ANALGESIA

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How often when operating in some deep dark wound, along the course of some great vein, with thin walls, alternately distended and flaccid with the vital current—how often have I dreaded that some unfortunate struggle of the patient would deviate the knife from its proper course and that I who would fain be the deliverer should involuntarily become the executioner, seeing my patient perish in my hands by the most appalling form of death.¹,²

This vivid description of an operation before the days of anaesthesia and analgesia illustrates the ordeal that both patient and surgeon endured. Only a person who has undergone such an experience can describe it accurately.

I asked a man once after an amputation if he felt faint during the operation. His reply was very curious and characteristic, "Did I feel faint? Why, of course I didn't. Neither would you if you had the same reason to keep you from fainting. It was a good deal too bad for that."

Man has always been searching for means of relieving pain and throughout the ages was singularly unsuccessful. The Peruvian Incas chewed coca leaves to numb the tongue and allay hunger. They argued that whatever came out of the coca leaves on chewing would relieve pain if dropped into wounds. In Roman times Nero's physician, Dioscorides, suggested the use of mandragora and similar atropine plants for the relief of pain in surgery.³

In the Middle Ages until the end of the 17th century the drugs and the methods used to relieve pain were much the same as the Romans, the Egyptians and the Chinese had used 2,000 years previously. Opium, henbane and mandragora were still being used in an uncontrolled way—by mouth or by inhalation from so-called soporific sponges. The results were so uncertain and sometimes so catastrophic that physicians distrusted these drugs and patients avoided them.

So much progress had been made in other sciences but so little in the relief of pain. Joseph Priestley's discovery of nitrous oxide in 1772 was the dawn of the age of analgesia. In 1800 Humphrey Davy⁴ reported the analgesic properties of the gas and suggested its use during surgical operations. But man was slow to grasp the knowledge and the means to relieve pain. Michael Faraday experimented on animals with ether and nitrous oxide and so did Henry Hill Hickman using carbon dioxide. Others, like Long, Wells, Jackson and Colton, played with the idea of relieving pain but did not realize the magnitude of their subject, and it is to Morton that history owes the pride of place as the man who introduced anaesthesia—on October 16, 1846—with his demonstration of surgical anaesthesia at Massachusetts General Hospital.

The dramatic introduction of anaesthesia swept the world as fast as communications would allow. This was but the beginning of man's era of the relief of pain and, like all the more wonderful discoveries of medicine, it brought with it is problems and complications. This was delightfully and prophetically expressed by Fleurens in the Académie soon after Simpson's publication of 50 cases of chloroform anaesthesia reached France in November 1847: 'If sulphuric ether is a marvellous and terrible agent, chloroform is more marvellous and more terrible.' During the next 100 years anaesthesia made great strides but simultaneously analgesia developed.

There are several important milestones in the development of analgesia. If Davy's observations on the analgesic properties of nitrous oxide was the first, then Frederick Sertuner's isolation of the active constituents of opium was the next. In 1806 he published his first paper on 'Principium Somniferum,' but this was ignored and it was not until he published his second paper that any notice was taken. In this paper he named the active alkaloid of opium—morphine, after the Greek god of dreams. The ability to use the pure crystalline drugs instead of the crude mixture was rapidly appreciated by physicians.

Wohler (1828) synthesized urea and so paved the way for the future production of chemically synthesized drugs. This and Leroux's discovery of salicin led to the introduction of the most widely
used analgesic of today, aspirin, and so many of this group.

It is so very strange that after years and years of ineptitude the absorption of drugs by inhalation, by digestion and by injection should all develop at the same time. Alexander Wood in 1843 reported that the use of morphine under the skin in the vicinity of a painful part afforded relief from pain. The introduction of the hollow needle by Rynd (1843) and the syringe by Wood of Scotland (1853) and Pravaz of France (1853) developed the technique of the introduction of morphine near the site of pain.

This was the introduction of anaesthesia and analgesia. Analgesia may be defined as insensibility to pain without total insensibility. This may be produced in the following ways:

1. Inhalation. By general anaesthetic agents.
2. Systemically. By analgesic drugs.
3. Topically. By local analgesic agents.
4. Local infiltration.
7. Epidurals.
8. Intravenously. Direct action on nervous tissue by analgesic drugs.

**Analgesia in Surgical Procedures**

The use of inhalation anaesthetic agents alone to produce anaesthesia enabled observers to describe the various stages of anaesthesia. The inability to use anything but low concentrations of the vapour made this a prolonged affair and even the earliest workers realized that before unconsciousness ensued there was a stage of analgesia. John Snow was, I am sure, aware of this judging by his views on the use of chloroform in midwifery. Guedel depicts it as a narrow band before entering Stage II—the stage of delirium. Nowadays this knowledge is still utilized in midwifery where analgesia to alleviate the pains of labour is produced by the inhalation of nitrous oxide or trichlorethylene. The difficulties in this technique are many; the greatest being the ability to anticipate the pains sufficiently in advance so as to give the drugs time to work. Another use of this band of analgesia occurred during the war when anaesthetists working abroad did not always have nitrous oxide to help them to anaesthetize patients for simple but painful out-patient minor surgical procedures, such as extraction of teeth and incision of septic fingers. The technique was briefly as follows: A piece of gauze 8 in. by 6 in. is rubbed up into a loose ball and placed in the patient’s open mouth so as to protrude slightly. Ethyl-chloride was sprayed on the gauze intermittently for 45 seconds (timed on a watch). The only sign of stage analgesia being reached was “blinking of the eye-lids.” This gave about 90 seconds of perfect analgesia. The chief difficulty is overdosage, precipitating the patient into the stage of delirium.

**Analgesia in Balanced Anaesthesia**

For many years the requirements of anaesthesia were fulfilled by using a single drug, and that drug had to produce sleep, analgesia and muscle relaxation.

It was unfortunate that in order to produce, say, muscle relaxation it was necessary to give far more of the drug than was desirable—the so-called toxic doses—with consequent disadvantages. The pursuit for the ideal drugs has gradually waned and in its place the search for a series of ideal anaesthetic agents has gone on; each having a specific action and preferably of short duration. Thus responsibility for the component parts of anaesthesia has been divided as Crile more or less suggested in his theory of 'Anoci-Association' propounded in 1911.

Sleep, of course, can be achieved by any of the anaesthetic agents but the introduction of sodium thiopentone has made this very pleasant for the patient and very easy for the anaesthetist. It is, however, a drug that requires a great care in its administration, for so easily can the anaesthetic dose approximate to the lethal dose.

In 1942 Griffiths and Johnson introduced curare and the problem of muscle relaxation was solved. Since then various muscle relaxants have been introduced, notably gallamine tri-i-iodide (Flaxedil), decamethion iodide and succinylcholine. They all work but their efficiency depends upon the skill of the administrator.

Pain has been divided into two components—the perception of pain and the reaction to pain. The perception of pain is, of course, obliterated as soon as the patient is anaesthetized, but it is the prevention of the reaction to painful stimuli that is the chief concern of the anaesthetist. Or as Gray puts it, the object of analgesia is not only to give freedom from pain but also freedom from autonomic response. It may be that the final answer is to block the autonomic ganglia deliberately and deal with the ensuing fall in blood pressure. Scurr suggested that pentamethonium and hexamethonium may be used in the prevention of shock during very major operations and Wyman noted its use in the treatment of established shock with the possible prevention of the occurrence of irreversible shock.

In 1938 Organe and Broad introduced the thiopentone/nitrous oxide/and oxygen technique, and this technique, with the addition of muscle relaxants, forms the basis of many of the general
anaesthetics given today. Others have since realized what a powerful drug nitrous oxide is in the prevention of autonomic response.

Neff, Mayer and Perales (1947) and Mushin and Rendell-Baker (1949) suggested the use of pethidine to augment the analgesic properties of nitrous oxide. The addition of this drug is widely used, though the given reasons are perhaps suspect.

Pharmacologically pethidine has three main actions—spasmolytic, sedative and analgesic.

The spasmyloytic action is due to a strong papaverine-like effect on smooth muscle combined with a weak atropine-like effect (mydriasis, inhibition of salivation and some antivagal actions)

It has a sedative effect with amnesia, but is not as powerful a hypnotic as morphia. Like morphia, it induces euphoria and is similarly a drug of addiction. As an analgesic it has been compared with morphia, but is only one-tenth as powerful. It is, however, especially useful in pain associated with smooth muscle spasm. It exerts a generalized depression on the central nervous system like morphia but much less on respiration. Respiration is slowed but not diminished in depth, and may sometimes result in total apnoea. It has given rise to the following generalization: if additional muscle relaxant is necessary during an apnoeic phase, then prolonged apnoea at end of operation is more frequently due to pethidine than to the muscle relaxant. Pethidine does not depress the cough centre but has a selective action in depressing the laryngeal reflex.

Its action on the circulation is slight, although large doses may cause peripheral vasodilatation with ensuing hypotension. It has a quinidine like action on the heart (80 per cent. as potent as quinidine) and increases the sensitivity of the vagal-pulmo-cardiac reflexes (atropine modifies the vagal effect). It has been used to abolish the arrhythmias associated with cyclopropane anaesthesia.

It may release histamine from tissues, producing a typical triple response causing urticarial wheals over veins into which it is injected. It also has considerable anti-histamine action. It has local anaesthetic action (70 per cent. strength of cocaine), but is not suitable clinically as it produces preliminary irritation.

Side effects may produce hypotension, vertigo, sweating, nausea and vomiting.

It may be given either by mouth, intravenously or intramuscularly. It does, however, take about 10 to 15 minutes to act and must be given in good time. Its action is prolonged and perhaps its greatest application to anaesthesia is the prolonged analgesic effect it has after an operation, thus ensuring quiet recovery from the anaesthetic.

It is destroyed by hydrolysis in the liver (80 per cent.) and 5 to 20 per cent. is excreted in the urine.

Other analgesic drugs which may be used to reinforce nitrous-oxide/oxygen anaesthesia are numerous, but for all its disadvantages pethidine is the most convenient and the most widely used. Other drugs are: (1) morphine; (2) amidone (Physeptone); (3) phenadoxone (Heptalgin), and (4) levorphan (Dromoran, Methorphinan).

Morphine has always been the most powerful analgesic known to man—first in its impure form, as opium, and then as a pure alkaloid. It causes the loss of pain by acting selectively on pain sensation in dosage that does not impair consciousness but does affect respiration. It is widely used as premedication and for relief of pain and reflex excitability post-operatively. It produces euphoria and so quickly becomes a drug of addiction. Side effects on medullary centres include stimulation of the vagal centre and the vomiting centre and depression of the cough and the vasomotor centres. It causes constipation by local action on gut. It is excreted mainly in the urine, though traces appear in the faeces and sweat.

Amidone (physeptone) and phenadoxone (heptalgin) are similar in action to morphine but without the sedative action of morphine and thus are not so useful as premedication.

Levorphan (dromoran) is a powerful long-acting drug even greater than morphine. It has little effect on the respiration and the intestines. It is not a sedative nor does it produce sleep. Euphoria is absent.

Local Analgesics

These are drugs which interrupt nerve conduction when applied to nervous tissue in suitable concentration. Their action is reversible and it is thought that as most of these drugs are usually hydrochlorides or sulphates the alkalinity of the tissues frees the base and this unites with the nerve tissue.

All local analgesics are vasodilators, with the exception of cocaine (vasoconstriction) and Xylocaine (no effect on blood vessels), and consequently have to be used with a vasoconstrictor such as adrenalin. This diminishes the blood flow, prolongs the action of the drug and slows the rate of its absorption. The last is very important as all the drugs produce toxicity if the blood concentration rises. This may lead to convulsions, circulatory collapse or such allergic phenomena as bronchospasm and urticaria. Detoxification of these drugs is thought to occur in the liver.

The drugs have a differential action upon nervous tissue dependent upon the size of the nerve fibres and the concentration of the drugs. Thus, in a mixed nerve, sensory nerves will be affected before motor nerves. The order in which the nervous tissue is affected is as follows: (1)
Proctocaine and anaesthesia for surgery have been limited their skill in the use of adrenalin. Halsted introduced nerve block using cocaine and tried the drug upon himself. He became addicted to the drug but, even more remarkable, overcame the addiction. Cocaine, however, was too toxic a drug to use other than topically and so a succession of new drugs appeared, Tropococaine (1891), Stovaine (1904). In 1904 Fourneau introduced Novocaine (procaine), a synthetic substance which is still the most widely used local agent. It is about one-quarter as toxic as cocaine and far less irritant. It is poorly absorbed from mucous membrane surfaces and thus cannot be used for topical analgesia.

Amethocaine (Decicain) was synthesized by Eislieb in 1928 and Nupercaine (cinchocain) was introduced by Meischer and Uhman in 1929. Both these drugs are far more toxic than cocaine but are said to be 20 times more potent in analgesic quantities and can be considerably diluted—this makes the effective dose safer than cocaine.

The introduction of lignocaine hydrochloride (Xylocaine) by Lofren and Lundquist in 1943 in Sweden has, at last, brought about a rival for procaine. It has several advantages, as it is extremely stable and not decomposed by acids, alkalis, boiling or autoclaving. Its effects come on very rapidly and last much longer than other similar drugs. It has better spreading qualities and though used in the same concentrations as procaine is more powerful. It may be used topically in a 2 to 4 per cent. solution, and for regional analgesia in ½ per cent. solution. It has no effect on blood vessels and so has to be used with adrenalin. It appears to have a central cerebral effect producing drowsiness and generalized analgesia.

There exists a need for a drug whose action would last for days rather than hours. Such a drug would help in the treatment of post-operative pain, the intractable pain of advanced malignant disease and many other painful conditions. Proctocaine and Efocaine are two compounds that attempt this but have sufficient disadvantages to limit their use.

The various techniques of using these analgesic solutions have been already mentioned. They supply an adequate alternative to general anaesthesia for surgical procedures. The increased skill in blocking nerves and ganglia has led to an extension of their scope beyond surgery to the treatment of patients and as an aid to clinical diagnosis.

Stellate ganglion block will cause sufficient vasodilatation of the cerebral vessels to be of real benefit to patients suffering from cerebral thrombosis, arterial embolus or arterial spasm. It has been used as an aid to diagnosis and therapy of vascular disorders of the upper limb such as Raynaud's disease, arterial embolism, the effect of cold, trauma to the vessels, etc.

Stellate ganglion block combined with upper thoracic ganglion block has been used with dramatic results in the relief of anginal pain, and Flothow's recommends it in the treatment of severe cardiac decompensation.

The lower thoracic ganglia may be blocked in for the treatment of visceral pain of the upper abdomen, such as acute pancreatitis, gastric crisis, renal colic and malignancy. The relief of pain that these methods produce is dramatic. Recently, in a case of porphyria, the intense abdominal pain which had been unrelieved by drugs for several days was obliterated in a few moments after a splanchnic block. The patient then slept for the first time for days and then awoke to have a meal.

Lumbar sympathetic blocks may be used as an aid to diagnosis, treatment and indications for surgery in vascular disorders of the lower limbs, such as Buerger's disease, arteriosclerosis, arterial embolism and thrombosis.

Caudal block may be used to obliterate the pains of labour and Kenny has recommended the use of proctocaine in the sacral canal for the relief of intolerable pain in malignant disease in the pelvis.

These are but a few of the ways in which the anaesthetist can help his colleagues in the treatment of their patients. Analgesia has taken a hundred years to reach its present stage and it is to be hoped that still newer drugs and newer techniques will render the analgesia better and safer. In a review such as this it has been necessary to quote many authors and workers, and I hope that this in itself is a humble tribute to all those who have worked to alleviate pain for mankind.

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the lung, when such sequelae may occur irrespective of the anaesthesia. The method seems to have been responsible for several cases of urinary retention occurring in men, several of whom required catheterization.

Many of the nursing and resident medical staff have come to prefer this technique for thoracic work. It is significant that when the routine use of this method was stopped after a trial period the surgeon at one hospital asked if it could be continued one week longer as he was operating on a surgical colleague; and that when the sister of one of the thoracic surgical wards herself underwent lobectomy, and later thoracoplasty, she chose chlorpromazine for herself.

**An Assessment**

The drug has undoubted value as an anti-emetic and has a place in the management of painful conditions and in psychiatry, but its continued administration carries the risk of damage to the liver and bone marrow. In anaesthesia the author’s experience is largely limited to its use in surgery of the lung. Here the combination of drugs used allows repeated endobronchial instrumentation, provides satisfactory operating conditions and seems to lessen the discomforts of the post-operative period. With adequate after care significant complications have not been increased.

While conventional methods in skilled hands allow a more rapid return to normality and make assessment of the patient’s condition easier, there is no doubt that several of the effects of chlorpromazine can conveniently fit into the pattern of anaesthetic requirements for major surgery. While grateful for this it would seem preferable to be able to control the extent of those various effects independently by manipulating the dosage of several different and shorter acting drugs. A sawn off shot gun may be effective but it is neither a weapon of precision nor is its use appropriate on all occasions.

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