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# INDUCED SLEEP---A HISTORY OF ANESTHESIA FOR NURSE ANESTHETISTS

by

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## PREFACE

One of the most rapidly advancing fields of medicine is that of anesthesia. The degree to which it developes in history is one index of social progress. The history of anesthesia, like the story of many useful contributions to mankind, is filled with hopes, disappointments, comedies, tragedies, and the very successes and failures involved in the process of accelerating this area of medicine.

The true value of anesthesia goes beyond the relief of pain as an end in itself. It has made the development of modern scientific and artistic surgery possible and has saved and is saving millions of lives. We live in a scientific age and further advances will take place and are continually developing as anesthesia experts see the use of observations and equipment in this and other branches of science. As our knowledge of anesthesia becomes more exact, the science itself will save more lives and alleviate suffering; but no matter how exact the science becomes, it will always reflect the words of S. Wier Mitchell in The Birth and Death of Pain when he wrote:

> ... The Birth of Pain! Let centuries roll away; Come back with me to nature's primal day.

What mighty forces pledged the dust of life!
What awful will decreed its silent strife!
When writhes the child beneath the surgeon's hand,
What soul shall hope that pain to understand?
Lo! Science falters o'er the hopeless task,
And Love and Faith in vain an answer ask,
When thrilling nerves demand what good is wrought
Where tortue clogs the very source of thought. ...
Recall this memory. Let the curtain fall,
For gladder days shall know this storied hall! ...
Then radiant morning broke, and ampler hope
To Art and Science give illuminated scope.
What angel bore the Christ-like gift inspired! ...
Made pain a dream, and suffering gently dumb!
This heaven-sent answer to the cry of prayer
This priceless gift which all mankind may share...
God's highest mercy brought by man to man(1).

I chose the topic, History of Anesthesia, in the hope that the reader may be able to analyze and reach a better understanding of anesthesia as it exists today. Also, I hope that this work will aid future students in nurse anesthesia programs as the history of anesthesia is part of the required curriculum for a nurse anesthesia program certified by the American Association of Nurse Anesthetists Council on Accreditation.

I express grateful appreciation to Dr. Robert E. McClintock, my thesis advisor for his patience and for his counsel. To Dr. Benjamin Rigor, former Chairman of the Department of Anesthesia at the University of Texas Medical School at Houston, Texas, I owe much for his help and assistance.

In writing this thesis, I attempted to acquaint the reader with a better understanding of the development of modern anesthesia and show its impact on our daily lives.

I hope this work will serve as a learning aid for future nurse anesthetist students. I strove for objectivity, but on this count I cannot claim to be really unbiased. However, the views expressed herein are mine and I assume full responsibility for what has or has not been said.

# CHAPTER I

## ANESTHESIA IN ANTIQUITY

Nature has given us pain for protection. It is the instinctive cry of the body at the onset of injury and disease. The word "pain" comes from the Latin word poena, which means punishment or penalty(2).

It has been claimed that the "deep sleep that the Creator caused to fall upon Adam is the germ of the idea of anesthesia(3)." Primitive peoples, in an effort to eradicate pain, treated it as a demon, and tried to frighten the demon away from their bodies. They often tattooed their skins to keep the demons outside the body. They wore rings in the ears and nose, as well as various ornaments on their person, such as talismans, amulets, tiger claws and charms, to ward off evil spirits(4). Primitive man also probably employed digital compression of the carotid arteries to produce a form of anesthesia. Indeed, the Greek and Roman words for the carotid artery meant "the artery of sleep(5)."

Although the Egyptians had a well developed legal code and considerable understanding of medicine, little evidence evolved that they developed any real proficiency in the

science of anesthesia, although scattered references came down through the writings of the Greeks. About 2,000 B.C., the Babylonians had a well developed legal code, the so-called Hammurabi Code. Admixed with rules governing daily life of the people and punishments for crimes were rules and regulations relating to the practice of medicine. It provided for severe penalties to be inflicted upon individuals who committed quackery and malpractice. Yet, these early cultures had little regard for the relief of pain and suffering, although there developed a gradual awakening of science and general medicine(6).

The Egyptians of the New Kingdom used Indian hemp and the juice of the poppy to cause a patient to become drowsy before surgical procedures. And the "sorrow-easing drug" which his comrades gave Ulysses may have consisted of a similar substance(7). The ancient Egyptians also applied a species of rock brought from Memphis which, when powdered and moistened with sour wine, they used to apply to painful wounds. This was the first known record of the use of carbonic acid as a local anesthetic(8).

Early Hindus inhaled the fumes of burning Indian hemp to produce a stupor. In that condition, they used it as a mind relaxant to endure pain. Cannabis is the botanical term for hemp. According to at least one writer, the mental effect of cannabis is that:

> ... the mind is immediately filled by a delicious succession of pleasant ideas. Until recently the American public has had no interest in and no

> knowledge of this ancient drug. It has been well known in Mexico and Central and South American countries by the name of Marijuana, the weed that intoxicates(9).

The Greeks worshiped Hypnos, the god of sleep, the fatherless child of night and the twin brother of death. Hypnos was the father of Morpheus, the god of dreams. From this belief, Hypnos came to be the most welcome of the Greek gods during times of sorrow, sickness, and especially during the pain of surgery. During these times, Hypnos slept and did not hear the prayers of the suffering patient(10).

The Greeks first used the term anesthesia, a term derived from two Greek words meaning the absence of feeling(11). Plato used the word in his writings(12). Unfortunately, Greek poets and dramatists made more use of the term in their literary works than the medical men made use of pain killing procedures in their practices. Not a single example of the use of anesthesia during an operation survived in known Greek medical writings. Theocritus alluded to Lucina, the goddess of the obstetric art, as "pouring an insensibility to pain down all the links of a woman in the throes of labour(13)." From the Greek word narkē, meaning "stupor," stemmed our word "narcotic(14)."

But the Greeks did not have an exclusive use of literary references to anesthesia. The Talmud used several passages which pointed out that the practice of easing pain of torture and death by stupefying the sufferer was quite ancient(15). In China, a physician named Hau T'o, who

lived about 230 A.D., came to hold a unique position in Chinese annals; he introduced surgery to that nation(16).

Until Hau T'o began his work, Confucian doctrine prevented the development of surgery in China because the priests considered the human body too sacred to be mutilated. However, Hau T'o developed into such a skillful surgeon that the Chinese people erected temples to him and he came to be worshiped as the god of surgery. Further, he discovered an effervescent powder called "ma-yo," which when dissolved in wine produced complete insensibility, thus enabling him to operate on any portion of the body without the patient's knowledge(17). To the sorrow of history, he did not leave the formula for his soporific powder to posterity.

Ibn Sina, known to the western world as Avicenna, dominated the Arabian school of medicine. His canon of medicine, after being translated into Latin, became the medical authority in Europe for six centuries. In one reference to the types of anesthetic agents to alleviate pain, he enumerated as follows:

> 1) those contrary to the cause of pain, which remove the pain. Examples: fennel, linseed made into a poultice;
>
> 2) those conteracting the acrimony of the humors, soothing, inducing sleep, or dulling the sensitive faculties and lessening their activity. Examples: inebriants; milk; oil; sweet water;
>
> 3) narcotics and somniferous drugs, the first of these is the most certain(18).

With the birth of Christianity came the concept of the relief of pain based upon divine healing through touch and

prayer(19). Some theologians believed mandragora to be the myrrh which, according to Saint Mark, the Romans offered with wine to Christ before they nailed Him to the Cross. Indeed, narcotic draughts were sometimes given to persons about to be crucified with the object of lessening their sensibility to the agony(20).

Theophrastus, in his early writings on botany, alluded to the virtues of mandragora. The Greeks called it circecum derived from the word Circe and they believed an evil spirit dwelt in the plant(21).

> Of all the roots nourished at the breast of Mother Earth, none was so mysterious as the mandragora (mandrake). The man-like form of the outspread, two legged root was awe-inspiring. It grew beneath the gallows, feeding on the flesh of felons; its pain easing sensation destroying death wine (wine of the condemned) was given on a sponge to those about to be tortured and hanged(22).

Disocorides (ca. A.D. 100), first mentioned mandragora as an anesthetic. He recognized the difference between the hypnotic and anesthetic affects of the drug(23).

During the centuries that followed the fall of the Roman Empire, little progress was made in the sciences or humanities except within the structure of the Roman Catholic Church. With civilization and culture at a low ebb, anesthesia as a science also remained immature. The so-called Middle or Dark Ages did produce much for which society should be indebted. Religion and philosophy did not disappear, as some historians would contend. The Renaissance, although a period of an awakening of science and the arts, based much of the knowledge of the time upon facts dis-

covered during the Middle Ages. But this period of history contributed little to man's search for an effective anesthesia(24). Saint Hilary, in the Fourth Century, distinguished between anesthesia due to disease and anesthesia resulting from drugs(25). Otherwise, there emerged no significant writings on the subject.

In 1490, Theodoric of Lucca mentioned a preparation which he called aleum de lateribus. He described it as "most caustic, and a soporific which, by means of smelling alone, could put patients to sleep on occasion of painful operations which they were to suffer(26)."

The mixture was placed on a sponge in hot water, and then applied to the nostrils of the patient. He called it the spongia somnifera. In writing about using the sleeping sponge, he stated:

> Take of opium, or the juice of unripe mulberry, of hyoscyamus, of the juice of hemlock, of the juice of the leave of mandragora, of the juice of the woody wig, of the juice of the forest mulberry, of the seed of lettuce, of the seeds of dock, which has round apples, and of the water-hemlock, each an ounce; mix all these in a brazen vessel, and then place it in a new sponge, let the whole boil as long as the sun lasts on the dog-days, until the sponge consumes it all, and has boiled away in it. ... As oft as there shall be need of it, place this sponge in hot water for an hour, and let it be applied to the nostrils to him who is to be operated on until he has fallen asleep and so let the surgery be performed(27).

When later tested by modern scientists, it was found the result would not "even make a guinea pig nod(28)."

In Brooke's Tragical History of Romelus and Julietta, printed in 1562, which some literary figures contend sup-

plied Shakespeare with much of the plot and material for Romeo and Juliet, the character Friar Laurence spoke to Julietta: "I have learned and proved of long time the composition of a certain paste which I make of divers somferous samples, which beated afterward to powdere and dronke with a quantitie of water, within a quarter of an houre after, bringeth the receive into such a sleep, and burieth so deeply the senses and other spirits of life that the cunningest phistian will judge the party died." In the same connection, the characters continued, "And, besides that, it hath a more marvellous effect, for the person which useth the same feeleth no kind of grief and, according to the quantitie of draught, the patient remaineth in a sweet sleepe; but when the operation is perfect and done, he returneth unto his first estate(29)." In Shakespeare's Romeo and Juliet, the lovely Juliet took a mysterious unnamed drug which produced such a profound sleep and such a perfect simulation of death that she was put in her tomb(30).

Thus it has been over the years. Anesthetic agents have played a part in literature, but very little influence derived from the actual practice and use of an induced sleep in the operating room. Of the ancient cultures, the Egyptians and Greeks placed a practical value on pain killing drugs. One method of pain relief for surgery was strangulation, used first by the Assyrians for the circumcision of their children. Anesthesia by strangulation to

the point of unconsciousness was practiced until the Seventeenth Century(31). Another method was cerebral concusion, achieved by placing a wooden bowl over the patient's head, and striking it until the patient became unconscious. The directions were simple. The surgeon merely had to strike the bowl with sufficient strength to crack an almond, but light enough to leave the skull intact(32). Other medical doctors diminished pain by the application of intense cold or by the compression of nerve roots(33). These were all primitive and less than effective methods of rendering the victim lethargic to pain. Anesthesia over the years progressed at about the same rate as surgery -- slowly. Therefore, it took modern man to perfect the uses and skills of both fields.

Even today an operating room can be viewed as a brutal and inhuman place. Modern anesthetic agents and operating room instruments may be considered by future generations as primeval as the use of hemp appears to our modern medical personnel. Accordingly, to understand better the historical evolution of anesthesia, consideration must be given to that period of time during which there was a distinct change from ancient medicine to current scientific uses of anesthesia.

# CHAPTER II

# INHALATION AGENTS

Present day choices of agents mirror the progress of the history and evolution of anesthesia. Ether, an early agent, continued to be used until the 1960s. Nitrous oxide, another early agent, is currently one of the most frequently used agents. Chloroform and Ethyl Chloride's popularity was short lived. The twentieth century brought us Vinethane, Ethylene, Trimar, Fluoromar and Cyclopropane. None of these agents are used today because they are either toxic or explosive. In the 1830s work began on the halogenated hydrocarbons. The first one released for clinical use was Halothane. It was followed a year later by Penthrane and three years later Ethrane was released. The most recent inhalation agent released for use is Forane. Much research led to the development of these agents and to those not yet released.

## NITROUS OXIDE

Although many people worked toward the development of modern anesthesia, early scientific investigation developed through a group of individuals from Great Britain. One of the primary motivations came from Joseph Priestly, a non-

conformist minister, who amused himself by experimenting with "fixed air" in a brewery next to his home in Leeds, England. There he isolated and described nine different gasses. In 1772 he obtained nitrous oxide from metals heated with nitric acid. Nitrous oxide is also called protoxide of nitrogen and nitrogen monoxide and "laughing gas." It is one of several oxides of nitrogen, but the only one which exhibits anesthetic properties(34).

It was not until 1799 that Sir Humphrey Davy, at the age of seventeen, experimented with and discovered that nitrous oxide had the ability to mask pain and suggested that it be used as an anesthetic agent(35). Also in 1799, James Wyatt designed a nitrous oxide container to assist in Davy's research. Davy was the first to refer to nitrous oxide as "laughing gas." He published a book on its effects entitled Researchs, Chemical and Philosophic -- Chiefly Concerning Nitrous Oxide and Respiration. In it are described methods for obtaining the gas and its effects on human beings(36).

But for forty-five years, Davy's suggestions lay unheeded. Then on December 10, 1844, a traveling chemist-lecturer, Gardner Q. Colton, visited Hartford, Connecticut, and gave a public demonstration of nitrous oxide. During the course of the demonstration a man named Cooley, who had just inhaled the nitrous oxide, fell over a bench. When he came to his senses, he noted his leg was lacerated and bleeding, but stated he felt no pain. Horace Wells, a

dentist who was attending the lecture, noted this and asked Colton to administer him some nitrous oxide the next day for a dental extraction. This Colton did and, following this successful experiment, Wells learned from Colton the method for producing nitrous oxide and used it in his dental practice for work on fifteen patients. In January, 1845, Wells attempted to introduce nitrous oxide as an anesthetic by giving a demonstration at the Massachusetts General Hospital. Unfortunately, the patient cried out and his colleagues ridiculed the experiment, thereby causing nitrous oxide to fall into disrepute(37). Wells eventually became deranged and an ether addict. He later committed suicide in a New York City prison by cutting his cubital vein. An ironic touch to the suicide act was the fact he inhaled ether while he did it, perhaps to relieve the pain of the incision(38).

In 1863, Colton revived the use of nitrous oxide when J. H. Smith, a dentist, heard his lecture and used the gas in his practice. Nitrous oxide was finally accepted and became widely used and continues to be the most widely used inhalation agent in anesthesia practice today(39).

During 1868, Edmund Andrews introduced the use of oxygen and nitrous oxide. He published, "The Oxygen Mixture: A New Anesthetic Combination," in which he described the efficiency of adding twenty percent oxygen to nitrous oxide. He concluded the mixture was safer and more pleasant. The techniques of administration were worked out by him and

by Paul Bert in 1879. Bert used positive pressure administration. As a result of Bert's investigation, the first accurate knowledge of the action of nitrous oxide became available(40).

The Johnstone Brothers, a medical supply business, began in 1872 to supply liquid nitrous oxide in metal cylinders. At a pressure of thirty atmospheres the gas condensed into a liquid(41). This led to the need for measurement of pressure and flow rate of gases which contributed to the eventual development of the anesthesia machine.

## ETHER: Diethyl Ether

The accidental mixing of two known substances gave the world ether. Its use and value was not fully realized for six hundred years. In the 13th Century, Raymundus Lillius, a Spanish chemist, mixed sulfuric acid and ethyl alcohol. The results when heated produced a product with a pleasant odor and, therefore, was called "sweet vitriol(42)."

In 1540, Valerius Cordus of Germany described the synthesis and properties of ether. He included in the use upset stomach, phelgm, dysentery, colic flatulence, hiccups, and whooping cough(43). Also in the 16th Century, Paracelus combined ethanol and sulfuric acid. He described the synthesized substance as a sweet sulfur compound. He told of how his chickens consumed the compound, fell asleep, and later awakened without any apparent ill effects. This inspired Paracelus to hypothesize that this substance "quiets

all suffering without any harm, relieves all pain, quenches all fevers and prevents complications in any illness(44)."

The name ether is attributed to a German scientist, Frobenius, who carried on experiments in 1730(45). However, the interest was short lived. It was not until 1818 that Michael Faraday called attention to the profound lethargic state that resulted from the imprudent inhalation of ether(46). By 1824, a surgeon, Henry Hill Hickman, had advanced the idea of using a gas to produce insensibility during operations(47).

Crawford Long first witnessed the effects of ether at an "ether frolic" in Philadelphia, Pennsylvania. This seems to have been an accepted pastime of well-to-do of the day. During January, 1842, he first used ether clinically. He gave a patient named James Venable ether before removing a tumor from his neck(48). Long continued using ether for minor surgery but not without making an impression on his friends. His use of ether threw the community of Jefferson, Georgia, into such excitement and fear of the gas that the people threatened to lynch him. Faced with this opposition, he abandoned operations under ether and later moved his office to Athens, Georgia. His work there received little recognition until publicized by Marion Sims(49).

Another pioneer of ether, William Morton, could not afford to go to medical school so he became a dentist. He established a good dental practice but was driven to seek a means to alleviate the pain of dental operations. Given a degree of financial security by his dental practice, he de-

cided to attend medical school at Harvard University(50).

While at that august school, Morton consulted with Professor Charles J. Jackson and learned that sulfuric ether had some effect in producing unconsciousness. Morton experimented on his dog, his fish, himself, and his friends. He finally convinced a friend to permit him to extract a tooth painlessly under ether(51).

As a second year medical student, he obtained permission from Dr. John Collins Warren, professor of surgery at Harvard to make a public trial of ether on October 16, 1846(52). This was a turning point in the history of anesthesia. The event was brief, but dramatic and world shaking.

Morton arrived late because he worked up until the last minute to develop a suitable inhaler. He arrived at the amphitheater of the Massachusetts General Hospital, now named the ether dome in honor of the event, and proceeded to anesthesize Gilbert Abbott. When the patient was unconscious, Morton said "Sir, your patient is ready." The procedure progressed quietly, and there was no struggling or screaming. At the conclusion of the procedure, Dr. Warren turned to the observers and said "Gentlemen, this is no humbug(53)." Dr. Henry J. Bigelow, an emminent surgeon of the day, declared "I have seen something today which will go around the world(54)."

Following Morton's demonstration of the effectiveness of ether anesthesia, the practice was generally accepted. Notwithstanding his experiments, Morton never received full recognition for the development of ether anesthesia during

his lifetime. But, the inscription on his tombstone reads:

> "Inventor and Revealor of Inhalation Anesthesia: Before Whom in All Time, Surgery was Agony: By Whom, Science had Control of Pain(55)."

Ether continued being widely used until the early 1960s.

## CHLOROFORM: Trichloro-methane

Chloroform was prepared in 1831 by Justus von Lerby in Germany, by Samuel Guthrie in the United States, and by Soubeiran in France(56). Jean-Baptiste Dumas described its physical and chemical properties in 1835 and gave it the name chloroform because of its relationship to chlorine and formic acid(57). Flourens discovered its anesthetic properties in 1847.

James Simpson and his associates introduced chloroform to clinical practice in November, 1847(58). Simpson's use of chloroform to relieve the pain of childbirth came under attack because it was felt by the Calvinist clergy that he acted in defiance of Divine Will(59). However, his opposition received a serious blow when John Snow administered chloroform to Queen Victoria for the birth of her eighth child, Prince Leopold(60). A wag of the day, in 1847, suggested a coat of arms for the obstetrician, which consisted of a newborn baby with the legend underneath, "Does your mother know your're out(61)?"

Many deaths occurred with chloroform because of apparent improper administration based upon misconceptions and incomplete knowledge of the drug's direct effect on the heart and circulation. The incidence of death with chloro-

form came to be at least twice that of ether(62). Yet its extreme potency, which in the hands of the unskilled led to the high incidence of unfortunate events, was at the same time the reason for chloroform's potential superiority as an anesthetic agent(63). Most of the black marks against the agent resulted directly from maladministration and lack of supportive therapy rather than any inherent property of the drug itself(64). Prior to 1890, the deaths were considered consequences of overdosage. After 1890, the sharp increase in the incidence of deaths in the post-operative period were thought to be from liver damage or delayed chloroform poisoning(65). Possible predisposing factors which occurred coincidently were:

1) introduction of opiates as premedication;

2) increasing length of surgical procedures; and

3) change in usage, according to surgical demand, from borderline analgesia to surgical anesthesia(66).

The relatively low level of deaths can be attributed to the skills and acute observations of these early physicians. The major surprise is that they were able to apply chloroform as successfully as they did, even if the success was only marginal. Even today, chloroform, with the exception of the drug halothane, relaxes a laboring uterus better than other drugs. It is the possibility of sudden inhalation of a strong concentration that makes chloroform extremely dangerous and a cause of cardiac depression.

## ETHYL CHLORIDE

Ethyl chloride was the last general anesthetic adopted in the Nineteenth Century. It was first prepared by Valentine in the Seventeenth Century and later by Flourenes, who described its anesthetic properties in February, 1847(67). Heyfelder first used it clinically in 1848; he found its action to be similar to ether and concluded that its extreme volatility, the difficulty of obtaining the pure compound, and the high price would preclude its frequent use(68).

The "Glasgow Committee" of the British Medical Association examined its action upon lower animals and in their report, published in 1880, concluded that it was unsuitable for human beings as it produced convulsions and respiratory failure. The disrepute into which ethyl chloride fell was largely due to impurities in the samples examined(69). As a local anesthetic, the drug leaves much to be desired. It has limited use today in dental practice.

## ETHYLENE

The anesthetic properties of ethylene were first noted by Hermann in 1864(70). It was not used clinically until 1923 when administered by Luckhardt, Carter, and Brown. Isabella Herb carried out the first clinical study in 1924 (71). Even after that date, few hospitals used it because of its high combustibility. Its explosive nature offset its slight advantage over nitrous oxide.

## VINETHENE: Divinyl Ether

In 1897, Semmler prepared the first Vinethene. In an attempt to make a hybrid molecule which would have the characteristics of parent agents ethyl ether and ethylene, Leake and Chen discovered its anesthetic properties in 1930(72). Ruigh and Major first successfully synthesized it in 1931 and Gelfen and Bell used it clinically at the University of Alberta in 1932(73). Many objections to this agent were associated with its breakdown products rather than with the original molecule(74).

## TRIMAR: Trichloroethylene

E. Fisher first described Trilene in 1864. As originally used in medicine to control the pain of tic douloureux, researchers found in 1935 that its analgesic effect was general and not specific on the trigminal nerve(75). Jackson described its anesthetic properties following experiments with dogs. Striker used it to anesthetize three hundred patients in 1935(76). Following an unenthusiastic report by the American Medical Association in 1936, it fell into disuse(77).

## FLUOROMAR: Trifluoroethylvinyl Ether

Fluoromar came to be the first inhalation agent to emerge from the group of fluorine containing hydrocarbons and ethers which Krantz developed and evaluated extensively(78). He first described it after initial investiga-

tion in 1953(79). The drug was introduced for clinical trial in 1954(80). This drug is no longer used. It had no apparent advantages over other agents that were available.

## CYCLOPROPANE

August von Freund first produced cyclopropane in 1882. Its anesthetic properties were not discovered for fifty years and then quite by accident. Professor Henderson and his staff in Toronto, Canada, worked with propylene in an attempt to find an anesthetic agent which would be potent and less toxic than ether. They stored the propylene in metal alloy tanks which consistently produced impurities. They believed these pollutions caused the myocardial depression and nausea associated with the use of the gas in general anesthesia. In 1927, a new member of Professor Henderson's staff, Dr. Lucas, was assigned to determine the toxic substances in the stored propylene tanks. He found mostly hexenes, but also an isomer of propylene formed during the preparation of propylene. He discovered cyclopropane and its anesthetic properties during tests for the contamination of propylene. He expected it to have toxic effects but, when tested on kittens, they went nicely to sleep and recovered rapidly without any significant problems. He concluded these tests during November, 1928. Subsequently, Professor Henderson volunteered to be anesthetized with cyclopropane, as first administered by Dr. Brown. In spite of excellent results, their first attempts to

introduce the drug clinically failed(81).

Later, Dr. Waters attended a meeting where an unknown physician suggested the use of cyclopropane as a general anesthetic. Following some correspondence, Dr. Waters became convinced of its effectiveness and started clinical studies at the University of Wisconsin where cyclopropane proved to have great promise. Waters and Rovenetine anesthetized their first three patients in August, 1930. The studies continued for three years with Dr. Waters and Dr. Schmidt publishing the first clinical report in 1934(82). Cyclopropane came to be used clinically until the advent of the nonexplosive agents.

## CHAPTER III

## IN SEARCH OF AN "IDEAL AGENT"

The initial work in the development of Fluothane began in the late 1920s. Scientists were looking for an "ideal agent" that would be nonexplosive, nonflammable, safe, potent, economical, compatible with other compounds and have no deleterious effect on equipment. They felt it should provide a rapid pleasant induction, have little or no depressant effect on vital organs and be easily and rapidly eliminated unchanged from the body with no side effects(83). Their agent was well termed "ideal."

Initial studies began with halogenated hydrocarbons. In 1929, Frederick Swatz discovered that fluorination added stability to the aliphatic hydrocarbons. He placed one fluorine atom on a carbon molecule(84). In 1932, Booth, Bixby, Gnong, and Birchfield showed that by increasing the temperature and pressure they could put three fluorination atoms on a carbon molecule(85). But, from 1932 to 1946 the primary use of fluorocarbons came to be with vehicular gases for aerosols and refrigerants. Progress remained slow because of the difficulty in producing pure gasses. Impurities were often present and caused more problems than the

gas itself. The development of the gas spectrograph in the early 1940s proved to be a great asset in the development of pure gasses(85). During this period most anesthesia research involved the medical aspects of World War II on trauma patients.

In 1937, Henne developed a method for combining fluorinated hydrocarbons with other aliphatic chains. This increased the number of possible compounds that could be formed(86). Following this, B. E. Brue began to add other halogenated chains and discovered some important relationships between fluorine, bromine, and chlorine. He found that increased fluorination produced agents with decreased boiling points and that decreasing the boiling point of an agent caused a greater incidence of convulsions in animal studies. The addition of chlorine or bromine increased the boiling point and decreased the seizure activity. He also found the bromination caused increased potency over chlorination(87).

During the middle 1940s Benjamin Robbins published a report on results of two years of testing of forty-six fluorinated compounds for their anesthesia activity. Of these he felt only four warranted further investigation. He made four important discoveries:

1) there was increased potency with increased boiling point,

2) the introduction of a second halogen atom (chlorine, bromine or iodine) to a fluorocarbon greatly increased the potency,

3) most of the agents did not support the blood

pressure in dogs, and

4) abnormalities in cardiac rhythm were frequently produced.

One of the agents that Robbins felt warranted further investigation was trifluorobromethane. It had good anesthesia properties and resembled the compound that was to become Halothane ten years later(87).

## HALOTHANE: Fluothane

D. W. Suckling, a researcher working for Imperial Chemical Industries Laboratories, synthesized a series of compounds in 1951; bromochlorotrifluorethane was one of these. It was introduced as an anesthetic under the aegis of the Committee on Non-Explosive Anesthetics, formed by the British Medical Research Council. In 1956, Raventous investigated the pharmacological use of the gas and actions of the gas on animals(87).

The Imperial Chemical Industries Laboratory did not release Halothane, but hired the highly qualified, experienced anesthesiologists Johnstone, Bryce, Smith and O'Bryan to test it and establish guidelines for its use. Johnstone and his associates published the findings of their research in October, 1956(88). They listed the advantages and disadvantages of Halothane. These studies led to the development of the Fluotec and other out-of-circuit vaporizers because they found Halothane too potent to be used in the conventional in-circuit vaporizers(89). They also determined that the various side effects could be decreased if

lower concentractions were used. Halothane was released in Great Britain in 1957 and in the United States and Canada in late 1958(90).

Between 1960 and 1962 a number of case studies reported Halothane as the suspected cause of severe hepatic necrosis and post-operative hepatitis. This created a great deal of concern and led to the largest research project ever to investigate an anesthetic agent(91).

In 1961, the Committee on Anesthesia of the National Academy of Sciences--National Research Council, designated a study group to report periodically on all clinical aspects of Halothane anesthesia and to give special attention to any evidence of association with fatal post-operative hepatic necrosis. The primary objectives were:

> 1) to compare Halothane with other general anesthetics regarding the incidence of fatal massive hepatic necrosis within six weeks of an anesthetic and
>
> 2) to compare total hospital mortality within six weeks of anesthesia(92).

The National Halothane Study produced facts and figures on over 800,000 anesthetic administrations. The conclusions indicated Halothane to be as safe or safer than other commonly used anesthetics. The effects of Halothane on the liver, if any, are clinically negligible. It has become the most widely used, potent inhalation agent we identify with the 1960s and is still an extremely popular agent today(93).

## PENTHRANE: Methoxyflurane

Penthrane, a relatively modern anesthetic agent, is a halogen substituted, methyl ethyl ether(94). It is the first unsymmetrical methyl ether used in clinical anesthesia(95).

Larsen first synthesized it in 1958, and Artusia used it clinically as early as 1959. He and his associates published the first pharmacologic and clinical results in 1960(96). They found Penthrane to be more susceptible to biogradation than Halothane and to produce renal and hepatic injury. Also, its high blood and tissue solubility rendered it less flexible and more likely to be toxic(97). This agent is rarely used today.

For some time the success of Halothane discouraged the search for new and better anesthetics. With time, scientists found that Halothane, too, had its limitations. It caused respiratory depression, sensitized the myocardium to arrythmias induced by epinephrine and isoproterenol and caused uterine relation which led to increased bleeding during delivery.

The primary criteria researchers sought in a new agent were nonflammability and chemical stability. Many researchers believed that stable chemicals would not be metabolized; therefore, possible toxic effects attributed to their metabolites would be eliminated. Other desirable criteria were minimal respiratory and cardiovascular depression, rapid and

pleasant induction and recovery, good muscle relation, not sensitizing the myocardium to catecholamines, no cellular toxicity and economy of production. Both enflurane--compound 347--and its isomer isoflurane--compound 469--satisfied most of these criteria.

## ETHRANE: Enflurane

Ethrane was synthesized by R. C. Terrell in 1963. It was the second methyl ethyl ether made available to the anesthesia community(98).

Ethrane differed from Halothane and Penthrane in its resistance to biogradation; as a consequence, organ injury is minimal. Rapid changes in alveolar concentrations are possible because of its low blood solubility. It provides heart rhythm stability and excellent muscle relaxation(99). It is the most widely used potent inhalation agent in the United States today.

## FORANE: Isoflurane

R. C. Terrell synthesized Forane in 1965. Because of the difficulty of synthesizing and purifying Forane, he developed it after the isomer Ethrane. The problem of purifying Forane was sufficiently great than the compound was almost abandoned. L. Spears first accomplished a separation of Forane from this contaminants introduced during manufacturing; this permitted biological testing. Initial testing in mice showed promise. Further studies by Rudo in

1967, by Dobkin and Byles in 1975 and by Stevens and Eger in 1975 were positive in outcome and suggested that no significant injury to the liver or kidneys would follow its use. Other studies of toxicity were negative. These findings led to trials in volunteers and the use of Forane with patients.

Forane was scheduled for introduction in 1975. However, a study by Corbett in mice suggested that Forane might be a hepatocarcinogen. A larger study with better controls failed to confirm Corbett's findings and the United States government released it for clinical use in 1980(100). Forane may constitute a major advance in the search for an "ideal" anesthetic(101). However, it is too early to determine what its future applications will be.

## CHAPTER IV

## ADJUNCTS TO ANESTHESIA

Over the years, various drugs have been used in conjunction with the inhalation agents. The barbiturates are still used today with Sodium Pentothal being the primary drug. The other group of drugs that are of significance are the neuromuscular blockers. They play a very important role in the practice of anesthesia. The muscle relaxants most used in the modern operating room are Curare, Anectine, Flaxedil, and Pavulon.

### SODIUM PENTOTHAL: Sodium Thiopental

In 1903, a German chemist, Emil Fisher, discovered barbiturates. The barbiturate first synthesized was Barbital. At the beginning of the intravenous barbiturate era, three long-acting drugs were investigated for clinical use. Bumm studied Pernosten in 1927, Zerfes and Lundy investigated Amobarbital in 1929, and Lundy experimented with pentobarbital in 1930. None of these drugs proved clinically satisfactory. Knopp and Taubb discovered the first ultra short-acting barbiturate, hexobarbital. Weese and Scharpff tested it clinically in 1932 and Lunday tested it clinically

at the Mayo Clinic in 1934(102).

Researchers also maintained an early desire to develop a drug that would produce profound hypnosis, but from which emergence would be prompt. As early as 1908, scientists detected that substituting sulfur for an oxygen atom on the carbon in the barbituric acid molecule produced a less stable and shorter acting drug called thiobarbiturates. Pentothal came to be the sulfur analogue of sodium pentobarbital. It was first prepared in the laboratory in 1929. Clinical trials with pentothal were begun in 1934 and it was first marketed in the United States in 1936(103).

A study covering the period 1934 through 1955 revealed that one-third of all surgical cases received pentothal. In 1950, an estimated 70% of all patients receiving general anesthesia were induced with pentothal. Pentothal suffered only one major decline in popularity. This occurred in 1941; the problem involved usage in the early months of World War Two and was due primarily to the drug being administered by untrained personnel(104). Pentothal is still used today as the main induction agent for general anesthesia. It can be found in all modern hospital operating rooms.

## CURARE: D-Tubocurarine

Indians along the Amazon and Orinaco Rivers in South America used blowpipes to shoot darts with tips which were covered with Curare. They used these darts for killing wild

animals and in warfare. About thirty species of plants are sources of Curare. The plants are found throughout northern and western South America. The Indians obtained the poison by soaking the roots and stalks of plants containing Curare in cold water, dissolving out the contents, and heating the mixture until it concentrated into a black paste(105).

In 1811, Sir Benjamin Brodie, an English scientist, while doing experiments on different modes of death from vegetable poisons, found that Curare altered respirations and that the heart continued to beat for some time after respirations ceased. Artificial respiration by means of a bellows revived some of the experimental animals. Brodie and Watterton, in 1815, found that asphyxia in Curare poisoning caused death(106).

It was in 1856 that Claude Bernard showed his colleagues that Curare exerted its paralyzing action by blocking the nerve impulses at the neuromuscular junction. Bernard demonstrated that Curare did not act on central or peripheral nerves, but acted on skeletal muscles(107). Dr. Carlos Chagus of the University of Brazil used electric eels, which had large neuronal endings, and radioactive C-14 to establish that Curare attached to a "transmitter substance" in the end plate making this substance insensitive to the actions of acetylcholine(108).

Initial clinical use of Curare was in the fields of psychiatry and neurology. Fiercelin and Benedict, French physicians, used Curare in 1866 to prevent epileptic

seizures in human beings. They had to discontinue their project because of a shortage of Curare(109). Intocostrin, the stable preparation of Curare, was manufactured by Sembil Laboratories in 1939. Richard Gill, with the help of Dr. McIntyre, developed a dependable Curare product(110). Curare evolved into an extremely useful drug in the practice of modern anesthesia.

## ANECTINE: Succinylocholine

In 1906, Reid, Hunt, and Taveau first described the pharmacological action of Anectine. Though they studied its effect on the blood pressure, they failed to observe that it caused neuromuscular block because they were using a previously curarized animal(111). Gluk established in 1941 that the hydrolysis rate for Anectine was high and that it was broken down by cholinesterase in horse serum. Bovet and his colleagues in Italy and Phillips in the United States independently described the neuromuscular blocking properties of Anectine in 1949(112). The drug was first used on man as a neuromuscular blocking agent by Thesleff at the Karolinska Institute in Stockholm, Sweden, in 1951. Foldes and his associates introduced it to the United States in 1952(113). Anectine is a very important adjunct to good anesthesia today. It is widely used in most hospitals.

## FLAXEDIL: Gallamine Triethiodide

Following the introduction of Curare into clinical

anesthesia, pharmacologists throughout the world sought to develop a synthetic drug with a similar action. In 1947, Bovet and his co-workers described the muscle relaxant properties of a synthetic product -- Flaxedil(114). This drug is rarely used today. It has no advantages over other muscle relaxants that are available.

## PAVULON: Pancuronium Bromide

While investigating a series of amino-steroids, Hervitt and Savage observed in 1964 that when they added an acetylcholine-like group to these biologically active compounds, pavulon appeared to be a very effective neuromuscular blocking agent. The pharmacology was studied extensively in animals by Bucket and Bonita in 1966. Boud and Reid introduced it into clinical practice in 1967(115). As a new muscle relaxant available to the anesthestist, this drug has received great popularity in recent years.

## CHAPTER V

## THE NURSE ANESTHETISTS

The shortage of personnel to administer anesthesia may well have started on March 31, 1842, the day after Dr. Crawford Long anesthetized James Venable. Physicians were not eager to learn the newly developed art of administering anesthesia. One reason for this is that the role of the anesthetist was considered subservient to that of the surgeon. Also, the pay was low.

In America the trend was established early for the administration of anesthesia by persons who were not physicians. This led to the practice of anesthesia being administered by nurses.

In 1877, Sister Mary Bernard entered St. Vincent's Hospital in Erie, Pennsylvania, to train as a nurse. She assumed the responsibilities of an anesthetist and did not complete her training as a nurse. During the next twenty years, many Sisters of the Third Order of the Hospital Sisters of St. Francis trained as anesthetists(116).

In 1889, a small hospital with thirteen patients, three surgeons -- the Mayos -- and five Sisters was opened by the Sisters of St. Francis in Rochester, Minnesota. The anes-

thesia was administered by Edith and Dinah Graham, two sisters who had graduated from nurses training in Chicago, Illinois. They were succeeded by Alice Magaw in 1893. In 1906, Miss Magaw reported on fourteen thousand Ether and Chloroform anesthetics without a single death(117).

In 1908, Dr. George Crile of Cleveland selected Miss Agatha Hodgins as his anesthetist. She was a very capable anesthetist, an excellent teacher and administrator. In 1915, Miss Hodgins established a school of anesthesia for nurses at Lakeside Hospital in Cleveland, Ohio. By the 1920s some thirty schools were in operation. Today there are about 130 programs for nurse anesthetists(118).

Miss Hodgins and fifty-three nurse anesthetists founded the National Association of Nurse Anesthetists on June 17, 1931. The association's objectives were "to advance the science and art of anesthesia, to develop higher educational standards, to facilitate cooperation between the nurse anesthetist and the medical profession, to publish periodicals, to maintain a central bureau of information and to educate the public to the need for proper administration of anesthetics." In 1939 they changed the name to the American Association of Nurse Anesthetists(119).

The first national qualifying examination was taken by ninety-two candidates June 4, 1945. In January, 1952, the school accreditation program was put into effect. In 1955, the U. S. Department of Health, Education and Welfare recog-

nized the American Association of Nurse Anesthetists as the accrediting agency for schools of anesthesia for nurses. Pressured by political, professional and educational forces to separate accreditation and certification from the parent socio-political American Association of Nurse Anesthetists core, the association relinquished control of the Council on Accreditation and the Council on Certification and established them as autonomous bodies in the late 1970s. Mandatory recertification was voted in by the membership and became effective August 1, 1978. To remain certified, each member must attend forty hours of continuing education every two years(120).

There are eighteen thousand active practicing nurse anesthetists in the U.S. today who owe much to the founders and leaders of their profession. Their objectives fifty years later remain "to advance the science and art of anesthesia, to develop higher educational standards, to facilitate cooperation between the nurse anesthetist and the medical profession, to publish periodicals, to maintain a central bureau of information and to educate the public to the need for proper administration of anesthetics(121)."

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