THE EVOLUTION OF ANAESTHESIA

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ETHER

The discovery of di-ethyl ether has been attributed to Jabir ibn Hayyan, an Arabian philosopher who flourished in the eighth century and was a close friend of Ja'far al-Barmaki, the Wazir to Harun ar-Rashid, immortalized in the “Thousand and One Nights”. Similarly, Raymund Lull or Lully, a Majorcan alchemist of the thirteenth century, has also been credited with the discovery, but there seems to be no evidence to substantiate these claims. The curious reader is referred to an article, “The Discovery of Ether”, Anaesthesia (1949), 4, 188, for a fuller consideration of these persons.

The first unequivocal description of ether, under the name, “oleum vitrioli dulce” (“sweet oil of vitriol”), occurs in Conrad Gesner’s edition of the works of Valerius Cordus, published in Strasbourg in 1561 (De artificiosis extractionibus, Lib. 3, Cap. 12). A second, and more accurate, edition was prepared by Peter Condemberg ten years later. “Oil of vitriol” was the name of what we now call sulphuric acid; the “sweet oil” was obtained by the distillation of sulphuric acid and spirits of wine. Cordus advocated the internal use of ether in a dose of one to three drops in a moderate quantity of wine as a remedy for such diverse disorders as ulcer of the bladder and pneumonia.

In 1605, there appeared the first edition of Paracelsus’ Opera Medico-chemica sive paradoxa. It contains an account of the action of ether on domestic fowls. “Of all the extracts of vitriol, this particular one is the most important, being stable. Furthermore, it has an agreeable taste, so that even chickens take it gladly, and thereafter fall asleep for a long time, awakening unharmed. In view of the effect of this vitriol, I think it especially noteworthy that its use may be recommended for painful illnesses, and that it will mitigate the disagreeable complications of these.”

Paracelsus had died in 1541, and Cordus three years later, the works of both appearing posthumously. It is generally believed that ether was discovered about 1540, at which time Cordus and Paracelsus seem to have been together. It is, therefore, impossible to apportion the credit for the discovery between them.

Ether was occasionally synthesized during the next two centuries; thus, the Hon. Robert Boyle describes the process in his Experiments and notes about the producibleness of chymicall principles (1680); and Sir Isaac Newton also mentions it in his Optics (1704). It was not, however, until the German chemist, Froben (Frobenius) wrote An account of a spiritus vini aetherus in the Philosophical Transactions of the Royal Society in 1730, that the “sweet oil of vitriol” became well known or acquired its present name. The place of ether in medical treatment became established in 1743, probably because in that year there was published An account of the extraordinary medicinal fluid, called aether, by M(atthew) Turner, Surgeon, in Liverpool, who recommended the administration of two teaspoonfuls of ether in wine for various complaints, and also for headache, of which he writes, “In stubborn cases, it will likewise be serviceable to snuff a little of the ether up the nostrils, either alone or mixed with equal parts of lavender water, Hungary water or Brandy, or it may be convenient to apply a bit of linen rag, wetted with aether, up the nostrils.” In 1795, Richard Pearson published his Short account of the nature and properties of different kinds of airs, in which he stated that he had found that the inhalation of the vapour of ether by patients with phthisis was very beneficial; “It abates the hectic heat, relieves and often removes the dyspnoea, and promotes and often
improves the expectoration.” By 1805, Dr. John Warren of Boston, Massachusetts, father of Dr. John Collins Warren, had adopted Pearson’s treatment for phthisis; and Nysten’s Dictionary of Medical Sciences (1815) speaks of the inhalation of ether as familiarly known for mitigating the pains of colic.

The stupefying effect of nitrous oxide had been described in 1800 by Humphry Davy. In 1818, the Journal of Science and the Arts, published by the Royal Institution, contained the following anonymous statement, “When the vapour of ether mixed with common air is inhaled, it produces effects very similar to those occasioned by nitrous oxide... It is necessary to use caution in making experiments of this kind. By the imprudent inspiration of ether, a gentleman was thrown into a very lethargic state, which continued with occasional periods of intermission for more than thirty hours, and a great depression of spirits; for many days the pulse was so much lowered that considerable fears were entertained for his life”. A method of vaporization of ether by means of a bottle, into the upper part of which a tube could be introduced for a variable distance, was also described. In 1819, there appeared, in the Annals of Philosophy, a Memoire on sulphuric ether, by John Dalton, and this is the classical description of the chemical and physical properties of ether.

Christison, in the second edition of his work, On Poisons (1836) related the case of a young man who had been rendered completely insensible by the vapour of ether, but such occasional accidents did not deter people from indulging in the inhalation of ether, which was by now well known, especially in the United States of America, as an intoxicant, and so-called “ether frolics” became popular in that country. From 1839 to 1841, William E. Clarke of Rochester, New York, then a student, and later a physician in Chicago, held a number of such parties, and it has been said, on what authority is unknown, that W. T. G. Morton was one of his guests on these occasions. Emboldened by his experience, Clarke, in January 1842, at Rochester, administered ether on a towel to a Miss Hobbie, and one of her teeth was then painlessly extracted by a dentist named Elijah Pope. Neither Clarke nor Pope published an account of the transaction, which seems to have been the first occasion on which anaesthesia with ether was undertaken, for we may discount the note in the Edinburgh Medical and Surgical Journal of April 1847, which refers to a case of ether anaesthesia “thirty years” before.

During an “ether frolic” at Anderson, South Carolina, in 1839, a youth named Wilhite forced a negro boy to inhale ether until he became insensible. Wilhite is believed to have given an account of this experience to Dr. Crawford Williamson Long of Jefferson, Georgia, already accustomed to such diversions, who, in March 1842, persuaded a patient, from whose neck he was about to remove a tumour, to inhale ether until insensible. The operation was performed without pain and recovery was uneventful. The event was recorded by Long in his ledger: “James Venable, 1842. Ether and excising tumour, $2.00.” Two similar operations were subsequently performed on Venable, and Long also used ether on three other patients in the following two years, after which he gave up its use, nor did he publish any account of his discovery until after the first public administration of ether by Morton.

According to the report of a select committee of the American House of Representatives in 1852, “Late in the autumn of 1844, Dr. E. E. Marcy of Hartford, Connecticut, as appears from his own affidavit and that of F. C. Goodrich of Hartford, suggested to Dr. Wells to substitute sulphuric ether for nitrous oxide, and informed him of its known effects and how to make it. Marcy ‘administered the vapour of rectified sulphuric ether in my (his) office to a young man... and, after he had been rendered insensible to pain, cut from his hand an encysted tumour of about the size of an English walnut’.” A slight doubt is cast upon this statement by the fact that it was not until December 10, 1844, that Horace Wells became interested in nitrous oxide; however, the story is probably otherwise true. A Dr. E. R. Smilie of Boston also asserted to the same committee “that he had employed successfully an ethereal (sic) tincture of opium to subdue pain under the knife. He states that he applied this tincture by inhalation in the Spring of 1844; that he opened a serious abscess on the neck of the late Mr. John Johnson, while he was rendered unconscious of pain from the operation by this tincture”. This story has little appearance of truth.
The committee further stated that in March, 1846, there appeared, in the Paris Medical Gazette, "an account of remarkable experiments performed by M. Ducos, by ether, on animals, exhibiting most of the phenomena since witnessed in the human body".

In July 1847, when the "ether controversy" between Morton and Jackson was developing, Morton presented, through M. Arago, a mémoire to the Academy of Arts and Sciences at Paris. This account is probably substantially correct. He stated that, in the summer of 1844, he being then in dental practice and also studying medicine under Dr. Charles T. Jackson of Boston, he discussed with the latter the problem of destroying the nerve of a tooth. Jackson told him that, some years before, he had successfully extracted a tooth after applying ether topically, and provided Morton with a bottle of the liquid. Morton used it by direct application. Jackson, on one occasion, saw Morton use it unsuccessfully in this way, but made no suggestion that he should get the patient to inhale the vapour. Later, however, Jackson did tell him what was then known concerning the inhalation of ether, and Morton, reading the subject up, came to the conclusion that there was nothing dangerous in the method. He became ill, and, while in the country convalescing, experimented unsuccessfully with some ether, locally obtained, on animals and birds.

In the winter of 1844-45, Morton assisted Horace Wells in the unsuccessful demonstration of nitrous oxide at the Massachusetts General Hospital. Morton's interest in ether was reawakened in the Spring of 1846 when one of his dental students, Thomas R. Spear, told him of his experiences at "ether frolics". Morton then administered ether to his dog, a water spaniel, "inserting his head in a jar having sulphuric ether at the bottom. This was done in the presence of two persons at my house at West Needham, where I reside during the summer months. After breathing the vapor for some time, the dog completely wilted in my hands. I then removed the jar. In about three minutes he aroused, yelled loudly, and sprung some ten feet into a pond of water". In August, Morton inhaled ether himself from a handkerchief, and also gave it, without success, to his two students, Spear and Leavitt.

Late in September 1846, Morton had the idea that the results might be more successful if he administered the vapour from a gas bag. Accordingly, he went to borrow a bag from Jackson whom he asked if it were possible to give ether vapour in order to relieve pain. Jackson said that it was, spoke of "ether frolics", advised him to use Burnett's ether, since this was the purest, and also gave him a flask and glass tube, considering this better than a gas bag. Morton now tried again the effect of ether on himself, with complete success.

On September 30, in the evening, a man called Eben Frost "came in, suffering great pain and wishing to have a tooth extracted. He was afraid of the operation, and asked if he could be mesmerized. I told him I had something better, and, saturating my handkerchief, gave it to him to inhale. He became unconscious almost immediately. It was dark, and Dr. Hayden (a dentist) held the lamp, while I extracted a firmly rooted bicuspid tooth. There was not much alteration in the pulse, and no relaxation of the muscles. He recovered in a minute, and knew nothing of what had been done to him".

Morton next called on Jackson, told him what he had done, and asked for a certificate to the effect that it was harmless; this Jackson refused to give. Morton also obtained permission to demonstrate his discovery at the Massachusetts General Hospital; meanwhile, he used ether several times in his surgery, but not very successfully. One child, who vomited, was pronounced by a physician to have been poisoned, and the patient's friends threatened legal proceedings.

On the morning of October 16, 1846, Morton obtained a glass inhaler from an instrument maker called Chamberlain, and used this on the patient, Gilbert Abbott, with that success which has since become so famous, and which proved the efficacy of ether as a reliever of pain during surgical operations. Morton subsequently administered ether at the hospital and elsewhere on frequent occasions.

On October 23, 1846, Jackson called on Morton and, having heard that a patent was being taken out, asked for payment for his share in the discovery. Eventually, Morton allocated a 10 per cent share in the patent to Jackson, which would seem to have been a generous award. Morton's account is corroborated at a number of points by
the evidence of his patients and colleagues and is probably reasonably accurate.

The subsequent efforts of Jackson to obtain the full credit for the discovery need not detain us here: it is sufficient to record that his pertinacity in this direction led to the defeat of Morton’s claims in the United States Senate so that the discoverer, whose patent had been tacitly ignored by the government, never received any financial reward.

News of Morton’s successful demonstration soon spread across the Atlantic; H. J. Bigelow’s letter, written on November 28, 1846, reached Boott in London in three weeks. The latter immediately sent a communication to the Lancet and wrote to Robert Liston, then Professor of Clinical Surgery in the University of London. On December 19, under Boott’s direction, his niece, Miss Lonsdale, had a tooth extracted by a Mr. Robinson. Ether was administered by means of an apparatus made by Hooper. Boott wrote again to the Lancet, describing the procedure, “the whole process of inhalation, extracting and waking was over in three minutes”, he said.

On December 21, 1847, Liston, at University College Hospital, performed two operations under ether anaesthesia, an amputation through the thigh, and an avulsion of the toe-nail. The apparatus employed, which was similar to Hooper’s, was designed by an instrument maker called Squire, who probably administered the anaesthetics, and who subsequently developed a practice as an “etherizer”. The success was such that the future of anaesthesia was assured.

Naturally, it was in London that the new idea flourished most in Europe, but the news spread: in December it had reached France; on the 24th de Lamballe had a successful anaesthetic at the Hôpital St Louis, and on January 12 J. F. Malgaigne described five anaesthetics, given by himself, before the Académie de Médecine in Paris. He used to administer ether through a tube inserted into the nostril, and this technique won a certain popularity in France, but was soon displaced by Charrrière’s apparatus, which was an improved version of Hooper’s and Squire’s inhalers.

The successful use of ether anaesthesia for surgical operations stimulated James Y. Simpson, Professor of Midwifery in the University of Edin-
dental, but his fertile brain was ready to respond to the stimulus, and the assiduity and eagerness with which he turned to the investigation of the new science are revealed in his writings: it is not too much to say that he was the first to understand and give clinical appreciation to the physical properties of ether vapour and its pharmacological effects. Among other things, his book contains a description of the stages of ether anaesthesia, an accepted classification which was to remain the basis of clinical anaesthesia with ether until it was modified by Guedel in 1920. Perhaps more important was Snow’s influence on the design of apparatus; he was later (1858) to write:

“When the inhalation of ether was first commenced, the inhalers employed consisted generally of glass vases containing sponge, to afford a surface for the evaporation of the ether. Both glass and sponge being very indifferent conductors of caloric, the interior of the inhalers became much reduced in temperature, the evaporation of ether was very much checked, and the patient breathed air much colder than the freezing point of water, and containing very little of the vapour of ether. On this account, and through other defects in the inhalers, the patient was often very long in becoming insensible, and, in not a few cases, he did not become affected beyond a degree of excitement and inebriety.”

In addition to facilitating the evaporation of the ether by maintaining it at a nearly constant temperature, Snow’s inhaler was designed with tubes of a sufficient diameter to minimize the resistance to airflow.

The introduction of chloroform towards the end of 1847 led to the virtual abandonment of ether in many parts of the world. The North American continent, however, generally remained faithful to ether, and it was there that, in 1853, Squibb revolutionized the commercial manufacture of this highly inflammable substance. In 1866, B. W. Richardson invented his ether spray, at first intended to be used with a volatile hydrocarbon called rhigolene, for the production of local anaesthesia by freezing.

The revival of ether on the Continent began in 1877 with the work of Gustave Julliard of Geneva, who adopted a semi-open technique, but it was
not until the late 1890's that the use of ether became general. In 1884, Mollière of Lyons resuscitated the rectal administration of ether, using, however, the technique of insufflation of the vapour instead of instillation of the liquid, as in the earlier methods.

By the beginning of the twentieth century, ether was firmly re-established and the famous nurse-anaesthetist, Alice Magaw, was able to report 14,000 cases in 1906, but the end was in sight. In 1910 W. D. Gatch developed an apparatus for the administration of nitrous oxide and ether simultaneously, also permitting the use of fractional rebreathing, of which he was a confirmed advocate. Teter, Gwathmey and others developed similar machines, and the use of a stream of nitrous oxide and oxygen to vaporize ether came into fairly general use at the time of World War I. The first Boyle machine, the outcome of a visit by H. E. G. Boyle to the United States of America, appeared in 1917, and his apparatus, with modification, is now that which is most commonly used in this country.

The cost of the new machines was considerable and, in Britain at least, the general standard of anaesthesia did not develop rapidly in the inter-war period. Ether, administered by open drop or by means of the Clover Inhaler, continued to be used alongside the "nitrous oxide with minimal ether" technique, a method in which the word "minimal" was interpreted very broadly. In 1920 Arthur E. Guedel issued the revised description of the stages of anaesthesia, including the subdivision of the third stage into four planes, and emphasizing the respiratory changes occurring with increasing depth of ether anaesthesia.

The rectal route once again became popular with the introduction of the "colonic oil-ether" method of Gwathmey in 1913, and this continued to be used, in obstetrics at least, until about ten years ago.

Some other drugs, rather similar to di-ethyl ether, have been introduced from time to time. B. W. Richardson, for example, experimented with a great many, as did Lawson Tait. One interesting development was the "construction" of divinyl ether, suggested by Leake and Chen in 1930. The successful use of ethylene, a rather weak anaesthetic, gave rise to the idea that an ether composed by the conjunction of two molecules of ethylene would prove a satisfactory compound. The drug was, at last, manufactured after considerable difficulty, and, while it achieved some measure of success and is still employed, especially for children, its influence on the discovery of new plastics was probably of much greater importance than the part which it has played in anaesthesia. Krantz and his co-workers have also sponsored the introduction of various ethers in the last twenty years, chief of which is N-methyl propyl ether, but none has proved popular.

Since World War II, the introduction of the relaxants and the extended use of the surgical diathermy apparatus have militated strongly against the use of ether, and it is now unusual for this substance to be used as the sole, or even as the main, agent of anaesthesia. Nevertheless, ether is still an important tool in the hands of the anaesthetist, and it will long remain so. More than a hundred years of almost continuous use have led to the building up of a body of experience with ether which is probably greater than that of any other drug used by the medical practitioner. Because of this knowledge, and because of its inherent property of safety, the experienced anaesthetist will often make use of ether in cases in which the patient's physical condition gives rise to alarm, and, should some great emergency necessitate the use of a number of untrained, or only partly trained, anaesthetists to cope with a sudden influx of casualties, ether will again be used, as it was by the inexperienced Morton, and with equal safety and success.

NITROUS OXIDE

Nitrous oxide was discovered by Joseph Priestley, whose pioneering experiments with gases have ensured him an honourable place in the history of science. He was the son of a cloth-dresser, and was born in London in 1733. After attending a Dissenting Academy at Daventry, he became a Unitarian minister, serving at Needham Market, Nantwich, Mill Hill (Leeds), Birmingham and Hackney. In 1794 he emigrated to America, where he died ten years later in his 71st year. Priestley wrote a number of religious works, and also dabbled in political affairs. His reply to Burke's Reflections on the French Revolution led to the burning of Priestley's house by the mob (1791).
It was during his stay in Leeds that he became interested in the nature of air, and his discoveries earned him the Fellowship of the Royal Society, of the French Academy of Sciences, and of the St. Petersburg Academy. The assistance of the Earl of Shelburne, who fitted up a laboratory for Priestley at his house at Calne, enabled him to pursue his experiments for some time without interruption.

Throughout his life, Priestley was bedevilled by the Phlogiston Theory of Stahl, and he thus never came to understand the nature of the chemical reactions which he demonstrated. The discovery of nitrous oxide (dephlogisticated nitrous air) is described in Priestley’s Experiments and Observations on Different Kinds of Air (1775); unfortunately the event is undated, but it ensued upon the discovery of nitric oxide (nitrous air), and is therefore to be related to the second half of 1772 or, at latest, early 1773.

Nitrous oxide remained a chemical curiosity until its further investigation was undertaken by Humphry Davy. This eminent scientist had been born at Penzance in 1778; in 1795 he was apprenticed there to a surgeon called Borlase. In 1798, he became superintendent of the Pneumatic Institute, opened in that year at Clifton, by Dr. William Beddoes, whence he moved to the Royal Institution in 1801. He became a Baronet in 1818 and was elected President of the Royal Society two years later. He died in 1829, at the age of 55. Davy’s interest in chemistry seems to have begun at Penzance in 1797, and it was there that his attention was drawn to nitrous oxide on reading an essay by Dr. S. Latham Mitchell of New York, in which nitrous oxide was denounced as the cause of febrile disorders. Davy prepared the gas, inhaled it, and, noticing its intoxicating effect, renamed it “Laughing Gas”. This investigation was the direct cause of Davy’s appointment to the Pneumatic Institute; while there, he pursued his researches with the gas, and, in 1800, published his findings in the important book, Researches Chemical and Philosophical chiefly concerning Nitrous Oxide . . . and its respiration, wherein he described the analgesic effect of nitrous oxide and suggested that it might be used during surgical operations “in which no great effusion of blood takes place”.

Davy’s advice fell on deaf ears, but the lay-public exhibited an increasing interest in “Laughing Gas”, an interest which was catered for, especially in the United States of America, by itinerant chemists. The medical profession held aloof from the gas, and there is no evidence that it was used by Hickman or anyone else until 1844. The actual use of nitrous oxide as an anaesthetic occurred in the following way. An itinerant chemist, Gardner Quincy Colton, visited the town of Hartford, Connecticut, and, on December 10, 1844, demonstrated the intoxicating effects of “Laughing Gas”. In the course of the demonstration, members of the audience were allowed to inhale the gas, and one of these, while still under the influence of it, knocked his shin against a bench with sufficient violence to draw blood. This incident was observed by a dentist, Horace Wells, who was also in the audience, and who noticed that, although the injury must have been extremely painful, the victim appeared to be completely oblivious to it; indeed, when Wells apprised him of it, he was at first incredulous. Wells immediately realized the significance of the incident and, on the following morning, he permitted Colton to administer nitrous oxide to him while another dentist, John M. Riggs, extracted one of Wells’ teeth. Riggs has another claim to fame for, 32 years later, he was to introduce a treatment of pyorrhoea alveolaris which was so successful that the disease came to be known in the United States as “Riggs’ Disease”.

The experiment of December 11, 1844, was a complete success. Emboldened by it, Wells used nitrous oxide on about a dozen patients, and Riggs also made use of it, the latter on one occasion extracting six teeth at a sitting, without causing any suffering. Wells now communicated his discovery to the chief surgeon at the Massachusetts General Hospital, John Collins Warren (1778–1856), an old student of Astley Cooper and of Dupuytren. Warren’s father, John Warren (1753–1815), had preceded his son as professor of surgery at Boston, and, it will be recalled, had advocated the use of the inhalation of ether in the treatment of phthisis. Somewhat reluctantly, John Collins Warren gave permission for Wells to address the students on his discovery and to demonstrate the anaesthetic effects of nitrous oxide on a volunteer. Unfortunately, the demonstration proved a fiasco: anaesthesia was insuf-
cient, and the volunteer emitted a scream as the tooth was extracted. Wells left the hospital amid the jeers and boos of the students.

The subsequent career of the discoverer of anaesthesia with nitrous oxide was short and tragic. Giving up dental practice, it is said after a fatality, he followed various occupations, became interested in chloroform to such an extent as to become an addict, and finally, in 1848, he took his own life in the Tombs prison at New York, whither he had been lodged following an act of an insane nature: at the behest of a chance acquaintance, he had thrown vitriol at a prostitute. The French Academy of Medicine belatedly acknowledged the importance of his contribution to the discovery of anaesthesia, but news of the award of a gold medal to him did not arrive in America until after his death.

The failure of Wells to demonstrate publicly the anaesthetic action of nitrous oxide led to the abandonment of its use. It had, however, one good result, for it caused W. T. G. Morton, who had been present at the fiasco, to turn his attention to more effective agents, and so to the discovery of the action of ether, the introduction of which obscured for a time the potentialities of the weaker drug.

One man alone seems to have retained his belief in the efficacy of nitrous oxide anaesthesia, and that man was Colton. It is true that both Bigelow and Nunneley gave the gas a trial in 1848: the former thought it inferior to ether, while the latter, who only experimented with it on animals, considered it to be so short acting as to be useless, and was worried by the cyanosis produced. Colton, however, remembered the success which he had had with Horace Wells and, continuing his career as a lecturer, frequently referred to that incident. In 1862, a lady who had attended one of Colton's demonstrations, asked him to administer gas to her for the extraction of teeth. The dentist, Dunham by name, was so impressed that he began to use this agent in his own practice, and, a year later, Colton gave up his lecturing and, in association with Dr. J. H. Smith, opened the Colton Dental Association in New York. Within a very short time, nitrous oxide became the accepted anaesthetic for dental extraction in the United States of America.

News of this development naturally came to Britain, and a few experiments were carried out, notably by Rymer at the National Dental Hospital. The results were encouraging, but little notice was taken, and the introduction of nitrous oxide anaesthesia to Britain was delayed.

One of Rymer's difficulties had been his inability to procure sufficient supplies of the gas. This problem was solved in America by A. W. Sprague of Boston, Mass., who devised an apparatus for the manufacture of nitrous oxide by heating ammonium nitrate, passing it through wash-bottles, and storing it in a small gasometer, from which the gas could be used direct or be drawn off into bladders for use outside the dentist's home. The apparatus was costly, but easy to manage, and gave satisfactory results.

In 1867 Colton demonstrated his apparatus and method at Paris, where he so impressed an American dentist, T. W. Evans, that the latter came to England in the following year, bringing with him Sprague's apparatus: he gave a series of demonstrations at the National Dental Hospital and elsewhere. Evans succeeded in persuading several dentists, notably Alfred Coleman, to make use of the gas, but there was some opposition from B. W. Richardson, who believed nitrous oxide to be unsafe. Following his lead, it was proclaimed that anaesthesia resulted solely from asphyxia when this gas was used, a conclusion which was disproved almost at once by Sanderson and Murray at the Middlesex Hospital, who compared the action of nitrogen with that of nitrous oxide, and showed that, with the latter, consciousness was lost sooner and before cyanosis was pronounced. Later in 1868, the Odontological Society formed a Committee to examine the question, but its reports were disappointing. Meanwhile, Joseph Clover turned his attention to the new agent, and modified his chloroform apparatus (really, Snow's apparatus) for use with nitrous oxide.

The extending use of nitrous oxide in 1868 led to the need for some simpler method for its distribution. The difficulty was overcome by compression into cylinders, not at first under sufficient pressure to cause liquefaction. Cylinders of compressed air had been used as early as 1833 by the Vienna fire-brigade, and in 1856, the Medical Pneumatic Apparatus Co. of London was offering nitrous oxide and other gases in this form, but without attracting much attention. Following the lead of
the Editor of the *British Medical Journal*, Ernest Hart, both Coxeter’s and Barth’s were providing compressed nitrous oxide in 1869, and, almost at once, the gasometer was abandoned, and the gas was taken direct from the cylinder to the patient. The liquefied gas became available on the American market in 1873.

By the end of 1868, nitrous oxide anaesthesia was firmly established in dental practice throughout Europe and America, and already it had become the custom to prolong anaesthesia by permitting the patient to breathe a limited amount of air. Early in 1869, Professor E. Andrews of Chicago described the use of a mixture of nitrous oxide and oxygen, and similar experiments were also made in England. It was at this time that Alfred Coleman introduced the economical use of nitrous oxide by rebreathing, passing the exhaled gases through slaked lime; this was the first use of carbon dioxide absorption in anaesthesia, although the principle had been understood since the days of the Abbé Fontana.

In 1871, at the time of the reintroduction of ether into English anaesthetic practice, Clover described his nitrous oxide-ether sequence: he developed various types of apparatus for this purpose, all of which were extremely successful, and this method of anaesthesia continued to be much used for some sixty years.

At this time, when the clinical use of nitrous oxide was increasing, and when the anaesthetic action of the gas had already been proved by Sanderson and Murray, French physiologists again put forward the theory that the anaesthesia with this agent was the result of asphyxia, and this remained the orthodox belief until the important work of Paul Bert, who showed that nitrous oxide was a true anaesthetic. In 1878, Bert read a paper to the French Académie des Sciences on the harmlessness of prolonged anaesthesia with nitrous oxide. He said:

> "The fact that nitrous oxide must be administered pure indicates that, in order to be absorbed by the organism in sufficient quantity, the tension of the gas must be equal to one atmosphere. In order to achieve this at normal pressure, the gas must be in the proportion of 100 per cent. But let us suppose that the patient is placed in an apparatus where the pressure can be increased to two atmospheres; then one could submit him to the desired tension by making him inhale a mixture of 50 per cent nitrous oxide with 50 per cent air. Thus one could achieve anaesthesia while maintaining the normal quantity of oxygen in the blood; and it follows that the normal conditions of respiration would be preserved. This is what, in fact, has been done; but I must add that, up to the present, I have only experimented upon animals."

Bert’s hypothesis was first tested in the following year. The pressure used was 920 mm Hg, an increase of rather more than 20 per cent of the normal; nitrous oxide and oxygen were given in the proportions of 85 and 15 per cent respectively. The result was so satisfactory that a mobile pressure chamber was constructed, but this failed to stand the test of time. Although the anaesthesia was excellent, the cost and complication of the apparatus caused it to be abandoned in the early 1880s. Bert’s original hypothesis was, however, borne out by the work of Faulconer, Pender and Bickford in 1949 (*Anesthesiology, 10, 601*).

About this time, the Russian obstetrician, S. Klikowitch, introduced nitrous oxide and oxygen as an analgesic in labour, a method which has found much favour in Scandinavia, and which led, indirectly, to the invention of a gas-air analgesia apparatus by Minnitr in 1934, self-administration of the gases being advocated by A. E. Guedel in 1912. Minnitr’s apparatus had the advantage that it could be used by relatively untrained midwives. In 1883, Bert had turned his attention also to the administration of nitrous oxide and oxygen mixtures at normal pressure, and similar work was done by a Viennese dentist, H. T. Hillischer, who, a few years later, produced an apparatus in which the percentage of nitrous oxide and oxygen could be regulated.

Meanwhile, other methods of prolonging nitrous oxide anaesthesia were being sought. Coxon in 1888 used a stream of gas directed into the patient’s mouth during dental extractions; in 1898, Coleman described the nasal mask, a method of administration, however, which both he and Clover had used many years before and which is substantially the same as that employed to-day; in the same year, Hilliard described the use of a naso-pharyngeal tube for the administration of gas during dental procedures.

It was Hillischer’s apparatus which stimulated Hewitt to construct a more portable and more easily regulated apparatus. Before 1893, Hewitt had designed an apparatus for administering nitrous oxide, employing a special stop-cock by which the patient could be made to rebreathe or
not, as desired. His nitrous oxide-oxygen apparatus embodied this valve, and was provided with two reservoir bags, one for oxygen and one for nitrous oxide, which were to be kept equally distended by manipulation of the foot-keys controlling the cylinder outlets. The two reservoir bags were separated from the stop-cock by a regulator which permitted a variable proportion of the gases to reach the patient by altering the sizes of the orifices. A modified regulator and stop-cock were described in 1897. Some fifty years later, R. R. Macintosh produced a somewhat similar apparatus, differing from Hewitt's in that, in order to equalize the pressures between the two bags, the oxygen reservoir was placed within the nitrous oxide bag.

Nevertheless, in spite of these developments, in 1901 Hewitt was still advocating the use of a gasometer filled with known quantities of nitrous oxide and oxygen for administering a constant mixture. The focus of development now shifted to the United States where anaesthetic apparatus underwent considerable improvement during the first two decades of the twentieth century. The first machine was designed by S. S. White; it appeared in 1899 and was essentially similar to Hewitt's apparatus. Three years later, C. K. Teter of Cleveland produced another machine along rather similar lines, but incorporating a device for warming the gases, and an ether vaporizer, a device in which he had been preceded by Coleman. In 1906, the Clark apparatus appeared, again incorporating a proportional regulator. This machine may be regarded as the direct ancestor of the first McKesson apparatus, which appeared in 1910, the brain-child of Elmer I. McKesson of Toledo, Ohio. This machine, which has undergone many modifications, was the first of the intermittent flow machines. McKesson introduced fractional rebreathing in the following year; his Naragraf apparatus appeared in 1930, and is still a popular machine in dental practice.

At the same time that McKesson was perfecting his mixing valve (1910), Boothby and Cotton opened the door for the modern continuous flow apparatus by employing a water sight-feed flow-meter. This was somewhat unwieldy, and was improved by J. T. Gwathmey in 1912. Boothby and Cotton also introduced the reducing valve into anaesthetic practice. Other apparatus was designed by Gatch, Heidbrink and Foregger soon afterwards.

American developments aroused the interest of H. E. G. Boyle in this country: his first apparatus was designed in 1917. After a continuous series of modifications, this apparatus is still the most popular machine in the British Isles. The Walton intermittent-flow machine was designed in 1925, while Magill's apparatus appeared three years later. This latter apparatus was fitted with Siebe Gorman dry flowmeters in 1931, and with rotameters in 1937. These latter had been used in industry for some years and their value to anaesthetists was realized first by Magill and, soon after, by Mr. Salt of the Nuffield Department of Anaesthetics at Oxford.

The gas ethylene is somewhat similar as an anaesthetic to nitrous oxide; although rather more potent, it has the disadvantage that it is inflammable. Its anaesthetic properties were first noticed by Luckhardt and Thompson in 1918, and it was introduced into clinical practice five years later, when it immediately became popular in the United States of America. It has not, however, achieved a similar popularity in this country.

This section must close on a more sombre note. After the extensive use of nitrous oxide with remarkable success, especially for dentistry, for three-quarters of a century, the warning of the dangers of anoxia was first sounded by C. B. Courville (Untoward Effects of Nitrous Oxide Anaesthesia, California, 1939). Experience has proved the truth of Courville's contentions, and it is now fully realized that nitrous oxide anaesthesia must not be accompanied by reduction in oxygen intake. This has led to the supplementation of nitrous oxide for almost all procedures, a technique which reached its apogee after the introduction of the relaxants. The satisfactory results obtained by this combination led to an extension of its use to the treatment of tetanus, and, once again, a warning has been sounded, this time by H. C. A. Lassen and his associates (Lancet, 1956, 1, 527), who have shown that prolonged anaesthesia with nitrous oxide may cause acute aplasia of the bone-marrow. Nevertheless, nitrous oxide is still one of the most valuable anaesthetic agents we possess, and its future place in anaesthesia would seem to be assured for many years to come.