

# From Out of the Primordial Soup: A Brief History of Anaesthesia

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## Abstract

Anaesthesia has been around in one form or another since around the 12th century and in some sense hundreds to thousands of years B.C. In the last 150 years however a revolution of anaesthesia has occurred with exponential growth in knowledge and substances available for use in anaesthesia making it one of the most advanced specialities in modern medicine. The following essay considers the core roots of our speciality and looks briefly ahead to see what the future may hold.

## PRIMITIVE ANAESTHESIA

Medieval anaesthesia was primitive and barbaric when compared to the standards employed today. The most common before the 15<sup>th</sup> century was probably the use of liberal quantities of alcohol plus or minus opium and a wooden stick to bite down upon. However some of the substances used in this period still hold strong today such as opium and some are even being 'rediscovered' such as Cannabis in chronic pain.

Arabic alchemist were perhaps some of the most advanced in their beliefs on anaesthesia in the 12<sup>th</sup> and 13<sup>th</sup> centuries employing techniques such as the soporific sponge which was a sponge steeped in hashish, opium and other herbal aromatics. When required for surgery it would be moistened and held over the face inducing a state of unconsciousness. Writings about this practice can be found in Sir Richard Burton's translation of *The Arabian nights* (1).

## Figure 1



Arabic Anaesthetists preparing to use the Soporific Sponge

(2)

Formal reference to the use of an anaesthetic agent for surgical intervention occurs around 1540 when dioscorides

refers in his pharmacopoeia to:

'Sleeping potions made from opium and mandragora root which may be used as surgical anaesthetics for such people whom be cut or cauteried' (3)

Mandragora continued to be a popular choice of anaesthetic upto the middle ages and was a mythical and respected plant. It was felt that the mandrake plant whose roots resembled a human form would kill the person who picked it if the screams of the root were heard. For this reason the plant was uprooted in novel ways such as tying the loosened plant to the collar of a dog and allowing the dog to uproot the plant, a practice that would be frowned upon by the RSPCA no doubt.

Mandrake was usually combined with a blend of opium and hemlock and either rendered the patient unconscious or dead, as hemlock shows zero order kinetics and is a toxic piperidine alkaloid.

Figure 2

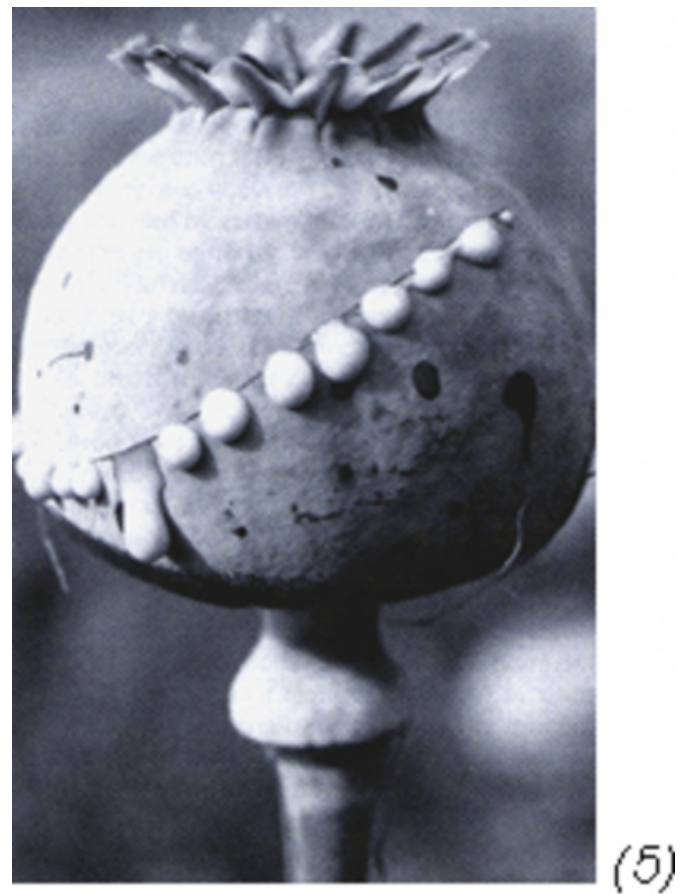


### *Mandrake Plant*

One of the commonest anaesthetic potions used was the 'Dwale Potion' from the medieval word dwale meaning confused or dazed. This comprised the gall from a castrated boar, lettuce, hemlock, henbane opium, mandrake and bryony.

Certainly the longest standing substance used in anaesthesia throughout history and into modern day are extracts from the opium poppy, *papaver somniferum* meaning the poppy of sleep.

Figure 3



### *Papaver Somniferum*

When the walls of the opium poppy are incised a latex like substance is secreted, from which many of the useful products are derived including opium and the isoquinoline alkaloid derivatives morphine, codeine, noscapine, papaverine and thebaine.

The Sumerians were the first to cultivate the poppy as far back as 3200 B.C. There is a feeling among some medical historians that the poppy itself is integrated into human culture and that this is one of the reasons that eradication of the illegal opium trade is so difficult. The first writings of opium overdose appear around 1037 A.D when the Islamic physician Avicenna died of an accidental overdose. A famous quote, which still holds true today, was in the 17<sup>th</sup> century when Thomas Sydenham wrote:

‘ There is no other pain killer that is so universal and efficacious as morphine’ (6)

As you can see from the above techniques the balance between life and death was even more tenuous during

anaesthesia than it is today. So when did things start to change?

### EVOLUTION

From these primitive beginnings little changed in anaesthesia until the end of the 18<sup>th</sup> century. During this time a rapid evolution occurred in the practice of anaesthesia largely due to certain key individuals who shaped the foundations of our speciality as it stands today.

The discovery of 'dephlogisated nitrous air' or nitrous oxide as we now know it, by Joseph Priestly was the catalyst for this evolution. The discovery occurred at the end of the 18<sup>th</sup> century but the relevance of the discovery was not stumbled across until a couple of years later in the early 19<sup>th</sup> century when a chemist, Humphrey Davy, conducted some 'physiological' experiments with the gas.

At the age of 21, Davy a keen chemist was employed as a superintendent of the medical pneumatic institution of Bristol to investigate the properties of various gases and their application to medicine. A quote in the diary of an observer at the time states, 'He breathed 16 quarts of the gas over a period of 7 minutes and became completely intoxicated.' (7)

**Figure 4**



*Humphrey Davy*

Davy was a remarkable if somewhat erratic chemist who was not only responsible for the above discovery but many others such as the Davy miners' lamp and many of the properties of the Alkali Earth metals. He died May 29<sup>th</sup>, 1829 at the age of 51 from a myocardial Infarction following

a prolonged illness considered to be brought on by the inhalation of many gases over his lifetime.

Despite Davy's work it wasn't until 45 years later in 1844 when nitrous oxide was used as an anaesthetic by Gardner Colton and Horace Wells. Colton was a travelling scientist who gave public demonstrations of his discoveries. Wells, a practicing Connecticut dentist, was at one such demonstration when he witnessed Colton administer Nitrous oxide to a man who then bashed his shin against a stone bench and displayed no sign of pain. Excited by this observation Wells invited Colton to his dental practice the next day.

Colton administered nitrous oxide to Wells and Wells' partner John Riggs extracted his wisdom tooth whilst under the effect of the gas.

**Figure 5**



(8)

*Horace Wells*

No pain was experienced during the extraction and Wells and Riggs pioneered the use of Nitrous oxide as a dental anaesthetic and went on to anaesthetise many more patients for wisdom tooth extraction.

During his career Wells was to influence the life of one of the most important names in anaesthetic history, William Morton. Unfortunately the rest of Wells' career was not so illustrious and in 1848 he committed suicide after being arrested for dousing a prostitute in sulphuric acid.

William Thomas Green Morton was born in 1819 in Massachusetts. From a young age he aspired to study medicine but unfortunately lacked the capital to do so and so chose the less expensive option of dentistry.

**Figure 6**



*William Thomas Green Morton*

He trained predominantly under the guidance of Horace Wells and together they started a dental practice that eventually turned out to be a financial failure. At this point in his life he separated from Wells and began studies at Boston medical school under the guidance of prestigious surgeon Charles Jackson. Here he began investigations into the properties of Ether. Unfortunately Morton's constitution was never strong and he suffered frequently with anxiety and stress. Early on in his studies of ether he was thwarted by a nervous breakdown and had to return to his family home for a period of respite.

After this set back he returned to his studies and was briefly reunited with Horace Wells when Wells gave an unsuccessful demonstration of the properties of Nitrous oxide as an anaesthetic for wisdom tooth extraction. The demonstration was a farce with the patient crying out and thrashing around and subsequently Well's work was rubbished.

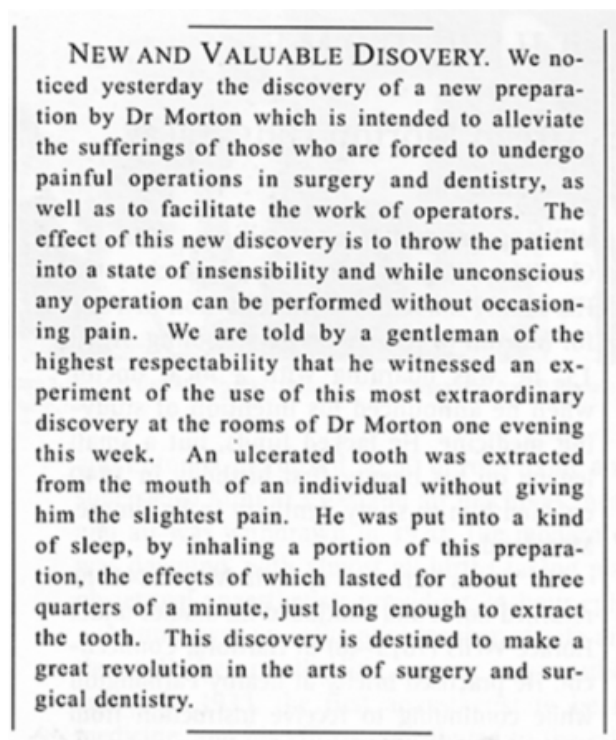
At this point Morton's' life began to flourish as he opened his own dental practice which was a financial success and even allowed him to open a factory which specialised in making

false teeth. With his continuing dental practice his interest in anaesthesia was again stimulated. The problem that he and his patients faced were that to fit the dentures the roots of the old teeth had to be removed at considerable pain to the individual undergoing the experience. He decided to return his interest back to ether which he had studied before. His experiments, which almost certainly did not have the approval of the ethics committee, ranged from testing the effects of ether on his goldfish, his pet terrier and himself.

Excited by his results from anaesthetising goldfish he was given a prime opportunity to test his research. On the 30<sup>th</sup> of September 1846 a patient named Ethan Frost came to his surgery for a painful wisdom tooth extraction and agreed to have it extracted under the influence of Ether. Morton held a handkerchief over the patients' mouth and dripped ether onto it (without accurate end tidal measurements!). The results of the experiment were published the next day in the Boston daily evening Transcript.

Morton's Article caught the eye of an up and coming young surgeon, Henry Jacob Bigelow. On the 16<sup>th</sup> of October 1846 Morton gave the first ever public demonstration of anaesthesia using sulphuric ether and Morton's Inhaler in the Ether dome at Boston whilst Bigelow removed a tumour from the jaw of his patient, Gilbert Abbot.

Figure 7



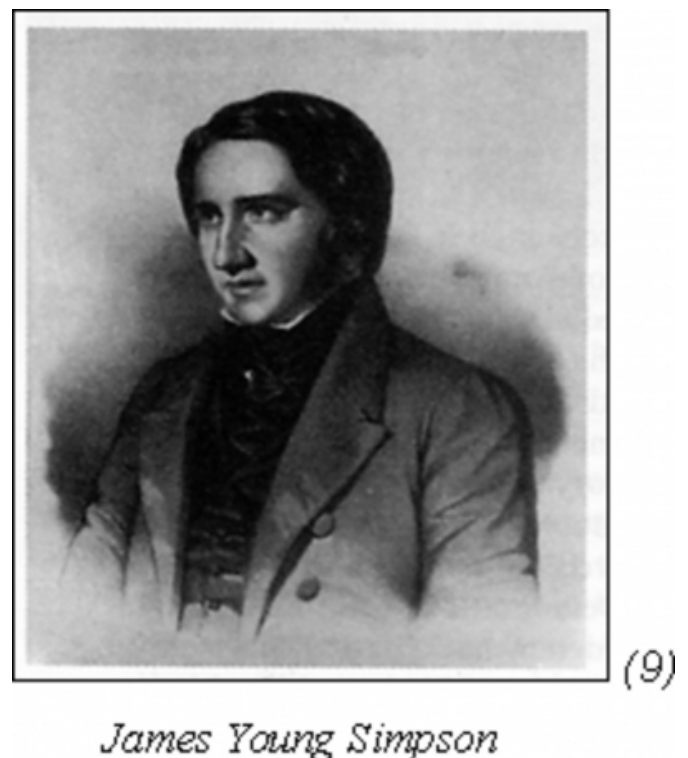
*Boston Daily Evening Transcript,  
October 1<sup>st</sup> 1846*

As with most historical names in anaesthesia Morton's tale is not a happy one. Because he was not a physician he did not receive full credit or financial reward for his discovery and spent the rest of his life in legal battles. He died in 1868 at the age of 49, a pauper. Bigelow kindly had inscribed on Morton's headstone:

'Before whom, In all time, Surgery was Agony  
By whom, pain in surgery was averted  
Since whom, science has control over pain'

One of the most notable in the history of medicine was James Young Simpson. Simpson was born in Bathgate in 1811.

Figure 8



*James Young Simpson*

His family were bakers by trade but sacrificed much of their earnings to allow the youngest and cleverest son, James, to go to University and be educated.

Simpson went to Edinburgh University at the age of 14 where he studied Greek, Latin and Maths for his first year before applying for Medicine in his second year. He was accepted with the handsome bursary of ten pounds per year. At Medical school Simpson was a feisty individual with a keen intellect and was never one to just sit back and accept the standard teachings of his seniors always keen to challenge accepted practice. He graduated from University with his LRCSEd and then for a short period worked in a few general practices before embarking upon and completing his MD thesis. After this he began work for an eminent Pathologist of the time.

From this point Simpson's keen intellect and voracity for his work lead him into the field of obstetrics and gynaecology where he challenged practices and produced a veritable cornucopia of publications, presentations and teachings on the subject. His esteem rose and in 1840 he was voted the Chair of Midwifery at Edinburgh University.

Shortly into this role Simpson heard of a discovery in London from his next door neighbour which was to change the course of his life. Robert Liston had performed a leg



amputation in December 1846 with the patient anaesthetised with ether (shortly after Morton's' discovery). Excited by this he travelled to London to find out more and when he returned to Edinburgh his mind was filled with great ideas of applying the use of ether to the relief of pain in Labour. This was revolutionary and in many circles, unpopular.

Simpson faced opposition from many angles. On the one side of the coin his professional colleagues opposed the idea saying that it would pose great risk to the mother and would certainly harm the child. On the other side many members of the public and clergymen opposed the idea on religious grounds. Simpson fought these ideas using his intellect to oppose them.

Professionally he opposed his colleagues by using the ether in his practice and collecting data from 800 other maternity patients who had had ether for both natural and instrumental deliveries and demonstrated clearly that it did have a place in obstetric analgesia. On the religious front he produced a leaflet with an equally valid counter argument to some of the religious objections. He used direct quotes from the bible to emphasise his points including:

For everything God created is good, and nothing is to be rejected if it is received with thanksgiving, <sup>(10)</sup> And Anyone, then, who knows the good he ought to do and doesn't do it, sins. <sup>(11)</sup>

Simpson found however that ether took too long to work and was not efficient in terms of the volume that had to be used during the course of labour. For this reason he searched for another agent. It wasn't until a pharmaceutical colleague suggested Chloroform that his mind focused on this. In November of the year after the discovery of ether, Simpson and two colleagues inhaled Chloroform over his dining room table and needless to say all fell unconscious and slipped under the table. Simpson's first thought on recovering (other than my head hurts) was how much more potent chloroform was than ether.

A few days later Simpson had progressed from his clinical trial to patient testing and by the end of the month had anaesthetised several patients with Chloroform. Simpson had first used chloroform on a patient by November 8<sup>th</sup> 1847. 2 months later on January 28<sup>th</sup> 1848, chloroform had claimed its first victim, a 15 year old girl called Hannah Greener. Investigation into this occurred but it was unclear whether the death was due to respiratory depression or some unknown effect on the heart. It wasn't until 60 years later

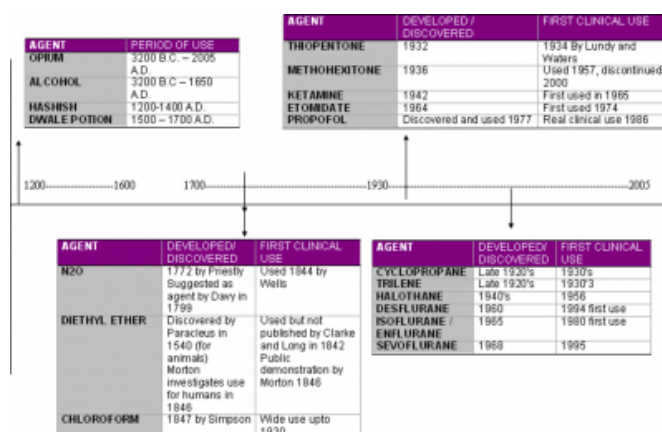
that Levy used animal experiments to prove that deaths from chloroform were:

'Not due to the direct respiratory depression but due to the cardio toxic effects resulting in cardiac fibrillation' <sup>(12)</sup>

Despite this discovery the popularity of chloroform rose well into the twentieth century and when Simpson died in 1870 he had already been Knighted and more than 30, 000 mourners lined the streets of Edinburgh as a mark of respect. His memory lives on with the dining room where he first used chloroform on himself being preserved to this day. Also there stands a statue in Princess place, Edinburgh, as well as a memorial plaque in Westminster cathedral. There is also an annual James Young Simpson gold medal awarded by the Royal college of Surgeons of Edinburgh and the winner gives the annual Simpson memorial Lecture.

## A TIMELINE OF ANAESTHESIA

Figure 9



## THE EBB AND FLOW OF THE TIDES

As we can see from the timeline there have been many changes in the use and popularity of anaesthetic agents over the centuries and none more so than in the last 50 years. What is it that has caused some agents to soar to heights of new popularity whilst others go from the most commonly used anaesthetic to being obsolete? The reasons are many and the changes are multifactorial. Perhaps the biggest reason has been a change in expectation as our knowledge and abilities develop. More recently a major driving force is the desire to have the absolute highest standards of safety possible before even considering anaesthetic agent for clinical use. Let us consider a few examples of change in popularity and consider the reasons why.

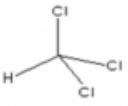
## CHLOROFORM VS DIETHYL ETHER

Chloroform was discovered by Simpson, as we have already discussed, in the middle of the 19<sup>th</sup> century. It largely replaced the anaesthetic at that time which was Diethyl ether despite numerous cases of cardiac fibrillation induced by chloroform. Up until the 1930's it remained popular when its use died out and the use of more sophisticated ethers and a new breed of anaesthetic agents based on either a hydrocarbon ring (cyclopropane) or a halogenated hydrocarbon chain (Trichloroethylene) superseded it.

So why did chloroform initially replace Diethyl ether? To answer this we need to consider the structure and properties of each

### PROPERTIES OF DIETHYL ETHER VS CHLOROFORM

Figure 10

PROPERTY	DIETHYL ETHER	CHLOROFORM
STRUCTURE	$\text{CH}_3\text{CH}_2 - \text{O} - \text{CH}_2\text{CH}_3$	
FORM	Liquid	Liquid
BOILING POINT	35 degrees Centigrade	61.3 degrees Centigrade
BLOOD / GAS PARTITION COEFFICIENT	12	10
OIL / GAS PARTITION COEFFICIENT	65	260
MAC	1.9%	0.5%

The above data demonstrates clearly why there was a move to Chloroform from ether and why despite adverse reports the agent remained popular for many years. Compared to ether, chloroform had a lower blood gas partition coefficient meaning that a stable alveolar concentration was reached faster and a smaller quantity was required to produce surgical anaesthesia. The much higher oil / gas coefficient shows that the agent would be far more potent and brain concentrations would rise rapidly producing a rapid onset of anaesthesia when compared to ether.

So in summary around the time of chloroform and diethyl ether the favourable physiochemical characteristics of chloroform made it the popular anaesthetic of that time and the fact that there was little choice of agent in that era meant that it stayed around for a long time despite adverse

reactions to the agent in some patients.

## CHLOROFORM BACK TO ETHER

By the 1930's chloroforms' popularity had waned and by the 1940's its use was almost obsolete largely due to its safety profile. In its place stepped a new breed of ethers and a group of anaesthetics based around hydrocarbon rings and halogenated hydrocarbon chains. The reason for the return of ether was the fact that the chemical modulation of the original diethyl ether molecule removed many of the problematic properties that limited its use in the past. A good example is divinyl ether.

### PROPERTIES OF DIETHYL ETHER VS DIVINYL ETHER

Figure 11

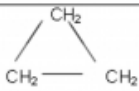
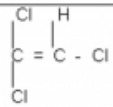
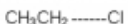
PROPERTY	DIETHYL ETHER	DIVINYL ETHER
STRUCTURE	$\text{CH}_3\text{CH}_2 - \text{O} - \text{CH}_2\text{CH}_3$	$\text{CH}_2 = \text{CH}_2 - \text{O} - \text{CH}_2 = \text{CH}_2$
BOILING POINT	35 degrees Centigrade	28 degrees Centigrade
BLOOD / GAS PARTITION COEFFICIENT	12	2.8
OIL / GAS PARTITION COEFFICIENT	65	60
MAC	1.9%	3%

By altering the hydrocarbon chain of the ether to an unsaturated one the molecule becomes less soluble in blood and so alveolar equilibrium is reached far quicker and less volatile was needed than with the diethyl ether.

The other three agents that were popular from the mid 1930's to the late 1950's were cyclopropane, trichloroethylene and ethyl chloride.

### PROPERTIES OF CYCLOPROPANE, TRICHLOROETHYLENE AND ETHYL CHLORIDE

Figure 12

PROPERTY	CYCLOPROPANE	TRICHLOROETHYLENE	ETHYL CHLORIDE
STRUCTURE			
BOILING POINT	-33 degrees C	87 degrees C	13 degrees C
BLOOD/ GAS COEFFICIENT	0.45	9	3
OIL / GAS COEFFICIENT	11.5	960	-
MAC	9.2%	0.17%	2%

These all had various advantages over chloroform and ether. Cyclopropane was extremely potent and gave a rapid onset of anaesthesia with cardiovascular stability. Ethyl chloride again gave a rapid onset of anaesthesia but was so volatile that it was difficult to control concentrations within the circuit. Trichloroethylene was never a particularly good anaesthetic having a slow onset with slow recovery, being unsuitable for use with a circle due to the production of a neurotoxic reactant. It was cardio stable however and had excellent analgesic properties and so was favoured for labour analgesia.

The main problem with both cyclopropane and ethyl chloride was that they were explosive and therefore posed a real hazard in the theatre setting to both staff and patients alike.

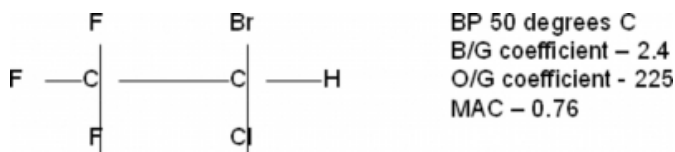
## THE HALOTHANE REVOLUTION

The search for a more stable volatile anaesthetic agent was on being further stimulated by several explosions in theatres in the 1930's due to surgery becoming more sophisticated with increasing use of electrical equipment (13)

The answer came from the research of a chemist during World War II who had extensive data on the chemical properties of the fluorinated hydrocarbons. Using this data the chemical manufacturing company ICI asked various leading clinicians what properties they would require from an anaesthetic agent. On of the main people instrumental in the development of the drug was Michael Johnstone. With the information ICI were able to select an agent which they felt would fulfil these criteria and this agent was 2 Bromo, 2 Chloro, 1,1,1 Trifluoroethane or Halothane.

## STRUCTURE AND PROPERTIES OF HALOTHANE

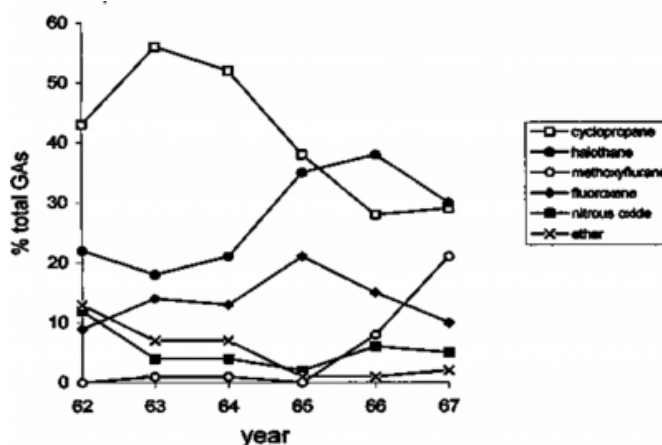
Figure 13



Halothane was ideal in many respects. It gave a rapid onset of anaesthesia with rapid recovery compared to previous agents. It was potent, it was none flammable and it had a none irritable pleasant odour. It superseded all agents at the time of its discovery and by 1956 was introduced into clinical practice in the USA and by 1959 was being used across the globe.

## ANAESTHETIC GAS USAGE IN THE 1960'S

Figure 14



(8)

(Note that halothane was also the first agent to employ the now standard out of circle vaporiser)

## ETHERS HERE TO STAY

So hadn't we discovered an extremely useful agent? Why then is the use of Halothane in the UK almost zero percent and why did it fade into the ether of time.

The answer was safety. Only a few years after its introduction the first case of Halothane hepatitis was documented. At this time there was still little else on the market and so it prevailed. The real damage came a decade later when the Americans conducted the national Halothane study which showed quite conclusively that the incidence of Halothane induced hepatitis was as high as 1 in 6000 and that liver enzyme derangement occurred in upto 20% of patients anaesthetised by Halothane. By 1986 the committee on safety of medicines recommended avoidance of



Halothane in certain groups of patients. Halothane may have survived this if it weren't for the introduction of a new breed of ethers that were feisty yet relatively safe. Enter the fluoranes.

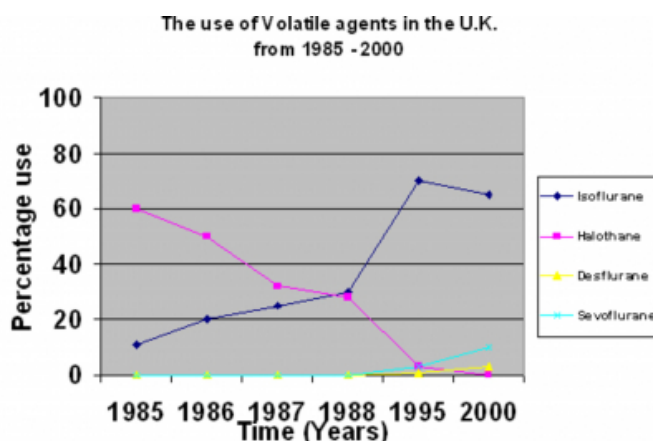
## PROPERTIES OF ISOFLURANE, SEVOFLURANE AND DESFLURANE

Figure 15

PROPERTY	ISOFLURANE	SEVOFLURANE	DESFLURANE
STRUCTURE	$\text{CF}_3\text{CH}_2\text{---O---CF}_2\text{H}$	$(\text{CF}_3)_2\text{CH---O---CH}_2\text{F}$	$\text{CF}_3\text{CFH---O---CF}_2\text{H}$
BOILING POINT	49 degrees Centigrade	58 degrees centigrade	23 degrees centigrade
BLOOD / GAS PARTITION COEFFICIENT	1.4	0.69	0.42
OIL / GAS PARTITION COEFFICIENT	97	53	19
MAC	1.15%	2.05%	7.25%
VAPORISER	STANDARD	STANDARD	PLENUM

Isoflurane came into clinical practice in 1980 but lacked one major feature possessed by Halothane which was none irritability to the airway. For this reason Halothane remained in use and was still the agent of choice for airway obstruction or gas induction. However a further nail in the coffin of Halothane was dealt in 1994- 1995 when two new halogenated ethers arose – Desflurane and Sevoflurane. Both were expensive but were none irritable to the airway, relatively safe (despite the compound A controversy) and following their introduction the use of Halothane has decreased to almost zero.

Figure 16



(8,16)

## MORE IV PLEASE WAITER?

The introduction of intravenous anaesthetic agents in the

1930's caused a major shift in the concept of anaesthesia from that of the production of anaesthesia to that of the induction and maintenance of anaesthesia. The first licensed IV agent used was Thiopentone (also known as Sodium Pentothal). This was developed and researched by John Lundy who published much data on the subject but the first report of clinical use was by Ralph Waters in 1936. Whilst IV anaesthesia seemed the ideal when it was first discovered it was soon realised that administration should only be by a trained anaesthetist and that the absence of adequate monitoring and resuscitation methods for traumatised patients would lead to almost certain death hence quotes like,

‘Spinal anaesthesia is the ideal form of euthanasia in war surgery’—then let it be said that intravenous anaesthesia is also an ideal method of euthanasia’ (14)

John Lundy was the first person to publish an article on balanced anaesthesia in 1926 and following the negative publications on thiopentone for trauma victims the standard practice of anaesthesia began to move to that of IV induction with gaseous maintenance.

Since then many induction agents have been developed all of which have waxed and waned in popularity. The most astonishing of these agents is Propofol which now forms the basis of 70-80% of general anaesthetic inductions in the UK, almost a 100% of sedation on ITU and an ever-expanding number of Target Controlled Infusions. One of the most interesting stories of IV induction agents is that of Etomidate.

Etomidate was the Propofol of the 70's and 80's. It had many highly favourable properties in that it was none cumulative, cardio stable and had a rapid onset of anaesthesia with no stimulation of epileptiform activity. For this reason it was ideal for the induction of trauma patients and also for the sedation of patients on ITU. It became highly popular until the mid to late 1980's when a general feeling that those patients on etomidate did not do as well as those who weren't. The introduction of Propofol in 1986 caused a decline in the use of etomidate and then in 1999 the fears about etomidate were confirmed in an article in Anaesthesia. The article demonstrated clearly that the mortality of patients sedated with etomidate was double compared to those sedated via other means and that this was probably due to adrenal suppression. Etomidates' fate was sealed and the gateway for propofol was opened and since then has never shut.

## WHERE ARE WE NOW?

Currently based on recent data from the Cost Effectiveness Study of Anaesthesia (CESA) around 85% of general anaesthetics given to adults are based upon a Propofol induction and gaseous maintenance with Isoflurane in day case surgery patients. A variety of other induction methods are used based upon the type of surgery and the clinical scenario as well as the experience of the anaesthetist.

Day case surgery has posed an interesting challenge to anaesthetists and has radically influenced the practice of anaesthesia in this setting. According to data from 1990 and 2000 respectively the incidence of day case anaesthesia and surgery has risen from 34% to 65% <sup>(15)</sup>. Day case is a consultant led service where the goals are the safe delivery of a suitable anaesthetic to patients upto ASA 3, with a quick recovery and the ability to be discharged home safely the same day with simple analgesia. During this development agents such as Sevoflurane and Desflurane initially rose in popularity as they were felt to be the ideal agents for day case anaesthesia. This is however a controversial issue and many now feel that this is not the case and that it certainly is not cost effective.

Another area of anaesthesia that is growing in popularity is that of Target Controlled Infusion as demonstrated below in the summarised data from the 2001 CESA survey.

## THE OPINIONS OF ANAESTHETISTS FOLLOWING THE CESA STUDY

**Figure 17**

	Considered to be	Patient acceptance	Cost-effectiveness	Avoidance of nausea/vomiting	Ease of use	Avoidance of adverse events on induction	Overall favourite
Propofol TCI	Overall best: 77%	0%	0%	100%	4%	50%	31%
	overall worst: 0%	58%	0%	65%	19%	31%	
Propofol/ isoflurane	Overall best: 54%	85%	23%	81%	46%	65%	
	overall worst: 8%	4%	4%	0%	4%	4%	
Propofol/ sevoflurane	Overall best: 50%	0%	23%	50%	58%	12%	
	overall worst: 0%	12%	0%	0%	0%	0%	
Sevoflurane/ sevoflurane	Overall best: 4%	12%	23%	12%	19%	0%	
	overall worst: 81%	20%	65%	31%	65%	62%	

(16)

Clearly this data shows that the advantages of TCI were being realised and thus leading to an increase in popularity. Hand in hand with this development goes the increasing amount of knowledge (and hence papers) on BIS monitoring

and the general drift towards BIS monitoring as part of the recommended minimum standards of monitoring.

## BRAVE NEW WORLD

So we have nearly reached the end of our journey through the time line of anaesthetic agents. We have looked at the primordial soup of basic and in most cases dangerous methods of anaesthesia from medieval times. We have looked at the evolution of the first real agents of anaesthesia under the influence of great minds like Davy, Morton and Simpson. We have seen how agents have risen and fallen over the last century until we finally reached the doorstep of our current practice.

So is this the end of the story. Is there anything to be discovered about anaesthesia that we don't already know. Of course the answer is yes and in all the developments over the years we still haven't answered the most basic question of all. How do anaesthetic agents work?

And on the horizon maybe the answer to this question is coming as new and exciting research is carried out at the University of Dundee by Professor J Lambert and his team. Their work is strongly suggesting that anaesthesia is receptor mediated and that the receptor involved is of the GABA<sub>A</sub> receptor subclass. In fact when the gene for this subclass was removed from mice and the receptor was no longer expressed it was shown that the IV induction agent etomidate had no anaesthetic effect. <sup>(17)</sup>

Clearly this is the start of a revolution of newer and better anaesthetic agents with receptor specific properties. Who knows, maybe we are on the brink of discovering the Holy Grail – the ideal Anaesthetic Agent.

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