Article

The Chemical History of Anaesthesia

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Introduction: The Age of Agony

The accounts and recollections of surgery before the discovery of anaesthesia are gruesome and it is difficult to imagine what such surgery was truly like. One of the best descriptions of a pre-anaesthesia medical procedure was provided by Fanny Burney, an English author, in a letter to her sister describing her mastectomy: *When the dreadful steel was plunged into the breast - cutting through veins - arteries - flesh - nerves - I needed no injunctions not to restrain my cries. I began a scream that lasted unintermittingly during the whole time of the incision - and I almost marvel that it rings not in my ears still! so excruciating was the agony.*[1]

While there *were* some techniques used to provide a type of primitive anaesthesia that included the barbaric methods of nerve compression, deadly intoxication, exsanguination, refrigeration, carotid compression, and even concussion, ultimately a good surgeon was a *fast* surgeon.[2] The great discovery came in the mid 19th century with Horace Wells, a dentist, observing that pain sensation was reduced while under the influence of N_2O (laughing gas). After experimenting on himself and some of his patients, he set up a formal demonstration of a *painless dental extraction* in a lecture theatre at the Massachusetts General Hospital in January 1845. By now, we know that nitrous oxide is a weak anaesthetic that requires the unachievable concentration of *ca*. 117% saturation to obtain true anaesthesia. As Wells attempted to extract the tooth, the patient cried out in pain, and amidst cries of *humbug*, Wells was jeered off the stage. Completely humiliated, he sold his dental practice and became a travelling salesman. Some two years later he was jailed for throwing sulfuric acid at two prostitutes and, subsequently in the jail cell, he inhaled an analgesic dose of chloroform, cut open his femoral artery, and quietly bled to death.[3]

On the 16th of October in 1846, William Morton, a dentist and a colleague of Wells, set up his own public demonstration in the same Massachusetts General Hospital lecture theatre, but used the slightly less cumbersome diethyl ether as his anaesthetic. After Morton anaesthetized the patient, a surgeon removed a tumour of the jaw. Afterwards, the patient reported having felt no pain, and the surgeon turned to the audience, declaring: *gentlemen*, this *is no humbug!* Morton is now acknowledged as the Father of Anaesthesia.[3]

Inhalational Anaesthetics

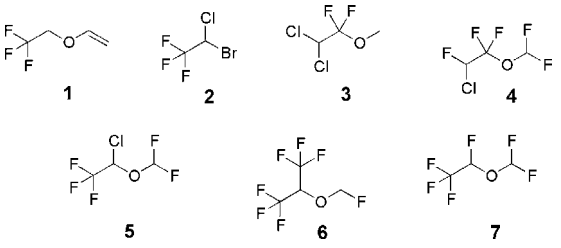
Despite its disastrous start, nitrous oxide became widely used and remains in clinical practice today as an adjuvant. The use of ether also spread quickly despite Morton's attempt to patent his discovery. James Young Simpson, a Scottish obstetrician, was among the first to use ether to relieve labour pain, but growing dissatisfied with it, sought a more pleasant anaesthetic. When a colleague suggested chloroform, Simpson and some friends inhaled it at a dinner party in Simpson's home. They fell promptly unconscious, and woke delighted with their success. Subsequently, chloroform anaesthesia became hugely popular, especially after being endorsed by Queen Victoria (who used it for her childbirths).

Other compounds that were trialled and used as anaesthetics include cyclopropane, ethene, ethyne, chloroethene, and ethyl vinyl ether. Most of these are quite flammable and/or explosive; the first report of a fire in an operating room dates back to 1850. The introduction and use of pure oxygen only increased the fire risk, and reports of explosions continued despite more stringent safety controls. The worst accident is possibly a 1964 cyclopropane explosion that killed two patients, two anaesthesiologists and two surgeons, with another surgeon losing an arm, and two nurses a leg each.[4] The search was on for better, safer and non-flammable anaesthetics.

The Organofluorine Revolution: Fluorinated Anaesthetics

Fortunately, at about the same time, great advances were being made in the field of ***organofluorine*** chemistry. Firstly, the discovery of the chlorofluorocarbons in the 1930s, then the serendipitous synthesis of polytetrafluorethene (Teflon®), and finally the demands of the Manhattan Project (requiring UF_6 for ^{235}U enrichment) led to a significant advance in the understanding of organofluorines. The C-F bond is stronger than C-C (average bond enthalpies 485 and 346 kJ/mol, respectively) resulting in the organofluorines being quite stable and making them the best candidates for new, non-combustible anaesthetics.[5]

Charles Suckling synthesized fluoroxene **1** in 1953 at the request of anaesthesiologists looking to replace the flammable diethyl ether. Although fluoroxene never became a widely used anaesthetic, many others followed, including halothane **2**, methoxyflurane **3**, enflurane **4**, isoflurane **5**, sevoflurane **6** and desflurane **7**; **5-7** remain in use today.



With the exception of **3** and **6**, these anaesthetics are synthesized and administered as racemates. This is surprising as biological systems are inherently chiral and the enantiomers of a chiral drug will interact differently with enzymes and receptors. However, interest in enantiomerically pure drugs is relatively recent, with the pharmaceutical

industry waking to the fact that neglect of stereochemistry leads to expensive and *highly sophisticated nonsense*.[6]

Interestingly, the absolute configurations of **5** and **7** were determined only in 1996 utilizing low temperature XRD methods. They provided a challenge being both volatile liquids needing cycles of partial melting and slow cooling at -98°C for 5 and -126°C for **7** to obtain single crystals. Ultimately, Schurig *et al*. showed that the dextrorotatory enantiomer of each has the *S*-configuration[7] and this triggered several groups to work towards the asymmetric synthesis of the major fluorinated anaesthetics. This is yet to be accomplished as the enantioselective syntheses that have been achieved each require a chiral resolution.[8]

Environmental Concerns

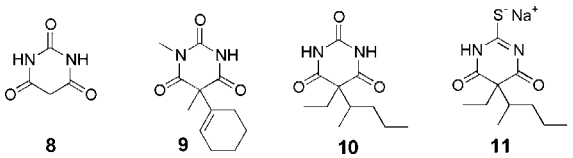
The anaesthetics **2-5** are hydrochlorofluorocarbons (HCFCs) related to the chlorofluorocarbons (CFCs) and, although their ozone depleting potential is less due to the presence of one or more hydrogens which speed up their atmospheric degradation, they are still of concern. The 1992 Copenhagen amendment to the Montreal Protocol (1987) requires the complete phase out of HCFCs by 2030. Fluranes **6** and **7** are hydrofluorocarbons (HFCs) and while not a threat to the ozone layer as they do not contain chlorine (the main ozone-depleting agent), are regarded as greenhouse gases. The Kyoto Protocol (1997) requires the reduction in HFC and N_2O (another potent greenhouse gas) emissions.[9] Thus, anaesthesiologists need to look for other, more environmentally friendly volatile anaesthetics.

An alternative might come from a surprising source, namely the noble gas xenon. It has been found to meet most of the criteria of a so-called *ideal anaesthetic*. It is an analgesic gas that is pleasant to inhale, has minimal-to-no side-effects nor is it biotransformed, yet is stable, non-flammable, non-explosive, and non-reactive. While it has a fairly low oil/water partition coefficient, meaning that it has low potency (anaesthesia is achieved at 60-70%), it is environmentally friendly, and with a low blood/gas partition coefficient has a fast onset of action. Unfortunately, its cost (from the fractional distillation of air - 8.7 x 10^{-6} % of the atmosphere) is prohibitive, thus limiting its use for anaesthesia.[10]

Intravenous Anaesthetics

The intravenous anaesthetics comprise a varied range of chemical structure types often called the hypnotics, as they cause sedation, unconsciousness, and amnesia. All are fast-acting.

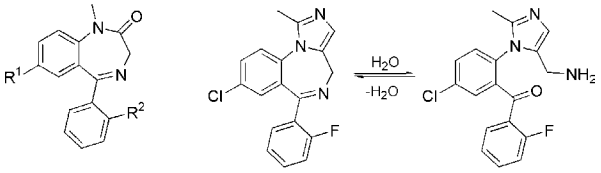
Based on barbituric acid **8**, the barbiturates were among the first hypnotics employed in medicine being used extensively during WWII. Sadly they are said to have killed more American military at Pearl Harbor than did the Japanese. At that time doctors did not know that the barbiturates, such as hexobarbital **9** and pentobarbital **10**, were potent vasodilators. Thus when administered to severely wounded soldiers at Pearl Harbor, they caused dilation of the blood vessels, magnifying the effects of bleeding and leading to higher mortality.[11]



8 **9** **10** **11**

Sodium thiopental **11** has gained notoriety as the *truth serum*, often being used to interrogate prisoners. Such barbiturates are known to inhibit higher cortical brain functioning and since lying is more complex than the truth, suppression of the higher cortical functions may lead to the divulgement of the *truth*. Yet the term *truth serum* is misleading on both counts: it is neither a serum,nor does it lead to the truth, with the subjects freely mixing fact with fantasy.

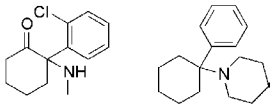
The benzodiazepines comprise the second group of sedative hypnotics, frequently used in hospitals for acute situational anxiety. Most famous is diazepam (or Valium®) **12**, that is often prescribed for sedation and sleep disorders. The related flunitrazepam **13**, known by its trade name Rohypnol®, has gained notoriety as the *date-rape drug* because of the abuse of its amnesic properties. Gaining popularity amongst the anaesthesiologists, however, is midazolam **14** due to some simple but useful chemistry. Most benzodiazepines are poorly water soluble and hence they are formulated in propylene glycol – and this is the prime cause of pain on injection. However, the imine midazolam **14** exists in equilibrium with its ring-open aminoketone form in water, thereby making it much more soluble and eliminating the need for glycol formulation.[3]



12, R^1 = Cl R^2 = H
13, R^1 = NO_2 R^2 = F

14

One unique member of the intravenous anaesthetics **15**, known as ketamine, was synthesized in the 1960s as a safer alternative to phenylcyclohexylpiperidine (**16**, PCP or angel dust) and it quickly gained popularity due to some unique properties. In contrast to most induction agents, **15** does not cause respiratory or cardiac depression and is safe to administer even shortly after a meal. This combination makes it an ideal agent for use in adverse field conditions and it was used extensively during the Vietnam War earning the nickname: *battlefield anaesthetic*.[12]



15 **16**

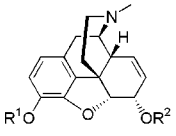
While still widely used for veterinary work, use of ketamine in general anaesthetic practice has fallen into disfavour due to some unpleasant psychological side effects. Because it induces anaesthesia *via* dissociation of the conscious mind from sensory input, **15** often causes *emergence delirium*, with vivid dreams and hallucinations, blurred and double vision, and feelings of floating and detachment from the body that have been likened to near death experiences. New research, however, indicates that

the *S*-enantiomer may be more potent and have a faster clearance than the *R*-form, reducing the extent of side-effects and making it an attractive alternative to the current racemic drug.[13]

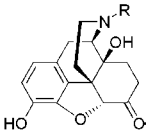
Opioids for Analgesia

Pain is *the unpleasant sensory and emotional experience associated with actual or potential tissue damage* and is a subjective experience accompanying nociception – the specific activity of the nerve pathways transmitting the noxious stimuli.[3] Nociception causes physiological changes such as increased heart rate, vasoconstriction, hypertension, increased skeletal muscle tone around surgical area, and others. It can be dangerous and even life-threatening to a patient, even one that is unconscious and not experiencing pain as such, and so needs to be controlled by analgesic drugs such as the opiates. *The influence of the opiates on modern society cannot be overestimated; they are used extensively as medicines to ease human suffering and are abused in equal measure as illicit narcotics*.[14] Records show the opium poppy to have been cultivated for extraction as early as 3000 BC. Opium, harvested from the exudate of unripe seed pods (*opos*: Gk. juice), is an analgesic drug containing three main alkaloids; morphine **17** (present at 10-15%), codeine **18** (3-4%), and thebaine **19** (0.1-2%).

Morphine, isolated by the German pharmacist Friedrich Sertüner in 1806, was named by him after Morpheus, the Greek god of dreams. It was the first natural product to be isolated, and it initiated the development of natural products chemistry as a discipline. While a blessing to those in pain, morphine is also addictive, and so its history is intimately linked with its abuse. In addition, German scientists from the Friedrich Bayer Company developed diacetylmorphine **20** as a cough remedy in 1898. This compound, now known as heroin, turned out to be particularly addictive, and its illicit use continues to this day.[14]



17, R^1 = H R^2 = H
18, R^1 = Me R^2 = H
19, R^1 = Me R^2 = Me
20, R^1 = Ac R^2 = Ac



21, R = Me

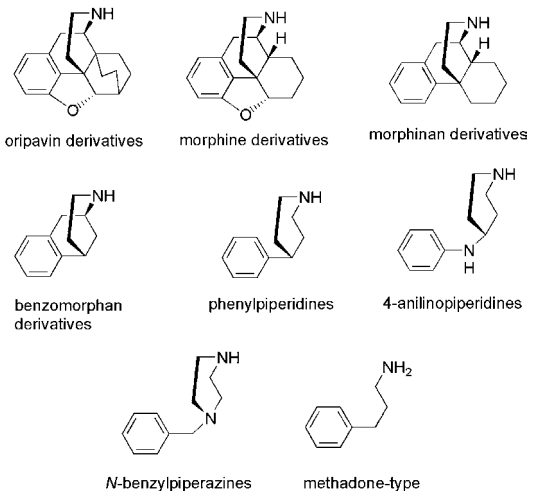
22, R =

23, R =

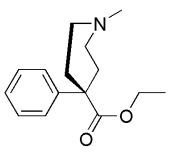
More recently, thebaine (**19**; the biogenetic precursor to codeine and morphine) has become more important as a synthetic precursor to several semi-synthetic opiates such as oxymorphone **21**, naloxone **22**, and naltrexone **23**. Oxymorphone is 10 times more potent than morphine, but naloxone and naltrexone are actually competitive antagonists, despite being structurally very similar. They bind to the opioid receptors with higher affinity but do not activate them. Because of this they are used to reverse the effects of opioid overdoses from, for example, heroin.

While the opiates are natural and semi-synthetic derivatives of morphine, the opioids form a wider class comprising of any agent that binds to the opioid receptor and mediates the pain response.

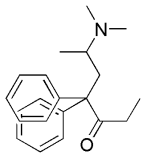
Chart 1



Many have been discovered serendipitously, others by systematic research, and they include a variety of diverse chemical types, as depicted in Chart 1.[15] Despite this, each retains structural similarity to morphine. Some well-known examples include meperidine **24** (Demerol®), which has but one-tenth the analgesic strength of morphine, but with fewer side effects. Methadone **25**, initially developed as an antispasmodic, is employed now as a long-acting oral analgesic for cancer sufferers and also in the treatment of heroin addicts. Most of the opioids used for anaesthesia are of the 4-anilinopiperidine type, often with potencies up to 800 times that of morphine. Most commonly used today is fentanyl **26**, but many other analogues, some of which have extremely high potency, are also known.[14]



24



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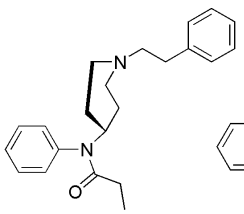

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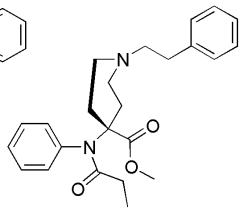


27

Likely, the reader will recall the 2002 hostage crisis in a Moscow theatre. Some 50 Chechen rebels had taken more than 800 people hostage and the Russian military stormed the theatre three days into the crisis, using a mysterious gas to incapacitate the rebels. During the rescue attempt, more than 120 hostages died. While the Russian authorities never officially revealed what the *gas* was, available evidence suggests it was an aerosol of carfentanil **27** that is marketed as a tranquillizer for large game animals; it is one of the most potent opioids known, being some 10,000 times more potent than morphine.

But why did the hostages die? Opioids do not cause death

directly as they have little or no inherent toxicity. However, they depress respiration and opioid-induced apnoea is the main cause of death with heroin overdoses; most likely this is what happened to the hostages. While simple ventilation and/or treatment with naloxone **22** and naltrexone **23** would have been life-saving for many of the hostages, the Russian emergency system simply was not prepared to receive and treat so many victims of opioid intoxication.[16]

Muscle Relaxants

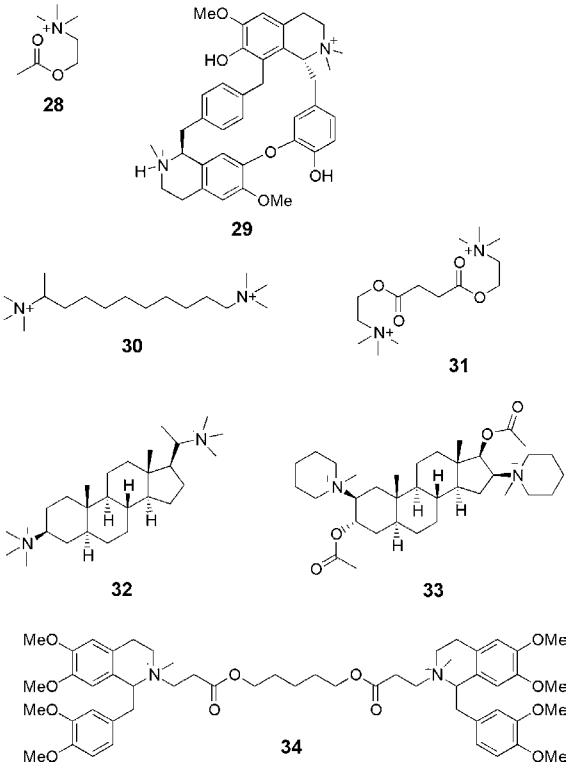
The Spanish conquistadores returned from the New World with stories of a powerful paralytic poison that the natives called *woorari* or *curare*. One European explorer, the eccentric British naturalist Charles Waterton, ventured deep into the Amazon to bring back with him this so called *flying death*. Intrigued by the toxin, Waterton performed a series of experiments to try to determine its mode of action. He administered curare to a donkey and was able to revive it after several hours of artificial respiration, clearly showing that death by curare occurs due to respiratory failure.[17]

Utilizing curare, the classic experiments of Claude Bernard (a French physiologist) and Sir Henry Hallett Dale (an English neuroscientist) led to the identification of the neuromuscular junction: the interface between the nerves and the muscle fibre. Intercellular communication occurs across this anatomical gap via chemical transmission. The neurotransmitter acetylcholine **28** is released by the nerve cell, crosses to the target muscle cell and binds to a receptor. Two molecules of **28** are needed to fully open the ion channel. This leads to an influx of Na^+ and an efflux of K^+ ions causing a change in ionic potential, which eventually leads to muscle contraction. By blocking this ion channel, curare causes muscle paralysis.

On 23 January 1942, Drs Griffith and Johnson revolutionized surgery by administering curare for the first time as a muscle relaxant for abdominal surgery. Until then, surgeons relied upon large concentrations of inhalational anaesthetics to achieve muscle relaxation suitable for surgery, but unfortunately, these often brought about dangerous levels of cardiac and respiratory depression. The use of neuromuscular blocking drugs allowed anaesthesiologists to achieve optimal surgical conditions at much safer inhalational anaesthetic levels.

Despite these obvious advantages, muscle relaxants were accepted into medical practice initially only slowly. Anaesthesiologists lived by the creed *dum spiro spero* - as long as there is breath, there is hope; spontaneous respiration was considered essential for anaesthetic practice. Fortunately, the early 20th century saw the invention of intubation, and with its widespread use anaesthesia was redefined as a triad of *narcosis*, *analgesia* and *muscle relaxation* that in essence remains in use today.[3]

Harold King isolated *d*-tubocurarine **29** from a museum sample of curare in 1935. He erroneously established its structure as having two quaternary ammonium groups at either end of a bulky, rigid molecule. This fortuitous error focused chemists on compounds with two or more such



centres, leading to the rapid discovery of decamethonium **30** and suxamethonium (succinylcholine) **31**. Both have curariform activity, but belong to a group of muscle relaxants called the *depolarizers*. Small and slender, they mimic the effect of acetylcholine **28** by opening the ion channel. Because they are not broken down as rapidly as **28**, they keep the channel open, first causing fasciculations – minute and random muscle contractions as the muscle fibres are continually stimulated – and then paralyzing when the ion source is exhausted. *d*-Tubocurarine **29**, on the other hand, binds to the same two acetylcholine sites on the ion channel but, being bulky, blocks any flow of ions across the cell membrane, causing *non-depolarizing* muscle block, free from undesirable fasciculations.[18]

In the early 1960s, malouetine **32** was isolated from the bark of the plant *Malouetia baquaertiana*. The bis-quaternary steroidal alkaloid was found to have non-depolarizing, curare-like activity, and inspired Dr David Savage, a medicinal chemist, to design a new and better neuromuscular blocking drug. He used the androsterone skeleton to provide a rigid scaffold and the required separation between two quaternary amine groups creating the first drug *ever to be successfully designed on paper using a rational structure-function approach*.[19] This non-depolarizing blocker **33** was named pancuronium and is still in use today.

Yet the design of new blockers did not stop at steroidal skeletons. Stenlake and colleagues were working on benzylisoquinoline structures similar to *d*-tubocurarine, and in 1981 synthesized atracurium **34**, which they found undergoes Hofmann elimination. While this elimination normally requires a high temperature and high pH, **33** reacts at physiological pH and temperature.[18] This simple chemistry has made atracurium a favourite of anaesthesiologists. Because its breakdown is under chemical rather than enzymatic control, it can be administered to patients

with enzymatic deficiencies. Patients with renal or hepatic failure, or organ transplant recipients, can also receive **33** without danger of prolonged muscle paralysis.

Local Anaesthetics

The conquest of Peru by Francisco Pizzaro in the 16th century brought to the attention of Europeans a plant the natives considered divine. Called *khoka*, meaning *the plant*, the locals chewed its leaves to appease hunger and thirst, and to increase strength and stamina. Interested in the stimulant effects of the coca leaf, the Austrian naturalist Carl von Scherzer collected a sizable sample of the leaves while exploring Peru. He passed them on to the German chemist Albert Niemann, who was able to isolate the main alkaloid of the coca plant, calling it cocaine **34**. Sigmund Freud soon became a great proponent of cocaine, advocating its use to overcome morphine addiction (!). He introduced it to Carl Koller, a Viennese ophthalmologist, who became aware of its numbing properties and was the first to use it in clinical practice. In 1884 he performed surgery with a local anaesthetic on a patient with glaucoma, usually a most difficult procedure because of the automatic blink reflex. Koller's success and the recent invention of the hypodermic syringe allowed the rapid spread of local anaesthesia for use in surgery and dentistry.[20,21]

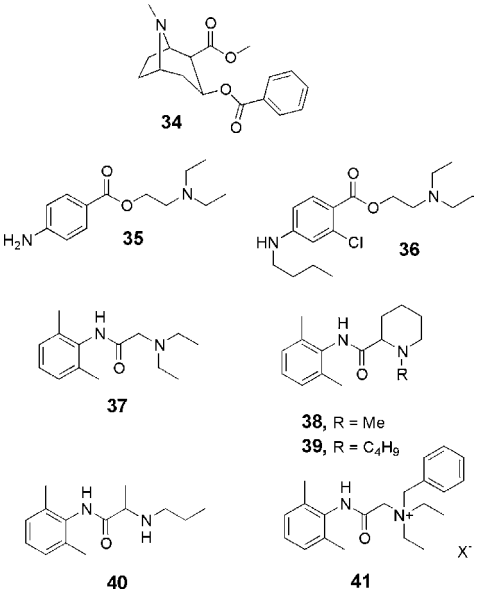
Simultaneously with its introduction into clinical practice, several unfortunate and undesirable effects of **34** (including toxicity and addiction) became apparent. New anaesthetic drugs were sought to replace it, and in 1904 the German chemist Alfred Einhorn patented 18 *p*-aminobenzoic acid derivatives such as procaine **35** and tetracaine **36**. Although they are good local anaesthetics with less toxicity than **34**, they are metabolized through ester hydrolysis to p-aminobenzoic acid, a known allergen. Lidocaine **37**, prepared in 1944, was the first in a new generation of local anaesthetics, incorporating the amide linkage instead.[20]

During the search for new amide-linked local anaesthetics (such as mepivacaine **38**, bupivacaine **39** and prilocaine **40**), salt **41** (X = benzoate, etc.) was also synthesized. Having no anaesthetic properties itself, **41** is, however, the bitterest substance known to man – as little as 10 ppm is unbearable. Because of this property, **41** is used to denature alcohol, and gets its name – denatonium – from this application. Today, amide-type local anaesthetics are used almost exclusively, although cocaine itself still finds application with ear-nose-and-throat surgeons because of its unique combination of local anaesthesia and intense vasoconstriction.[20]

The Ether Monument

Today, we think nothing of asking the dentist for local anaesthesia for every small procedure, yet only a few generations ago patients would submit to surgery only as a last resort. Anaesthetics have made elective surgery – if not quite pleasant – certainly bearable, made major life-saving operations possible, allowed the alleviation of chronic pain, and in general revolutionized the world of medicine.

In 1868, the grateful citizens of Boston erected the Ether



Monument *as an expression of gratitude for the relief of human suffering occasioned by the discovery of the anaesthetic properties of sulphuric ether*. This splendid 40-foot obelisk remains the oldest statue in Boston's historic Public Garden and is possibly the only monument to a chemical in the world. It displays the description: *There shall be no more pain*.[1]

Acknowledgement

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