# ONE HUNDRED YEARS OF ANÆSTHESIA

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ANÆSTHESIA has grown from a scientific curiosity in early nineteenth century to an indispensable weapon in the armoury of modern medicine. This article attempts to give a general account of the development of anæsthesia and anæsthetics during the last hundred years. From the most remote periods, surgeons have sought the means to relieve the pain of operations. The internal administration of drugs seems to have been the time-honoured method. In China Indian hemp was used for this purpose. The stupor produced by compressing carotids and thereby producing anæsthesia with the aid of carbon dioxide was employed by the Assyrians, and hypnotism was practised in the East. In later times advantage was taken of the intoxication produced by alcohol. However, the discovery of the means to achieve complete and safe anæsthesia is an accomplishment of the 19th century (1842-1847). The credit of the discovery must be divided among several investigators: Sir Humphrey Davy for his brilliant researches on the chemistry and pharmacology of nitrous oxide, and for suggesting the possibility of using it as a means of anæsthetising patients during surgical operations; C. W. Long for discovery of the anæsthetic properties of ether; Horace Wells for application of nitrous oxide as an anæsthetic; C. T. Jackson and Morton for successful demonstration of the use of ether as a surgical anæsthetic, and Flourens and Sir James Simpson for the introduction of chloroform.

After the discovery of chloroform no major advance was made in general anæsthetics, until about 1923. Since then active researches have recommenced. Ethylene, cyclopropane, evipal and some thio-barbiturates have been introduced, and a wide variety of methods on basal narcosis have been investigated.

## Mechanism of Action of Anæsthetics

During the last decade or two, anæsthesia has encroached more and more upon the domains of organic and physical chemistry as well as of physiology and biochemistry. In the days gone by, anæsthesia was accepted as such, and no explanation was sought for its action, but now nothing is taken for granted. It has been realised that until some insight is gained into the mysteries of consciousness, our appreciation of the phenomena of anæsthesia will remain inadequate. Strictly speaking anæsthesia means loss of sensation. But the drugs which cause a general loss of sensation also cause loss of consciousness, and this is their most obvious effect. Anæsthesia may be produced in several ways: (1) by temporary paralysis of the sensory nerve endings in the immediate neighbourhood of the part to be operated on (local analgesia), (2) by temporary suspension of the conductivity of the main nerve trunk supplying the affected area (spinal or regional analgesia). But by neither of these methods the patient is rendered unconscious as is the case with (3) administration of a volatile substance through inhalation or (4) by injecting certain substances into the rectum, veins, etc.

Several theories have been advanced, and they are all concerned with the explanation of changes in the nerve impulse and with consciousness. Anæsthesia resembles sleep in many ways, and many of the theories of sleep may with slight modification explain anæsthesia as well. The most important of these are (1) the accumulation of waste products, (2) consumption of intramolecular oxygen, (3) toxin theories, (4) the neuron theory and (5) the anæmic theory. In all these theories it is assumed that there is either a depression of the irritability of the brain cells or the exclusion of stimuli from the periphery or both. Anæsthetic activity is responsible for both of these conditions. The "Mayer-Overton Theory" assumes that anæsthetics act by their solubility in the lipoids of the nerve tissue with consequent fall in conductivity and irritability of the nerve. "The theory of Moore and Roaf" accepts the lipoid solubility but states that the anæsthetic dissolved in lipoid is rendered inactive. According to this view anæsthesia is caused by a loose combination of ether, chloroform, etc., with the protoplasm of the brain cells. The lipoid material, however, absorbs and holds the anæsthetic in contact with the protein and in this way aids the production of anæsthesia. "Verworn's theory" accepts the Mayer-Overton theory to the extent that it explains how the anæsthetic reaches the field of action; but this view holds that real action is due to depression of the activity of the cerebral cells through reduction of their power to carry on oxidation.

## Modern Anæsthetics

The constant increase in the complexity and severity of surgical operations has demanded more and more from anæsthesia, and many of the surgical procedures carried out at the present time require a very high degree of technical skill.

The choice of anæsthetics is a complex problem and is determined particularly by the condition of the patient and the type of operation. Safety is the first consideration, but the depth and duration of anæsthesia, the comfort of the patient and the convenience of the operator are also important.

The several agents that are now in use will be very briefly dealt with, and only certain salient features touched upon. Those that deserve consideration are general anæsthetics, *e.g.*, ether, chloroform, ethyl chloride, vinyl ether, trichlor-ethylene, nitrous oxide, ethylene, avertin with or without morphine and scopolamine and barbiturates, spinal anæsthetics and local analgesics.

The merits and demerits of the volatile anæsthetics are well known and need not be

elaborated here. Suffice it to say that chloroform has been found to be far more dangerous than ether or nitrous oxide, although in the hands of the expert, the acute dangers may be greatly reduced. The chief immediate risks are the induction period. The danger of post-anæsthetic toxæmia makes its employment in prolonged operation almost inexcusable. Ether and nitrous oxide are practically safe in ordinary cases, but nitrous oxide is perhaps the safest form for short operations and in sequence to ether.

A large variety of volatile soluble hydrocarbons has anæsthetic properties and many of them have been studied pharmacologically and clinically. Those that have achieved some practical prominence may be mentioned. *Ethylene* has been used extensively in America, and most observers claim that it possesses many advantages over ether or nitrous oxide. The rapid action and recovery, however, demand close attention on the part of the anæsthetist.

*Cyclopropane* or trimethylene has been found of great advantage in thoracic surgery although recently it has been largely replaced by kemithal. The supporters of cyclopropane claim that it produces fewer toxic effects than other powerful anæsthetics. It has been used clinically with good results in a considerable number of cases, especially in Wisconsin and Montreal. *Venyl ether* is unreliable in the production of full muscular relaxation, but is largely used for small operations of short duration.

It is well known that the introduction of halogen atoms increases the anæsthetic properties and toxicity of aliphatic narcotics. Mention may be made of ethylchloride, trichlorethylene, and avertin (tribromethanol). The utility of *Ethylchloride* as a general anæsthetic is mainly limited by its extremely volatile nature. Anæsthesia is induced very rapidly, and recovery is equally rapid. It is, therefore, particularly suited for minor operations. The main use of ethylchloride is for local anæsthesia—by freezing the tissue with a fine spray of the liquid. The impossibility of dissecting the frozen tissues restricts its use to simple incisions (opening boils and abscesses). The analgesia is imperfect, and thawing painful.

*Trichlorethylene* is now generally recognised to have a definite place in anæsthesia in spite of certain disadvantages. It has been given extensive trial, but is probably not a desirable agent for general anæsthesia. It acts as a prompt central analgesic and is used (self-inhaled, using a simple "Draw over" apparatus such as Freedman's) to relieve the pain of trigeminal neuralgia. Muscular relaxation is very poor. It should not be used to produce deep anæsthesia. For light anæsthesia, used as an adjuvant to nitrous oxide, it is probably quite safe. It is very useful in minor surgery and dental practice where surgical anæsthesia is unnecessary or undesirable. Trichlorethylene analgesia is also tending to replace nitrous oxide and air in midwifery in many parts of Britain.

*Tribromethanol* was introduced under the name "avertin" as a fixed-dose anæsthesia for rectal administration to produce rather evanescent surgical anæsthesia. Reports regarding the safety of avertin are conflicting. It was originally recommended for use as a full anæsthetic, but it is now considered to be dangerous in doses needed to produce this effect. It is used, at present, as a basal narcotic, full narcosis being produced by the administration of nitrous oxide and oxygen.[1]

Many of the derivatives of barbituric acid have been used in medicine for years as hypnotics and sedatives. Since the central effects do not differ in principle from those of the other aliphatic narcotics, certain of the rapidly acting barbiturates can be used alone or in combination to produce true general anæsthesia. The chief difference lies in the non-volatality. They cannot, of course, be administered by inhalation but by mouth, rectum, hypodermically or intravenously. The non-volatility also entails a more prolonged and continuous action. This secures steadiness but restricts flexibility. The latter is a distinct disadvantage, as the anæsthetist can do nothing to lighten the effects if they are too severe. The duration of anæsthesia is also another disadvantage. The use of barbiturates as the chief agents of anæsthesia has, therefore, been considered to be unjustified, although those with relatively brief action are employed in special techniques. Barbiturates in conjunction with inhalation anæsthesia are a definite accession to anæsthetic technique. They are now generally administered to induce sound sleep on the night prior to operation to soothe the patient, and remove nervousness and to secure smooth induction and finally to contribute to the action of the anæsthetic itself.

The common barbiturates that are used to produce general anæsthesia are sodium evipan, pentothal and kemithal. The choice of preparation involves chiefly the duration of effects, the toxicity and the personal experience of the anæsthetist with the drug.

*Evipan* (cyclohexanyl methyl barbiturate of sodium) was introduced especially for intravenous anæsthesia. It acts very quickly and is rapidly broken down in the body. In a good number of cases death has occurred by depression, and it must be used with great discrimination. The chief objection to its use is that it is liable to produce clonic twitching. It may be used with fair safety, however, in a relatively narrow field of analgesia. The action of thio-barbiturates is generally similar, but much shorter.

*Thiopentone* (pentothal) has largely replaced evipan. This drug is used to produce prompt unconsciousness with rapid recovery so that the depth of anæsthesia may be fairly controlled, an advantage over evipan. But, nevertheless, it is dangerous and should not be used indiscriminately. This drug is not well suited for long operations. Obstetric analgesia has been reported to be fairly good with pentothal; excitement is absent and no harmful effects have been observed in the mother or child.

A new thiobarbiturate "Kemithal" (5-cyclohexanyl-5-allyl-2-thiobarbituric acid) has recently been introduced. It has been given a

fair trial, and the results have so far been very satisfactory. Carrington and Raventos have carried out pharmacological investigations and consider it to be half as potent as thiopentone, and slightly less potent than hexobarbitone; but owing to its lower toxicity kemithal has a wide margin of safety. Equiactive doses of these drugs produce a similar duration of action and onset of anæsthesia. Clinical experience supports the experimental findings.[2] Kemithal has been used as an anæsthetic agent in a number of cases. It has been used for induction before cyclopropane anæsthesia, as the principal anæsthetic agent in combination with nitrous oxide and oxygen; as a sole anæsthetic agent with or without oxygen, and to produce hypnosis in association with regional anæsthesia. The results have been satisfactory—post-operative recovery is rapid and is marked by the absence of complications. This drug has been found to have a particular advantage when anæsthesia has to be prolonged. It is especially indicated in thoracic surgery. In such operations there is usually a diminished vital capacity, and anæsthesia in any form tends to cause further embarrassment. There are many other problems too which the anæsthetist has to face. No real advancement towards the solution of these problems had been made till recently when cyclopropane with oxygen anæsthesia was introduced. But long continued use of cyclopropane has its disadvantages. Trials with thiopentone did not prove satisfactory. Kemithal has recently been used on a number of cases of major thoracic operations, and it has been noted that the drug has distinctly many advantages over other barbiturates. There is no respiratory depression and laryngeal spasms are absent. Recovery is very rapid, and there are no post-anæsthetic complications. This technique is undoubtedly a big step forward in the field of anæsthesia. The use of *d*-turbocurarine chloride along with Kemithal has been very promising.

Attempts to blend the actions of volatile anæsthetics by mixing them have been unsuccessful mainly because the ingredients do not volatilise with equal rapidity. The composition of the inspired anæsthetic is, therefore, quite uncertain. A more rational method of combining the advantages of different anæsthetics is to employ them in sequence. Thus anæsthesia may be induced by the pleasant and promptly acting nitrous oxide and then continued with ether. These may be preceded by a sedative dose of morphine or a full hypnotic dose of a barbiturate, to produce lasal narcosis. This probably presents the nearest approach to an ideal anæsthesia.

Many recent advances have been made regarding administration of general anæsthetics. Most inhalation anæsthetics are given with nitrous-oxide-oxygen-ether apparatus. The flow of the gases is regulated and measured fairly accurately by flow-meter (the Rotameter is the present favourite). The Nuffield Department of Anæsthetics has produced a device, the Oxford vaporiser, which is calibrated to deliver known proportions of ether vapour up to 25 per cent. The ether is kept at a constant temperature over a water-bath. A brief pictorial survey of the evolution of anæsthetic apparatuses by A. Charles King is given in the *British Medical Bulletin* (Vol. 4, No. 2, 1946). This is very instructive and gives a clear idea of the advancement in the technique of administration of various anæsthetics.

Side by side with the advancement of general anæsthesia, there has been a revival of interest in local and regional anæsthesia. Mushin[4] has described the bilateral vagal nerve block at its point of emergence from the skull, for such operations as laryngotomy. For upper abdominal surgery, bilateral intercostal nerve block, combined with light general anæsthesia or extradural caudal block has been found especially valuable.

Spinal anæsthesia has been less frequently used during recent years. Nupercaine is the drug of choice, but amethocaine and procaine have also been used.

No reliable statistics of anæsthetic mortality are available. The existing figures give only a rough idea of the relative danger. According to the various compilations, the acute mortality for chloroform is given as 1 in 1,000 to 1 in 5,900, a fair estimate would seem to be 1 in 3,500. This does not take into consideration the delayed deaths. For ether, the figures are 1 in 5,100, to 1 in 23,200—the average would be perhaps 1 in 16,000; for ethyl chloride, 1 in 3,000 to 1 in 7,000; for nitrous oxide in short operations less than 1 in 5,000,000. Beecher (1938) gives 1 in 2,000 for avertin and for chloroform, 1 in 3,500 for cyclopropane, 1 in 5,000 for ether and 1 in 50,000 for nitrous oxide.[5]

With the development of the art and science of anæsthesia operations which were once few in number, have greatly multiplied. At the present day, with our advanced knowledge and experience and constant dependence on the various agents at our disposal, it is difficult to understand how surgical practice could have been conducted without them. Anæsthesia has enabled the surgeon to attack almost every region of the body, and, instead of the operation being hurried over as in the pre-anæsthetic period, the surgeon can now undertake to carry on with deliberation and accuracy. The recent advancement in the field of anæsthesia has been a definite boon to mankind.

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1. Hewer, *Brit. Med. Bull.*, 1946, **4**, 2, 108. 2. Macintosh and Scott, *Lancet*, 1946, **1**, 767. 3. Halton, *Ibid.* 1946 **1**, 771. 4. Mushin, *Proc. Roy. Soc. Med.*, 1945, **38**, 308. 5. Sollmann, *Manual of Pharmacology*, 1942.