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Local anesthetic agents

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LOCAL ANESTHETIC AGENTS.

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HISTORY

INTRODUCTION

The desire to reduce pain is as old as the history of man. The search extends over many centuries, as is indicated in the writings of Hippocrates. The use of local anesthetics by the ancient Egyptians depended more upon superstition than upon local anesthetic properties. Their method depended upon the topical application of such agents as the fat of the crocodile, or the dried and powdered skin of the same animal, and attended with much religious ceremony. They also used a certain kind of 'Stone of Memphis' which was probably a carbonated rock. This they wet with vinegar and applied to the area to be operated, possibly producing carbonic gas.

The sedative and anodyne properties of many plants were known to the ancient Greeks, from which they made ointments and lotions, the most prominent being Mandragora atropa. The Chinese early recognized the sedative action of opium and hyoscyamus.

ANESTHESIA BY COMPRESSION

Of the methods developed in ancient times, probably the first to render any real service was the compression of nerve trunks. It was thought first to be developed by the Arabs, revived by Pare in the seventeenth century. Throughout the succeeding ages one sees it occurring in one form or another, only to be discarded again. No doubt it accomplished its

purpose to a limited degree, but was practical only upon the extremities for amputations or minor surgery. Usually the pain produced by compression of nerve trunks was as severe as the actual operation.(1)

It was noted that the binding of the limbs to prevent hemorrhages caused disturbances of sensation. This method was advocated by many but continually fell into ill-repute. In 1874 J.Moore, of England, devised a constricting apparatus, consisting of pads compressing the sciatic and the anterior crural nerves, which were left in place one and a half hours. This was combined with the use of large doses of morphine, thus permitting painless peripheral operations. Other surgeons found the method defective, as it caused severe pain and intense venous compression.(2).

ANESTHESIA BY MEANS OF COLD

In the sixteenth century, the application of cold as a means of reducing sensibility was noted by Severinno, an Italian surgeon, and introduced by his pupil Thomas Bartholinus, by the use of ice and snow. It was forgotten, but revived again by J.Hunter, who carried out painless experiments on animals. Two French military surgeons, during Napoleon's time, reported that with a temperature of 19 degrees below zero, the limbs of the wounded men could be amputated with no sensations, but in no specific instance was cold used as an anesthetic.(3)

The rapid chilling of tissues by rubber bags and pig's bladders filled with ice and salt was early

replaced by the rapidly evaporating fluids. Richardson in 1866,(4) devised an atomizer for the purpose of using ether and chloroform in a finely divided spray on the skin. This apparatus consisted of a finely pointed metal tube through which a strong stream of air was passed, blown by the means of rubber bulbs, this being mixed with the ether sucked through another metal tube from a glass container. The temperature rapidly drops to minus 15 to minus 20C., sufficient to turn a test-tube of water into ice. The freezing of tissues occurs very rapidly and the thawing and return to sensation is very slow. Other hydrocarbons than ether can be used in the Richardson apparatus such as ethyl bromide, carbondisulfide, and ethylene chloride.

Quoting from Braun(5) based on the work of Gruetzner, Gendre,Heinzmann and Fratscher, the physiological effect of cold on nerve substance is as follows:"slightly cooled nerves retain their property of reacting to stimulation for a considerable time; cooling to plus 5 degrees centigrade inhibits the stimulation of all nerve fibers; cooling to the point of ice formation intercepts nerve function, the nerve, however, regaining its property of reacting to irritation on thawing. Sudden intense cold acts as a stimulus; slow cooling even to a minus 4 to a minus 6 degrees does not stimulate. It is undoubtedly the cooling alone which brings the molecular change and injury to nerves, which requires a normal temperature for a normal action."

The sense of pressure remains intact for a long time in the presence of cold; the sense of touch is less resistant than the temperature sense. The sense

of pain is lost more quickly and more completely than any of the other senses.

For the practical application of cold, very low temperatures are necessary for the rapid dissipation of heat from the tissues. The rapidity of freezing the tissues depends upon the heat dissipation, also on the nature of the tissues, such as the amount of blood in them, and the rate of blood flow through the tissues. The sensory nerves lose their function when the tissues are cooled below the freezing-point. There is a terminal anesthesia and the degree depends upon the duration of the freezing process. When the tissues are rapidly cooled, anesthesia is preceded by pain; upon thawing, sensation returns provided there has not been permanent damage to the parts, the insensitive area is changed into one of marked hyperesthesia due solely to the freezing process. The freezing process applied to nerve trunks blocks their conduction and thus produces anesthesia, but at the expense of great pain. Its field of usefulness is limited to superficial incisions,as in opening an abscess, furuncle, incising fistulae, and aspirating cavities of the body. This method of anesthesia survives today by the use of ethyl chloride spray which was first described by Rottenstein in 1867.(6).

ANESTHESIA BY LOCAL APPLICATION OF HYPNOTICS

The theory existed until recent times that sleep-producing drugs would produce local anesthesia when applied locally. This accounts for the use of opium,

hyoscyamus, the juice of indian hemp, of the poppy seeds, and aconite in the preparation of plasters, washes, and salves. It was demonstrated that the skin could be saturated by the application of chloroform, which resulted in the idea that local anesthesia could be easily produced with the volatile inhalation anesthetic agents. This is only partially true as these agents set up more or less irritation or destruction of the skin, with fleeting disturbances of sensation even when the effect of cold from evaporation is prevented.

This line of thought stimulated Richardson to advocate the use of electric current in aiding the absorption of these agents. It was soon proved that these non-conductive agents failed to respond to cataphoric action of the electric current. It is hard to believe by these means a sufficient amount of drugs mentioned above could be absorbed by the unbroken skin to produce a useful anesthesia.

DISCOVERY OF HYPODERMIC SYRINGE

It is not difficult to understand the attempt to produce local anesthesia by direct application to nerve trunks of a sleep-producing drug. This naturally followed the discovery of the hypodermic syringe. The discovery of the hypodermic syringe was erroneously attributed to Wood. It was really discovered by F.Ryand,(7) an Irish surgeon in 1845. Wood was really the first to apply its use by the injection of solutions around nerve trunks(8). He believed it would be of decided

advantage to inject a narcotic by direct application to the nerve affected by disease. This was attempted by means of acupuncture needles superficially, but without success. He recalled his attempt to remove a naevus by injection of the acid solution of perchloride of iron. In order to do this he procured what he described as an "elegant little syringe", constructed by a Mr. Ferguson of Gillspur street, London. It occured to him that this instrument might supply the means of bringing the narcotic more directly than he had hitherto been able to accomplish on the affected nerve in neuralgia. The first patient to receive an opiate by injection was an old lady suffering severely from cervico-brachial neuralgia, who had the idiosyncrasy of not being able to take opium by mouth. The syringe was inserted in the angle formed by the clavicle and the acromion, and about twenty drops of a solution of muriate of opium was injected. The patient complained of giddiness and confusion within ten minutes, and the pain subsided with half an hour.

ESMARCH BANDAGES

In 1874 Esmarch (9) described a method of "kunstliche blutleere" by means of elastic bandages, in which local anesthesia followed a short period of local ischemia. He used this procedure on small operations on fingers and toes. He mentioned that Stokes removed a carcinoma of the back of the hand by this

method. The probability of producing anesthesia is too uncertain and evil consequences as gangrene, permanent motor and sensory paralysis are avoided with difficulty.

COCAIN

This takes us up to the real beginning of modern anesthesia when cocain was introduced by Karl Koller (10), in 1884. The cocoa plant is native to Peru and Bolivia, and was regarded as a gift of God by the natives. The response obtained by chewing the leaves of the plants were well known to the natives before the Spanish invasion. Dr. K. Scherzer, (11) was the first to bring back a large quantity of these leaves to Europe, when he accompanied the Austrian frigate "Navarro" on its expedition circumnavigating the world. A supply of these leaves were received by the chemist Woehler and in 1858 his assistant Albert Niemann and Loessen isolated cocain from the cocoa leaves. Scherzer was the first to notice that chewing the leaves caused a numbness of the tongue, which was also noted by Niemann, who described its anesthetic properties.

B. von Anrep in 1879,(12) studied the pharmacological effects of cocain and found that when it was injected subcutaneously the area of the skin above the injection became insensitive to pain from the prick of a pin, and he actually recommended its use clinically as a local anesthesia. However, he did not follow up his own suggest-

ion. Upon the instillation of a solution of cocain into the conjuctival sac of animals he noticed only the previously well-known midriatic action.

The earliest record to be found of any cocoa preparation for its anesthetic effect is a letter published by Moore(13) of New York, in 1885, who states that for the past ten years Dr.Fauvel, (address not given) had been using the fluidextract of cocoa applied to the pharynx and larynx by a brush or a spray as a local anesthetic to these parts.

However the real introduction of local anesthetics into the practice of medicine and surgery dates from 1884, when Karl Koller and Sigmund Freud,(10), two young Vienese physicians made a systemic study of the various alkaloids in hope of finding a substitute for morphine. One of their friends a young physiologist, had through a painful affection a neuromata in the stump of an amputated thumb, become the vistim of the morphine habit. While working with cocainKoller realized that he had in his possession the local anesthesia for which he had been previously striving. In Stricker's laboratory he made his solution of cocain and instilled a few drops in a frogs eye, and afterwards of a guinea pig. He found the cornea and the conjunctiva insensitive to mechanical, chemical and faradic stimulation. Then he repeated these experiments on himself, some colleagues, and many patients. His first publication was read at the German Ophthalmoligical Society at Heidelberg. He recommended it to his colleague,

Jellineck, who used it in the surgery of the nose and throat.

CONDUCTION ANESTHESIA

Knowledge of the new remedy spread quickly. Within six weeks it was being used in America. and the most active of its advocates, William Halstead, was able to report within less than a year, successful anesthesia in over a thousand surgical cases. R.J.Hall with the assistance of Dr. Halstead,(14) developed conduction anesthesia. They noted that the conductive power of nerve trunks could be interrupted by cocain solutions, with the result that the areas innervated by these nerves became anesthetic. Halstead made practical use of this method in the extraction of teeth. The first attempt being the introduction of cocain solution in the vicinity of Dr. Hall' infrorbital foramen in order to anesthètize his sensitive dentine for a dental operation.

Halstead in 1885 also experimented with dilute cocain solutions injected into cutaneous and subcutaneous tissue by infiltration and thus developed local tension sufficient to produce anesthesia and really antedating Schleich in the use of very dilute solutions of cocain.(15).

SPINAL ANESTHESIA

Like many new discoveries, spinal anesthesia resulted from an accident. (16). In these experiments Corning had aimed to inject the fluid between the spinous processes, and permit it to be carried by the veins to the cord. He first experimented on a dog, injecting a 2% cocain

solution in the lower dorsal region and obtained paralysis of motion and sensation in about five minutes, followed by complete recovery without noticeable ill effects. He next injected a man suffering from sexual disturbance using 30 minims of a 3% cocain solution, between the 11th and 12th dorsal vertebrae. There was no result in 8 minutes, and the injection was repeated, producing anesthesia and incoordination of the lower extremities. The passage of a uretheral sound caused no pain and the uretheral electrode caused no inconvenience. An hour later the patient was able to leave with sensibility still impaired but none the worse for his experience. Corning in conclusion states, "Whether the method will ever find an application as a substitute for etherization in genito-urinary or other branches of surgery further experience alone can show. Be the destiny of the observations what they may, it has seemed to me, on the whole, worth recording." Corning's intention was to make the injection into the neighborhood of the cord; he did not aim to puncture the membranes, whether this occurred or not, he must have entered the canal, else it is hard to understand how anesthesia resulted, as it could not take place by diffusion, because the cord is well isolated from its perivertebral surroundings.

The first operation to be performed under spinal anesthesia in America was probably by R. Matas of New Orleans.(17) The patient was a young, male negro, upon whom a hemorrhoidectomy was performed in 1899. The subarachnoid space was reached between the fourth and fifth vertebrae, and spinal fluid was allowed to escape. A volume of 1 cubic centimeter of 1% cocain in normal saline was injected twice during a 5 minute interval. The

anesthesia was complete from the waist down, and the patient made a good recovery.

In 1898, Bier(18) described the technique of spinal injection of cocain solution used on a patient suffering from advanced pulmonary tuberculosis, and another from osteomyelitis of the leg. The anesthesia was highly successful. Then Bier, with admirable courage, tried the method upon himself to more accurately observe its effects. The only ill effect was a slight headache which soon disappeared.

COCAIN POISONING

The wave of enthusiasm for cocain and local anesthesia was quite remarkable. As a result much carelessness was involved as to concentrations and volumes injected. Soon, mild, severe, and fatal cases of cocain poisoning were observed in great numbers following the use of the drug subcutaneously, internally, and by local application to mucous membranes. The first compilations of the published cases by cocain poisoning was made by Falk(19) Naturally these cases represented only a small portion of the entire number observed.Corning had early served warning by stating: "a remedy which has such a strong affinity for nerve substance must also effect the heart and central nervous system when introduced into the circulation in concentrated solution." According to the tendency of the time concentrated solutions were used and often the size of the absorbing surface to which cocain was applied was relatively large.

To overcome the toxicity following the injection of cocain in concentrated solutions, Schleich, perhaps was

the most prominent in developing the use of dilute solutions and the infiltration method of producing anesthesia.(20). It was discovered that the anesthesia of the skin proper by intradermal infiltration as distinguished from subcutaneous method is the key to success. This fact seems to have suggested itself at the same time to several observers, particularly Halstead, Corning, Reclus, and Schleich.

The rapid progress made in local anesthesia soon met with almost insurmountable difficulties. The use of dilute solutions was not applicable in all fields of minor surgery. Mild, severe and fatal cases of cocain poisoning were observed in great numbers. Cocain poisoning, the habit forming properties of the drug, the instability of its solutions, as well as fluctating supplies and high cost led to an intensive study with a view to discovering other substances which would be equally efficient as a local anesthesia withouth the serious effects of cocain.

TROPOCOCAIN

The first synthetic product was benzoylpseudotropein, produced by C. Liebermann in 1892, although the alkaloid was actually discovered by Giesel the year before. Later this drug was given the name tropococain. It was found to be less toxic than cocain, to be one-fifth to one-eighth as potent, and produced anesthesia of shorter duration. No serious cases of poisoning were observed in man, but due to its fleeting action is was never extensively

used.(21).

ALPHA-EUCAIN AND BETA-EUCAIN

The first of the cocain substitutes to have widespread practice before being supplanted by procain were alpha-eucain and beta-eucain. A-eucain was synthesized by Merling in 1897 and B-eucain by Vinci.(22) They were good local anesthetics, even for mucous membrane and less toxic than cocain, but had a tendency to cause local edema and hyperemia of the tissues. The undesirable local reactions were greater with A-eucain than with B-eucain. Synthetic products such as holocain, akoin, orthoform, nirvanin, stovain, alypin, etc. were used for a short period of time. Their usage was cut short by the introduction of procain in 1905 by Einhorn.(23). His synthesis of procain may truly be said to have introduced the modern era in local anesthesia, and is considered next in importance to Koller's introduction of cocain. Einhorn demonstrated that the esters of aminobenzoic acid have local anesthetic properties when brought in contact with nerve endings and that their water-soluble basis are effectual substitutes for cocain.

ADRENALIN

Many of the early investigators were aware of the fact that the toxicity of local anesthetics could be reduced by preventing the drug from being absorbed by the general circulation. Corning and others suggested the value of the Esmarch bandage in this respect, and mentioned the prolonged anesthesia that followed when making a limb ischemic.

Upon the discovery and preparation of adrenalin in 1901 and knowledge of its vaso-constrictor power, H.Braun was quick to realize the value of adrenalin. To him is due the credit of first introducing, developing, and perfecting the use of this agent in combination with a local anesthetic. Today it is indispensable in the surgical field, particularly in nose and throat surgery.

Toxicology

The extended use of local anesthesia in surgery has forced the question of toxicity to the front, and it is now generally recognized that the various drugs and methods have their own dangers just as in a general anesthesia. Next to the production of a suitable non-irritant anesthesia, the most important property of a local anesthesia is its toxicity.

Although data are available of the toxicity to animals of all the local anesthetics, undesirable reactions have occurred much too frequently in humans. It must be remembered that local anesthetics are protoplasmic poisons possessing special affinity for the nerve tissue. The injection of large amounts of solution into the general circulation will naturally affect the brain and vital centers.

RESPIRATION

The systemic toxic effects of local anesthesia appear to be due primarily to three main factors, first in importance being respiration. Local anesthetics in small doses usually stimulate respiration in laboratory animals, where-

as with larger doses, the period of stimulation is short, followed by paralysis of the respiratory center. This is the chief cause of death for most of the anesthetic agents such as procain, cocain, alypin, stovain, metycain, tutocain and others. (24) (25).

CIRCULATION

A second important action is on the circulation. Here again small doses of most anesthetic agents produces slight stimulation with a rise in blood pressure. Mosso(26) showed that the factors responsible for this was the central stimulation of the cardiac accelerator and the vasomotor centers and peripheral vasoconstrictors, but that the central effects were more prominent. Large doses are followed by marked fall in blood pressure, which is attributed to central and peripheral vasomotor paralysis and to depression of the heart muscle. The most toxic for this system appears to be nupercain which according to Lipschitz and Laubender,(27) most commonly produces death by cardiac depression.

CONVULSIONS

The third action is the production of convulsions as a result of their stimulant effect upon the central nervous system. The convulsions are generally said to be confined to stimulation of the cerebral cortex, but the "running movements" so frequently seen is still present after cerebral hemispheres are removed. (28).The period of stimulation is followed by one of depression especially after large doses. The higher the animal in the developmental scale,

the greater the depression and hyperpyrexia and death may follow, probably due to exhaustion. All the local anesthetics can produce this effect. The following quotation taken from Allen's book of local anesthesia gives an excellent description of the toxic symptoms:

(29)The symptoms of mild intoxication in man may be evident in loquacity, laughing, or singing, later slight nausea, vertigo, faintness, thoracic opression; as the severity of the symptoms increase the pulse which at first is stimulated becomes rapid and weak, respiration may be opressed or quite rapid, great mental excitment and anxiety may occur, the patient becoming very restless and twitching or trembling of muscles, these symptoms indicating the onset of convulsions; at times the state of excitment may manifest itself by maniacal delerium, the patient becoming violent and uncomfortable; convulsions with unconsciousness may now supervene and be followed by death. During the onset of symptoms the pupils are usually dilated, but may at times be contracted. The order and character of symptoms may vary greatly in different individuals, the stage of excitment may be absent, unconsciousness coming on at once, followed by convulsions. In some cases where the toxic dose is very large, or the patient is particularly susceptible, death may occur almost immediately from cardiac inhibition."

Eggleston and Hatcher(30) have shown that the toxicity of local anesthetics for the cat, and this presumably holds for man, depends up on the ratio between rates of absorption and elimination. They have shown that an animal will succumb to a smaller dose of procain given by rapid intravenous injection than of cocain given by slow intravenous injection. Farr has shown that the rate of absorption from subcutaneous tissue or mucous membrane increases with increase in concentration. From the standpoint of elimination, the commonly known local anesthetics may be divided roughly into two groups, first

cocain, nupercain and holocain, which are not destroyed or eliminated rapidly by the organism, and second, alypin, procain, stovaine, tropococain which are rapidly destroyed or eliminated by the organism.

ROLE OF LIVER

With the wide modern usage of local anesthetics, it is surprising that more attention has not been given to the role of the liver in the occurrence of toxic reaction. That liver damage is a contraindication to the wide use of local anesthetics is concluded from the findings of Ellinger and Hof,(27) who have shown that liver damage increases the sensitivity of animals to cocain, procain and tutocain. Thus it is reasonable to assume that sick human beings are more sensitive to the systemic effects of local anesthetics than are healthy normals. It is well known that the exsanguinated and cachetic patients may show toxic symptoms on comparatively small doses.

Unquestionably some people are susceptible to local anesthetics, and death has occurred from the mere application of trifling amounts of solutions to mucous surfaces. For example, cocainization of the nasal septum in asthmatics may initiate a violent paroxysm, and this can even prove fatal,(31). Idiosyncrasy to the cocain substitutes is less common, but undoubtedly occurs. (32).

The toxicity of local anesthetics varies greatly, depending upon the method of application. Accidental intravenous injections have, no doubt, accounted for a number

of fatalities. Greater care must be utilized when local anesthetics are applied to highly vascular areas, such as the nose, throat, and urethera. Absoprtion particularly from the gums, where the fluid is under great pressure is more rapid than from a less vascular area. Therefore dentists may encounter reactions from a few cubic centimeters of procain which would never give any symptoms elsewhere. The sitting position of the patient may also be a factor in the reactions. (33). Mayer reports that more deaths occur when anesthesia is applied to the throat and urethera than when applied anywhere else in the body. It has been noted that injured defective mucous membranes seem to absorb the anesthetic more quickly.

SAFE HUMAN DOSAGE

For prevention of toxic reactions from local anesthetics, the Committee for the study of toxic effects of local anesthesia of the American Medical Association have laid down the following recommendations: cocain should not be used for injection, but should be used for surface anesthesia in a concentration not greater than 5 to 10 % with a maximum dose of from 0.06 to 0.1 gram; for injection anesthesia procain should not be used in a concentration greater than 1 percent; butyn should not be used for injection anesthesia, the maximum dose to be used should not exceed 0.06 gram for topical application. The committee advises that local anesthesia should not be employed in the presence of trauma or stricture.(34).

Bieter (35) has noted that the safe doses for patients were about equal in amounts as the minimal fatal doses per kilogram of guinea pig administration by subcutaneous injection. It is his opinion in the absence of any definite criteria for determining the safe human dose, that the minimum lethal doses for guinea pig be used as total safe human doses. Also it is generally concluded that the safe dose of procain for spinal anesthesia should be much smaller. The maximum safe dose of 200 milligrams is employed by Lundy at the Mayo clinic.(36)

VASOCONSTRICTORS

EPINEPHRIN

Braun(37) in 1903 demonstrated that minute quantities of epinephrin added to local anesthetics solutions greatly prolonged the duration of anesthesia for infiltration and block. This was later confirmed by Sollman(38) who showed that for cocain there was actually a potentiation, but for most of the remaining drugs he studied, it was a simple prolongation. The beneficial lengthening of anesthesia is very striking with procain. For example, a one percent percain solution for infiltration anesthesia lasts approximately 15 to 20 minutes, while the addition of a 1:100,000 epinephrin will easily prolong the anesthesia to an hour or longer. This action is due to the constriction of blood vessels which greatly reduces the flow of blood, thereby slowing the absorption. As a result, much smaller concentrations of the local anesthesia may be

used, the resulting anesthesia is greatly prolonged, and the danger of toxic symptoms occurring is markedly reduced. The concentration of epinephrin ordinarily added to local anesthetic agents for this purpose may vary from a part in 50,000 to a part in 200,000 or even less.

Bieter(35) has made an interesting study in regard to the varying concentrations of epinephrin and the relative effect on prolongation of anesthesia. A uniform increase of duration of anesthesia does not occur with the proportional increase of epinephrin. The explanation of this variation may be that the more concentrated ephenephrin solutions tend to produce a local acidosis which hinders the continuance of the anesthesia. A lowered pH, as shown by Gerlough(40), greatly reduces the duration of anesthesia, which is explained by the decreased hydrolysis in an acid medium. He has definitely showed that alkalosis increases the hydrolysis of local anesthetics and prolongs anesthesia, the liberated alkaloid base being more readily taken up by the nerve structures.

Although epinephrin serves a valuable purpose in producing a bloodless field and in delaying the absorption of a local anesthesia, especially procain, yet, it is not entirely free of danger. (40) There may be a danger, locally, in using too great a concentration of epinephrin. This has been shown by Serafin(41) who described a local slough of tissue from the accidental use of a local anesthetic solution containing epinephrin in a concentration of about 1:20,000.

The addition of epinephrin in amounts of one milligram or more to a solution of cocain often results in a greater degree of toxicity than from cocain alone when rapid absorption takes place. Lundy(42) is of the opinion that the use of larger doses of epinephrin with cocain is deemed unsafe and epinephrin should not be used in a greater concentration than 1:10,000 and of this not more than 10 minims with cocain. Somewhat larger total amounts of epinephrin may be used with solutions of procain, but not more than 1 milligram of epinephrin should be used, and even this dose may be unsafe for patients suffering from hyperthyroidism. (34) Sollman (43) believes that for most surgical purposes the maximum concentration should not exceed 1:50,000. In certain regions, such as in the fingers and toes, a vasoconstrictor is contraindicated, and a tourniquet should be applied.

In excitable or susceptible patients, epinephrin may produce minor toxic symptoms, such as palpitation of the heart, opression and often a feeling of dread or alarm, difficult respiration and a fulness and a throbbing in the head. These symptoms are frequently noted by dentists and surgeons doing nose and throat work. It is well known that epinephrin is absorbed rapidly from highly vascular tissues such as the face, nose and throat. This no doubt is the probable cause of the symptoms so often seen by these workers. Dental workers also tend to use higher concentrations of epinephrin in their local anesthetic solutions. As a result, there has been a plea from

the dental profession for a less toxic vasoconstrictor, one which would not cause a sudden collapse with a fall in blood pressure, which sometimes occurs in "adrenalin-sensitive" patients.

COBEFRIN

Hartung(44) in a classic review of epinephrin and allied compounds, has demonstrated that an isomer of epinephrin, which possesses the same pressor activity of epinephrin is much less toxic, and is active when administered orally. This substance, which has been identified for some time, was formerely known as non-homoepinephrin, or 3,4-dihydroxyphenylpropanolamine. It is now known as cobefrin. Hartung and Munch(45) found that when cobefrin was injected into rabbits, its toxicity was less than a hundredth as great as that of epinephrin and that its effect on the circulating system was indistinguishable from that of epinephrin, however it is less potent in its action, being 1-12th as active as levorotatary epinephrin. This drug, according to Tainter(46) has 1-12th the degree pressor activity of epinephrin, and in white rats, 1-53rd the toxicity of epinephrin.

Cobefrin has been used clinically in combination with a solution of procain to produce local anesthesia by several German workers. Hirsch(47) has employed this substance combination for tonsillectomy and various other operative procedures on the eyes, ears, nose and throat.

He commented that the advantage in the case of cobefrin is that it does not cause a sudden drop in blood pressure through a vagal reflex. This, he asserts, is responsible for the lack of untoward symptoms, such as tremor, dizziness, palpitation and minor syncopal reactions. Lundy and Tuohy (48) state that if epinephrin is pure and fresh it does not have certain undesirable vagus influence. Furthermore, Hirsch said that cobefrin may be given to individuals who have an idiosyncrasy to epinephrin, without fear of any unusual symptoms or reactions. Cobefrin is widely used in the United States today by the dental profession as a vasoconstrictor in place of epinephrin. They tend to substantiate the above comments. Cobefrin as it is supplied comercially is said to be 7.5 times less toxic than epinephrin when injected into the albino rat and its average pressor action one-fourth to one-fifth that of epinephrin. Thus a 0.5 percent solution of cobefrin should be equal in strength to a 0.1 percent solution of epinephrin. Correspondence with the Winthrop Drug Company states that cobefrin is stable only when in solution with procain.(Personal letter)

EPHEDRINE AND NEOSYNEPHRIN

Other hemostatic agents that are sometimes used include ephedrine and neosynephrin. Ephedrine produces the longest vaso-pressor effect of the four drugs, but it has one disadvantage in that it does not give adequate hemostasis. The effect of ephedrin lasts about forty-five minutes and its is therefore more useful in connection

with spinal anesthesia than ephenephrin, the effects of which last about fifteen minutes. Neosynephrin, or laevo-α-hydroxy-β-methyl amino 3 hydroxy ethyl benzene hydro chloride is thought by Bittrich(49) to have a number of advantages compared to ephedrin. Ephedrin often produces disagreeable reactions, such as nervousness, and cardiac irregularities occur. It is not well tolerated by arterosclerotics in whom very marked arrhythema with extrasystoles may occur. Neosynephrin slows the heart rate, but raises the blood pressure by increase of stroke volume and peripheral vascular constriction, whereas ephedrin produces tachycardia. Neosynephrin does not become less efficient upon repeated injections. The effects last for 30 to 45 minutes. Bittrich finds the superiority of the drug so marked over ephedrin, clinically, that the use of ephedrin has been entirely discarded.

PREMEDICATION

Since most local anesthetic agents produce death by respiratory paralysis, artificial respiration was the routine procedure in the treatment before the use of hypnotics became prevalent. Also the administration of respiratory stimulants such as caffein, strychnine, and atropine had long been advocated as antidotes, but now, a much more effective method for both prophylactic premedication and immediate treatment of intoxication is the use of narcotics and soporific drugs.

BARBITURATES

As early as 1890, Mosso(26) noted the fact that

chloral hydrate diminished the sensitivity of rabbits to cocain. It was common practice, particularly in the dental profession, to recommend the administration of a small quantity of alcohol to patients before the local anesthetic as a p rophylactic. The real importance of this action was not properly emphasized, however, until Tatum(50) and co-workers demonstrated that a member of the barbital group could actually raise the lethal dose of cocain in animals two or three times, protect against the onset or even stop the convulsive procedures. This protection is augmented by increasing brain development. (51) Later, Knoefel, Herwick and Loevenhart,(52) confirmed these observations, and showed that sodium amytal conferred a greater degree of protection than either sodium barbital or sodium phenobarbital. These findings have been repeatedly confirmed by reports of the clinical use of the barbital hypnotic preliminary to the administration of a local anesthesia. These hypnotics have been greatly responsible for the reduction of toxic symptoms. It is probable also that the preliminary administration of morphine and scopolamine which Farr(53) used almost continually to quiet his patients has a similar protective effect, and that this accounts for the relative freedom of his patients from toxic symptoms, in spite of the large doses of procain and other local anesthetics which he used routinely. Although de Takats is of the opinion that the use of morphine is not logical as one is frequently impressed by the salivating, nauseated, highly uncomfortable patient

arriving at the operating room, worse off for the morphine. Also the use of morphine and scopolamine to produce twilight sleep contradicts the true principle of local anesthetics.

THE PSYCHIC ASPECT.

Modern surgery is just as concerned with the protection of the patient from mental discomfort in the pre-operative period as it is with his protection and comfort during the actual surgical procedure. There should be a minimum of fear of the impending operation and a maximum of confidence in its success. The assurance of a fearless, confident, psychic state is undoubtedly one of the purposes of pre-anesthetic medication. There are numerous records of patients in good health, posted for minor operations, who have died before any manipulation was instituted, apparently from sheer terror. (54) This applies particularly to children for whom too often the use of pre-medication is neglected. Even the value of a good nights rest before the day of operation must be stressed. Before a major surgical operation, the restless night, fear and anxiety may cause definite body harm and certainly exhaust the patient. In the over-anxious hyper-thyroid or mentally deranged patient the best drug is his ignorance of the time of operation. Whenever pain is present a sedative should be supplanted with an analgesic if mental and physical comfort are to be obtained.

While many anesthetists find the opiates objectionable for preoperative medication, others find some fault with the barbiturates. In the presence of pain, the barbiturates may

cause excitment instead of sedation. One barbiturate will effect one individual entirely differently from another, and the same individual may not react alike to the different forms of the barbiturates.

TREATMENT OF TOXIC SIGNS

What to do for the patient who is showing signs of toxic symptoms such as mild convulsions and respiratory depression is still debatable. According to the survey of fatal toxic cases by Mayer(34) and co-workers, a number of deaths could be blamed on the use of morphine, which was used in a mumber of patients showing toxic symptoms. Ether appears to be of little value. According to the evidence presented by Tatum(50) and others(54), the barbiturates, if given intravenously will stop the convulsions and offers definite protection to the respiratory centers from the paralyzing action of the local anesthetics. With severe decrease in respiratory excursion, the administration of oxygen and carbon dioxide is undoubtedly of value. When respiration ceases, artificial respiration is, of course, the only means left.

Of the many valuable drugs available, it is unfortunate that no one will adequately fulfill all the requirements for satisfactory pre-anesthesia preparation. Individualization for each patient, giving careful consideration to all factors involved, is essential. Such pre-medication cannot be done by rule or set down in tables of doses for any drug or combination of drugs. Increasing the possibility of successful preanesthetic medication will depend largely upon

experience in the use of any of these drugs, particularly with regard to the adjustment of dose and time of administration.

DRUGS USED IN LOCAL ANALGESIA.

The discussion of the individual local anesthetic agents will be limited to those that have fairly common usage, as the total number of compounds that have been patented and trade-marked are represented by approximately sixty-five to seventy different synthetic agents. Many of these agents have never been accepted by the medical profession, some have had a limited wave of popularity. Eventually the better anesthetic compounds replaced the poorest ones of which many have been permanently discarded. Some of the more recently discovered agents which possess excellent anesthetic properties which have not been on the market for a sufficient length of time to become well known, and also, compounds which have proved their worth are not easily replaced by the newer and less tried agents. Many new compounds are being synthesized each year in quest of an agent which possesses all the ideal qualities. To date, there is not one compound known which meets all of the requirements. The criteria upon which the ideal anesthetic should be based are:

1. Practical non-toxicity in relative large doses and absence of idiosyncrasy.
2. Rapidity of action in order that the injection itself may be painless and that complete anesthetization of the area may be induced within a reasonable length of time.

3. Good powers of diffusion and penetration.
4. A duration of anesthesia sufficient to enable the most extensive operation without reinjection.
5. An ideal quality would be prolonged period of dulled sensibility after the anesthesia proper has passed away.
6. There should be no impairment of tissue vitality or retardation of healing.
7. The substance should be readily eliminated or destroyed.

In addition to these characteristics the local anesthetic should have the following physical properties:

1. It should be stable, both in solid and in the dissolved state.
2. It should be unaffected by exposure to air, or by exposure to heat, for the purpose of sterilization, or by admixture with saline, epinephrin, and such subatance as may reach it from the walls of the vessels, instruments and syringe.
3. It should be readily soluble in water and the general pH of the tissues.

An attempt to obtain a compound that has all the ideal qualities has resulted in a constant search in the chemical world for a new synthetic anesthetic agent. This in turn is reflected by the large number of local anesthetic agents on the market today. The greater portion of the following list of such compounds is taken from Gutman's book on drugs.(55)

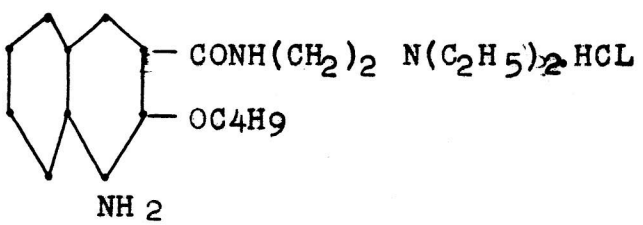
Acoine, Adrocain, Allocaine-S, A.L.A., Alypin, Anesthesin, Anisocain, Antidolorin, Apocain, Apothesine, Benzyl alcohol, Benacol, Benzocain, Benxoinal, Beta-eucain HCL, Beta-eucain lactate, Borocain, Butesin, Butesin-picrate, Butyn, Carbinol, Chlorbutanol, Chloretone, Cycloform, Diothane, Dunocaine, Holocain, Kelene, Larocain, Metycain, Monocain, Neocain, Novocain, Nupercain, Oleocain, Orthoform, Pontocain, Panthesin, Phedrocain, Phenocain HCL, Phenolain, Phenol-procain, Phenylcarbinol, Procain-borate, Propoesin, Psicain, Quinine and Urea HCL, Saligenin, Scuroform, Spinocain, Stovain, Suprcain, Trichlorethylene, Tropocain, Tutocain.

A detailed account will be made, particularly of the more recently discovered compounds, which, at the present time present considerable evidence in their favor of being eventually accepted for extensive and wide usage by the medical profession.

Percain.

Percain is the name applied in Europe, while nupercain is the name given to the drug in this country. It was synthesized and discovered by Karl Meischer, an industrial chemist in Germany in 1929. The first publication if its properties was made by Uhlmann in June, 1929.

Percain differs from cocain and novocain groups in being a derivation of quinoline, its actual structure being the hydrochloride of the diethylethylendiamide of alpha-butyloxy-cinchoninic acid with the formula:



Percain forms colorless, tasteless crystals, with a melting point of 97 C. It is readily soluble in water and alcohol, and may be repeatedly boiled for sterilization without decomposition. It is neutral in reaction. In the preparation of such solutions, however, care must be taken that no alkali comes in contact with them lest precipitation should occur, a particularly serious event where the concentration is so low. It must be kept in alkali free glass. The syringes, needles, etc., must be boiled in water free from sodium bicarbonate. Solutions which must be stored are best kept by the addition of a trace of hydrochloric acid.(56).

Regarding toxicity, Uhlmann(57) found that percain is about five times as toxic as cocain when injected subsutaneously in rabbits and guinea pigs. The toxicity by intravenous route on rabbits is about doubled that for cocain. Lipschitz and Laubender(27) found the toxicity on dogs and cats was about one-half as poisonous as for rabbits. The lethal dose for rabbits being 2 to 4 milligrams/killogram; for cats, 4 to 8 milligrams/kilogram intravenously and 15 to 20 milligram/kilogram subcutaneously; for the dog 20 milligrams/ kilogram subcutaneously. For very rapid intravenous infusion the lethal dose for the cat, the dose is 2 milligram/ kilogram. Israels and McDonald(58) found percain to be about 25 times as toxic as procain. Moller(59) found the toxicity to vary depending upon the species of animals used. He states

that roughly speaking, the toxicity of percain is 2 to 3 times that of cocain and 15 to 30 times that of procain. The toxicity was also found to be the same when given subcutaneously, or in the bladder. The reason for the greater sensitivity in the rabbit may be the more sensitive circulatory system, particularly the heart. In all species the heart is more often seriously affected with percain than with cocain. The first signs of intoxication appear as early as one-sixth of the fatal dose. Small repeated doses very early show cumulative effect. The disappearance of percain is too small to be of practical value or signifigance. The dog shows only 12 percent excretion in a twenty-four hour period, which may account for the sharp boundaries in the minimal fatal dose.

The main characteristics of percain are its extremely long duration of action and potency. It was found to be effective as a surface anesthetic in the rabbit's eye in a concentration about one-fiftieth of the concentration of cocain necessary for abolishing the corneal reflex. A 0.02 per cent percain solution produces an anesthesia of similar depth and much longer than a 2 percent solution of cocain.(60) Dillion and Greer(61) found that a 1:1000 dilution was equal to a 3 percent cocain solution. In the rabbit's eye this concentration abolished the corneal reflex in 4 minutes, and lasted an average of 58 minutes, while one drop of 1:5000 abolished the reflex in 98 seconds with a return of the reflex in one hour and 48 minutes. In man

there is no pupillary change, no corneal change or reaction other than slight vasodilation of the conjunctival vessels. Bochner(62) noted only slight drying of the corneal epithelium and no alteration in the intraocular tension. There is a slight smarting sensation after the first drop is instilled which is also true of cocain. Although loss of corneal sensibility begins within one minute, the maximum effect does not take place for at least ten minutes. The addition of boric acid solution is found to be less irritating to the eye for instillation. Epinephrin in the solution is essential to counteract the rather marked vasodilator action.

P ercain is gradually being accepted by a high percentage of the ophthalmologists, particularly for operative procedures or conditions followed by long periods of severe discomfort, such as removal of pterygiums or foreign bodies. A popular form is one percent percain ointment. One application results in anesthesia in 3 to 5 minutes and the patient remains comfortable for 24 hours. In one patient with a severe corneal ulcer the daily application for sixteen successive days was followed by progressive improvement.(63).

One and two percent percain is more effective than five to ten percent cocain for nasal operations, as resection of turbinates, removal of polypi, etc.(64) Zeidler(65) carried out an extensive investigation evaluating the use of percain as a surface anesthetic in nose and throat surgery. He believed the optimum concentration to be a 1.5 percent solution with one-third epinephrin,(1:1000) which compares favorably

with "ephraim" mixture,(20 percent cocain with one-third epinephrin). Kochmann was able to confirm his report.(66). (In spite of these findings, for the sake of safety, concentrations of epinephrin greater than 1:10,000 are not generally used in the United States.) Increasing the concentration to 2.5 percent increased the rapidty of onset of anesthesia all out of proportion to increase in strength. Because of this and because the use of a solution of this concentration seems entirely devoid of danger, Gatewood,(67) used it routinely in a clinic where rapidity of action was more important than in private practice.

Several objections have been made to percain by laryngologists. With high concentrations, inflammatory reactions are noticed, particularly in the larynx. More bleeding is also thought to be noticed after tonsillectomies. For diagnostic purposes in the nose, percain cannot substitute cocain because of the hyperemic effect. Ischemia is very important in making a correct diagnosis at nasal examinations and therefore the elimination of cocain for diagnostic purposes is not as yet possible. But percain is excellent where shrinking of the membranes is not necessary or even contra-indicated, as in the removal of nose polyps and adenoids.(68)

P ercain is found to be equally effective on mucous membranes elsewhere. A 1:1000 concentration gives excellent anesthesia of urethera and bladder for cystocopic examination and operation, also for diathermy and papillomata. It is very

useful to relieve post-operative pain in ano-rectal surgery. R.R.Best(69) used a one-fourth of one percent immediately after the operative procedure and gives the patient a one percent solution to apply locally as necessary for relief of any distress. For anesthesia and alleviation of post-operative pain in hemorrhoidectomies the use of one percent percain in oil produces prolonged anesthesia and cuts down on the need for morphine.(70)

Percain finds its greatest attraction in spinal anesthesia and has even resulted in a new technique called the "Howard Mones Technique" (71) and gives results which are much more consistent than the old method of injecting small quantities of concentrated solutions and depending upon the gravitational diffusion for the necessary spread. In spinal work a 1: 500 ~~percent~~ is an adequate strength and this renders it possible to use a trulyhypobaric solution. The subarachnoid space can be treated in exactly the same was as the tissues in infiltration analgesia and this solution can be injected without the withdrawl of any cerebral-spinal fluid, the heighth of the resulting anesthesia being proportional to the volume injected. One curious result of using hypobaric solutions is that if a patient is turned immediately on his back after the injection is made, a preponderating anterior root block will occur, owing to these roots being soaked thoroughly, in spite of the fact that sensory roots are more easily affected than motor fibers by any analgesic drug. This anomaly can be prevented by placing the patient on his face for five

minutes after the injection. (72) The advantages of percain used in this manner are no nausea or vomiting, prolonged anesthesia, slow return to sensation, low concentration of drug which means slower absorption into the blood stream, less fall in blood pressure, and less expensive. The disadvantages are that it requires ten to fifteen minutes to act, and headaches are more frequent.(73) (74)

Hoefer(75) was the first to report the use of percain for infiltration anesthesia. The optimum concentration to be from 1:1000 to 1:2000 ~~percent~~ with 10 minimums of epinephrin per ounce, which produces and anesthetic period of three to six hours. In general, most workers limit the total dosage to 200 milligrams for local infiltration.

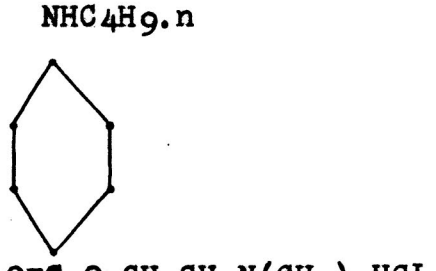
Very early in its use fatal cases of poisoning with percain were reported.(76) The large majority of these were due to using it in concentrations and volumes that were too high. It was difficult to become accustomed to a drug which to date is the most potent to be discovered. The average fatal dose in humans is considered to be o.7 grams.

Henschen,(77) as early as 1929, in comparing percain with cocain and procain made the following statement: that the duration of anesthesia is longer, the depth of anesthesia is greater, the toxic clinical dose is less, the same substance serves simulatenously for injection and surface anesthesia, with the possibility of good anesthesia in very dilute solutions and no after pain or neuralgia.

PONTOCAIN

Ever since Einhorn introduced procain in 1905 a search has continued for an anesthesia of similar, but more prolonged action, with less blood pressure depression when used intraspinally. It was early believed that all amino-benzoic acids, alkyl-amino-benzoic acids, di-amino benzoic acids and amino-cinnamic acids could form the basis of alkamine esters which would produce as satisfactory, but more prolonged anesthesia than procain. Pontocain is one of the results of this search. It was synthesized in Germany by the I.G. Farben company in 1931. The distributor in this country is the Winthrop company, New York. For spinal anesthesia the drug is marketed in 2 cubic centimeter ampules containing 20 milligrams of drug. It can also be purchased in crystalline form. The various synonyms of pontocain, are pantocain, tetracain, butethanol, and decicain. The name most prevalent in this country is pontocain.

Chemically it is of the procain series and is known as butylamino benzoyl beta diethylamino ethanol hydrochloride, with the following chemical structural formula in comparison with procain:



Pontocain

Procain

This new compound exists chemically in the form of small colorless, odorless, crystals with a slightly bitter taste, which are easily dissolved in water or saline solution.It makes a

crystal clear solution with a hydrogen-ion concentration of 5.8 and a specific gravity of 1.0068, for a 1 percent solution in an 0.8 percent saline solution at 25 degrees C. It is not affected by alkali in glass and withstands prolonged and repeated heat sterilization. It is considered more stable than procain.

The pharmacological action of pontocain has been carefully investigated as to toxicity, anesthetic potency, etc. Weidhopf (78) demonstrated in a comparative study the toxicity of similar agents upon intravenous injection as presented in the following table:

M.L.D. Rabbit-Milligram/kilogram body weight.

	Procain	Cocain	Percain	Pontocain
Intravenous	55-60	7.5	2-4	6-10
Subcutaneous	450	75	5-10	20-30

Fussganger and Schumann(79) conclude that pontocain is 2.5 to 3 times more toxic than cocain, and that comparing it with procain, the intravenous is about 9 times, and the subcutaneous is about 20 times as toxic as that of procain. Laubender and Ost(80) in comparing the toxicity of pontocain and percain state that the latter is about 2 times as toxic as pontocain on rapid intravenous, but on slow intravenous injection the toxicity of pontocain becomes much less, indicating destruction within the body. Marvin(81) states that if procain is given a value of 1, on intravenous toxicity tests then pontocain is 5.8 times more toxic. The results of Essex and Lundy(82) agree closely with the German work.

Regarding action on circulation, pontocain produces

only a decrease in blood pressure, and considering its toxicity, relatively large doses are necessary to produce this drop in pressure. Wiedhopf(78) working with dogs found that pontocain with a dose of 4 milligrams/kilogram body weight produced a blood pressure drop from 110 to 70 millimeters of mercury for 4 seconds, which returned to normal in 3.5 minutes. Percain of the same dosage produced a blood pressure fall from 70 to 20 millimeters of mercury followed by a rapid return to normal. This dose, however, produced cardiac irregularities and convulsions.

In all experiments, respiratory paralysis is the cause of death, and in non-fatal doses produce stimulation of respiration.(82) If artifical respiration is instituted when respiration ceases, a much larger dose is necessary to produce cardiac failure. The various anesthetic agents fall into classes:(1), those anesthetics which have a narrow margin of safety, if any, between respiratory paralysis and circulatory failure, including chloroform, percain and probably cocain, (2), drugs such as ether, procain and pontocain, which seem to have a wider margin of safety. The fate of pontocain is analogous to that of procain on which extensive studies of Dunlop and Essex proved that it is the liver which removes procain from the blood.(83)

The anesthetic potency and duration is fairly well established. The following table taken from Hirsch(84) gives the relative anesthetic potency's of cocain, percain and pontocain in the various concentrations.

Surface anesthesia in minutes.Rabbit's Cornea.

Concentration	Cocain	Percain	Pontocain
1:10,000	---	2-6	10-12
1:6,000	---	10-12	---
1:4,000	---	60	30-40
1:1,000	10-12	130	60

These figures compare favorably with those obtained by Laubender and Ost(80), who state that in all concentrations percain is approximately 2 times as effective for duration of anesthesia and that the depth of anesthesia is the same. Even a 2 percent pontocain solution produces no corneal damage nor inflammation of the conjunctiva.(79) It appears to be about ten times as active as cocain for anesthesia and about twice as toxic. On this basis the relative toxicity or therapeutic index is 5 times less with pontocain. Marx(85) made a detailed study comparing 1 percent pontocain with 5 percent cocain and came to the following conclusions regarding the advantage of pontocain: greater depth of anesthesia, less smarting upon instillation, less corneal irritation and damage, does not dilate the pupil, no increase in intraocular tension, and does not effect accomodation. All of these points have been verified by Wilmer and Paton(86). Although not as potent as perc-ain there is definitely less local reaction in the eye. Only a few cases of hypersensitivity have been reported.(87)(88)(89)

The above properties have secured for pontocain a permanent place in the examining and the operating room, and in

spite of the many new local anesthetics on the market, pontocain is a very valuable addition to the armamentarium of the ophtholmologist. In fact many of them have entirely discarded cocain since pontocain has proved itself definitely superior.

As a surface anesthetic, in nose and throat work, 2 percent pontocain gives a much better anesthesia than 10 percent cocain or 2 percent percain.(90) The onset of anesthesia is slightly more rapid than cocain, almost the same with pontocain and last with percain. Percain also produces more local reaction, while pontocain causes neither hyperemia or ischemia. It is considered as an excellent substitute for cocain, being 5 to 10 times less toxic in the useful strength, not habit forming, more stable and economical.

Ernst (91) was the first to use pontocain in a 1:2,000 solution with satisfcation as an infiltration anesthesia, in 120 major operations. The anesthesia is comparable to that obtained with 1 percent procain and lasts decidedly longer than the later.(92) Percain the same concentration, while slower in onset, produces longer anesthesia than pontocain, but shows some local reaction or inflammation which is absent with pontocain. In spite of its potency, the relative toxicity is still higher than with procain, which is more important in infiltration anesthesia where the total amount of drug injected is greater. There is only a small advantage to be gained with a somewhat longer lasting effect of anesthesia. For that reason it is quite likely that pontocain will not be used extensively for infiltration anesthesia.

In the field of spinal anesthesia, pontocain perhaps has its most ardent supporters. The first studies in America for its use in this respect occured at Mayo's clinic, by Lundy and Essex.(82) They made the following rules regarding its usage for spinal anesthesia: one milligram of pontocain for each 10 pounds of body weight, plus 5 milligrams as the dose used for the average adult. The maximum dose is limited to 25 milligrams. The solution is aspirated into the syringe in 1 percent solution, 10 milligrams to the cubic centimeter; the syringe is attached to the spinal needle, and an equal quantity of spinal fluid is added, so that the solution injected is then of 0.5 percent concentration. It is usually injected one intervertebral space higher than that when procain is used for the extent of diffusion of the smaller amount of drug seems limited. Stockwell and Smith(93) inject 1 cubic centimeter of 1 percent for each 100 pounds body weight, and to this is added one-fourth cubic centimeter for prolonged cases, the maximum dose being two cubic centimeters. They find the average working dose is 1.75 cubic centimeters for short cases and 2 cubic centimeters for long cases. The amounts used by others fall within the range suggested by the two workers mentioned above.

Besides a more prolonged anesthesia, another advantage is a smaller drop in blood pressure, which has been noted by many observers. (81) (94) (95). In clinical dosages, a comparison showed that 20-30 millimeters of mercury is the average systolic fall after procain, but 0 to 10 millimeters fall after pontocain. For this reason most workers have reduc-

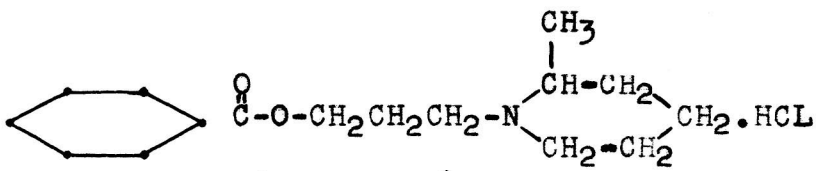
ed the dose of ephedrin one half for maintaining the proper blood pressure level.

The onset of anesthesia varies from 2 to 8 minutes, produces but few headaches, reduces the gastro-intestinal complaints and leaves a normal neurological sequence. Although the duration of anesthesia is not as long as that of percain in equivalent amounts, the toxicity is three to four times less. To date only three deaths have been attributed to pontocain, all of these were due to respiratory paralysis and each instance was thought to be due to faulty technique. (94) (96).

Pontocain is an excellent local anesthetic agent, which will probably replace cocain entirely as a surface anesthesia, and is definitely superior to procain for spinal anesthesia. Procain is still preferable for infiltration anesthesia.

METYCAIN

Metycain or neothesin is a relatively new local anesthetic drug, synthesized by McElvain of the University of Wisconsin in 1927.(97) It is trade-marked "Neothesin" and produced by Eli Lilly company of Indianoplis, Indiana. It is the hydrochloride of gamma(2 methyl piperidino) propyl benzoate and belongs to the group of substituted piperidino-alkyl benzoates with the following structural formula:



"Neothesin"

It is an odorless, white crystalline powder, and is readily soluble in water, alcohol, and chloroform. It does not deteriorate with exposure to air or sunlight. The solution remains stable after boiling or sterilizing in the autoclave. The aqueous solution is slightly acid and is comparable with epinephrin.

The pharmacological studies were carried on in the research laboratories of Eli Lilly company by C.L.Rose, and H.W. Coles.(98) They found the toxicity of metycain to be nearer that of procain than of cocain, and its margin of safety equivalent to that of procain when administered subcutaneously. Meeker(99) using the human intradermal wheal test compared its anesthetic potency with procain. With one-sixteenth percent solutions anesthesia from procain lasted 5 minutes, with metycain 14 minutes. Procain solutions were ineffective in weaker solutions, whereas metycain produced anesthesia in dilutions down to 1-128 percent solutions, the minimum effective concentration. When combined with small amounts of epinephrin, procain in 0.5 percent solution gave anesthesia for 70 minutes, compared to 96 minutes for metycain in the same strength.

In the rabbit's eye, Rose and co-workers found that the corneal anesthesia with metycain was of slightly shorter duration than with equal concentrations of cocain.

Metycain is rapidly eliminated by the urine of the dog, very little of it being unchanged. The ether extract of urine produces prolonged corneal anesthesia. A convulsive dose is entirely excreted within 8 hours.(100)

A survey of clinical reports made by Woodbridge(101) indicates that metycain acts more rapidly than cocain, is free of objectionable side reactions such as dilatation of the pupil and dessication of the cornea, and does not deteriorate if kept in solution as long as six months. A few drops of a 2 percent solution produces a momentary stinging, superficial anesthesia appears within one minute, and lasts about ten minutes. Repeated applications give deeper anesthesia suitable for major operations.

In nose and throat surgery, metycain produces excellent anesthesia, when applied topically in a 10 percent solution. Anesthesia develops more rapidly than with cocain, but does not last quite as long. Local anemia is absent unless epinephrin is added. There were no signs of toxicity even for those patients who had previously had moderately severe reactions from cocain.

In genito-urinary surgery, solutions ranging from 1 to 4 percent were employed. They agreed that metycain produces anesthesia as deep as that of cocain, that its onset is more rapid, its duration is somewhat longer, and that it is not accompanied by signs of toxicity.

Over 200 operations under local infiltration, field blocks, and nerve blocks were reported by Meeker(99) The largest amount of the drug used in any one case was 250cc. of one-fourth percent solution, for herniorrhaphy. After sacral injection, for which he used 30 cc. of one-half percent solution with epinephrin, he frequently observed evidence of mild toxicity, such as he would expect from

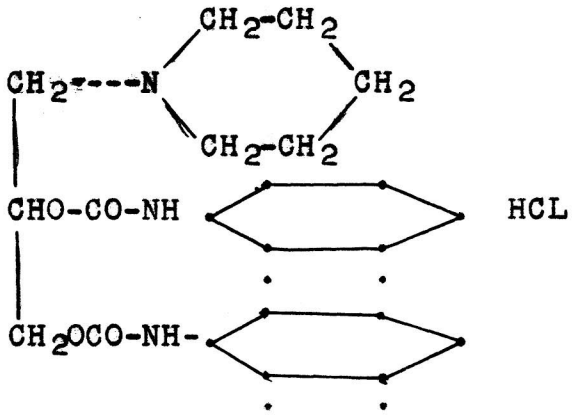
a one percent procain solution, namely pallor, palpitiation and perspiration. Other signs of toxicity were absent. It is to be noted that palpitation is rather an effect of epinephrin, and that pallor may be caused by either. He is very favorably inclined toward the drug.

Metycain(102) in spinal anesthesia is injected the same way as procain. Pure crystals, in a sterile ampoule are dissolved in 3 to 4 cc. of the patients spinal fluid, then partially injected, and further mixed by aspiration. The time elapsing between the completion of spinal injection and the beginning of the operation varies from 12 to 18 minutes. The Trendelenburg position is used. An inspection of blood pressure readings show a circulatory depression about the same as for procain. A dose of 100 milligrams of metycain administered according to the above technique is equivalent to 120 to 150 milligrams of procain. The post-operative response is about the same as with procain.

Since the introduction of percain and particularly pontocain, metycain with the limited usage it has had, has been largely displaced as a surface anesthesia and spinal anesthetic agent. Although less toxic than cocain and pontocain, the duration of anesthesia is somewhat shorter. The advantages offered by it for infiltration are not sufficient to displace procain from the market, even though metycain is suitable for both infiltration and surface anesthesia.

DIOTHANE

Recent research has developed a chemical compound the hydrochloride of piperidinopanediol di-phenyl urethane, which has shown considerable local anesthetic properties. The originator is Dr. T.H. Rider, (102) Professor of Pharmcology of Yale University. The first results were published in 1930. The compound has the following structural formula:



Diothane

Diothane occurs as dull white, fluffy needle crystals, melting at 195.6 C. The crystals dissolve slowly in water to give a saturated solution which, at room temperature, has a concentration of 1.03 percent. Solutions of 1 percent and 0.5 percent have a pH value between 5.1 and 5.6 Such solutions are perfectly stable for indefinite periods when stored in non alkaline containers, (pyrex glass); alkalies precipitate the anesthetic free base, and even minute traces of alkali present in a solution will, in time, lead to a deposition of crystals of the free base. Diothane has a quinine-like taste. The one percent solution of diothane is easily made by dissolving the crystals in hot distilled water. A two percent super-saturated solution can be prepared which does

not precipitate for several hours, and if it does precipitate, can be reduced by gentle heating. Sterilization by boiling, autoclaving and the action of diffuse light are without effect on the anesthetic properties.

The toxicity of diothane as determined by the subcutaneous minimal lethal dose for mice is 1200 milligrams/kilogram, as compared to 700 milligrams/kilogram for procain and 100 milligrams/kilogram for cocain. The same ratio of toxicity is demonstrated by the minimal lethal dose for the guinea pig. There is less tendency to produce convulsions, as is demonstrated by injecting large doses of the compound intravenously into rabbits, causing complete collapse usually without a trace of convulsions. In all types of laboratory animals death from lethal doses of diothane was due to respiratory paralysis, the heart beat continuing for some minutes after respiration had ceased.(104)

The relative anesthetic efficiencies were determined by use of intra-dermal wheals, rabbit's cornea and frog's motor and sensory nerves. According to McKim(105) and co-workers, the duration of anesthesia by intradermal wheals produced by diothane is approximately three times as long as that with procain of the same concentration. Hertzler(106) using a 1 percent solution to form wheals found that the onset of anesthesia almost immediate and that the anesthesia does not completely disappear for four days. The injection of a 1 percent solution into a rabbit's ear produces a perceptible edematous feel which is present for three days.A tissue section

of this area shows an amorphous edema with some perivascular round cell infiltration. The duration of anesthesia is parallel with the persistence of this edema which disappears in a week without leaving a trace. Diothane shows a definite affinity for protein substances. A solution of egg albumin is actually precipitated by a solution of this compound such solutions become clear again upon dialysis, showing the drug-protein combination is a reversible one. This tendency to unite with protein undoubtedly explains, in part at least, the unusual duration of anesthesia obtained with diothane. The anesthesia wears off very slowly in contrast to the usual abrupt passing of anesthesia with procain.

On the rabbit's cornea, diothane is exceeded in anesthetic activity only by nupercain, which is about 10 times as active, but its toxicity is about 20 times as great. A 0.25 percent solution of diothane is equal to a 0.5 percent cocain solution, and there is less drying and pitting of the cornea. Freshly prepared solutions of diothane appear to be less injurious to tissues than solutions stored in containers of ordinary glass.

The use of diothane clinically has not been very extensive. Diothane has proved to be a practical anesthetic in ophthalmology.(107) The application of a 1 percent solution produces a mild hyperemia and irritation of the conjunctiva which rapidly passes away and is easily overcome by the action of epinephrin. There is no change in the size of the pupil, no dessication or softening, of the corneal epithelium and no change in intraocular pressure. The onset of anesthesia

is slower than with butyn, cocain and pontocain, but is remarkably longer. There has been no evidence of toxicity or idiosyncrasy toward a 1 percent diothane solution. The degree of anesthesia was satisfactory in all cases. The disadvantages are slowness of induction and the initial irritation to the conjunctiva.

Still (108) found that it was necessary to prolong the application of diothane compared to cocain for nose and throat anesthesia. The onset of anesthesia was slightly slower than with cocain, although the duration of anesthesia appeared to be definitely longer. The shrinking of the mucous membrane and the resultant anesthesia are as satisfactory as that obtained with a 1 to 2 percent cocain solution. The use of diothane in a spray is not very satisfactory. Instead, cotton pledgets soaked with a 1 percent solution should be applied and held in contact with the tissues for as long a period of time as is feasible. No toxic or other undesirable effects were noticed, and the headaches and giddiness which so often follow the use of cocain were entirely lacking.

In the field of urology, diothane has been given a fairly comprehensive clinical trial. It was used in concentrations varying from 0.25 to 1 percent in amounts varying from 5 to 50 cubic centimeters. After instillation, ten minutes was allowed to pass before instrumentation. There was a complete absence of any initial stinging sensation or post-anesthetic discomfort, characteristic of certain other local anesthetics. The optimum concentration appeared to be about 0.5 percent. Within certain limits, the intensity of anesthesia appears

to be directly influenced by the time the anesthesia is allowed to remain in contact with the uretheral and bladder mucosa. It does not appear to be very efficient in the presence of severly inflamed conditions of the bladder and urethera, which is true of many other anesthetic agents. Examinations with diothane anesthesia may be frequently repeated without any evidence of toxicity.(109)

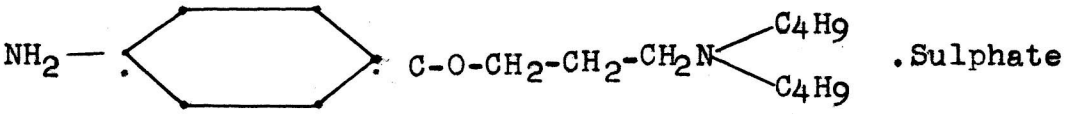
Diothane in concentrations varying from 0.25 to 1 percent has received but limited usage as an infiltration anesthesia. There has been no suggestion of toxic symptoms or local tissue irritation. A definite delay in the appearance of post-operative pain has been noted. This property has been attributed to a reversible drug-protein combination. The surgical anesthesia compares favorably with that of procain. No references were found regarding the use of diothane as a spinal anesthesia.

Diothane to date is not being used extensively. It appears to have excellent possibilities in infiltration and topical anesthesia in urology, nose and throat. Pontocain, according to the literature is definitely superior as an anesthetic agent for the eye. Diothane is less toxic than procain and more potent, which gives it an excellent therapeutic index.

BUTYN.

Butyn was introduced and described in 1920, as a result of prolonged experimentation by the staff of the Abbott laboratories of Chicago, working in collaboration with Professors

Adams and Kamm of the University of Illinois. The chemical name of the compound is para-amino-benzoyl-beta-di-n.butyl amino propanol sulphate and represented by the following structural formula:



Butyn.

Butyn in the form of the sulphate is the most stable form, being saturated in a five percent solution. It is heat stable, as boiling for sterilization does not destroy its anesthetic potency. The toxicity of the compound varies with the species of animals used. With mice, butyn is 2 or 3 times as toxic as cocain, with guinea pigs the two substances are about equally toxic. In cats butyn is about 15 percent less toxic, and in dogs from 25 to 30 percent less toxic than cocain. It is concluded that in man, butyn is still less toxic.(110) (111) In small doses, butyn first produces slight stimulation of blood pressure, with larger doses the decrease in blood pressure is pronounced with a slow return to normal. The fall of blood pressure and convulsions can be prevented by injection of pituitary extract. It is less depressing on respiration or respiratory center than cocain. Butyn is thought to be more toxic on circulation than on respiration.

This compound produces complete anesthesia on surface application to mucous membranes, such as the conjunctiva,

in concentrations about one-half those of cocain, one-tenth those of procain, or about the same as holocain. The following conclusions are quoted from Bolson:(112)

"1.Butyn is more powerful than cocain, a smaller quantity being required.
2.It acts more quickly than cocain.
3.Its action is more prolonged than that of cocain.
4.Butyn in the quantity required is less toxic than cocain.
5.It produces no drying effect.
6.It does not change the size of the pupil.
7.It has no ischemic effect and therefore causes no shrinking of the tissues."

Beaumont(113) more or less confirmed the great optimism and lack of precaution expressed by Bolson. Hill(114) in the clinical use of butyn found that about 5 percent of the people fail to respond with anesthesia to the eye. He also found hyperemia and tumefaction of the mucous membranes of the nose and throat.There is considerable lacrimation with the hyperemia of the conjunctiva, which in some cases proves to be rather annoying to the patient.(115) However, Gradle does not believe this to be a serious factor.(116) O'Brien(117) found the use of butyn very satisfactory for instillation anesthesia if one drop of a fresh sterile solution is instilled every 2 minutes for five doses and instilling 1:1000 ~~percent~~ epinephrin between doses. This not only prevents hyperemia, but enhances the action of the drug. Conjunctivitis and dermatitis are frequently reported following the use of butyn in the eye. (118) (119)

Death has been reported from a five percent solution instilled upon nasal mucosa and other deaths have been

reported especially in cases where the toxicity of the drug has not been duly regarded. For this reason, its use in nose and throat surgery has been rather discouraging.(120)

Butyn has been used but little for infiltration anesthesia. The anesthetic potency is not sufficient to overcome the toxicity although Rochelle,(121) used as high as 250 cubic centimeters of a 0.1 percent solution without signs of toxicity.

Butyn finds its use limited to the field of ophthalmology and with the introduction of even more potent and less irritating coumpounds, it is gradually being crowded out of the field of local anesthetics.

Table of Anesthetic and Minimal Lethal Doses

Drug	Minimal Effective concentration in percent		Duration of anesthesia in minutes				Toxicity (M.L.D. in gm. per Kg)				Therapeutic Indices	
			Rabbit's cornea		Human Intracutaneous		Mouse	Guinea Pig	Rabbit			
	Rabbit's cornea	Human Intracutaneous	1%	Other %'s	0.125%	0.5%	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous	* Intracutaneous Human	**Surface anesthesia
Cocain	0.32	0.02	22	2% 35	6-15	12	0.189	0.05	0.126	0.0149	0.5	1.00
Procain	4.00	0.038	0	2% 0	5-10	16	0.800	0.43	0.46	0.055	1.0	0
Percain	0.003	0.0025	-	0.01% 51.5	-	100	-	0.0112	0.01	0.0025	0.4	20.00
Pantocain	0.01	-	-	0.1% 60	-	25	0.04	-	0.020	0.0060	-	8.00
Metycain	-	0.0077	22	2% 34	16	25	0.8	-	-	0.028	5.0	4.00
Diothone	-	-	-	0.5% 65	-	48	1.200	-	-	-	-	-
Butyn	0.312	0.020	30	2% 40	15	45	0.120	0.07	0.05	0.012	0.3	0.62

* $\frac{\text{M.E.C. procaine}}{\text{M.E.C. Drug}} \div \frac{\text{Toxicity of procaine}}{\text{Toxicity of drug}}$ = therapeutic index on basis of procaine for injection anesthesia.

** $\frac{\text{Duration of anesthesia of drug of same concentration}}{\text{Duration of anesthesia of cocain of same concentration}} \times \frac{\text{Toxicity of drug}}{\text{Toxicity of cocain}}$ = Therapeutic index

SUMMARY

No attempt will be made to discuss in detail other anesthetic agents. Detailed discussion of cocain and procain has been purposely omitted. The anesthetic properties of these two compounds are well known. The frequent reference to them as standards of comparison has added much to our knowledge regarding their qualities.

It seems quite possible that cocain may be permanetly removed from the list of local anesthetic agents as a surface anesthesia. There are several compounds, pontocain and percain, which have definitely proved their superiority in this respect, and have therapeutic indices in their favor, which is particularly true when volumes and concentrations are considered. Butyn is inferior to cocain and has the added disadvantage of being quite expensive. Diothane is definitely inferior to pontocain in eye surgery, but appears to be the agent of choice for the surface anesthesia of the urinary tract. It will be many years before cocain is definitely discarded, in spite of its many disadvantages.

Procain is still the anesthetic agent of choice for infiltration anesthesia. In the field of spinal anesthesia other anesthetic agents such as pontocain and percain are gradually replacing procain. The only anesthetic agent that approaches the surface anesthesia of cocain and the safety of procain for infiltration anesthesia is metycain, although the other agents discovered are superior in their limited fields of usage. Thus, if only one anesthetic agent were available

for surface, infiltration, and spinal anesthesic, metycain would be the agent of choice.

The toxicology of the local anesthetic agents has been thoroughly discussed. The three main effects being:1: respiratory depression and paralysis, which is the chief cause of death, 2, circulatory depression through vasomotor paralysis and cardiac depression, and 3, convulsions due to the stimulating effect on the central nervous system followed by depression and exhaustion.

The avoidance of toxic symptoms led to the use of vasoconstrictors. Epinephrin is the most widely used of the vasoconstrictors. It is not without danger, being contraindicated in anesthesia of fingers, toes and hyperthyroidism. The optimum concentration appears to be about 1:100,000 solution with the total dosage limited to 1 milligram. Because of the frequency of toxic symptoms due to epinephrin, new vasoconstrictors have been introduced. Cobefrin while less active and much less toxic has been highly praised by the dental profession. Ephedrine finds its use limited to the field of spinal anesthesia for maintenance of blood pressure. Its hemostatic activity is insufficient for a hemostatic in infiltration anesthesia. Neosynephrin does not produce the cardiac irregularaties and disagreeable actions attributed to ephedrine and is gaining favor as a vasopressor substance in spinal anesthesia.

Premedication by the use of hypnotics was discussed. The conclusions were made that the barbiturates were superior to all other forms of hypnotics, including morphine and scopolamine, for the prevention of toxic symptoms. Sodium amytal is the most efficient of the barbiturates for premedication use.

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