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Anesthesia and analgesics and their relation to fetal asphyxia

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"ANESTHESIAS AND ANALGESIAS AND THEIR RELATION TO FETAL ASPHYXIA"

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HISTORY

"And the Lord God caused a deep, deep sleep to fall upon Adam and he slept. And he took one of his ribs, and closed up the flesh instead thereof." (Genesis 2:28). Thus is described the first case of anesthesia on record.

The term "anesthesia" was introduced into medical nomenclature in 1847 by Sir James Y Simpson. It means the state of being without sensation. To produce this condition artificially, substances known as anesthetics are employed. We therefore define an anesthetic as, "any agent which possesses the property of abolishing sensation." Willard (70)

The anticipation of a pain-destroying agent was a medical dream, older, more persistently pursued, and more enticing than the fancies of the fabled lotus-eaters. The belief in and the search after some agent by which pain might be alleviated is as old as medicine itself. The atmosphere of mysticism, charms, chasticism, and incaritations that surrounded the early history of pain-destroying agents, tended to discredit the whole matter, and in part, at least, explains why the age that produced Sydenham and Pare' was barren in this respect. There too were the religious ideas, based on the primeval curse. Patton (49)

Pliny and Dioscorides speak of a wine of the root of the mandragora, which was used to induce sleep. Lucius Apulcius, who lived about A. D. 160, writes that "If a man has to have a limb mutilated, sawn or burnt, he may take half an ounce of this wine, and whilst he sleeps, the member may be cut off without pain or sense." Willard (70)

Hoa-Tho who flourished under the dynasty of Wei, between 220 and 230 of our era, gave to the patient a preparation of hemp, after a certain number of days the patient found himself reestablished without having experienced the slightest pain during the operation. The ancient Scythians were in the habit of inhaling fumes of hemp several centuries before the time of the Hoa-Tho, and also by the practice of the Hindoos at present, who inhale the fumes of hemp from a pipe. As early as 977 the Hindus knew of several narcotic drugs. It is said that they administered a drug called sammolini to render patients insensible. Theodoric, a monk who practiced surgery, mentions in 1490, a preparation used by his father, Hugo of Lucca, a Tuscan physician, and called the "Spongia Sommifera." It is stated that often a patient who had taken this substance would often sleep two or three days.

In 1540, sulphuric ether was discovered by Valerin Cordus, but its anesthetic properties were not recognized until three centuries later.

About 1579, Geanbattesta Porta, a surgeon of Naples, used an extract made from lyoscyamus, solanum, poppy and belladonna, enclosed in a leaden vessel, which when the lid was removed and the patient allowed to inhale the fumes, sent him into a deep sleep. Webster (69)

Hypnotism was known to the ancient Egyptians, Persians, and Indians as early as 1617, for the purpose of surgical anesthesia. Grevtrokes as early as 1661, produced magnetic sleep, by passes over the subjects body. The theory of "animal magnetism", of Anthony Mesmer in 1766. Potet, in 1839 introduced hypnotism, under the name of mesmerism. The Greek physicians must have recognized the principle of hypnotism, for in the Greek Anthology we have, "Touching them with his hands the physician quickly makes them whole". Patton (49)

The tardy progress thus far noted toward the discovery of a really satisfactory method of producing artificial anesthesia was no doubt due to the rudimentary condition of chemical science. Willard (70)

In 1776, Priestly discovered nitrous oxide gas and the discoveries of Cavendish, Lavoisin and others,

respecting the nature of atmospheric air, and the more important gases, gave an impetus to research and experimentation on this subject. Davy in the course of his experiments, having an inflammation of his gums which caused him severe pain, found that this was completely relieved by the inhalation of the gas. And because of this he published the following, "As nitrous oxide in its extensive operation seems capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place." Webster (69)

In 1818 Farady showed that inhalation of ether vapor produced anesthetic effects similar to those of nitrous oxide. Crowford W. Long of Georgia, in 1842 used ether to produce anesthesia during surgical operations. Two years later, Horace Wells had a tooth extracted while under the influence of nitrous oxide. Morton used ether for surgical anesthesia in Massachusetts General Hospital in 1846, and made the first public announcement of its use for this purpose in January 1847. Simpson first used ether to produce analgesia in mid-wifery. Flourens, in March of the same year, announced the anesthetic properties of chloroform, and Simpson, in November, read his paper

entitles, "Nature of a New Anesthetic agent as a substitute for Sulphuric Ether in Surgery and Mid-wifery". Davis (16)

The use of anesthesia in surgery developed very rapidly. On the other hand, owing to the opposition of the clergy and, to a lesser degree, the medical profession, the analgesia in obstetrics was slow at first. Simpson was Knighted by Queen Victoria after she had experienced painless childbirth, but had he lived in the sixteenth century it is probable that he would have fared as badly as the witches.

The desirability of pain relief in surgery and obstetrics is no longer a matter of discussion. Severe pain is not essential to childbirth, and it is the duty of the obstetrician to give the maximum relief which may be obtained without sacrificing the safety of mother or infant. Davis (16)

The modern history of pain relief in obstetrics dates from the work of Simpson in 1847. Ether, Chloroform and Hypnotism were all used during the decade which followed. Klikowitsch a Russian, applied nitrous oxide-oxygen analgesia to 25 cases in 1880. The following year Winchel of Dresden used the nitrous oxide-oxygen analgesia in 50 cases. Nitrous-oxide was not

used as an anesthetic at this early date for various reasons, among which were; its cost, the impurity of the gas, the crudeness of the apparatus used, and to the fact that it was often given to the stage that it produced asphyxia.

In 1902, Van Steinbuchel of Gratz first suggested the use of scopolamine, and morephine analgesia in obstetrics, and in the following year made a report of its use in 20 cases.

Gauss made a similar report in 1906, after some 12 years. The lay press discovered the use of scopolamine and morphine, and the women of America were told of the wonderful Dammershlof and painless childbirth. So, within a few months, twilight sleep became a fad. Davis (16)

In 1899 Sinclair, Hopkins and others were using spinal anesthesia in operative obstetrics.

The anesthetic effect of ethylene was discovered by Luckhart and Carter in 1923. Heaney at the Presbyterian Hospital, Chicago, began the use of ethylene-oxygen analgesia and anesthesia in obstetrics.

In recent papers by Guedel, George and Trussler, and by Harris and Waters, they have called attention to the importance of the control of CO2 and O2 content

in the mothers lungs as a means of protecting the respiratory center of the fetus from apneic tendency. Davis (16)

PHYSIOLOGY

Asphyxia neonatorum is one of the most important and yet one of the least understood of all the phenomena connected with child-birth. It is important not only for its frequency but for its deadliness. It is little understood because the investigation of its elements, phases, and etiologic conditions is frought with difficulties that are many times insuperable.

Previous to the 18th century, asphyxia meant no pulsation in an artery, in particular below a tourniquet. In the 18th century, it applied mostly to drowning, and soon after, it included death from strangulation and noxious gases. Obstetrically speaking, in its present day usage, we apply it to any baby who fails to breathe at birth, irrespective of cause.

However, the clashing together of a few theories may clear the atmosphere.

Due to the fact that such little work has been done on respiratory-like movements in fetuses, there is still some doubt, at least by many, that they do exist.

In a recent article by Barnett, Bonar, and Blumenfeld, (3), we find the ideas of various men summerized; Preyer in 1885 stated that Vesalius had observed such movements, when the fetal circulation had been interrupted, and that Winslow in 1787 observed rhythmatic

dilatations and contractions of the thoracic wall in the fetus in the amnionic sac following exposure of the uterus. Beclard made similar observations about 1815. From this time nothing was done until about 1905, when Ahlfeld published some work in which he stated that there were rhymatic pulsations of the abdominal wall of pregnant women which seemed unrelated to maternal respirations or pulse. In 1911, Reifferscheid confirmed these observations with graphic record. However, in 1933, Klemperer failed to observe these movements in anesthetized animals in which the uterus had been exposed.

Some further work done along this line by Snyder and Rosenfeld (59), in which they proved quite conclusively that respirations is not initiated in the child at birth, but extends far back into embryonic life. And instead of there being a state of complete apnea during intra-uterine life the human fetus shows spontaneous respiratory movements for periods lasting many minutes. In some of their experiments of the intact but exposed uterus of rabbits, they found that there were rhythmic excursions of the thorax and abdomen, which, while shallower, resembled quantitatively the respiratory act in the new-born. They later made

observations on unopened abdominal walls of pregnant animals and observed the same situation.

Eastman (20), has also observed these movements in the cat, guinea pig, and the monkey.

Barnett (3), and others, by their work have come to the conclusion that "Intra-uterine respiratory movements of the fetus occur, and that they are physiologic, that they are not initiated by asphyxial changes in the fetal blood nor by stimulation as a result of handling". These investigators made their observations on ten rabbits, five dogs, and seven rats. They also showed, as did Rosenfeld and Snyder, that through the intact uterus periodic rhythmic excursions of the fetal thorax and abdomen were observed. During their course of experiments they also found that in premature fetuses the respiratory activity was not as great as in full term animals; that during any movement of the fetus itself or of the uterine musculature the respiratory movements stopped all together. They also found that after five minutes of light anesthesia the fetal respiratory movements stopped, and that at the beginning of the anesthetic the respiratory rate was somewhat increased, and with the withdrawal of the anesthetic, within twenty minutes, regular respiratory rate had resumed.

Further observations were done by Snyder and Rosenfeld (60). In these they used rabbits and cats and observed that in full term fetuses within the uterus, the respiratory system is found to be in a state of marked activity as shown by the occurrence of regular respiratory movements. There were rhythmical excursions of the chest wall and diaphragm, continuing throughout the periods of observations lasting many hours. In their experiments the fetus was placed from the uterus into a saline bath, and the placenta remaining intact. It was found the respiratory movements continued vigorously, and that the respiratory movements occured during periods of general body activity as well as when the fetus was at rest. It was also shown that if the fetus was exposed to the air that the respiratory movements continued as before, and that the blood in the umbilical artery became a bright red.

Other investigators (2), observed that the respiratory movements become rhythmic, instead of being a single mass reaction envoked by a specific simulus, or perhaps by two such reactions in quick succession. The youngest fetus observed of this phenomenon was, age, 38 days, 31 mm. long. Therhythm described is spoken of as spontaneous. The rate of rhythm bore no

relation to that of the rhythm of the mothers respirations.

It was also noted during their (59), experiments that anesthetics profoundly influenced fetal respiratory movements. In anesthetized animals prolonged apnea was characteristic of the fetus before birth. Narcosis may mask the true physiological activity of the respiratory system of the fetus. In animals in which ether was used for anesthesia, it was noted that apnea was interrupted by spontaneous respiratory movements of the fetuses at times when the depth of anesthesia was minimal.

Kustner (40), during his experiments, observed that general anesthesia of the mother may cause asphyxia in the child by paralyzing the respiratory center.

Henderson (33), also thinks that the fetus makes distinct rhythmatic respiratory movements. But these movements are ineffective in expanding the lungs and keeping them expanded. He then asks the question: "How are respiratory movements of the fetus transformed into effective breathing of the New Born?" In trying to answer this he believes that a certain function is quickly developed at birth and is then continually maintained throughout life. This is the muscle tonus

theory of respiration, metabolism and circulation.

At birth external stimuli increase muscle tone. Without muscle tone, blood would stagnate in the tissues and circulation would fail. Henderson's first experiments with dogs thirty years ago, proved that over-ventilation killed, and that collapse consisted in failure of circulation rather that heart injury, and it was the venous return that was impaired due to a complate failure of muscle tonus. He observed that when a man or animal dies, the muscles lose their tonus within five or ten minutes and that when tonus is lost, the cubic capacity of the chest decreases and the lungs are correspondingly deflated. At birth the circulation undergoes a fundimental change. As the placental vessels contract, the blood is sent in full volume through the lungs. Due to the increased action of the left heart, the arterial pressure rises and because of this, muscle tonus is maintained. When this fails, there is asphyxia.

The full term fetus in-utero exists normally in a state of cyanosis with a mean capillary oxygen saturation of 11.1 volumes percent (the threshold for visual cyanosis being at 6.5 volumes percent.)

Clifford and Irving (13) found that the normal fetus at birth, due to the impaired circulation of the

placenta by the retracting uterus, is in an even greater state of cyanosis with a capillary unsaturation of 13.9 volumes percent.

At birth the arterial blood of the fetus contains less oxygen than the blood in the maternal arm vein. Therefore the normal fetus exists in-utero in a state of cyanosis. Because of its rhythmatic respiratory movements, we expect it to continue these movements spontaneously as extra-uterine breathing.

There has been much controversy in the literature regarding the roles played by oxygen and carbon dioxide in the causation and cause of asphyxia. One author (13) believes that intra-uterine anoxemia of the fetus, whatever its cause, is accompanied by an accumulation of lactic acid in the fetal blood proportional to the degree of anoxemia. In some cases this may reach a concentration which is incompatible with life.

There is some implication that an accumulation of carbon dioxide is as much a cause of death as lack of oxygen. Haldame and Prestley's demonstration proved that carbon dioxide rather than oxygen is the chief immediate factor in respiration. Eastman (19) has found the carbon dioxide tension in the asphyxiated infant to be twice that of the normal. He also thinks

that the fetus in-utero is definitely less sensitive to carbon dioxide. It has been proven quite conclusively that excess of carbon dioxide and inadequate oxygen is very injurious to the higher centers. (64)

The response of the fetus to increases of carbon dioxide was less pronounced than that of the adult. The level of carbon dioxide which stimulated maternal respirations, did not increase fetal respirations beyond normal limits. Other investigators (59), also found that with depletion of carbon dioxide the respirations of the mother slowed to the point of apnea. They established the fact that normal fetal respirations are not maintained below certain minimal tensions of carbon dioxide. The fetal center is less sensitive to excess of carbon dioxide, but carbon dioxide depletion is qualitatively similar to the adult.

Other investigators, Trusler, Guedel and George (67), come to the conclusion that the accumulation of carbon dioxide in the new-born, constitutes the normal mechanism of respiratory stimulation, but there may be several factors which may be depressing the respiratory center, namely, drugs, and anesthetic agents.

Wilson and his co-workers (71), believe the onset of true respiration is caused by chemical rather

than by physical factors. An explanation of this phenomenon is, "That immediately after delivery, the placental circulation is markedly impaired by the contracting, retracting, uterus. This results in a diminution of the oxygen supply to the baby and a marked increase of the carbon dioxide tension in the blood, which stimulates the respiratory center to action."

Snyder and Rosenfeld (60) think that the respiratory failure, or "asphyxia neonatorum", must be regarded as a suppression of previous activity rather than failure of some new mechanism to begin functioning at birth.

Snyder and Rosenfeld also feel that the fetal respiratory center before birth is sensitive to the depressant effect of anoxemia and narcosis. In their experiments in "intra-uterine respiratory movements", they found "that general anesthetics profoundly influenced fetal respiratory movements, and that in their anesthetized animals prolonged apnea was characteristic of the fetus before birth".

Still other men, Burge, Neill and Ashman, (12), in their paper bring forth the idea that was brought out by Hewitt in 1907, in his book on anesthetics in which he states, "That it is not at all improbable that

future experimental research may lead us to the conclusion that general anesthetics produce their characteristic effect by limiting the normal process of oxidation."

In Snyder's and Rosenfeld's work many of the volital and non-Volatile anesthetics were used, e.g., nitrous-oxide, dramyl-ether, paraldehyde, phenobarbital, chloral hydrate, and it was found that the fetuses were extremely sensitive to the depressant effects of the ordinary anesthetics. Intravenous Pento-barbital Sodium, was also tried but there was a depression or abolition of respiratory movements of the fetus.

The least depressant anesthetic which these investigators found was cyclopropane and oxygen. In their experiments they maintained deep surgical anesthesia without depression of the fatal respiratory movements.

Patton (49), found the effects of anesthesia on the respiration vary exceedingly according to the nature of the agent, the type of the subject, and manner of administration.

For some time argument of the anesthetic and its effect upon the fetus has been discussed.

About 1902 and for some time following, the ques-

tion of the asphyxiating effect if any, by an anesthetic, remained under the dictum of Ballentyne who stated, "While there is evidence to show that chloroform may pass over and enter the blood of the fetus after prolonged administration to the mother, there is no strong evidence that when there it produced any serious effects. As with chloroform, so with ether, its transmission through the placenta, if not entirely proven is probable, but there is no reason to apprehend a toxic effect unless the anesthetic by very deep- or greatly prolonged". (53)

It has also been shown by Reed (53), by experiment with, "curare, hydrocyanic acid, and nicotine, that the blood of the umbilical vein of the fetus becomes markedly dark in appearance when asphyxia of the mother occurs, which indicates that oxygen is being drawn from the fetus to the maternal organism. The same holds for anesthetics, which are administered for a long period of time. The fetus may be seriously endangered and if administered up to the point of saturation, the fetus may be killed".

Leff (42), in his article "Theory as to the cause of Asphyxia", states that the respiratory apparatus does not function intra-uterine, it is not subjected to any

strain and is therefore not likely to be out of order. When it fails to react, it is due to a lesion in some vital structure or to a failure of the proper stimulus to reach the respiratory center. As the stimulus to the respiratory center goes through the circulation, it is the circulatory system that we must give our attention and determine the factors that disturb it. He also maintains that the contractions of the uterus forces a variable amount of blood out of the placenta into the fetus, this raises the arterial and venous tension in the fetal circulation, and thereby a slowing of the fetal heart. When this overloading occurs with the last few labor pains, the babies heart is over-loaded and dilated. When the infant starts breathing and the lungs expand, there is a stasis in the pulmonary circulation due to the dilated heart, and as a result of it, pulmonary congestion occurs. Therefore, delayed respiration of improper heart action causing a stasis in the circulation at birth may so interfere with the proper oxygenation of the vital centers and the brain as a whole, that they may become damaged in a very short time.

It would probably be wise before going further in the discussion to find out something as to the cause of

narcosis. Trusler, Guedel, George, (67), refer to the respiratory centers as, "an animated chemical indicator and that we find its reactions dependent upon two conditions; 1. The sensitivity of the indicator itself, and 2. The chemical properties of the solution acting on it. The respiratory processes of the fetus are entirely internal. Normally the mechanism of this internal respiration continues till birth has been accomplished at which time the respiratory center responds and external respiration carries on. A marked delay in respiratory effort must be attributed to depression of the respiratory center".

In answer to this many theories have been advanced in attempts to explain how anesthetics produce narcosis and depression of the respiratory centers.

In Websters book (69), we find the explanation, "During narcosis there is an increase of fat in the blood, probably brought about by the action of the anesthetic on the fatty tissue. It has been shown that the more soluble an anesthetic is in fats and lipoids the more readily it produces its effects".

Burge, Neill, Ashman, (12), have also called attention to the fact that, "Anesthetics are fat solvents, so they come to a conclusion that narcosis is produced

by the direct removal of the fat like substances, or lipoids, from the brain". Due to the fact that no one has been able to prove this theory has rendered it intenable.

Other investigators, Spegel and Speigel, Adolf (62), working on this same theory believed that lipoids and probably their state of dispersion play an important part in the mechanism of the central nervous system depression. This seemed tobe indicated by the fact that in experiments with electrods placed in the brain substances of cats found "that the index they found changed under the action of the narcotics, namely, the defference in conductivity at low and at high frequencies could be initiated in their studies on biocolloid membranes only, by such membranes that contained lipoids (cephalin, lecithin) in fine dispersion. This fact is an increase in density of the cellular surfaces film, is still controversial". It has also been stated that the action of narcotics is not limited to the cell surfact and that an influence upon the colloids within the cells plays a part also.

Oxidation of the nerve tissue and cells is decreased or prevented entirely according to the depth and duration of the anesthetic. It has been shown by

numerous experiments on frogs which were narcotized, and whose spinal cords were mildly poisoned by strychinine, ether chloroform, alcohol or carbon dioxide; the presentation of oxygen did not relieve the fatigue of the cord, as shown by electrical stimulation, until the animal was allowed to recover from the anesthetic: when the presentation of oxygen speedily relieved the fatigue, showing that while under narcosis, living tissues are unable to utilize the oxygen offered to them. Webster (69)

According to this then it would seem logical to assume that what ever other changes may occur, the factor which produced the characteristic symptom complex of narcosis is under all circumstances the suppression of the power to carry on oxidation.

Quoting again from Webster (69), who states some work done by Mossa, tends to uphold the above theories, we find, "In a case of a large defect in the skull over the frontal lobe, the cerebral pulsations could be graphically recorded. When he compressed the carotid arteries in the neck so that the cerebral pulsations ceased, consciousness was lost in five seconds without disagreeable sensation. On releasing the arteries, consciousness returned at once. Thus, it is shown

that the ganglion cells of the cerebral cortex are exceedingly sensitive to lack of oxygen, and to deep narcosis which completely inhibits oxidation processes, and may, if prolonged, do permanent injury to the brain".

The nervous system shows the first and most marked effects of an anesthetic, and the most highly organized part of this system is first and chiefly affected. There is irritation, depression and finally paralysis of the nervous system. The effect to the areas of the brain are in the following order as listed by Patton (49); "the cerebral cortex, the cerebellum and ganglia, the sensory tracts, centers of the cord, the cerebrospinal motor tracts and centers, the respiratory center, and then the cardiac centers".

No topic in obstetrics is more provocative of discussion than that of analgesia and anesthesia. Journals are filled with reports of assorted methods and new combinations and every patient who comes to register wants first to know, what will be done to eliminate the pangs of labor. She wishes to go to sleep with the first pain and wake up with her baby in her arms, and she is sure from her reading that this is not only feasable but that it is her rightful privilege. (Montgomery T.) Therefore there is an ever increasing demand of the modern woman for painless child-birth, obstetricians and anesthetists have been increasingly diligent in the search for an ideal analgesic that will meet the demand. But it has been stated, (52) that the risk of anesthesia falls chiefly on the mother where as the drugs used to produce amnesia and analgesia are seemingly more dangerous to the fetus.

The ideal anesthetic or analgesia, should be safe for both the mother and the child and should not interfere with the efficiency of the uterine contractions or the patients co-operation, so as to decrease to any appreciable extent the number of spontaneous deliveries. Up to the present time there has been no one drug, or combinations of drugs, that will meet these requirements.

DRUGS AND THEIR ACTION

With this in mind then, we will attempt to bring together some of the most commonly used drugs, in the field of obstetrics today, and see what various men over the country have found as regards their use.

All anesthetics, hypnotics and narcotics diminish the sensitivity to stimuli, but these drugs vary widely in the relative degree to which they depress sensitivity to the various kinds of stimuli. It is obvious then that the drugs employed should have a minimum tendency to depress respiration. In general, the volatile anesthetics decrease sensitivity to afferent stimuli, while exerting comparatively little influence of a depressant character upon respiration, unless they are administered in excess. It has been demonstrated also that the most drugs administered to the mother pass also to the child. This has been demonstrated by Irving and his associates showing that all of the children born of mothers who have not had drugs, less than two percent failed to breathe spontaneously; on the other hand with some of the drugs now frequently used, the depressant effects are so powerful that a large minority (35%) of the children born under their influence failed to breathe immediately at birth. (71)

With this in mind then, the following discussion

on drugs will be limited to those that are the most commonly used in the field of obstetrics to produce anesthesia and analgesia.

GAS ANESTHESIAS

"The term general anesthetics is employed to indicate substances used to produce unconsciousness sufficiently complete to allow of surgical operations being performed. In the history of medicine there are repeatedly obscure allusions to substances used for this purpose, but it was not until the end of the first half of the nineteenth century that the era of surgical anesthesia really opened. In 1798 Davy advised the use of nitrous oxide as an anesthetic, but no practical use was made of his suggestion, and Wells may be said to have rediscovered this property of the gas in 1844, though his efforts to introduce it into general use met with no greater success than Davy's. Long used ether in 1842-1843 in surgical operations, but did not give any publicity to his discovery, and the honor of demonstrating publicly the practical use of ether in surgery must be awarded to Jackson and Morton in 1846.

In 1847 Simpson introduced chloroform to the medical profession as a substitute for ether, over which he supposed it to possess several advantages. Its Pharmacological action had been examined some months earlier by Flourens, but Simpson appears to have made his investigations quite independently. Chloroform soon ousted ether in popular favor in Europe, and although

in America a considerable number of surgeons continued to use it, ether had practically fallen into complete disuse throughout Europe, save in Lyons, until a few years ago. The continually increasing number of accidents in chloroform anesthesia has, however, caused a reaction to set in, in favor of ether, and it has been once more reinstated as the rival, and perhaps as the superior, of chloroform throughout the world". Edmunds and Gunn (79)

In the field of obstetrics the general anesthetics, as they are used today, are usually only employed during the second stage of labor, or during the time when the head is presenting over the perineum, or at times when a version is to be done, or a forceps manipulation is expected.

Of the large variety of general anesthetics that are at the disposal of the obstetrician today, the following are the ones most commonly used; Ether, Chloroform; Nitrous oxide, and a rather new-comer to the field, Cyclopropane.

ETHER

Ether alone, is never used as a volatile anesthetic in obstetrics, unless it is in combination with some other gas or air. When it is used, it is usually used in combination with some form of the barbiturates or narcotics.

Clifford (13) has stated that any patient receiving less than one ounce, has not shown any effects on the infant.

Irving, Berman, and Nelson (36) in a report of a hundred cases in which they had used rectal ether and oil showed that fifty-nine percent of the babies breathed immediately at birth. Other investigators (74) believe that this method is safest of all satisfactory analgesias. The baby suffers no ill effects and it incurs no complications of labor or post-partum pathologic conditions.

Eastman (20) also found no proven effect on the infant attributable to the use of this form of anesthesia. He also found that ether anesthesia produces a slight depression of the oxygen saturation of the fetal blood, but it is not a sufficient degree to injure the fetus through anoxemia. Wilson and his coworkers (71) found that ether is relatively safe un-

less present in the fetal blood in high concentrations for a long period of time.

Ether in combination with morphine was introduced in 1923 by Gwathmey of New York. This method is still used and does not seem to have any outstanding effects on the baby. (73)

CHLOROFORM

Chloroform is Trichlormethane ($CHCl_3$). It is the most rapidly acting and most powerful of the inhalation anesthetics, but at the same time by far the most poisonous. It was discovered in 1831 by Lieberg.

"The effects of chloroform upon respiration are reflex. All parts of the nervous system are paralyzed, and eventually killed by chloroform, but in the intact animal, death occurs through the action on the centers, before the peripheral structures are markedly affected. The cerebral centers of consciousness are first lost, then those of the cerebral sensation and voluntary motion. Later reflexes are lost and finally automatic movements, such as those of respiration". (61)

Eastman (20) has emphasized that chloroform had quite a benign effect on the child, and that ether as well as chloroform passes readily through the placenta, and exerts considerable anesthetic effect upon the child. He also found that chloroform anesthesia, when administered to mothers at the time of delivery, has no demonstrable effect on the oxygen saturation of the fetal blood, but due to its toxic effect on the mother, it is not to be recommended as an obstetrical anesthetic.

Findley (25) in a report of cases, found that when

chloroform was used during labor, narcosis of the baby in varying degrees was frequently observed.

NITROUS OXIDE

Nitrous oxide, formerly called "Laughing gas", was discovered by Priestley in 1772.

Chemically it is nitrogen monoxide (N20) and is quite stable. It is well absorbed only through the lungs, and is carried in the blood, probably a larger proportion being held in the plasma. It is evenly distributed through the body, and less gathered in fatty organs than ether or chloroform. With moderate concentrations the effects on the respiratory center are asphyxial, but if the gas is administered under pressure, direct paralysis of the center results". (61)

Eastman (20) has shown that nitrous oxide and oxygen in proportion of eighty-five to fifteen, weaker, did not cause harmful degrees of anoxemia. And he also showed that four to five breaths of pure nitrous oxide to produce analgesia probably causes less anoxemia than eighty-five to fifteen concentration continued for five minutes.

Other investigators (13) in their reports on cases where nitrous oxide and oxygen were used, the length of anesthesia seem to bear no relation to the condition in the infant is found at birth. Clifford and his associates (13) found no relation between the duration

of nitrous oxide and oxygen administration and the infant's condition.

R. R. Ferguson (27) collected reports on some seven thousand cases from all over the country. In a letter from Dr. Carl H. Davis of Chicago, he got a report stating, "There is no apparent effect on the baby. A critical study of all cases delivered in the maternity department of the Presbyterian Hospital during a period of six months, shows that the babies of mothers treated with the analgesias, lose less weight during the first week than did those of mothers not given the gas. There is the variation in fetal heart tones of over five per minute and then only once in a case where gas was used for ten hours. Less effect on babies than either chloroform or ether". In a letter from Dr. Darling of Milwaukee, observed, "The first cry is earlier and lustier and general condition is better than other babies". Henderson of Louisville, "No danger to baby if mother does not become cyanotic."

There are numerous other reports from other prominent men, all with the same conclusion, that there is no deleterious effect on the baby. So, in summing up the reports that he obtained, Ferguson came to the conclusions that 1. "That nitrous oxide oxygen gas in their

proper percentages for each individual case, this to be determined at the bedside, is a most wonderful help to the mother, and may even annihilate all labor pain; but that it is impossible to rule out all danger to the baby even though the mother may show no cyanosis". 2. "That nitrous oxide oxygen gas when used longer than three hours becomes dangerous to the baby by reason of the hemolysis which occurs in the mothers blood. This may also occur in the baby's blood". 3. "That the babies are safe for three hours of a gas labor providing the mother is never allowed to become cyanosed and nitrous oxide is not used above ninety percent, the other ten percent being oxygen, not air." (27)

Findley (25) (24) in speaking of nitrous oxide oxygen analgesia, stated, "this seemed to be highly efficient as an analgesic, and caused no ill effects in the babies". He also found that when the gas was not given in quantities to produce cyanosis, that the babies when delivered, breathed spontaneously and seemingly showed no ill effects.

CYCLOPROPANE

Cyclopropane is a cyclic hydrocarbon gas, with the empirical formula (C_3H_6), was developed in 1929-30.

Eversal U. and others (23), who have been working with this gas give the following report; "Absorption of cyclopropane through the lungs is quite rapid, and unconsciousness is usually reached in one to two minutes, but is slow to reach saturation. The probable explanation for this slow saturation lies in the high oil to water ratio of this gas, hence the very rapid absorption by the lipoids of the body.

Elimination from the blood is probably quite rapid. It does not have the respiratory stimulating effect which is so evident with nitrous-oxide and ethylene, and due to the fact that there may be periods of apnea indicate that there may be a slight respiratory depressant.

The effect on the blood chemistry is very slight. There is slight rise in blood sugar, as is true with most anesthetic agents, but the level very quickly returns to normal and there is practically no change in the acid base balance.

The reports of cyclopropane in obstetrics are quite favorable. Its use in intermittent administration

to relieve labor pains and for manual and instrumental delivery is fast gaining recognition. There is a relatively low toxicity for the mother, and very infrequent necessity for the use of any type of resuscitation proceedure for the baby".

From their conclusions these authors (23) think that this type of anesthesia is good from an obstetrical standpoint because of the large amount of oxygen which may be administered with it and because of its rapid, smoothe induction.

Knight (38) states that "Because cyclopropane does not impair the respiratory center this factor is not present after obstetrical operative proceedures, to hamper resuscitation of the child. Furthermore, as cyclopropane is used with a very high percentage of oxygen the color of both the mother and the child is always excellent unless the cord circulation has been interfered with, and even if a partial impingement has occured, the danger is lessened because of the excess of oxygen".

However, Wright (73) believes that the margin of safety of nitrous oxide oxygen as a supplementary anesthetic in the third stage, is much greater than with cyclopropane.

NON-VOLATILE ANESTHETICS

AVERTIN

Avertin, or tribromethanol, was first described as an anesthetic and demonstrated by Eichlialtz in 1927. A dosage of 60mg. per kilogram dose was used.

In a series of some 120 cases as reported by Cochran (14), six of the babies required resuscitation, the others showed no evidence of cyanosis or narcosis, each breathing and crying vigorously immediately after birth.

In a series of 100 cases reported by another author (25), there was no effect on the babies when the drug was given at time of complete dilatation of the cervix. Its disadvantages as seen by this man were the postpartum hemorrhage and very little relief of pain.

The use of this form of anesthesia in the field of obstetrics has been more or less disbanded, and is therefore only used in selected cases.

PARALDEHYDE

Paraldehyde ($CH_3CHO)_3$, was introduced by Cewello as a powerful hypnotic about 50 years ago. This polymer of acetaldehyde (CH_3CHO) is a volatile, colorless, transparent, inflamable fluid slightly soluble in water. (18) It resembles ethyl alcohol, absorbs rapidly from mucous membranes and is excreted rapidly from the body in the lungs and kidneys without damage to these organs. It is characterized by its absence of respiratory and cardiac depression and prompt hypnotic action. DeCosta (17)

In a large number of cases in which paraldehyde was used, this author (17) found only six babies out of a large number that had fetal apnea, all of these began to breathe and cry as soon as mucous was removed from the larynx.

In the use of paraldehyde in labor, a study was begun by Moore (76) in the Cleveland City Hospital, in June 1934. A study of 50 cases was used. The drug was given rectally with an equal amount of olive oil, the usual dose being six drachms, repeated every three to four hours. In some cases it was combined with morphine, sodium amytal, or sodium pentobarbital. He found that in 64% of the cases, results were good and

in 22% the results were poor. In all cases in which paraldehyde was used, there were surprisingly few complications which might have been attributed to the medication. There were no maternal deaths and no still births or neonatal deaths. In all cases the new born breathed spontaneously or with slight stimulation and seemed to be entirely free from the effects of the drug. The odor of the drug persisted on the breath of the new born child for several hours. Paraldehyde, therefore, is recognized to be a powerful hypnotic of low toxicity.

Wright (73) believes that paraldehyde given in 1 cc. doses for each one and one-half pounds of body weight appears to be a better hypnotic than morphine-scopolamine, and there is less pain than with avertin.

He also observed that paraldehyde may be observed on the infants breath, but very few cases of infantile asphyxia have been observed or reported.

Rosenfield and Davedoff (57) in their series of three hundred cases found that there was complete amnesia throughout labor in 285 patients (95%), and there was no maternal mortality. Of the babies born alive, 264 (86%) breathed or cried readily immediately following delivery.

Other men believe that paraldehyde used alone in

labor will not produce satisfactory analgesia or amnesia, even in large doses, but acts only as a basal anesthetic.

Rice, of Oklahoma (55), is one who upholds this belief and he combines nembutal with the paraldehyde, and he has found that there is less asphyxia of the new born and no cardiac or respiratory depression.

Findley (25) states "Paraldehyde in doses of two to three drams was concluded of no use -- only when used with ether or some form of the barbiturates".

Wilson and his co-workers (71) in stating their views on the value of paraldehyde say, "No other available drug is so harmless".

NARCOTICS

The only narcotic that is used to any length in the field of obstetrics is morphine. This drug can hardly be discussed alone without also discussing scopolamine, because these drugs are so closely linked together in the field of anesthesia and analgesia.

MORPHINE

Morphine is an alkaloid of opium, of which it is about 10 percent of the total quantity of the alkaloid present. It is the most dangerous of the opium alkaloids because death is produced in the narcotic stage through asphyxia. (71) states that morphine exerts a more powerful depressant effect in decreasing the sensitivity of the respiratory center, to be stimulated by the gases of the blood. And Kreds (39) experiments seem to prove that the use of alkaloids of opium are likely to interfere with the prompt establishment of respiration of the new born.

Mussey (44) makes a statement that "the routine use of morphine during labor is followed by a higher incidence of fetal asphyxia". He also advised against the use of morphine and its derivatives during labor, as it distinctly delayed the initial respiration of the child.

Clifford and Irving (13), at the clinic of the Boston Lying-In Hospital, found that the use of opium derivative drugs, given within four hours of the birth of the premature infant was associated with a doubling of the death rate, and that the use of morphine or pantopon as a method of obstetrical analgesia would

appear to be not only unsatisfactory for the mother but dangerous to the infant. It was concluded that the size of the dose and the time interval of medication were definite factors influencing the infant at birth.

DeLee (18) says "narcotics may affect the child adversely when given in the second stage of labor, but only when the drugs are improperly administered and in doses that would endanger the mother; if they are given at the proper time and in the proper dosage the child is not in danger, and the mother is made more resistant to exhaustion".

Shute and Davis (58) have reported that narcosis may be exaggerated following the administration of morphine to the mother during the time when the drug is supposed to act most strongly on the baby, only 50 percent of the infants are affected by it to any noticable degree. They also believe that it is a safe drug to use during labor when adequate means of resuscitation are at hand. Other investigators (36) in studying a large group of patients believe that morphine or any of its derivatives has no place during labor as they distinctly delay the initial respirations of the child.

Rongy (56) in a study of 2000 reported cases found,

that "this method when used as outlines by Bauss, the results were uniformly favorable to both mother and child".

Wilson (71) states that when morphine is used, it should be in moderate dosage and should not be administered less than two hours before delivery.

SCOPOLAMINE

The drug was first reported by Gauss in 1906. In 1909 Newell of this country reported 112 cases, but later discontinued it because of asphyxiated babies. McPherson in 1908 at the Lying-In Hospital of the City of New York, tried it out and he also got a high infant mortality. (66)

Scopolamine has two actions. The primary of which is amnesia and the secondary one the analgesia. It acts chiefly upon the central nervous system, quiets the cerebrum and diminishes the reception of pain, but does not affect the involuntary muscles directly. The action of scopolamine upon the baby is very slight when given in proper doses to the mother. It does flush the skin and prevents some shock to the baby in operative work. (66)

Scopolamine anesthesia has always been somewhat of a step-child in the anesthetic world. The scopolamine-morphine anesthesia has the reputation of being responsible for what is known as "blue Baby" as morphine is entirely responsible for asphyxia in the new born in cases where the anesthesia is produced by the combination. It would seem quite rational that if the morphine was eliminated, asphyxia would not occur. Hoosen's (34), observations, showed there was no effect

on the fetus, and its disadvantages lay in the control of the patient herself, and the length of time it took for the drug to take its effect.

Freeling (28) in stating his belief in the use of scopolamine in labor and the effect on the child stated, "that resusitation of asphyxiated infants was not required oftener in the scopolamine than in the other cases". In a review of 410 cases, the fetal mortality was 2 percent and these cases were due to a cerebral hemorrhage, and could not be attributed to the drug. Others (13) have also found no proven effect on the infants attributable to the dose used of this drug.

Taylor (66), in a study of a number of cases found that ninety-two percent of the babies were pink and cried spontaneously. Eight percent required some resuscitation, of these, two were due to the scopolamine and morphine.

SCOPOLAMINE AND MORPHINE

Scopolamine and morphine was introduced by Steinbrichel of Germany in 1902, being most popular about 1915. No matter in what dosage it was given, many babies were narcotized and some could not be resuscitated. Edwards (21) found that the use of narcotics with scopolamine, that the babieswere quite cyanotic and hard to get them to breathe properly.

However Krebs and his co-workers (75) think there is no disadvantages of the method to either mother or child. Fetal asphyxia is not increased, although children are occasionally born in a state of oligopnea, from which usually they promptly recover on appropriate stimulation.

Lewis (43), in a series of 575 infants, out of this group 109 mothers received morphine-scopolamine, ninety-three or eighty-five percent were not narcotized; sixteen or 14.6 percent were. He believes that "the size of the dose of the analgesia plays a minor role in the incidence of narcoses. The time between the administration of the analgesia and the delivery of the infant does not seem to have any direct bearing on the incidence of narcosis except for those in the operative group, and the effect of the drug on the mother is no

indication of its effect on the new born". Findley (25) also agrees with this view. In reviewing 1500 cases in which morphine and scopolamine were used, found that serious complications in the baby were relatively rare. Another investigator (52) found that no disastrous effects followed morphine-scopolamine analgesia unless the treatment is begun too late or the dosage is too large or too long maintained.

Others (36) used pantopon and scopolamine and they believe that pantopon is less toxic to the fetus in-utero than is morphine. In 100 cases, 1/3 gr. pantopon was used and the effects on the babies were striking only 33 percent breathed immediately at birth. In another series it was found that 1.9 percent of babies did not breathe, as soon as they were born. Irving, Bermen, Nelson (36), in reviewing one hundred cases in which pantopon and rectal ether was used found the effect on the baby was not as marked as that of pantopon and scopolamine, since 53 percent of the babies breathed immediately at birth.

BARBITURATES

Barbital was first introduced into medicine by Emil Fisher and Von Mering under the name of Veronal. (15). Since their introduction the barbiturates have the most extensive clinical use of any of the agents now commonly employed to cause sleep. During the last three or four years the barbiturates have become increasingly popular, either as the principle hypnotic or as adjuvants to morphine and scopolamine. They are slowly eliminated, and their action as hypnotics is not only prompt but prolonged. (73)

Small doses are sedative to the higher cerebral centers, larger doses are somnifacient, and still larger amounts produce anesthesia. The diverse therapeutic application of these compounds is largely the result of the successful development of substituted derivatives of the parent substance, barbituric acid, which vary among themselves in the rapidity and duration of their action. It is possible to select from the series one or more preparations which are particularly well adapted to any medical or surgical indication. (22)

The use of various barbiturates has been steadily increasing in labor. It has been found that the use of the barbiturates in doses large enough to produce com-

plete analgesia or complete amnesia is not without risk of respiratory and vascular depression. (22) "the barbiturates are very valuable, however, during the first stage of labor to relieve anxiety, lessen the acuity of pain, and cause perineal relaxation between labor pains. They are usually combined with a more potent analgesic, such as morphine, paraldehyde, or a gaseous anesthetic, when the second stage of labor begins. Rectal ether-oil is being widely adopted to supplement the use of the barbiturates during the latter part of the first stage of labor".

There is much divergance of opinion regarding their action on the fetus and infant. Wright (73) "believes that in therapeutic doses they do not materially affect the respiration of the mother or the circulation of either mother or child, though some narcotized babies have been reported".

Animal experiments by Berutti (5) in which he studied the permeability of the placenta (in these animals) to the various barbiturates, namely dial, veronal, luminal, somnifen, evipal and pernocton show that the placenta is very permeable to these drugs. By repeated hysterotomes, he was able to determine the barbiturate concentration of the blood of the mother,

the placenta and the fetus at intervals of three, five and twelve hours. The maximum concentration in the placenta was reached in three hours, and in the fetus in five hours. None could be found at the end of 36 hours. This permeability was more so to luminal and less so to evipal.

Eastman (20), in his study of barbiturate analgesia versus no analgesia, has shown, as is illustrated by the following table, that an average of two percent required some method of artificial resuscitation before respirations became normal. And in the narcotized that gasp shortly after delivery, the respirations are shallow and frequently after the first breath a considerable period may elapse before normal respiration is established.

	No analgesia	pentobarbital scopolamine rectal ether nitrous oxide
Maternal amnesia--------	0	84%
Neonatal mortality------	0	0
Infants physiologically normal-------	73	62
Infants artificially resuscitated-------	0	2
Infants abnormally cyanotic----------	23	21
Minutes to first breath-	1.0	1.0
Minutes to first cry----	1.6	4.7

Although there are a large number of the barbituric acid derivatives in use today, there are only two that are outstanding in the field of obstetrics at the present time, namely sodium amytal and nembutal (pentobarbital-sodium). Others have been used but do not have seemed to have obtained the expected results so have fallen by the wayside.

SODIUM AMYTAL

Of these two compounds, sodium amytal is more generally used in obstetrics. It may be given by mouth or by retention enema. Dosage has ranged from three to six grains as an initial dose, followed by additional amounts of three to six grains as indicated. In small amounts, sodium amytal will allow rest and sleep between pains, the perineal muscles relax, and there is rapid softening of the cervix. (22)

Clifford and others (13), have been able to demonstrate no relationship between either the size of the dose or the time of administration of the barbiturates and the condition of the infant at birth.

Barnett (3), found in his experiments that sodium amytal in doses sufficient to produce analgesia and drowsiness was found to affect the fetal respiratory movements, stimulating them at first and then retarding them, and gradually slowing them down.

Friedman (29) has therefore come to the conclusion that "the drug produces no harmful effect on the baby, and labor is actually shortened rather than prolonged.

Cases in which sodium amytal and scopolamine were used, Irving and others (36) found in analgesia of 160 cases that "sodium amytal nine to twelve grains and

scopolamine one one-hundreth, 45 minutes after the amytal, the effect on the baby was good, since sixty-one percent breathed immediately".

NEMBUTAL

Nembutal has a profound sedative but short hypnotic action. Contrasted to most other barbiturates, nembutal produces surgical anesthesia in the lower animals with a smaller dose and shorter duration of effect, resulting in comparatively more rapid recovery, usually with little excitement or delirium.

The use of nembutal in obstetrics was started as a routine at the Boston Lying-In Hospital by Clifford and Irving (13), in 1931. The patient received pentobarbital without scopolamine or rectal ether. Since this use of the barbiturates the still birth rate has fallen from 65 in the preparbiturate era to 56 per one thousand births for the past five years. So from this report it would appear that the general use of barbiturates and expecially of nembutal, in this clinic has had no ill effect on the life of the fetus.

Findley (24-25) in reviewing two thousand cases in the Philadelphia Lying-In Hospital found "that fetal distress attributed to the drug was not meet. Nearly all babies, save in complicated deliveries, were of good color when delivered and required no resuscitation. Although the initial dose given the mothers was nine grains".

Other men 21; 77; 78; 4; 36; in their series of cases in which the baby was born of mothers who had received nembutal found that over 80 percent of the babies were living and breathed spontaneously. They also seem to agree that nembutal is the safest of the barbiturates, and due to the fact that the drug is excreted more rapidly than is sodium amytal, is therefore much less toxic.

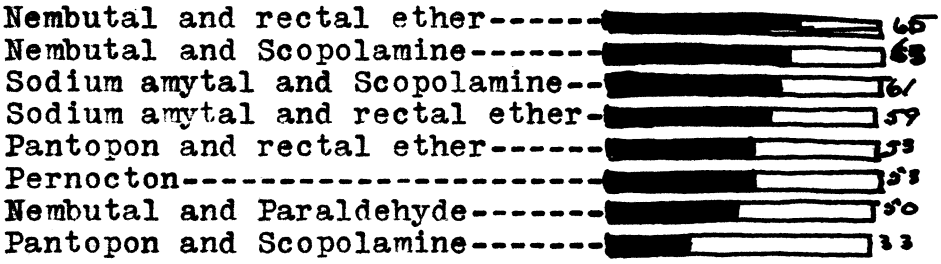
The action of the nembutal can be markedly prolonged by the use of scopolamine. As Clifford and Irving (13) report "that when scopolamine is combined with either nembutal or sodium amytal a more successful analgesia results in so far as complete maternal amnesia is concerned, and there has been no significant change in the condition of the infant at birth".

Other men 1; 44; 37; also agree with Irving that scopolamine when combined with the nembutal prolongs the action of it and does not seem to materially effect the child, as the mortality, with or without the scopolamine is not increased.

The following chart made at the Evanston Hospital by Galloway and his followers (30) on the fetal mortality of a group which the mothers received nembutal.

	Total of 3 years
Nembutal	1415
Gross fetal mortality	31
Unavoidable deaths	22
Obstetric Mortality	9

Another chart brought out by Irving, Berman and Nelson (36), in which they compare the various analgesias in relation of the effect on the initial respirations of the infants.



CONCLUSIONS

CONCLUSIONS

1. The modern history of pain relief in obstetrics dates from the work of Simpson in 1847.

2. That the fetus exerts respiratory like movements in-utero, that these are phypsiologic, and are not initiated by changes in the fetal blood nor by stimulation as a result of handling.

3. That the full term fetus in-utero exists normally in a state of cynosis with a mean capillary oxygen saturation of 11.1 vol. percent. (the threshold for visual cynosis being 6.5 vol. percent.)

4. That prolonged apnea was characteristic of the fetus before birth, when anesthesias were used.

5. If the mother does not receive more than one ounce of ether during labor, there is no effect on the infant.

6. That chloroform is more toxic to the mother than to the child.

7. Nitrous-oxide when used in concentrations of 85:15 of NO2 - O2 there are no harmful degrees of anoxemia.

8. Cyclopropane is quite promising because of the high O2 used with it.

9. Paraldehyde is only good when used with some form of the Barbiturates.

10. Morphine causes distinct delayed innitial respirations of the child, and should not be given within 2hr. of the expected delivery.

11. Scopolamine-Morphine analgesia dose not seem to have any outstanding effects on the child.

12. The Barbiturates give the greatest percent of maternal amnesia and the lowest fetal mortality.

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