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President of the Ulster Medical Society 2008–09

Presidential Opening Address
Ulster Medical Society
9th October 2008

CLOUDS OF UNKNOWING

This is the Coat of Arms of the College of Anaesthetists in Dublin granted to the College in 1999 (fig 1). In central position, representing anaesthesia is a shield containing poppy heads. The cloud above

Fig 1. Coat of Arms of the College of Anaesthetists

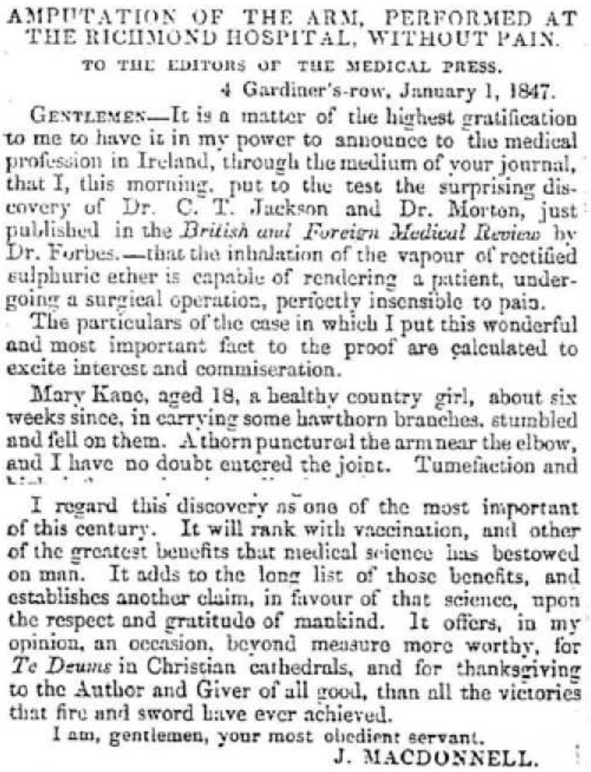
represents the downwards drift to unconsciousness with the healing hand of the physician in attendance. The cloud might have another interpretation for there can hardly be a treatment in medicine which is so widely applied and yet so little understood. The supporters are unusual in heraldry taking the form of dolphins and these provide a link to one of the founders of this Society, James MacDonnell (fig 2a) whose family coat of arms also bears this heraldic symbol (fig 2b).

As most of you will know James was a son of the Glens and the first of a family of doctors all of whom rose to distinction in different ways. His thesis entitled ‘On the Drowned’ is the first formal account of resuscitation methods, and perhaps he might have been attracted to emergency medicine or even anaesthesia, had he lived a generation later. As it happened, it was his surgeon son, John, who administered the first anaesthetic to a patient in Ireland, at the Richmond Hospital in Dublin.

Fig 2. Bust (left) and coat of arms (right) of James MacDonnell

MacDonnell broke the news in a letter to the Medical Times on New Year’s Day 1847 (fig 3a, 3b). It was not just a New Year; it was indeed a New Dawn. The details of the case were these: An 18 year old girl from the Drogheda area, Mary Kane, had been carrying hawthorn branches when she tripped and a thorn punctured her elbow. Over some weeks this became septic to the point where it threatened her life and the only recourse was amputation. MacDonnell had obviously heard about the new discovery and must have thought that Mary Kane being a strong young country girl would be an ideal subject. One or two days before administering the ether, MacDonnell decided to ‘ascertain on myself’, as he put it, the effects of the vapour and was assisted in this by a colleague, surgeon Alexander McDonnell. ‘I rendered myself unconscious for some seconds, five or six times’. On the day of surgery itself, it took more than one attempt to get it right and we can but imagine the scene and the sense of relief, when at the end, Mary Kane opened her eyes. Far from congratulating himself, MacDonnell concludes his letter with great humility, writing, ‘It offers in my opinion an occasion beyond measure more worthy for Te Deums in Christian Cathedrals…than all the victories that fire and sword have ever achieved’. Te Deum Laudamus indeed!

The synthesis of ether was first described in modern times by the German apothecary Valerius Cordus in 1540. He called it “sweet oil of vitriol”.



AMPUTATION OF THE ARM, PERFORMED AT THE RICHMOND HOSPITAL, WITHOUT PAIN.

TO THE EDITORS OF THE MEDICAL PRESS.

4 Gardiner's-row, January 1, 1847.

GENTLEMEN—It is a matter of the highest gratification to me to have it in my power to announce to the medical profession in Ireland, through the medium of your journal, that I, this morning, put to the test the surprising discovery of Dr. C. T. Jackson and Dr. Morton, just published in the *British and Foreign Medical Review* by Dr. Forbes.—that the inhalation of the vapour of rectified sulphuric ether is capable of rendering a patient, undergoing a surgical operation, perfectly insensible to pain.

The particulars of the case in which I put this wonderful and most important fact to the proof are calculated to excite interest and commiseration.

Mary Kane, aged 18, a healthy country girl, about six weeks since, in carrying some hawthorn branches, stumbled and fell on them. A thorn punctured the arm near the elbow, and I have no doubt entered the joint. Tumefaction and

I regard this discovery as one of the most important of this century. It will rank with vaccination, and other of the greatest benefits that medical science has bestowed on man. It adds to the long list of those benefits, and establishes another claim, in favour of that science, upon the respect and gratitude of mankind. It offers, in my opinion, an occasion, beyond measure more worthy, for *Te Deums* in Christian cathedrals, and for thanksgiving to the Author and Giver of all good, than all the victories that fire and sword have ever achieved.

I am, gentlemen, your most obedient servant.

J. MACDONNELL.

Fig 3. Extracts from the Medical Times letter

Maybe it's too far-fetched to imagine that this gave rise to the expression 'Sweet Dreams'. Raymond Lully, a 13th Century alchemist almost certainly came across it before this and probably many others. The basic ingredients are wine and sulphuric acid. We've always had wine and sulphuric acid was synthesised by the Assyrians as early as the 7th century BC. It is, therefore, conceivable that ether was available to ancient civilisations.

In modern times, in Europe, the Swiss physician-alchemist, Paracelsus, observed the narcotic effects of ether in chickens. He noted that they "undergo prolonged sleep and awake unharmed". Unfortunately, Paracelsus failed to grasp ether's potential. Inimical to the potential was the concept. Henry Hickman (1800–1830) was a young Shropshire GP (fig 4), who had graduated from Edinburgh about 50 years after James MacDonnell. He had no knowledge of ether but in 1825 he suggested in a letter to a local newspaper that 'suspended animation' might be used as a means of reducing pain during surgery. He had developed a technique which involved asking the patient to re-breathe from a bag. Taken to extremes rebreathing will produce narcosis and this was the basis for Hickman's suggestion, although of course he didn't know the physiological basis for it. Needless to say, his results were not entirely satisfactory and he was roundly denounced in a letter to the Lancet in September 1826, under the caption ' Surgical Humbug'. Hickman's patients were described as being 'doomed to come under his care', that he was a disgrace to his profession, dishonourable, and a 'quack'. The correspondent signed himself off, not entirely honourably, as 'Antiquack'.

Fig 4. Henry Hickman

Crawford Long (1815–1878) was an American GP practicing in Jefferson, then a remote outpost in the southern state of Georgia. Long is now credited as being the first doctor to administer ether as a general anaesthetic to a patient for a surgical operation. It took place in 1842. Had he announced his initial case report in the literature, he might now be hailed as the discoverer of anaesthesia. On the other hand he might have attracted a torrent of abuse like Hickman, and shortened his life. For whatever reason, Dr Long left the first public demonstration of ether anaesthesia to others.

The first successful public demonstration of ether anaesthesia took place on 16th October 1846 in what has come to be known as the 'Ether Dome' in the Bulfinch Building of the Massachusetts General

Hospital in Boston (fig 5). The following is a paraphrased account of what took place:

On Oct. 16, 1846, in the operating theater on the top floor of the building, one of the greatest moments in medicine occurred., William Morton, a Boston dentist, demonstrated the use of ether during surgery, ending the indescribable pain — and the overwhelming dread — that had been associated with the surgeon 's knife.

Using a specially designed glass inhaler containing an ether-soaked sponge, Morton, administered the anesthetic to Gilbert Abbott, a printer who had come to the MGH for removal of a vascular tumor on his jaw. After several minutes, Abbott was rendered unconscious. John Collins Warren one of the most widely respected surgeons of that time, removed the tumor. Upon wakening, Abbott informed the curious and skeptical physicians and medical students in the theater that he had experienced no pain.

Fig 5. Mass. General Ether Dome

As the patient was carried from the operating theatre, Warren turned and faced the incredulous onlookers, remarking as he did so, "Gentlemen, this is no humbug," a suitable riposte to the scurrilous Surgical Humbug letter penned some 20 years earlier by Antiquack. News of the discovery spread quickly, and within days it was hailed in the popular press as the "greatest gift ever made to suffering humanity." In the case of ether anaesthesia, the species jump from chicken to man had taken 300 years.

The first recorded use of ether in Belfast was on 21st January 1847 for the amputation of the arm of a young woman. The next day the Belfast Newsletter published a detailed description of the proceedings in which it was stated that 'her only intelligence of the operation was being sawn through'. The ether was probably administered by Dr Horatio Stewart for surgeon Alexander Gordon who later became the first Professor of Surgery at The Queen's University.

Although ether may have been, in John MacDonnell's words, 'the greatest gift ever made to suffering humanity' it was difficult to use well. (fig 6). Stewart and Gordon would have been feeling their way, trying as best they could to avoid cyanosis without the aid of oxygen or any knowledge at all as to how to maintain a patent airway, or avoid aspiration. These early ether anaesthetics must have been sporting affairs to say the least and no doubt some patients succumbed. One surgeon, Syme, in Edinburgh said of ether: 'It will not do', preferring to do his amputations without it. His patients, had he asked them, might have taken a different view.

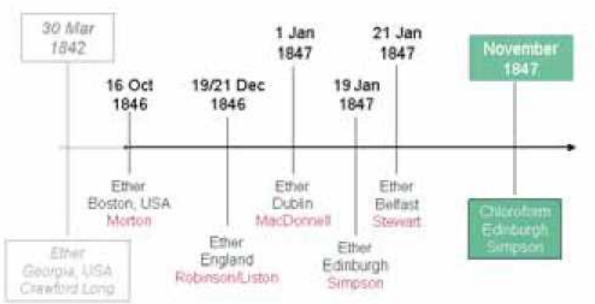


Fig 6. Early chronology of Ether and chloroform

By way of a summary, within 10 weeks of the Boston demonstration, ether was being used London in UCL, surgeon Robert Liston remarking that 'this Yankee Dodge beats mesmerism hollow'. Within a month of this, ether had reached Dublin, Edinburgh and Belfast. The world's first chloroform anaesthetic was to follow towards the end of 1847.

James 'Young' Simpson (fig 7), an Edinburgh man, entered the University at the age of 14 years, and graduated MD in 1832 at the age of 21 years. Seven years later he became Professor of Midwifery at Edinburgh University, a post he held for over 30 years. Hence he was nicknamed 'young' as in 'young Simpson'. So ubiquitous did this usage become that he incorporated 'Young' into his name. Simpson's many notable achievements in obstetrics were to be overshadowed by his discovery of the anaesthetic properties of chloroform.

Like surgeon Syme, Simpson was dissatisfied with ether, a drug he had used in obstetrics, and sought a more pleasant and more rapidly acting anaesthetic. David Waldie, a medical man and an apothecary, suggested chloroform and Simpson and his friends inhaled this at a dinner party in Simpson's house on 4th November 1847. (Just how such a party would be viewed by professional regulators these days is hardly

Fig 7. James Young Simpson

a matter for conjecture). Not surprisingly all became unconscious and awoke delighted at their success. Within weeks Simpson published in the Lancet.

It is well known that Simpson was attacked for advocating general anaesthesia to relieve pain in childbirth. The Old Testament injunction that 'in sorrow shalt thou bring forth' was as strongly advocated as it was merciless. It was not until John Snow administered chloroform to Queen Victoria for the birth of Prince Leopold that anaesthesia for this purpose was accepted by the church. As Monarch she was Supreme Governor of the Church of England so the bishops were left with little option. Simpson was the first person to be knighted for services to Medicine and be became one of the most famous doctors of his day, much loved by patients and colleagues alike. At his death funding for a new maternity hospital, the Simpson Memorial Maternity Pavilion, was raised by public subscription.

In the latter years of the 18th century France was heading for Revolution. It was indeed the best of times and the worst of times. It was a time of change on many fronts in 'natural philosophy' and for those interested in the chemistry of gases in particular. Why do I show this beautiful painting by the incomparable Jacques-Louis David of Charles Lavoisier and his wife (fig 8) at a lecture like this?

Charles Lavoisier was the first to reveal the true nature of oxygen, a gas beloved of anaesthetists. In experiments on guinea-pigs he showed that respiratory gas exchange was a combustion describing it 'like a candle burning'. In so-doing he

Fig 8. The Lavoisiers

blew away the phlogiston theory of oxygen so beloved of Priestley. Secondly, he was the first to use quantitative methods in chemistry; measurement is close to the hearts of all anaesthetists. Thirdly, he introduced the double-barrelled nomenclature we use to describe inorganic salts, e.g. sodium chloride, sodium bicarbonate. Fourthly, he wrote the first chemistry book, an important book in itself and one which had an influence on an even greater scientist, Humphry Davy (fig 9).

Sadly, as an aristocrat, Lavoisier found himself on the wrong side in the years that followed. Trumped up charges were levelled against him. As Robespierre put it at the tribunal. 'The Revolution has no need of chemists'. At his execution at the age of 51 years in 1794 one of his friends remarked: 'It took but a moment to cut off his head, but it may take 100 years to produce another like it'.

Well, as is so often the case, the French underestimated the Anglo-Saxons. At the time of Lavoisier's execution, Humphry Davy (1778–1829) was 16 years of age and destined to become the greatest scientist of his day. Davy was a polymath. As a chemist he isolated, amongst other things, potassium, and a few days later, sodium: he was the first to show that all acids contained hydrogen; he postulated that chemical forces were fundamentally electrical, and demonstrated electromotive forces in a cell. Outside of science he was highly regarded as a poet, a friend of Wordsworth, and an archaeologist. He became famous in his own lifetime but now is

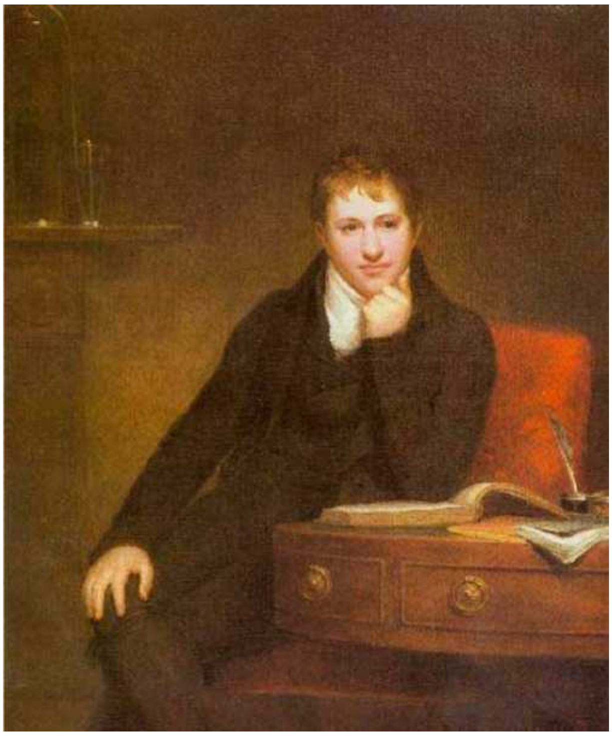


Fig 9. Humphry Davy

remembered chiefly for two things: the indispensable miner's lamp, and discovery of the analgesic properties of nitrous oxide. Unaccountably, for as a young man he had been a surgical assistant, Davy failed to grasp the potential of nitrous oxide as a means of alleviating the pain of surgery. What an irony that at the very time the much maligned Dr Hickman, only 50 or so miles away, was experimenting with carbon dioxide narcosis, Humphry was administering nitrous oxide to treat 'hysteria' in his Medical Pneumatic Institution in Bristol.

On 11th December 1844, Gardner Quincy Colton (1814–1898) an erstwhile medical student, administered nitrous oxide as a general anaesthetic for the removal of a tooth. The patient was a Connecticut dentist called Horace Wells (1815–1848) who, on waking up afterwards, proclaimed: 'a new era in tooth pulling'. The experiment was performed at Wells' suggestion, a fact which Colton was always careful to acknowledge.

A few weeks later in January 1845, at the Massachusetts General Hospital, Wells himself attempted to repeat Colton's experiment. Unfortunately, the patient moved and then cried out and Wells became a subject of ridicule. It is not clear what went wrong, if they rushed, or if the patient held his breath, or the gas mixture was dilute. Whatever the reason, the failure affected Wells very deeply and although he continued as a dentist for a time, he became profoundly depressed and ended up taking his own life. Although Wells failed in one sense, he was the first person to submit to the only 19th century anaesthetic drug still in use in 2008. In that sense both he and Colton should be remembered as important pioneers of anaesthesia. When the flamboyant and entrepreneurial Colton returned empty handed from the Californian Gold Rush, he set up dental 'offices' in many American cities. The photograph (fig 10) shows an example of one of these with the cylinder of nitrous oxide on a bench to the left.

Fig 10. A Coulton dental office

In 1867 Colton visited Paris to attend the First International Medical Congress. At that meeting he met a dentist, TW Evans. Evans, a Philadelphian emigre was by 1867 a fashionable Parisian practitioner numbering amongst his patients the President of the 2nd Republic himself, Louis Napoleon. Colton instructed Evans in the use of nitrous oxide and soon after the Paris Congress, Evans travelled to London where he, in turn, demonstrated nitrous oxide at the London Dental Hospital.

Nitrous oxide quickly found a place in obstetric practice and the Russian, Stanislav Klikovitch in St. Petersburg, was amongst the first to advocate it for self-administration by women in labour. Klikowitch's methods were taken up by an eminent obstetrician, Paul Zweifel in Leipzig, and by one of his juniors, Albert Doderlein. Doderlein saw the need for some form of monitoring and was the first to measure blood pressure during administration. He also recognised the potential for hypoxia and checked the oxygen content of whole blood using a new spectrometric method recently developed by Felix Hoppe-Seyler (1885).

Doderlein's prescience was well judged as the risk

Fig 11. The Minnitt (left) and the Lucy Baldwin (right) apparatus

of hypoxia has always been a major concern during nitrous oxide administration. It was not until the 1930s that machines were constructed which were capable of giving fixed percentages of nitrous oxide in air to women in labour. Ralph Minnitt of Liverpool gave his name to the most widely known of these. Another was named after Lucy Baldwin, later Countess Baldwin of Bewdley, wife of British Prime Minister, Stanley Baldwin (fig 11a,b). She was a forceful advocate for pain relief in labour in the1930s, possibly not unconnected with the fact that she gave birth to six children.

Fig 12. John Snow

I have digressed. Important as obstetric analgesia was and is, it is only a small part of anaesthesia. So we will return to the 1850s to see something of how anaesthesia developed as a specialty.

John Snow (1813–1858) of Broad Street pump fame (fig 12), was the first professional anaesthetist in these islands and was a powerful advocate of the physician anaesthetist. He was the first to apply scientific method to the administration of volatile drugs. He calculated dosages and kept detailed records of all his cases. Most remarkably he established that the potency of an inhaled anaesthetic is inversely related to its solubility in the blood. The opposite of what, at first sight, might be expected.

Following Snow's early death at the age of 45 years, leadership of the embryonic specialty in England fell to another remarkable man. Joseph Clover (1825–1882) was an innovator par excellence who would find the straightjacket of modern research governance incomprehensible (fig 13). He experimented with combinations of nitrous oxide/ether in air and he designed many different types of breathing apparatus to facilitate this, including means by which concentrations could be adjusted.

Here he is inducing anaesthesia with chloroform, with a finger on the patient's pulse (fig 13). [When I started as an SHO in the main theatres in the Royal Victoria Hospital in 1973, palpation of the pulse, careful observation of colour and temperature, and a sphygmomanometer were the only forms of monitoring available for routine surgery. ECG monitors (single lead) were rare, unreliable and highly susceptible to diathermy interference]. In the photograph he is using his famous inhaler which remained in use, in its various modifications, right up to the Second World War.

During the 100 years from 1850 to the mid 1950s, ether and chloroform were the only volatile anaesthetics in general use. Of the two, ether was the more widely used, because it was relatively safe and, by the standards of the time, its administration could be entrusted to young doctors, medical students or even nurses.

In contrast, chloroform was intrinsically hazardous. It induced dangerous cardiac arrhythmias and was associated with fulminant liver failure. However, it provided excellent anaesthesia and was certainly preferred in Scotland and Ireland. It was

Fig 13. Clover — hand on pulse

Fig 14. Sir Frederick Hewitt

never popular in USA probably because of a shortage of doctors; the administration of chloroform could not be entrusted to medical students and nurses.

Despite the higher risk of death with chloroform (estimated at 1 in 4,500 compared to 1 in 21,000 with ether) its popularity soared in the UK and in many other European countries. Such a situation could not be allowed to continue and the Hyderabad Commission 1890 concluded that it caused hypoxia. This was the beginning of the end for chloroform. It was the correct result but for entirely the wrong reasons.

You may have noticed that I've drifted across the Atlantic Ocean—the last American I mentioned was the 'American Dentist' who brought the good news from Paris to the London Dental Hospital. The fact is that during all of this time, not only did Britain rule the waves, but British anaesthesia ruled as well. Its pre-eminence up to the beginning of World War II was largely the result of the efforts of three men, Snow, Clover and Frederick Hewitt. Writing of them, the late Rod Calverley of University of California had no doubt that they were exceptional. Not only was that indeed the case, but British anaesthesia, indeed British surgery too, was fortunate that the professional lives of these three overlapped in such a way as to provide continuity.

It is not generally known that Clover (who died in 1882) was the first to perform an emergency cricothyroidotomy. He averted disaster by inserting a curved cannula of his own design through the cricothyroid membrane, thereby bypassing a large oral tumour. He remarked afterwards that 'I never used it before although it has been my companion at some thousands of cases'. That was Clover, obsessed with patient safety, and unusually for his time, well prepared for trouble. Frederick Hewitt was a man of like mind.

The successor to Snow and Clover, Hewitt (1857–1916) was the leading English anaesthetist of his day and an outstanding clinician (fig 14). We might remember him for a dozen things. He perfected Clover's portable inhalers, and most importantly invented the first apparatus capable of delivering oxygen and nitrous oxide in variable proportions. Apart from his clinical contributions Hewitt should be remembered for his contributions to anaesthetic

Fig 15. King Edward VII

training and education. It was on his insistence that anaesthesia became part of the curriculum in all British medical schools. In 1893 he wrote the first anaesthetic textbook, a book which subsequently ran to five editions.

Hewitt was the first anaesthetist to be knighted, possibly on account of his ministrations to the future King Edward VII whom he anaesthetised for a perforated appendix on the eve of his planned Coronation. The future King, and here he is in his Coronation robes (fig 15), was not an ideal anaesthetic subject, being obese, bearded and much given to tobacco and strong drink. Most of us today would baulk at anaesthetising him. To do it with open-drop ether without any form of airway protection would have been a considerable challenge, even for a clinician of Hewitt's skill.

The subsequent reigns of Edward VII and his son George V saw great upheavals in the world and everything was caught up in them. The years from 1914–1934 saw advances in anaesthetic equipment, notably Henry Boyle's machine and the arrival of Ulsterman, Sir Ivan Magill's tracheal tube. But why 1934? To understand that we must go back to another era, to another starting point, a starting point

Fig 16. The Royal Chelsea Hospital

which was central to the evolution of modern anaesthesia.

Sir Christopher Wren's Royal Chelsea Hospital was completed in 1692 and is still in use for the purpose for which it was built. With its magnificent chapel, it stands in stark contrast to the inhuman designs of modern hospitals (fig 16). Wren gave patients, their relatives and the staff something to lift their spirits, perhaps even their souls. The earliest intravenous administrations of substances were performed in the neighbourhood of Oxford around 1656 and were attributed to Wren. What a polymath he was! Robert Hooke said of him:

'Since the time of Archimedes there scarce ever met in one man so great perfection, such mechanical hand and philosophic mind'.

He injected opium and other substances into dogs to see if substances could be given directly into the circulation and still exert their characteristic effects. If they did it would explain the rapid collapse following bites by venomous snakes.

Henry Oldenburg, a civil servant associate who was present at the time recorded:

'he thought he could easily contrive a way to conveigh any liquid thing to the blood by making ligatures on the veins... and putting into them slender

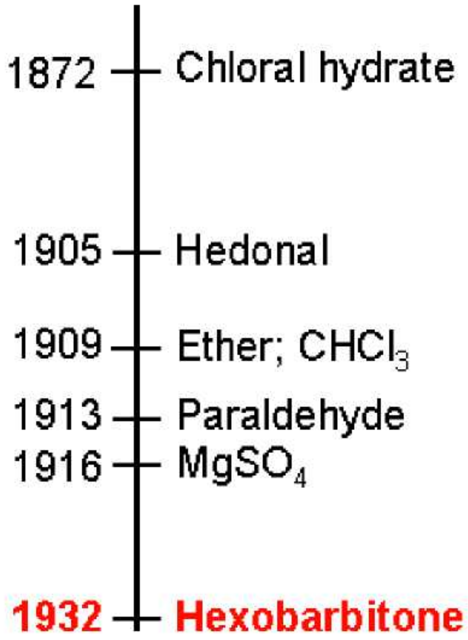


Fig 17. Intravenous 'anaesthetics'

syringes... fastened to bladders containing the matter to be injected'.

Oldenburg went on to say that they used 'big, lean dogges that the vessels might be large enough and easily accessible'. Given opium in this way the dogs were temporarily stupefied, but they survived, though probably not for long.

What excitement there must have been in the minds of Wren, Harvey, Hooke, Willis and others, as they began to uncloak these secrets right at the beginning of the scientific age. Those who wish to read more can find refer to Norman Bergman's paper or enjoy Iain Pears' very well researched historical novel, 'An Instance of the Fingerpost'.

Many circumstances had to change before intravenous drug administration could become a reality, including the concept of aseptic technique. An early hypodermic syringe, dating from 1860 and described as English, can be seen in the Science Museum in London. It was designed by an Irish physician (Francis Rynd) and made in Dublin by an Austrian silversmith. Rynd had already invented the hollow needle in 1844.

Dr Alexander Wood was the first physician to use a hypodermic syringe to inject narcotic drugs into a patient. In 1853 he injected morphine into 'painful points' and published a report in the Edinburgh Medical and Surgical Journal. So far as we know he did not inject morphine intravenously (fig 17).

Intravenous anaesthesia was very slow to

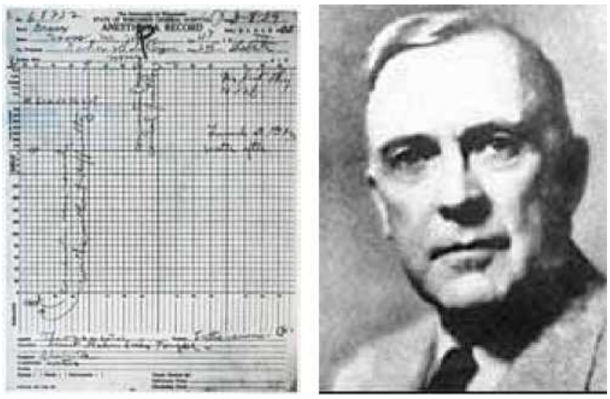


Fig 18. Reproduction (left) of the anaesthetic record of the first administration of Thiopentone, 8 th March 1934 by Ralph Waters (right)

establish itself, partly due to the absence of suitable drugs, partly due to the difficulty of preventing sepsis. The arrival of barbiturates in the 1930s revolutionised anaesthesia. For the first time there was a drug which could induce anaesthesia in one arm-brain circulation time—normally around ten seconds. Hexobarbitone was the first of these drugs to achieve popularity and in the twelve years following its introduction it was used to anaesthetise approximately 10 million patients.

However, the barbiturate which would be the gold standard for the next 60 years or so, was yet to come.

This is a record of the first administration of thiopentone (Pentothal). It took place on 8th March 1934 at the University of Wisconsin Hospital and the anaesthetist was Dr Ralph Waters (fig 18a,b). He was another exceptionally gifted doctor and went on to become the world's first University Professor of Anaesthesia. Waters was a strong believer in the concept of research-led teaching and did much to encourage the development of academic anaesthesia in Britain. It is notable that a man of Waters' stature could, almost 80 years after the death of John Snow, write this about that great man:

'He is my idol, the more I try to do various things, the more respect I have for him. We need not hesitate to say that John Snow was and remains the greatest anaesthetist as well as the first'.

The use of ether to induce anaesthesia declined rapidly after 1934 and thiopentone was soon the standard method. Of course, ether, and if you were brave, chloroform, remained the only means of maintaining general anaesthesia.

The next great advance in anaesthesia originated in the jungles of Ecuador. The first medical uses of curare were for relieving muscular spasms due to

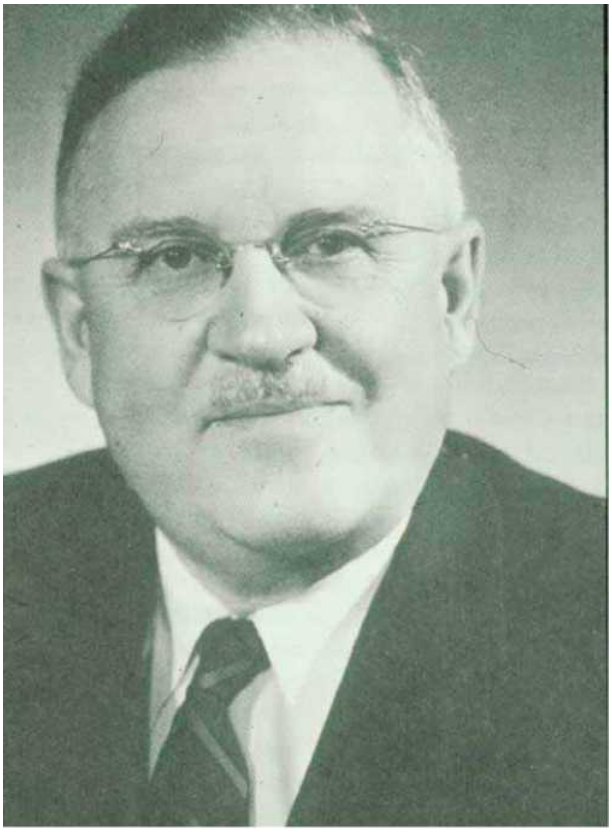


Fig 19. Harold Griffith

disease, or the spasms induced by EEG in psychiatric patients. Drs Manny Papper and Stuart Cullen were the first to use curare in anaesthesia. They gave it to two patients in Bellevue Hospital, New York City, in 1941. After the operation they were horrified to be confronted by two patients who could not breathe, and who had to be resuscitated overnight. Apnoea was not regarded as lightly then as it is now, and the concept of reversal was some way off. Papper, who later became the first anaesthesiologist Dean of an American Medical School was so shocked by the whole experience that he went so far as to say that curare had no place in anaesthesia.

Papper may have thought curare had no place in anaesthesia, but Harold Griffith in Montreal was confident that he could deal with respiratory paralysis if it occurred (fig 19). In July 1942, Griffith and Johnston reported the successful use of curare in a series of 25 cases performed in the Homeopathic Hospital, Montreal. This series marked a second revolution in anaesthetic practice.

Combined with tracheal intubation, which it facilitated, curare transformed surgical operating conditions.

The third revolution, had to wait for the Second World War and the Manhattan Project. In order to generate sufficient quantities of fissionable uranium for the atom bomb, Ur^{238} had to be enriched using uranium hexafluoride. The researches in fluorine chemistry which were necessary to bring this about were the springboard which gave rise to our modern heavily fluorinated anaesthetic drugs.

Halothane was first synthesised in 1951 in the laboratories of ICI by Charles Suckling. He began by asking anaesthetists what they wanted and it is a measure of his knowledge of organic fluorines that halothane was one of the first six anaesthetic compounds he synthesised. Halothane was revolutionary in being non-flammable, non-irritant, and much more potent than ether. Initial studies confirmed that it was rapidly acting with rapid recovery characteristics.

Revolutionary as it was, halothane was not perfect. Being similar to chloroform structurally, it had similar side-effects although generally these were much less pronounced. Fulminant liver failure on repeat administrations, although rare, became a growing concern in the 1970s, and a quest for better alternatives gained pace. Ross Terrell synthesised over 700 fluorinated ethers, of which just three, enflurane, isoflurane and desflurane became available for routine practice. Of these three only isoflurane and desflurane remain in regular use today. Terrell remains largely unknown to the general public despite the great service he rendered to mankind.

Sevoflurane was not one of Ross Terrell's ethers. It was discovered in the 1960s, not long after halothane, and was initially promoted in Japan. For regulatory reasons it was not licensed in the UK until 1995. Its properties are close to ideal although it has been associated with toxic degradation products when used in closed circuits with standard soda lime. This possible disadvantage can be circumvented by using carbon dioxide absorbents which do not contain strong alkalis. Sevoflurane has become the standard volatile agent for most purposes in the UK and much of Western Europe.

The question now is, has anaesthesia reached such a state of perfection that nothing more remains to be done? I do not think so. Whilst time does not permit me to delve into local anaesthetics, or the newer generations of opiates, non-opiate analgesics, muscle relaxants or relaxant reversal drugs, the fact remains that we are still heavily reliant on opiates, with all their pharmacological baggage, to control severe pain. Our understanding of pain mechanisms, and of anaesthesia itself remains superficial. Our ability to control postoperative emetic symptoms is

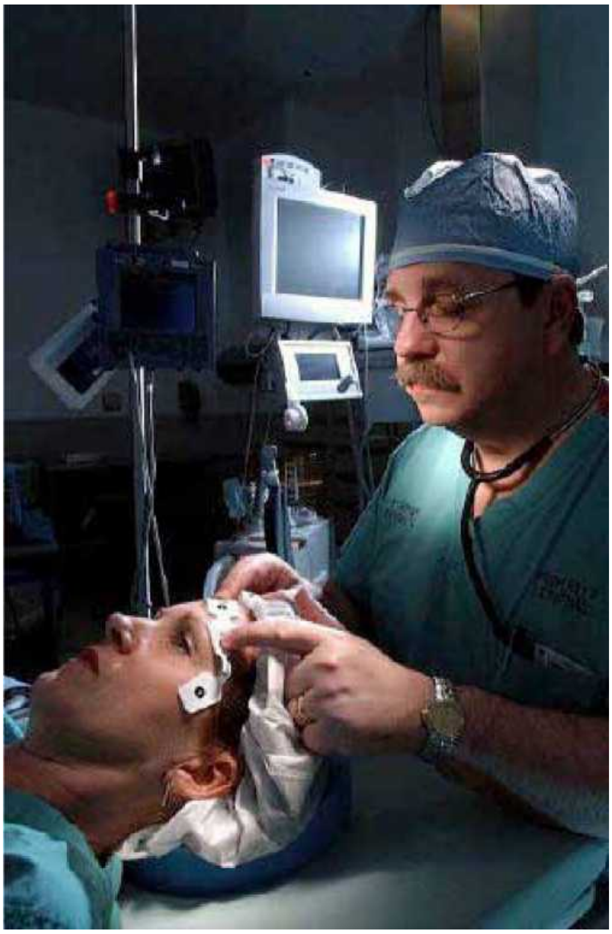


Fig 20. The BIS monitor

often ineffective and whilst we can keep people alive in intensive care units, we often lack any depth of understanding of the therapies we apply. Worse still, and surely the most serious gap in our knowledge, is that we cannot tell for sure if our patients are anaesthetised or not. We perform certain manoeuvres which we know from experience will in most cases result in an anaesthetic state, but we do not have a reliable, quantitative measure of 'depth' or even an adequate definition of what is meant by the term.

A large prospective trial of over 11,000 adult patients reported in the Lancet eight years ago quoted a figure for explicit awareness of 1 in 1000 overall, but almost twice this when muscle relaxants were used. This year, an alarmingly high incidence of 1 in 100 was reported in a very carefully performed study of 4001 adult patients in the University Hospital in Valencia. This group excluded patients most at risk so even this high figure may underestimate the true incidence. A prospective study of 184 children aged 5–18 years this year revealed no explicit recall but two children responded positively under the modified isolated forearm technique, an incidence of around 1 in 100.

The risk factors are well known and include: caesarean section, absence of benzodiazepine premedication, emergencies, young patients, cardiac surgery and difficult intubation. The consequences include nightmares, post traumatic stress, depression, anxiety and flashbacks. One third of the patients in the Valencia study experienced one or more of these.

Can anything be done? At present the adequacy of anaesthesia is either deduced from end-tidal concentration values in the case of volatile anaesthesia, or indirectly from algorithms used to calculate target infusion dosage in the case of total intravenous techniques.

The bispectral index (BIS) monitor (fig 20) displays a realtime electroencephalography (EEG) trace, sampled from the fronto-temporal area. It generates a dimensionless number with 100 representing normal activity. Studies have shown that the probability of awareness is very low when the BIS is kept <60 intraoperatively but there are serious problems in applying this universally. Firstly, there is no gold-standard against which the bispectral index can be measured and judged. Secondly, there is marked patient variability. Thirdly, there is no clear-cut transition value which can be used to differentiate between sleep and awake. Finally, our current knowledge of the primary sites of action of anaesthetics suggests that these are distant from the fronto-temporal cortex.

Furthermore, there is no agreement on the value of BIS as a means of reducing anaesthetic awareness. A Cochrane Review last year reported that when intravenous or volatile-based anaesthesia was guided by bispectral index monitoring, there was less awareness, and there were significant improvements in the quality of the anaesthetic overall. In contrast, a more recent US study reporting a comparison of bispectral and end-tidal agent monitoring concluded that BIS monitoring conferred no advantage. Nor could the Cochrane review have examined a recent Australian study. This showed that during anaesthesia, the EEG in infants is fundamentally different from the EEG in older children. The authors concluded that we lacked the necessary information to allow us to use anaesthetic depth monitors in infants.

So, I come back to the original question. What, if anything, can be done?

The problem for anaesthetists is that if we adopt protocol-driven methods based on bispectral indices, then in order to keep the monitor reading where it

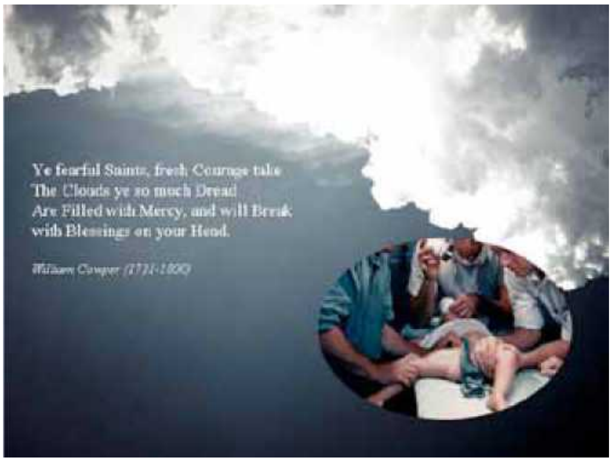


Fig 23. Clouds of Unknowing

should be, we will inevitably administer higher concentrations of potent drugs than are necessary, or safe, for some patients. We do not have data which would allow us to develop patient-specific or condition-specific protocols. These we need.

In a recent editorial, Beverly Orser, from the University of Toronto, spelled out the obstacles to a reliable depth of anaesthesia monitor. Anaesthetics have complex actions involving memory, pain, consciousness, vascular autonomic responses, etc. These responses require specific drugs for their suppression and the doses used are often very critical. Orser warns of the dangers of handing over critical elements of patient care to a 'black box' and concluded that we won't get anywhere until we knew a lot more about how and where anaesthetics work.

Although our knowledge of the mechanism of anaesthesia is sketchy it is advancing rapidly. For example, we know with certainty that the ß3 subunit of the $GABA_A$ receptor mediates both volatile and intravenous anaesthesia.

By creating mutations in the beta sub unit, we can produce mice which are resistant to specific anaesthetics. Figure 21 represents a beta subunit of a $GABA_A$ receptor. The N265 mutation shown here renders an affected mouse completely resistant to propofol, a modern day thiopentone (Pentothal). This particular mutation had no effect on other intravenous anaesthetics.

Second, we are reasonably sure that the thalamus and its projections (fig 22) are important in the anaesthetic state. The neuronal pathways within the pink shaded oval are all GABA-ergic and are more active during sleep. We know that the ventrolateral preoptic nucleus (VLPO) is activated by anaesthesia and we hypothesise that it in turn activates sleep promoting pathways to the basal forebrain and

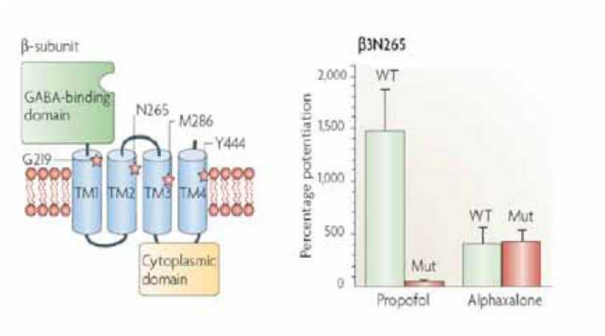


Fig 21. GABA mutation. Reproduced by permission from Macmillan Publishers Ltd NRN. Copyright 2009.

anterior hypothalamus.

Thirdly, from PET studies it would seem that anaesthesia resembles normal sleep. As in normal sleep the largest decreases in blood flow during anaesthesia are in the thalamus, brainstem and basal ganglia. The precuneus appears to be involved in a range of highly complex tasks, including the monitoring of the world around us. It is profoundly

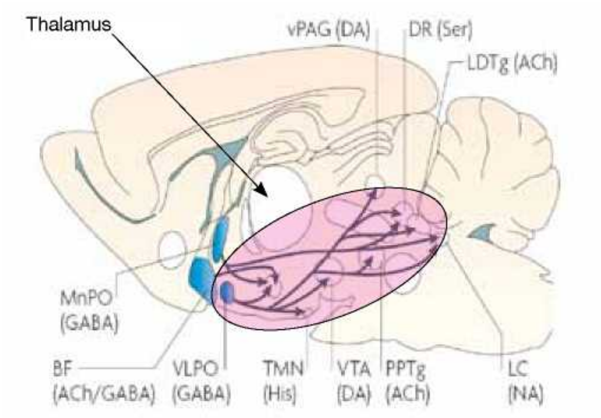


Fig 22. Thalamic projections. Reproduced by permission from Macmillan Publishers Ltd NRN. Copyright 2009.

de-activated both in deep sleep and anaesthetic-induced unconsciousness.

As I come to the end of the lecture and look forward, it is hard to know if doctors of my generation are labouring in the twilight of a golden age of medical practice, or witnessing some new dawn. There are many dark clouds including the likelihood of economic decline in the next 50 years, climate change and burgeoning population growth. The profession itself will be challenged by part-time practice, increasing patient expectations and ever more intrusive regulation and control.

What will be the consequences of the current decline in traditional research-led education and training of medical students? What a tragedy it is that the intellectual freedoms which in the past have delivered so much are now so undervalued. How regrettable it is that the freedoms which allowed generations of my clinical colleagues to conduct small research projects on the basis of a clinical observation, or even a hunch, have effectively been lost. It is worth remembering that it was those very freedoms which gave us modern anaesthesia, not million pound research grants or research strategies.

We have travelled a long way from the clouds of vapour and gas which first induced a state of unknowing in 1846. I've mentioned our lack of knowing as we struggled to find safe drugs, and good methods of administration. I've referred to our ignorance when it comes to patient awareness and the mechanisms of anaesthesia. I've alluded to storm clouds on the horizon. But I would like to end on a positive note, not just because it is a better way to end, but because I believe that there is always the potential for good, no matter how trying the circumstances.

And as this child struggles, in very trying circumstances, against the choking cloud of ether the words of the English poet clergyman, William Cowper, would seem to resonate, for her, and for us: (fig 23)

Ye fearful Saints, fresh Courage take
The Clouds ye so much Dread
Are Big with mercy, and shall Break
In Blessings on your Head.

My thanks are due to the following who either directly or indirectly assisted with the preparation of my lecture: Dr Rod Calverley (the late), Professor Richard Clarke, Professor Nick Franks, Professor Rajinder Mirakhur, Professor Sir Keith Sykes, Dr David Wilkinson, The College of Anaesthetists of Ireland, The Royal College of Surgeons in Ireland and The Royal Society of Medicine.