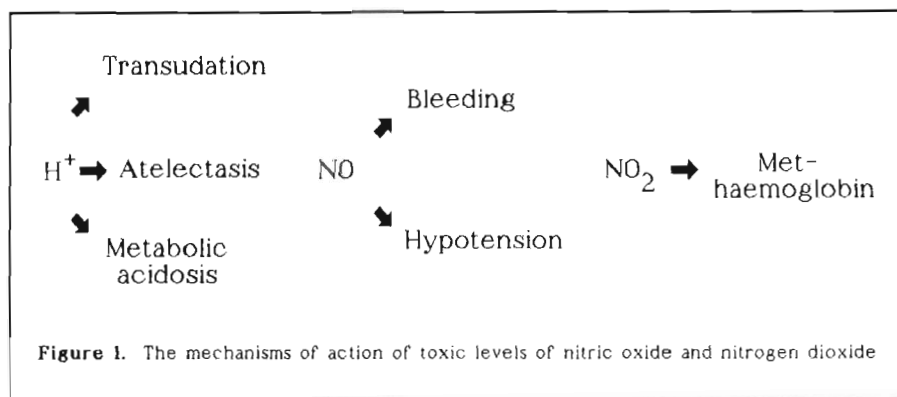
Decomposition of ammonium nitrate also forms ammonia and nitric acid and several other decomposition routes allow nitrogen, nitric oxide and nitrogen dioxide to be formed:



If the system temperature is carefully controlled, these alternative products account for less than 1% of the ammonium nitrate breakdown. The commercial production of nitrous oxide includes acid and alkali scrubbing of the gas and continuous testing of the product gas. Nevertheless, all safety systems can fail.

On the morning of 5 September 1966, two patients in Bristol inhaled nitrous oxide from a cylinder which was later found to be severely contaminated with nitrogen dioxide and nitric oxide. The first patient died, but the second was saved by the late Professor J Clutton-Brock recognising that the cyanosis resistant to oxygen therapy, hypotension and fall in lung compliance were caused by poisoning that had to be due to contamination of nitrous oxide with nitric oxide and nitrogen dioxide. Severe methaemoglobinaemia was also recorded.⁴ Similar events happened simultaneously to two patients in Plymouth.

A group headed by J F Nunn examined the effects of 2% nitric oxide and 2% nitrogen dioxide in the anaesthetised dog. Severe metabolic acidosis and pulmonary oedema were produced, plus severe hypotension and methaemoglobinaemia with both oxides of nitrogen.⁵ The mechanisms are shown in Fig.1.



The current interest in nitric oxide therapy therefore requires awareness of the risks of methaemoglobinaemia, airway inflammation and prolonged bleeding time, and the necessity for strict rules and precautions in its administration.

References

1. Frostell C. Nitric oxide inhalation - future drug or an invitation to disaster. Review article. *Paediatric Anaesthesia* 1994; **4**: 147-150.
2. Vallance P, Collier J. Biology and clinical relevance of nitric oxide. Fortnightly review. *British Medical Journal* 1994; **309**: 453-457.
3. Austlin AT. The chemistry of the higher oxides of nitrogen as related to the manufacturers storage and administration of nitrous oxide. *British Journal of Anaesthesia* 1967; **9**: 345-350.
4. Clutton-Brock J. Two cases of poisoning by contamination of nitrous oxide with higher oxides of nitrogen during anaesthesia. *British Journal of Anaesthesia* 1967; **39**: 388-392.
5. Greenbaum R, Bay J, Hargreaves MD, Kain ML, Kelman GR, Nunn JF, Prys-Roberts C, Siebold K. Effects of higher oxides of nitrogen on the anaesthetised dog. *British Journal of Anaesthesia* 1967; **39**: 393-404.

DR RUTH EVELYN MANSFIELD, MBE FFARCS 1902-1994 AN APPRECIATION

Dr D Howat

Dr Mansfield died at her home near Haslemere, Surrey, on 10 December, aged 92. A few hours before, she had attended the celebratory symposium recorded in these Proceedings where she spoke from the floor to give a brief account of seeing McKesson's technique of secondary saturation used at the Royal Dental Hospital over fifty years ago.

Ruth Webster was born on 1 August 1902. After attending Streatham Hill and Clapham High School for Girls, she studied medicine at King's College, London, and the Westminster Hospital, one of the few women accepted there immediately after the first world war. She married Leonard, an accountant, the year before she qualified in 1926 and it is reported that she was pregnant when she passed her finals. She spent the next seven years bringing up her children, working for a time as a clinical assistant at the Belgrave Hospital for Children in South London. She became house anaesthetist at the Westminster Hospital in 1935 and obtained the DA in 1936. Inspired by the late Sir Ivan Magill, she decided to make her career in anaesthetics.

Dr Mansfield worked in the Emergency Medical Service during World War II, at the Mayday Hospital, Croydon, and the Chest Unit at Horton Hospital near Epsom. In 1946 she became Assistant Anaesthetist at the Brompton Hospital and was made a Consultant when the National Health Service was introduced in 1948. In the same year she was awarded the Fellowship of the new Faculty of Anaesthetists of the Royal College of Surgeons.

She had considerable expertise in local anaesthesia for thoracoplasty, and had sessions at Milford Sanatorium, King George V Hospital, Godalming, King Edward VII Hospital Midhurst, and also visited Sully Hospital near Cardiff. In those days thoracic anaesthetists were not many in number and in great demand. She covered the whole field of lung, oesophageal and later intracardiac surgery, working with Lord Brock, Sir Clement Price-Thomas, and many other well-known surgeons.

Dr Mansfield wrote several papers on the control of secretions in lung surgery and designed a bronchoscope for endotracheal intubation. In 1967, she was co-editor of a textbook *Practical Anaesthesia for Lung Surgery*. She worked voluntarily for six-month periods at the Lady Templar Hospital in Kuala Lumpur, Malaysia, and at the Nazareth Mission Hospital in Israel.

After retiring from the Health Service in 1967, she spent ten years at the Christian Medical College Hospital, Vellore, in South India, introducing anaesthesia for intracardiac surgery there and making only brief trips home; for this work she was awarded the MBE in 1977. In 1979, at the age of 77, she went for two years to the Miraj Medical Centre, Maharashtra. In 1986 she was awarded the Pask Medical of the Association of Anaesthetists.

Dr Mansfield was a person who did good work unobtrusively. She and her husband were Nonconformists and did not drink or smoke, but never inflicted their views on others. They were kind and generous hosts, especially to junior colleagues and their families. Mrs.M, as she was known to all her colleagues, enjoyed playing tennis, gardening and swimming; the last two she pursued into her eighties. She always kept her interest in anaesthesia and was a regular attender at the meetings of the History of Anaesthesia Society, of which she was an honorary member and to which she gave two papers recounting her reminiscences.

Dr Mansfield's husband died in 1958. She is survived by her son Charles, a doctor, and her daughter Mary, an artist, as well as by seven grandchildren and six great-grandchildren.