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INHALATION ANESTHETICS
WITH SPECIAL CONSIDERATION OF
THEIR COMPLICATIONS

by

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INTRODUCTION

In this paper I shall discuss the five major anesthetic agents which produce their effect after absorption into the blood stream from the alveoli of the lungs, with special consideration of the complications arising as a result of their administration.

The five major inhalation anesthetics I consider to be chloroform, ether, ethylene, nitrous oxide, and cyclopropane. Ethyl chloride is sometimes used to induce anesthesia, but in this section of the country is so seldom used that I have not included it in this paper. Chloroform is not used extensively anymore, except in rural communities because of its convenience. I have included it because of the important place it has had in the study of liver damage and physiology.

A complication shall be considered to exist when changes are produced in the individual by the anesthetic agent which are manifest by an untoward symptom or group of symptoms occurring during the anesthesia or in the post-anesthesia period which have a physiological or pathological basis of explanation. They will be considered complications resulting from the

anesthetic whether from a direct toxic action of the anesthetic agent or from an indirect effect of altered physiology resulting from the presence of the agent.

HISTORY

The use of various agents to relieve the pain of surgical procedures dates back to antiquity. The Egyptians probably used narcotics. The Assyrians strangled their children to insensibility before circumcision. The Chinese used hashish. During the middle ages, all kinds of drugs were used, especially opium and hyocin containing drugs.

Sir Humphrey Davy first suggested the use of Nitrous oxide for surgical anesthesia in 1799. There is no record, however, of it being used for this purpose until 1884 when Horace Wells, a dentist, noticed an individual who had inhaled "laughing gas" was insensible to the pain of a leg injury during some kind of public performance. He conceived the idea of painless dentistry and set about to try it. He was quite successful and the gas was soon introduced into the practice of dentistry. A breast amputation by a Dr. Bigelow in April 1848 was the first surgical operation with nitrous oxide anesthesia. The gas was used alone until 1867 when Dr. E. Andrews of Chicago suggested the use of oxygen with it.

Ether was used for surgical anesthesia by Dr. Crawford Long in 1842 but he failed to report its use and the credit usually falls to Wm. Morton, a dentist

and friend of Wells. Morton was not entirely satisfied with the results of nitrous oxide and consulted a chemist, Charles T. Jackson regarding anesthetic substances. Jackson suggested the use of sulphuric ether and after a period of experimentation, Morton applied to John Warren, Chief Surgeon of Massachusetts General Hospital for permission to demonstrate a new anesthetic which he called "letheon". He was granted permission and in spite of his efforts to mask the odor of the ether with essential oils, a Dr. Bigelow recognized it and immediately spread the news abroad and ether was soon being used throughout the world. Ether had been discovered in 1540 by Valerius Cordus and Morton got a patent on it in 1846.

Chloroform was discovered independently by Samuel Guthrie of New York, and Liebig Germany in 1831. It was tried on animals by Flourens in 1847, and in the same year by Simpson on man.

The anesthetic qualities of ethylene were quite accidentally discovered in 1908 by two Botanical chemists investigating the cause of a condition simulating sleep in plants stored in green houses in Chicago. Luckhardt and Carter (73) experimented with the gas and reported on its anesthetic qualities in 1923.

Cyclopropane was first prepared and its structure proved by Freund in 1882. It was reported first as an anesthetic agent by Henderson and Lucas in 1929. (71)

THEORIES OF NARCOSIS

Narcosis was defined by R. S. Lillie, to be a physiological condition in which the normal responsiveness or automatic activity of the living system --organism, tissue or cell-- is temporarily decreased or abolished. He considered it synonymous with anesthesia. Such a definition emphasized the reversibility and possibility of recovery.

Bibra and Harless, in 1847 (108) immediately after the discovery of the anesthetics, drew attention to the fact that they were nearly all fat-solvents. He suggested that these substances dissolved the fat from the nerve cells to produce narcosis. The rapid recovery from the effect of the anesthetics could hardly be made to coincide with such a theory. There were definite association of the lipoid-solubility of an anesthetic agent, however, and others showed there was a quantitative relationship. Bernard in 1853, suggested a semicoagulation of the protoplasm of the nerve cells. Such a suggestion was prompted by the fact that he had noted that aliphatic narcotics coagulate proteins. Cerebral anemia, the same explanation offered by Durham, for natural sleep, was suggested by Bedford and Brown in 1860. In 1866, Hermann showed

that all the aliphatic narcotics dissolve red blood corpuscles, and connected this with their lipid solubility and narcotic action, whereas Richet in 1895 believed the narcotic efficiency to be inversely proportional to the solubility in water. Meyer and Overton combined the two later theories and showed a close parallelism between the relationship of the solubility of the substance in fat to its solubility in water and the narcotic action. They showed that the higher the partition coefficient, the greater the narcotic action of the agent.

$$\frac{\text{Solubility in Fat}}{\text{Solubility in Water}}$$

Thus according to their theory, a substance which is less soluble in the watery plasma of the blood than in the lipoids of the brain cells, it leaves the blood and accumulates in the latter. Meyer suggests that here they render the lipoids more liquid and thus alter the physiology of the cell with a consequent impairment of function which depresses the activity and narcosis is the result. Cushney has pointed out that morphine and other basic and saline narcotics do not obey the law and must act by entirely different mechanisms, but this does not of course impair the validity of the relationship when applied to the aliphatic narcotics.

Froelich showed, in agreement with this theory, that an excised nerve loses its excitability in an atmosphere free from oxygen. He and his associates also showed that oxygen deprivation delays recovery from anesthesia.

Nernst explained stimulation of the nerve cells as being due to a change in the electric polarization of the cell resulting from a change in the concentration of the ions on the surface brought about by a sudden increase of the permeability of the membrane at the moment of stimulation. Lillie showed that anesthetics lessen the permeability of cell membranes, and suggested narcosis as being due to an interference resulting from the altered permeability.

Many other theories have been suggested but at the present time no one theory is entirely satisfactory. Perhaps a combination of the lipoid - water solubility, membrane permeability, and reduced oxidation theories provide the best possible explanation in the light of present knowledge.

RESPIRATORY COMPLICATIONS DURING
ADMINISTRATION

Nausea, retching and vomiting during the anesthesia are usually due to faulty induction with disproportionate anesthetic mixtures or to faulty technic.

The most common type of complications are those associated with the respiratory and circulatory systems. Mechanical obstruction to respiration, caused by dropping back of the tongue, or by mucous, blood, lung exudates, or stomach contents is easily relieved by the introduction of an airway and by aspirating the obstructing fluids. Laryngeal spasm may result from a too concentrated mixture of the agent early in the induction, or even later with ether in some individuals, if added too suddenly. Reduced oxygenation of the blood with varying degrees of anoxemia, especially with nitrous oxide, may result in generalized muscle spasm, including laryngeal spasm. Such spasm may usually be relieved by the inhalation of oxygen or by the use of helium in the anesthetic mixture (36). If asphyxia is resulting from tracheal compression or other obstruction below the larynx it must be relieved by the use of an

intratracheal catheter.

Intra-abdominal explorations and traction on the viscera set up reflexes which sometimes have an inhibitory effect upon the respirations. This is especially true in an acute abdomen in a robust individual with improper preoperative preparation. The condition is usually temporary, however, and will correct itself when the cause is removed or the narcosis deepened. Deep narcosis to compensate for the rough handling is neither good anesthesia nor good surgery.

Threatened cessation of the respirations from whatever cause, characterized by slow, shallow respirations, dilating pupils, and other signs of threatened collapse, is combated by inhalation of carbogen with whatever other restorative or stimulating measures seem necessary. Cessation of respiration is not infrequent with cyclopropane and may occur early in the induction period. (8) Probably two factors are concerned in such apnea; the first being the high oxygen content of the inspired mixture and second, due to irritative properties of the anesthetic agent when given in too high concentrations. Such apneas are frightening, though they are usually temporary. Regardless of their temporary character,

artificial respiration with oxygen by means of the rubber re-breathing bag is better therapy than waiting for the carbon dioxide tension to rise sufficient to stimulate the respiratory center.

Complete respiratory failure with its attendant asphyxia is usually due to the lethal effect of a dose of the anesthetic agent upon the vital respiratory and cardiovascular centers. The respiratory muscles which are responsible for the normal chest excursions first become paralyzed, and finally by paralysis of the respiratory center. The heart may continue to function for a variable period. Before complete breakdown, active measures for effective artificial respiration may save the life of the patient.

Surgical shock is rarely considered an anesthesia complication. But, the anesthesia is sometimes considered a contributing factor.

Sudden death on the operating table is sometimes ascribed to primary cardiac failure, which is a very rare condition. When it occurs it is usually due to the lethal effect on the cardiovascular mechanism of a toxic dose of an anesthetic which is definitely a cardiac depressant. Chloroform, ethyl chloride and cyclopropane in high concentrations

fall into this group.

Other causes of sudden death on the table, such as embolism are hardly ascribable to the anesthetic and an etiological factor is usually demonstrable. Unexplained deaths have been ascribed to "status lymphaticus", but it is hard to comprehend or to explain the cause of these deaths.

Postoperative pulmonary complications are sometimes attributed to the anesthesia as will be discussed in the next section of this paper.

PULMONARY COMPLICATIONS

Pulmonary complications following a surgical procedure have always been a very real factor in postoperative morbidity and mortality, but it has not been until fairly recently that attention has focused on it with an attempt to understand the cause and prevention of such complications. The literature of early surgery has not considered the subject, perhaps the operations were so short, or anesthetics so new that the relationship did not occur, or the interest in the surgical aspect overshadowed other factors as a cause of morbidity.

Factors other than the anesthetic agent have an important influence on such complications and I shall consider the following as being influential.

(1) The anesthetic agent, (2) the duration of the procedure, (3) the depth of anesthesia, (4) the preoperative condition of the patient, (5) sex, (6) the site of the operation.

The effect of the anesthetic agent has been thought by many to bear a direct relationship to the occurrence of pulmonary complications. Ether has been considered a serious offender because of the irritation of the bronchial mucous membrane with the consequent hypersecretion. This, however, is open to question as is shown by King. (65) in the following table

Anesthetic	Operations	Complications	Per Cent Complications
Inhalations	1198	158	13.1
Spinal	227	42	18.5
Local	79	15	18.9

Such a group of statistics is not conclusive without knowledge of how the cases were selected, if other factors are admitted to be involved in the production of the pulmonary complications. It does indicate, however, that spinal and local anesthesia are not without attendant pulmonary complications and that other factors than the agent or manner of administration of the agent must be considered.

The problem of deciding which agent is the greatest offender is difficult to solve, since ether is used with both ethylene and nitrous oxide when good relaxation is to be obtained. The gases are used alone, but in such cases the surgical manipulation is of a minor character and the duration of the anesthesia is short.

The use of cyclopropane has been reported by various authors to have reduced postoperative pulmonary complications. Waters, Bennett, and Taylor (111) reported an incidence of 1.9 per cent with ether, out of 2,431 cases compared to 0.95 per cent of 5,889 cases using cyclopropane. Burford (12) reports an incidence of 0.97 per cent with cyclopropane out of a

total of 1,333 cases, but when abdominal operations only were considered he found the complications percentage to be 2.07 of 625 cases. On the other hand, Moffitt and Mechling (83) report no complications in 172 abdominal operations. Fuller, (40) in 1930 reported an incidence of 8.3 per cent with ether. Eliason and McLaughlin (33) report 1.68 per cent of 7,326 cases showed pulmonary complications following the various anesthetics with nitrous oxide gas-ether to be the most frequently followed by such complications. They placed open drop ether second and local anesthesia third. They did not use cyclopropane.

Ether used as a supplement to other anesthetic agents tends to raise the incidence of pulmonary complications if the report of Burford (12) is authentic. He reports that 303 abdominal operations performed with ether supplement were followed in 2.9 per cent of the cases by pulmonary complications, whereas with cyclopropane alone they occurred in only 0.93 per cent of 214 cases.

I can find no statistics concerning the incidence of complications following ethylene or nitrous oxide alone, but from the report of Sollmann(108), one could expect them to be as free from such effects as cyclopropane.

In summarizing the effect that the individual anesthetic agent may have in the production of pulmonary complications, one may say that factors other than the agent must be considered, but ether is probably the one most frequently followed by such complications. The incidence of complications seemsto be no higher following inhalation anesthesia than following spinal or local, in cases selected for its use.

The duration of the operation or the time under anesthesia has been proved to have a very decided effect on respiratory complications. Taylor, Bennett and Waters (111) report an increase in all complications from 2.9 per cent for an operation of thirty minutes through successive stages for each half hour the operation is prolonged, to 30 per cent for operations lasting three to three and one-half hours. Rovenstine and Taylor (102) present statistics show that the incidence for operations lasting one and one-half hours is twice that following operations of one hours, and the incidence for two hour operations is triple that of the one hour. Raginsky and Bourne (94) show the relationship existing between liver damage and the duration of ether and chloroform anesthesia.

Eliason and McLaughlin (33) state that the length of the anesthesia has a definite bearing on the number of pulmonary complications.

Taylor (111) and his associates have compiled statistics to show that there is a progressive increase in the incidence of pulmonary complications from 5.9 percent in the stage of anesthesia to an incidence of 15.4 per cent in the fourth plane of the third stage. Their statistics also show, besides the increasing pulmonary morbidity with increasing depth of anesthesia, the tendency for the greatest number of surgical operations to be performed in the upper planes of anesthesia. Surgeons in the past have been dissatisfied with anesthesia that did not provide them with complete relaxation which requires profound anesthesia. But, in their effort to reduce operative morbidity they are heeding the advice of the anesthesiologist and training themselves to work with not quite so complete relaxation.

Guedel (45) states that anesthesia relaxing skeletal muscles to the point where their tone is lost, will also relax vascular tone. This tends to peripheral circulatory failure and shock. He believes that

fifteen minutes in lower third plane anesthesia is

depressing than two hours in the first plane.

Henderson (56) added further that loss of vascular tone resulted in venous stasis with a diminished return of blood to the heart.

Burford (12) sites 626 abdominal operations requiring a fairly deep anesthesia, and 707 non-abdominal operations which did not require such relaxations. The incidence of pulmonary complications in the first series of cases was 2.07 per cent, whereas in the other series it was zero.

According to one school of thought, postoperative pulmonary complications are produced by the aspiration of infected material into the bronchial system. The factors cited as favoring this theory will be an aid in the preparation of the patient for the anesthetic, whether the theory is completely true or not. Among those factors presented are:

(1) Experimentally and clinically, material from the mouth may gain access to the trachea and lungs during anesthesia. (2) In animals under ether, colored matter in the stomach may reach the lungs if the animal is allowed to vomit. (3) The pneumococcus, type IV is responsible for the majority of postoperative complications and it is well known to be a common organism in oral secretions.

(4) Pre-existing lung lesions frequently flare up with anesthesia. (33) These authors also report a series of 120 cases, 19 of which had colds or chest signs at the time of operation. They state, however, that all but 5 of these were acute surgical cases in which operation could not be postponed. Of the 19 patients 6 succumbed directly as a result of a respiratory complication, and 4 others died with their pulmonary complication contributing to their death.

King (65) is of the opinion that sepsis anywhere in the body at the time of operation contributes to a higher incidence of pulmonary complications. In 127 cases of appendectomy alone, pulmonary complications developed in 9 to 7.1 per cent. Appendectomy with drainage, was accompanied by a higher incidence. Out of 68 such cases there were 19 who developed pulmonary complications, or 27.9 per cent

Such figures emphasize the importance of the removal of all septic foci in the nose, mouth, pharynx, larynx, etc. before an anesthetic be administered. Unfortunately many emergency cases come to the hospital on whom an operation can not be postponed and the foci iradicated, but operations of election and chronic cases do not present such an emergency.

Patients with a temperature above normal who have no other signs of a septic process are good prospects for an upper respiratory infection and operations may wisely be postponed until the course is determined. (33)

The age of the patient is an important factor in the probability of respiratory complications. Butler, Feeney, and Levine (13) found the operative mortality three times as great in patients over fifty as in those under fifty. Miller (81) found death occurring eight times more frequently in those over fifty.

The surgical and anesthetic risk, as classified by the International Anesthesia Research Society is as follows; A: The good risks: patients free from organic diseases, whose surgical condition is not likely to prove fatal. B: The fair risks: patients suffering from organic disease, but whose surgical condition is not especially serious. C: The poor risks: patients whose surgical condition is so serious and so far advanced as likely to result in fatality. Woodbridge (121) objects to such a classification on the grounds that it offers no place for the classification of patients with extremely severe "organic disease" nor mild "surgical conditions". He feels that additional letters to such a classification only add confusion

and he suggests a classification using numbers 1, 2, 3, and 4, meaning respectively slight, moderate, marked and extreme risk. (1) means Good risk: nothing found in patient's condition that adversely affects the risk; (2) means Fair Risk; one or more adverse factors are present, but are not serious; (3) means Poor risk; prepare the patient carefully for operation, choose the least surgical procedure that will give the needed relief, and select the anesthetic drug and method with special regard to the patient's condition, (4) means Extreme Risk; so seriously sick that death is likely unless the downward progress is quickly reversed. He feels that such a classification considers the patient from both his medical and surgical condition and takes no account of the severity of the proposed operation, so that a patient with severe hyperthyroidism is a grade 3 surgical risk, whether the proposed operation be thyroidectomy or merely reduction of fracture of phalanx.

Woodbridge (121) suggests it is a good idea to listen to those individuals who have a premonition of death, in order that the powerful autosuggestion be prevented by proper medication. Bourne (6) believes that the emotional reaction of the patient should be adequately controlled by sedative drugs before the

trip to the operating room. Ledbetter (24) states that fear will diminish the patient's power of resistance. According to Crile (24) psychic shock should be avoided as assiduously as traumatic shock. He questions the ability of a single anesthetic to exclude all nocuous or harmful stimuli of the brain. He states that a combination and selection of anesthetics is an attempt to attain the anesthesia that will exclude all stimuli from the brain and thereby attain anoci-association.

The weight of the patient has a bearing on the outcome of the surgical procedure. The women, "fair, fat, and forty" with gall bladder disease present a problem to both surgeon and anesthetist. The thick fat neck, with obstructed air-way, results in a difficult induction and maintenance of the anesthetic, and muscle tonus and abdominal movements produced by the labored respiratory movements, are difficult to abolish. To overcome the interference in the abdomen the patient must be placed in a lower plane of anesthesia which immediately increases the probability for the development of some pulmonary complications.

A loss of weight which is more than a slight pathological loss, usually means some tissue starvation with the glycogen reserve somewhat depleted.

These patients show an increase in postoperative complications and mortality. Studley found a mortality rate of $33 \frac{1}{3}$ per cent in a series of 50 patients operated for peptic ulcer who had lost 20 per cent of their body weight. In those who had lost less weight he found the mortality to be about 3.5 per cent. +

Males develop pulmonary complications post-operatively at least twice as frequently as do females. Others have quoted percentages as high as 70 per cent for the males. (33) The administration of anesthetics to males is agreed to be more difficult than females. Difficulty of induction has been shown by Guedell (44) to result largely from an elevation of the metabolic rate. Burford (12) states that the metabolic rate represents the degree of reflex irritability and oxygen want. It represents a fair approximation of the depth of anesthesia to be traversed before the stable planes of third stage anesthesia are reached, and the greater the depth to be traversed the greater the likelihood of an uneven struggling induction. The struggling results in still further change in oxygen metabolism. To avoid such difficulty, Burford (12) advised premedication to the point where the patient is nearly asleep when he arrives in the operating room and then, because of

its rapid action, choose cyclopropane for the anesthetic.

King (65) states that sex and type of operation are the most important factors in the occurrence of postoperative pulmonary complications. He states that complications follow laparotomy and herniorrhaphy twelve times as frequently as after operations in the non-abdominal group. For this reason he considers all menhaving operations on the stomach and duodenum, gall bladder, and intestines as "bad risk" patients. In the non-abdominal group he found those patients having thyroid operations to run the highest incidence of pulmonary complications.

Burford(12) in his series of 626 operations involving the peritoneum, had thirteen cases who developed pulmonary complications. This was a series of 1,333 cyclopropane anesthetics and there were no complications in the non-abdominal operations. Joslin and Gage (61) report 75 per cent of their pulmonary complications followed abdominal operations.

The main factor to which is attributed the high incidence of pulmonary complications following abdominal operations is the decreased ventilation and vital capacity of the lungs (16) subsequent to opening the peritoneum, together with the voluntary restrictions of respiration resulting from pain subsequent to the peritoneal irritation.

The main factor to which is attributed the high incidence of pulmonary complications following abdominal operations is the decreased ventilation and vital capacity of the lungs, (16) subsequent to opening the peritoneum, together with the voluntary restrictions of respiration resulting from pain subsequent to the peritoneal irritation.

Eliason and McLaughlin (33) suggest the use of a midline incision for all gastric and duodenal surgery instead of a right rectus or papamedian incision.

They feel that in their service the patient is more comfortable after operation and that there is less splinting of the upper abdomen and diaphragm with this incision, which may serve in part to prevent postoperative hypoventilation.

Bronchopneumonia is the most frequent and the most serious of the pulmonary complications. Eliason and McLaughlin (33) reported it as occurring in 45 cases of the 120 cases showing any pulmonary complication. Atelectasis was noted 23 times, lobar pneumonia 18 times and embolism and infarction 9 times. They observed also that the lower lobes were the most frequently effected and the two, the right was more frequently involved than the left.

Coryllos (19) believes that the complications usually described as postoperative bronchitis, atelectasis and pneumonia generally follow one another in the order named and are evolutionary phases of one and the same pathological process. Stated briefly he believes that pulmonary complications follow a collapse of a portion of the lung.. Following collapse, if there is an existent infection of the bronchus present, there will be a pneumonic process follow. The severity of the process depends on the area of tissue collapsed and the number and virulence of the organisms present in the bronchial secretions. His theory of bronchial occlusion, based on extensive experimental work and confirmed by others, is that atelectasis results from bronchial occlusion by stagnant bronchial secretions and exudates follow-

ing operation. He does not exclude the possibility of postoperative pulmonary complications secondary to embolism, but believes such a condition should be differentiated from inflammatory lesions. He has made a very extensive study of the process and considers only two theories to be supported in any way, as causative in the production of massive atelectases. One, "a nervous reflex theory," and the other the "mechanical occlusions of a bronchus by bronchial secretions.

The nervous reflex theory may be divided into (1) the bronchoconstrictor theory, (2) the diaphragmatic and muscular theory, and (3) the vasomotor. None of these various theories have much to support them according to Coryloss (19) who firmly believes that the only explanation of massive atelectasis lies in the mechanical plugging of a bronchus with the absorption of the alveolar contents distal to the plug. Jackson (62) stated that complete obstruction to a mainbronchus with normal pulmonary circulation is essentially the cause of all cases of massive collapse, and that such an obstruction must be one of two types; a stop valve type, with no air passing in or out; or a check valve type preventing inflow but not outflow. In the stop valve mechanism, gases

trapped below the obstruction are absorbed slowly and atelectasis occurs after several hours. In the check valve type, with some expression of air with each expiration, atelectasis occurs much more rapidly. No collapse occurs when a bronchus is not completely obstructed. Coryllos explains massive collapse on the operating table on the basis of the rapidity of absorption of the gases. The coefficient of absorption of the various gases as discussed Teschendorf, quoted by Coryllos (20) are found to be very rapid for carbon dioxide and nitrous oxide and only slightly slower for ethylene. After the plug is established the absorption of these gases is nearly instantaneous. It is with this fact in mind that the inert and slowly absorbed gas, helium, is being used as a diluent in cyclopropane anesthesia.

Pneumonitis is perhaps a better term than pneumonia for the inflammatory processes following operation, for besides lobar pneumonia, are found so many atypical forms which run an atypical course that any differentiation is nearly impossible.

The etiology of such pulmonary complications has been ascribed to, aspiration of septic contents of the mouth; hypostatic congestions; chilling embolism; and retention of mucous secretion in the bronchi.

Regarding the aspiration theory, some authors believe that this alone can hardly explain the condition since patients aspirating barium sulphate through a bronchoesophageal fistula never develop atelectasis.

Coryllos (19) states that postoperative pneumonia is rare after tonsillectomy and here there is frequent aspiration of material from the throat. Myerson (86) found blood in the bronchi of 75 per cent of cases bronchoscoped after tonsillectomy. Others have shown that aspiration produces suppuration and gangrene, but does not explain the occurrence of pneumonia within a day or two of operation. However, in spite of such reasoning the incidence of complications occurring in individuals operated during some upper respiratory infection, makes one consider the possibility as one not definitely disproved.

Pulmonary hypostasis is a decided factor in the incidence of pulmonary complication in the aged group, and in those who have a failing pulmonary circulation. It does not, however, explain it for the young and healthy male group.

The embolic theory has had many supporters, but Coryllos (19) again takes the other side and argues that the pathology of what is considered postoperative pneumonia is different from embolism with infarction.

He states further that the signs of minor emboli develop later than the first 12 to 24 hours and that the attack then comes on suddenly without physical signs until the second or third day after the onset. The physical signs of greatest importance are friction rub and an impairment of the percussion note. Following this in two or three days there is improvement. Pneumonitis, however, has its onset within 12 to 24 hours and is accompanied by cough, dyspnea, often cyanosis and some rise in temperature, without friction rub. The signs of consolidation are never absent. These signs are present whether the condition be atelectasis or pneumonia, especially if the mucous plug which caused the atelectasis has been removed. (65) If the plug is intact, King (65) states that the breath sounds are diminished over the atelectatic area. King (65) disagrees with Coryllos, stating that they have found no evidence that atelectasis necessarily precedes pneumonitis. In their series of pneumonias they could prove atelectasis in only 47 per cent of their cases.

Thus the explanation of the etiology of pulmonary complications is much disputed and after reading both sides and attempting to evaluate their statistics, I have come to the conclusion that one

can not exclude any of the possible and proposed explanations. The proponents of all theories have points in their favor and whether the complications result from aspiration, emboli, or atelectasis it behooves the surgeon and anesthetist to do all possible to avoid all three.

In summing up the various methods of avoiding postoperative pulmonary complications it is evident that many factors present themselves.

It is necessary, first of all, to remember that the patient is not well and, in such a condition, finds himself in new and fearful surroundings. The apprehension of the patient who is having a surgical procedure thrust upon him should not be treated lightly. His preparation for the operation should begin with the treatment he receives at the hands of the hospital staff, and allowance for the peculiarities of the patient should be made. Perhaps he sleeps in his underwear at home, and even though it does not conform to the standards of sanitation to which the hospital attendants are accustomed he may avoid an upper respiratory infection by continuing the habit until operated upon.

A complete physical examination for pulmonary

pathology, patency of the air-way and the efficiency of the circulatory system are essential. This requires that he be in the hospital at least 12 hours before his operation, which allows time for adequate preparation.

The preoperative medication should be selected to fit the anesthetic and should be given in sufficient doses, and far enough ahead of the time of operation, that the patient may be in a semi-sleep when he arrives in the operating room. On the other hand he should not have such large doses that his respirations are slowed beyond the rate that will permit him to take the anesthetic safely.

The anesthetic should be selected with the patient in mind rather than the disposition of the surgeon. The surgeon and anesthesiologist should cooperate and the anesthesiologist should be competent to direct the anesthesia, rather than follow it, and capable of diagnosing the warning signs of approaching danger in time to stop the operations or take steps to prevent a progression of untoward symptoms. The anesthetic should be so administered that as little time should pass, as possible with the patient in the lower planes of anesthesia, and the surgeon should appreciate the

efforts of the anesthetist in this endeavor.

The use of helium or other inert gases in the prevention of atelectasis has been discussed.

The patient should be protected from drafts and exposures, and is entitled to a warm cart and warm bed when he returns from the operating room. In an effort to further protect the patient from accidents, the anesthetist should accompany him to his room after the anesthesia. He should be watched by a competent nurse when he returns to the floor. Under no circumstances should a patient returning from surgery be entrusted to a probationer.

A mixture of 5 per cent carbon dioxide in oxygen, administered before he leaves the operating table is physiologically sound if properly administered; first because it hastens the exhalation of the anesthetic and thereby shortens the recovery period; second, hyperventilation tends to allay the postanesthetic nausea and vomiting; third, the bronchi are forced open and atelectasis is avoided. This should be followed by deep breathing exercises after consciousness has returned.

To avoid stasis in the bases of the lungs, his positions should be changed every 45 minutes to an hour.

Tight abdominal binders should be avoided and the patient should be instructed to breath deeply in spite of the discomfort it may cause.

If all of these factors were observed and complete cooperation of the hospital staff existed, in an attempt to prevent a complication in every patient, the incidence of postoperative pulmonary complications should be greatly reduced.

Disorders of the
circulatory system occurring during
anesthesia.

During the early stages of anesthesia with ether the pulse rate and blood pressure are increased by the reflexes, excitement and asphyxia from holding the breath.(8) During the anesthesia, however, the blood pressure is normal to somewhat above normal, and the pulse is between 80 and 110.(108) The pressure in the pulmonary arteries rises even if the carotid pressure remains the same, Wood 1911. These actions which are quite favorable, persist through the stage of surgical anesthesia, even if this be prolonged for hours. (Mann 1916) claims there is seen a marked and progressive arterial dilatation of central origin. Sollman (108) states that in the paralytic stage the vasomotor center becomes gradually depressed. The blood pressure begins to drop and the respirations may fail, but the heart is usually unaffected. A patient may usually be revived with artificial respiration if there is not too long a delay. The vascular effects are central; the cardiac changes are mainly the indirect result of vascular disturbance. Concentrations which injure the heart directly can be reached only

in perfusions.(108) ✓

Asphyxia is not tolerated in ether anesthesia and a venous congestion with extensive bleeding from severed vessels occurs. Severe grades lead to extreme cardiac dilatation by paralysis of the vasomotor center and heart.

In light ether anesthesia, 12 to 16 per cent carbon dioxide in the air raises the blood pressure but slows and weakens the heart. (108) Sollmann. Cathart and Clark state this effect is much less pronounced in deep ether anesthesia. In light ether the heart rate tends to vary inversely with the blood pressure as it does in the normal individual; a response involving the accelerator mechanism in the carotid sinus and aorta. In deep ether, with anoxemia of the medulla, such a coordination fails and the pressure and pulse rate fall together. Ether should not be used in shock because of its effect in such conditions, to lower the blood pressure still further (108) Krough states ether tends to paralyze the capillaries with concentrations slightly greater than those existing in the blood in anesthesia. Sollmann believes this may account, in part, at least, for the greater tendency to shock that ether anesthesia is believed, by surgeons to entail.

The effects of chloroform on the heart, as on the liver, are much more severe than those of ether. Even with smooth anesthesia, the pressure falls markedly by central vasomotor depression. Careless induction with the sudden inhalation of a highly concentrated vapor will produce sudden and permanent arrest of the heart. (108)

In normal chloroform anesthesia the pulse and blood pressure are somewhat irregular in the early stages, but as the anesthesia progresses there is a marked progressive drop in pressure. In an hour of anesthesia the pressure may fall to one half the original pressure and continue to fall to as the anesthetic is continued. Sollmann states the pressure fall is due to depression of the vasomotor center. The splanchnic vessels are dilated with the cerebral vessels constricted. The heart beats slowly but regularly even when vasomotor paralysis is complete. Sollmann states that the heart muscle is affected directly by the chloroform in prolonged administration and even though respiration has ceased the heart may continue to beat, but too weakly to maintain the circulation.

Both ether and chloroform produce some hemolysis during anesthesia and reduce the hemoglobin. DaCosta and Kalteyer (108) found that diminution of the hemoglobin to 50 per cent is dangerous and for that reason patients with a hemoglobin of only 60 per cent should not be given either of these anesthetics.

The coagulation time of the blood is shortened by ether; chloroform will not affect a normal coagulation time, but will prolong one that is abnormally short.

Ethylene has no deleterious action on the circulatory system, the blood pressure usually is elevated about 10mm, showing that there is no damage to the vasomotor center. The heart muscle of experimental animals is not injured by saturating the perfusion fluid with ethylene. (108) Ethylene causes less tendency to acidosis than ether or chloroform, but about the same as nitrous oxide.

Nitrous Oxide is without injurious effects on the circulatory system in the absence of asphyxia. It has only feeble chemic affinities, is very soluble in blood, and is practically free from side actions and herein lies its value. (108) Sollmann. A further discussion of nitrous oxide will follow in a discussion of its effect on the cerebral cortex.

The effect of cyclopropane on the circulatory system has not been fully determined. Cardiac irregularities are frequently noted and the pulse rate decreases as the anesthesia deepens. Kurtz, Bennett, and Shapiro (66) found in their electrocardiographic studies that multiple focus ventricular tachycardia occurred in 10 per cent of the cyclopropane cases in their series. This is an interesting finding since Seevers, Meek, Rovenstine and Stiles (105) report this irregularity in two ~~dogs~~^{MAN}, under deep cyclopropane anesthesia, just before fatal ventricular fibrillation.

In writing the section on the effects of the various anesthetics on the blood, I neglected to include a recent opinion of Bourne (6) and though out of place in sequence, I believe it important enough to include here.

He considers two changes produced in the blood by anesthetics, to be of especial importance. The first is blood concentration. He states that ether anesthesia causes the blood solids to increase by 2 to $3\frac{1}{2}$ per cent of the total weight of the blood. This, he found to be due to migration of fluid from the blood to the tissues under both ether and chloroform.

He makes no mention of it occurring with the gas anesthetics.

His second consideration is that of acidosis. He and Stehle (4) demonstrated that phosphoric acid leaves the muscle during ether anesthesia and was found to be neutralized by the bases, sodium and potassium with a consequent decrease in the base of the blood. Other authors have given evidence that the lactic acid of the blood is increased during anesthesia.

To return now to the sequence of this paper I will continue with a discussion of ventricular fibrillation.

Guedal and Knoefel (46) say that the occurrence of ventricular fibrillation depends upon an increased activity of the sympathetic system, and the resultant increase of adrenalin in the blood, together with a probable increase in the irritability of the ventricular muscle. The adrenin may be poured into the blood stream by the suprarenal glands, or epinephrine may be introduced intravenously.

Death from ventricular fibrillation is due to cardiac anoxia. If the fibrillation passes before the reserve oxygen in the heart tissues is consumed the heart will regain its normal activity almost immediately. Guedel. If, however, the fibrillation persists until the reserve oxygen is so depleted that anoxia depression prevents the reestablishment of normal cardiac activity, the heart will fail to contract again.

Ventricular fibrillation, according to these authors, occurs without warning. Probably it either passes in less than a minute or death results.

The approach to a surgical operation and induction of anesthesia provide favorable circumstances for the occurrence of ventricular fibrillation. Emotional excitement, as fear, produces an increased activity of the sympathetic nervous system and a consequent increase in output of adrenalin. This sets the stage for fibrillation in response to any added stimulus such as the delirium of the second stage of anesthesia, noises, or any physical disturbance of the patient during the induction period.

The most likely place in anesthesia for the occurrence of ventricular fibrillation is in the stage of delirium, immediately after consciousness is lost. It is here that the peak of sympathetic hyperactivity is reached (44). It has been shown that there is an increased probably becomes less as anesthesia progresses in time or into the deeper stages.

Ventricular fibrillation is most likely to occur in the periods of life where general physiological activity is greatest, that is, between the ages of five and thirty years.

Clinical recognition of the phenomenon depends largely upon the appreciation of predisposing circumstances surrounding the case at hand. If the pulse stops without warning during induction, the cause is probably ventricular fibrillation (46) Respiration stops almost immediately after the ventricles fibrillate. Unless the anesthetist has his finger on the pulse constantly, fibrillation will be well advanced before it is recognized. The respiratory cessation will likely be mistaken for one of the frequent respiratory pauses occurring at this stage of anesthesia and death occurs almost before the anesthetist is aware that anything is wrong.

If during any period of light anesthesia when epinephrine is being used by the surgeon for hemostasis, the pulse stops without warning, there is probably a fibrillating ventricle.

Embolism, acute cardiac dilatation and apoplexy might be confused with ventricular fibrillation but in one of these will the pulse go from normal to nothing between two heart beats.

Guedel states that artificial respiration with oxygen should be instituted at once because one can never be sure, at the time, that the circulation has ceased entirely. If the abdomen is open at the time,

the circulation may be maintained by rhythmic compression of the heart between the anterior thoracic wall and the hand, through the diaphragm. This direct cardiac massage, in the presence of adequate artificial respiration with oxygen, will prevent serious anoxemia for from half an hour to an hour. If the fibrillation should pass during this period, it is more than likely that the normal rhythm would be reestablished.

Ventricular fibrillation which does not pass in less than a minute is usually fatal, although the fibrillation may continue for many minutes beyond this period. Probably short periods of ventricular fibrillation with spontaneous recovery of normal rhythm have occurred many times without being recognized.

The prevention of this condition, according to Guedel, lies in holding down the activity of the sympathetic nervous system and thus the output of adrenalin, and the avoidance of any external stimuli during the induction of the anesthesia. Any preanesthetic medication which will prevent sympathetic hyperactivity is of value. Morphine fails to do this. Deaths have occurred from ventricular fibrillation in individuals who had the usual preanesthetic dose. The barbituric acid derivatives are effective depressants of the sympathetic system. Guedel. The degree

of protection afforded by these drugs is in proportion to the dose administered.

Atropine and scopolamine are of value in that they prevent reflexly excited activity of the cardiac excitability.

Too much emphasis cannot be placed on the necessity of avoiding any disturbance of the patient during induction. Such things as beginning the preparation of the operative field, or surgical procedure itself, before anesthesia is complete, are dangerous. Knowing the danger zone to be the second stage of anesthesia, it must be passed through as rapidly as possible.

The use of epinephrine in amounts sufficient to control bleeding during general anesthesia is to be condemned. When epinephrine must be used in the surgical procedure it should be sparingly.

Although chloroform is the greatest offender, ventricular fibrillation must be considered a potential danger in every anesthesia, no matter what agent may be used.

LIVER DAMAGE

Clinical observation, functional tests and experimental investigation have demonstrated that certain anesthetic substances are injurious to the body. Depressed kidney function and a depressed liver function may result from an anesthetic, but this is perhaps partly an expression of a generalized depression of cell activity of the organism. (18) Certainly the fall in body temperature accompanying anesthesia is evidence of a generalized effect.

Casper (15) was the first to suggest chloroform poisoning as a cause of death. Since that time much has been done to prove the severe damage produced by chloroform, and it is now universally agreed that chloroform is not a safe nor a non-toxic anesthetic agent. Chloroform results in fatty changes in the liver, heart and kidney. Parenchymatous damage varies in extent with the individual, and the duration of the anesthesia. Davis and Whipple (20) showed that the glycogen content of the liver and the general nutrition of the patient were important factors in liver damage in relation to the amount of chloroform absorbed.

Williamson and Mann (118) show, however, that the characteristic symptoms which follow hepatectomy are

observed after poisoning with chloroform, although the results of the poisoning may be fatal. They found that hypoglycemia occurred in very few of their cases of poisoning and uric acid in the majority. They concluded from the results of their experiments that the poisons, though greatly injuring the functions of the liver, do not produce complete hepatic insufficiency.

Other tissues and organs are undoubtedly profoundly affected and in many instances the functional damage to the liver is probably not the primary cause of death. (5) The study of liver damage produced by the various anesthetic agents has been studied by means of various dyes by Abel and Rowntree (1) Whipple and Speed (117) Rosenthal (99) and many others. Rosenthal and Bourne (100) report a series of experiments in which they studied the effect of the various anesthetics on liver functions by the use of the bromsulphalein test and studies of bile pigment disturbances. They found that a half hour of chloroform anesthesia produced a transient bilirubinemia and urobilinogenemia that returned to normal in three days. The bromsulphalein test, however, showed dye retention for eight days. With two hours

of chloroform the icterus index rose to 11 on the following day and required ten days to return to normal. The urobilinogen dilution index in the urine rose, from the normal value of 5, to 100 on the following day and required ten days to return to normal. The dye test showed 100 per cent retention in the blood for the first two days and required six weeks for recovery.

With ether, they found there was always a slight impairment of function as shown by the dye retention or excretion test, but there were no abnormalities of the bilirubin or urobilinogen determinations. Functional impairment resulting from ether depends on the duration of the anesthesia, as with chloroform, but the striking difference is that with ether, function returns to normal, as shown by the dye excretion tests, the next day, whereas with chloroform the damage progresses and does not reach maximum until the day after the anesthesia.

There is a difference of opinion regarding the toxicity of nitrous oxide mainly, I believe, because of the practice to use the pure gas in some cases, especially dentistry. Rosenthal and Bourne (100) proved experimentally, however, that neither nitrous

oxide nor ethylene produced either immediate nor delayed impairment of liver function even after two hours. But, if during the administration, cyanosis was permitted to exist there was immediate impairment of hepatic function, which did not return to normal the next day as with ether, but required several days for recovery. There was also an increase in blood bilirubin for two or three days following the anesthesia.

Cyclopropane anesthesia has been proved to be free from the possibility of producing liver damage to the normal liver, even after repeated administrations, or after long periods. It does not enhance the liver damage purposely produced by chloroform, nor impede the usual recovery of the liver from chloroform poisoning. (94)

ANESTHESIA IN CHILDREN

Children require relatively larger doses of anesthetic agents, but the margin between safety and danger may be narrower and it is here that experience in caring for children under anesthesia plays such an important part in their safety. (96)

Children are more liable to the postoperative condition of acidosis (107). Depletion of the glycogen reserve predisposes to such a condition, hence neither ether nor chloroform should be administered to a child in such a condition. Fortification of the liver by use of glucose, either in fruit juice or by intravenous infusion should be routine procedure in children.

Deaths have been reported from asphyxia by aspirated food particles following operation. When food has been taken shortly before an emergency operation of some kind the stomach should be emptied by some method. Washing the stomach is not always satisfactory because pieces too large to pass through the stomach tube remain to be vomited. Use of apomorphine is frowned upon because of its depressant qualities. Any induced vomiting in the conscious state usually results in exaggeration of the pain at the site of injury or disease and is therefore

not satisfactory. Robson (96) advises placing the patient on the side on the operating table and inducing anesthesia to the point where the swallowing reflex is abolished. The mouth is then opened with a gag and in a short time the pharyngeal reflex returns sufficiently that vomiting may be induced by means of a tongue depressor and the stomach empties itself without distressing the semiconscious patient.

In the case of the infant to be operated for pyloric stenosis, the fluid contents of the stomach is drained off through a small stomach tube while the patient is in the conscious state. This should never be neglected because surgical manipulation of the stomach containing fluid will cause the contents to pass up the esophagus and obstruct the airway.

Mental comfort may be established, induction made smoother and the amount of anesthetic used may be reduced by proper administration of sedatives and hypnotics. Robson(96) denies the statement that morphine is not tolerated by children. On the contrary, he states ~~that~~ they require relatively larger amounts than adults to obtain necessary therapeutic results. He advises the use of morphine and nembutal with either gas or ether, giving somewhat larger doses

when the agent is gas than when ether is used.

He uses codeine in children under four.

The use of atropine in children to precede anesthesia is discouraged by several authors on the grounds that it serves no useful purpose and has many disadvantages; dry mouth and throat; loss of normal moisture from alveolar wall preventing a free interchange of gases; it definitely retards ciliary activity of the respiratory mucosa; probably contributes to the rise of body temperature. I do not consider myself in a position to criticize an opinion of these men, but I believe the obstruction to respiration resulting from the accumulation of copious amounts of mucous in the oropharynx and mouth of those children above the age of six who have not had preoperative atropine should not be entirely disregarded. Morphine should not precede anesthesia for tonsillotomy because it prevents the rapid return of the pharyngeal reflexes.

Cyclopropane is replacing nitrous oxide as an anesthetic agent for children and because of its rapid action many of the dangers of the early periods are eliminated.

A child should not be returned to the floor until the vomiting spell has passed, and the anesth-

until the vomiting spell has passed, and the
anesthetist should accompany him when he goes.

CONVULSIONS OCCURRING IN GENERAL ANESTHESIA

Convulsions occurring during general anesthesia have been reported from time to time, there being some three hundred cases reported. These cases all fall into the category known as convulsions associated with general anesthesia, though many were originally reported as "ether convulsions", and ether is the agent that has been most frequently associated with the syndrome, although frequently it has been administered as a vapor, with oxygen or with nitrous oxide and oxygen. Bull (11) reported one case in which chloroform was used.

Although there is wide diversity of opinion regarding the cause of this complication there is uniformity in the description of the syndrome. The patients are frequently children or young adults; many are suffering from acute infections associated with pyrexia. In some of the cases the patient was known to have or found later to have had epilepsy (112) The condition has also been confused with heat stroke (91)

It has been noted that as the convulsion starts the respiration is usually rapid and labored to some extent, but frequently the first un^oward sign noted is twitching of the muscles of the face, occurring

during the maintenance of anesthesia. The pupils are widely dilated and the globe is fixed in position. The twitching spreads to the muscles of the neck, shoulders and arms, finally to the legs and abdomen. As the twitching spreads it becomes more active. Finally violent and sustained epileptiform convulsions occur, associated with cyanosis of a varying degree. Administration of oxygen, even under pressure, often fails to alleviate the cyanosis of the extremities. Hyperpyrexia develops and some authorities maintain that this sign must be present if the untoward reaction is to be considered typical. Deepening of the anesthesia does not usually relieve the condition. Following cessation of administration, recovery from the anesthesia is delayed. Recurrence of convulsions later, when the patient is in bed has been noted. Death may occur while the patient is in the operating room or later from exhaustion associated with deficient oxygenation. The convulsive seizures may disappear, but the patient may fail to regain consciousness. Death may supervene within three to five days with bronchopneumonia as the salient feature. Weber (115) reported one case in which a child two years of age, failed properly to regain

consciousness, and when seen two years later, idiocy of the most severe grade had developed. Wilson (119) was of the opinion that the convulsions were toxic in origin and that acetaldehyde and peroxides in the ether were the offending agents. Gwathmey (49) disagreed with his opinion and presented some experimental evidence to show that lack of adequate preliminary medication was a factor. Hornabrook (60) took the position that atropine was responsible for the reaction, but a report of the Hospital for Sick Children in London shows that no convulsions occurred during a two year period even though the total dosage of atropine for all children more than six years of age was 1/80 grain administered by mouth. Concentrated ether vapor with an excess of carbon dioxide has also been suggested, but Hewer (58) presents arguments to refute the theory.

Fairlie (37) thought superheating the ether might be a factor. Pinson (92) pointed out, however, that convulsions occurred without the superheating method and offered the opinion that the reaction was the outcome of the extensive action of carbon dioxide in patients who are sensitive to it naturally, and who are under the influence of ether. McDonagh (8) wrote, " it would appear the anesthetic substances

act by subjecting protein particles in the plasma to sudden dehydration and then to an equally sudden hydration...the actual state in which the patient's protein particles happen to be, before the anesthetic is administered must play a greater part in the production of toxic symptoms".

Hadfield (50) suggested that heat, sepsis or other toxemia, impurities in ether, and youth might be accessory factors to the unexplained tendency to convulsions, but he could not explain the absence of reported cases previous to 1926. Rood and Webber (97) thought that perhaps the impurities in ether might have increased as a result of the widespread use of various machines in which fresh supplies of ether are likely to be added to old residues. MacKenzie (78) proposed that three factors call for careful consideration. (1) Impurities in the ether, (2) carbon dioxide imbalance, and (3) acute suppuration or toxemia. Simon (106) was of the opinion that the septic element was very important. Thomas (112) and Pinson (92) both expressed the belief that late ether convulsions could be avoided by careful and judicious administration of the anesthetic.

That ketosis could be a factor was suggested by Frasier (39). Clarke (17) advanced the hypothesis

that "increased vascularity of the cerebral cortex, more the Rolandic area than elsewhere, produced by a histamine effect is the underlying cause. Haworth (53) was inclined to believe that toxemia and instability of the nervous system were the most probable causes.

Daly (28) reported a case in which convulsions ceased when the head was raised, suggesting that congestion of the brain had been present. Haworth (53) reported cessation of convulsions after the foot of the bed had been raised. Kemp (64) stated that, "theoretical and practical treatment of ether convulsions indicates that acapnea or carbon dioxide deficit is the causative factor in many instances". Sears (104), following a study of thirty-four cases of "thymic death", suggested that local and general anesthetics may be the source of allergic anaphylactic symptoms. Riddell (95) considered three factors to be causative; susceptibility, ether vapor, and oxygen above the content of atmospheric air. Rovenstine (101) gave his view that the convulsions may sometimes be attributable to trauma. Rosenow and Tovell (98) experimented with streptococci taken from the nasopharynx of patients having a convulsion. A culture was made and then injected into a rabbit which was then anesthetized with ether. They felt that the results of

their experiments suggested that ether convulsions were attributable to a neurotoxin or poison produced by some strains of streptococci in insufficient amounts to cause spasms in the absence of anesthesia, but which in the course of general anesthesia sufficed to incite the muscle spasms characteristic of this condition. They also suggest, on the basis of their clinical and experimental evidence, that the barbiturates, administered intravenously, be used to control the convulsions.

NITROUS OXIDE POISONING

The symptoms of nitrous oxide poisoning referable to the nervous system may be mild or severe. There may be mild muscular twitchings or gross uncontrolled muscular movements or even convulsions. At times stupor or mental cloudiness may persist for a variable interval after the anesthetic is withdrawn. Restlessness, irrationality, hysterical outbursts, or more prolonged psychosis have also been described. Among the more serious eventualities are more or less persistent neurologic manifestations of psychic, motor, or sensory character. Persistent manifestations indicative of injury to the lenticular nucleus may be present in some cases. Such patients succumb after an interval of days, weeks or even months after anesthesia. It is in this group of cases that cerebral damage can be demonstrated postmortem (23). In another group of cases, sudden death occurs during the anesthesia. Excluding those cases with an advanced surgical lesion, the immediately fatal issue has been attributed to persistent thymus, idiosyncrasy to the drug, pressure on the carotid sinus, or the direct depression of the respiratory center by the gas.

The mechanism whereby nitrous oxide produces cerebral damage is still in a state of controversy. Some believe it a result of some toxic action of the gas; others contend the phenomenon is due to the anoxemia which accompanies nitrous oxide anesthesia.

In order that the damage to the cerebrum result from anoxemia, Lowenberg (69) and associates believed it must occur in one of two ways; either from lowered oxygen tension in the blood--anoxic anoxemia, or as a result of collapse of cerebral vessels.

Their discussion of the anoxemic factor rather disregarded it as a factor since there was no indication during the administration of an existent anoxemia and they contend that an anoxemia due to oxygen lack should be promptly relieved by the administration of oxygen.

Regarding vascular collapse, there experiments showed that under 90 per cent nitrous oxide with 10 per cent oxygen there was at first a vasoconstriction which, as the anesthesia progressed, changed to a vasodilation of the entire capillary bed. The arterioles were engorged with a slowing of the blood

stream and they state that the condition remained even in prolonged anesthesia. There was no collapse of the blood vessels and stasis did not occur and the manifestations could be relieved by the administration of oxygen. They state that these findings differ from those produced by an asphyxiating mixture of nitrogen and oxygen which readily produces a vascular collapse and stasis. From this they reason that the effect of nitrous oxide is not a result of asphyxiation. The authors also indicate a parallel in the histologic picture between that found in nitrous oxide poisoning and that in poisoning by excessive doses of pantopoon, morphine, and ergoapiol. They conclude that the symptoms may be due to destruction in the cortex and basal ganglion as a result of sometoxic action of nitrous oxide, rather than from asphyxial causes.

Courville (23) who has done more on this subject than anyone else, does not agree with Lowenberg. Courville states that in delayed deaths following nitrous oxide anesthesia there are demonstrable pathological changes in the cortex and lenticular nucleus (22) which result from asphyxia and not from any toxic action of the gas. As evidence, this author

suggests that the earliest effect is observed in the interstitial tissue about the pericellular spaces as well as in the nerve cell itself, which is characteristic of asphyxia and not of narcosis. The patchy character of the necrosis, which is not observed after narcotic poisoning, are comparable to the necrotic areas following experimental temporary-ligation of cerebral arteries. He states further that lenticular degeneration is a common effect of asphyxia. In concluding his article, he states, "the cerebral damage is a direct result of asphyxia, even though at times the cessation of respiration and cardiac action may be due to a depressant action of the gas on the vital centers. In some of these cases, cardiorespiratory failure is due, not to the narcotic effect of the gas but rather to the development of some intercurrent lesion such as pulmonary embolism. In cases without cardiorespiratory failure, cerebral damage is probably the result of prolonged accumulative anoxemia of a dangerous degree, due to inherent predisposing factors in the patient, to defects in the apparatus, to impurities in the gas or perhaps at times to improper administration of the anesthetic.

The extent of cerebral anoxemia during anesthesia, however, is difficult to determine because of a lack of information regarding the concentrations of oxygen, carbon dioxide, and the anesthetic gas in the blood before and after it has passed through the human brain. Since in small concentrations it produces a narcotic effect it is not unreasonable to attribute at least part of its effect to a direct action. Such a concentration, however, is not sufficient to produce surgical anesthesia and hence the question; is the rest of the effect due to a cerebral anoxemia?

As early as 1899 Hewit (59) attributed respiratory difficulties to obstruction produced by the anoxemia accompanying nitrous oxide anesthesia. Green (43) found that the depth of the anesthesia with nitrous oxide did not depend so much on the concentration of the gas as it did on the percentage of oxygen. Brown (9) and his associates believe that there is always a severe degree of anoxemia in patients anesthetized with nitrous oxide and that this is an unhealthy state. Macklin (79) realizes the oxygen deficiency and also the danger, but in his mind any anesthetized patient is in an unhealthy state, no matter what the agent. He calls attention

to the fact that all of the theories proposed to explain narcosis consider the final effect the result of reduced tissue or cellular oxidation, whether it be by a change in the permeability of the cell membrane, a change in cellular proteins, or whatever, and he believe it is better to reduce the percentage of oxygen in the gas mixture than to give a greater concentration of oxygen with a poison which renders the cell unable to utilize it. Crile (25) agrees with this point of view when he states, "We found that in the state of deep ether anesthesia which interferes with the permeability of the films around the cell and hence interferes with oxidation, the temperature of the brain and liver fell steadily till death occurred. On the other hand, we found that in nitrous oxide anesthesia which interferes with oxidation itself, but does not interfere with the permeability of the lipid films surrounding the cells, the temperature of the brain fell much more slowly."

So the battle wages, and the only definite conclusion I am able to reach is that there is, at least some danger of neurological complications following nitrous oxide anesthesia.

Review of the inhalation agents

ETHER

The circulatory system of normal individuals is but little effected by ether unless its administration is prolonged. However, after an hour of ether anesthesia, a marked and progressive peripheral arteriolar dilatation takes place (85). The effect of the anesthetic upon an organism suffering from shock is, however, different. Cannon showed that etherization of a shocked animal to the point of disappearance of the corneal reflex, reduced the blood pressure from sixty-five to thirty-five points (108)

The effect of ether on the gastro-intestinal tract was studied by Miller (82) and he shows that during ether anesthesia, peristaltic action is abolished and muscular tone diminished, that recovery is slow and normal activity is not resumed until several hours after the administration of the drug has been stopped.

Ether produces many changes in the blood. They are, an increase in its solid elements, reduction of its oxygen carrying power, ten to twenty, five percent (57 b), reduction of coagulation time, increase in icteric index and sedimentation of red

cells, reduction of alkali reserve, increase of acetone bodies, sugar, lactic acid, uric acid, and inorganic phosphates (57).

Stander (57 e) has demonstrated with dogs and shown that there is tubular degeneration in the kidney. Many investigators have reported fatty changes in the liver occurring always in the central portion of the lobules and sometime throughout the lobule following ether anesthesia.

Lundy (76) reporting a parallel series of 600 cases with ether and ethylene shows bronchitis occurring in 2.5 per cent of cases with ether and 0.6 per cent with ethylene. Also with ether bronchopneumonia occurred in 3.6 per cent of cases and with ethylene only 1.5 per cent.

Blood concentration and reduction of coagulation time may be a factor in thrombus formation when ether is used(57 b). He reports 0.98 percent frequency following ether, against 0.24 per cent when local was used.

NITROUS OXIDE

The functions of the respiratory and circulatory systems, excepting the blood itself, are unaffected by nitrous oxide, any changes occurring in them during anesthesia being always the result of asphyxia (108)

If cyanosis develops, the motility of the gastro-intestinal tract may either be increased or abolished (82). Nitrous oxide causes changes in the blood similar to those produced by ether, except no concentration of the blood nor reduction of coagulation time has been observed. The gas produces pathology in the liver and kidney identical with that caused by ether, but to a lesser degree. Nitrous oxide and morphine, however, protect the brain against infection (25), but ether increases the damaging effects of infection.

Nitrous oxide produces a venous congestion which results in disturbances in the circulatory system. In a series of cases reported by Miller (81) coronary embolism occurred twice as frequently after nitrous oxide and oxygen; cerebral embolism and cerebral hemorrhage - seven times more frequently and pulmonary embolism about one-half times more frequently following nitrous oxide, than after ether.

Haveman (52) states that nitrous oxide is the least harmful of inhalation anesthetics. He states its only effect is its interference with oxidation, producing no change in the blood; not injurious to the lungs and having no effect on the glandular system. States when nitrous oxide causes death it does so by oxygen deprivation. It does not kill suddenly and

without warning, since the color of the blood is a sufficient index of safety. He emphasizes the importance of psychic shock with its resultant cardiac dilatation, and believes control of this factor would do much to reduce anesthetic mortality.

ETHYLENE

Ethylene produces narcosis by direct action and the symptoms of asphyxia do not occur during its administration. The drug has no effect on the respiration and does not interfere with intestinal movements, nor with kidney function (72).

The nervous system, respiratory system, and circulatory systems are not injured by this drug. The same changes occur in blood as occur following nitrous oxide, but these changes are in a lesser degree. Stander (57 e) states that the changes in the liver are less marked than occurs with ether and nitrous oxide and there are no changes in the kidney. Sollmann (108) states that if the concentration of the gas is pushed much beyond 90 percent the animal stops breathing, but the animal may be resuscitated by means of artificial respiration as the drug itself has no toxic actions.

Luckhardt and Lewis (72) report postanesthetic vomiting occurring in 30.2 per cent of their cases

anesthetized with ethylene, against 76.6 per cent in those patients having ether. Gas pains occurred in only 4.2 percent with ethylene against 36.6 per cent with ether.

Henson states(57) there is no evidence to believe that the use of ethylene is attended by any more danger from explosion than the use of ether.

In the first six year following the use of ethylene as an anesthetic twelve explosions supposedly due to it were recorded with three fatalities. The first was due to the use of a cautery on a carbuncle of the neck (32). The anesthetizing machine had been removed from the room before the occurrence of the explosion . The second (57 c) fatality was caused by an explosion during administration of nitrous oxide and ether, but as ethylene had been in use earlier during the anesthesia, the occurrence was attributed to its use. The third fatality (32) occurred in Evansville, Indiana, and ethylene recieved wide publicity through the newspapers regarding its explosive properties. The facts in that case are, that the explosion took place in a tank known to contain nitrous oxide which was not attached to the machine at the tiie. It was thought that as it had been attached, some ethylene hight have flowed into it

EXPLOSIONS

through the connecting tubes.

Ethylene unmixed with other gases will not explode (72). It must be mixed with air in certain proportions in order to explode. When mixed with air, the lower limit of ethylene necessary for explosive possibilities is 4 per cent and the upper limit, twenty two per cent, according to the U. S. Bureau of Standards. When mixed with oxygen, the mixture must contain between 5 and 70 per cent ethylene. Hence in anesthetic mixtures, 80 - 90 per cent, it is above the explosive range. (35). For this reason

the gas in the tank, and in the tubes leading from the tank, cannot explode. That in the cylinder or bag may explode, if directly ignited, but it is not under sufficient pressure to do serious damage. In the room, the concentration is below that necessary for an explosion. Bevan (57 a) states that explosion may be avoided by having the humidity over sixty per cent in the operating room and have the machine grounded.

CYCLOPROPANE

Cyclopropane is an isomere of propylene, having a ring structure. The gas is heavier than air having a density of 1.46 and hence sinks to the floor

instead of diffusing throughout the atmosphere as does ethylene.

The gas is inflammable and when mixed with oxygen, may form an explosive mixture. As stated before, an explosive mixture with oxygen exists between 2.5 per cent cyclopropane and 50 per cent cyclopropane. Hence, the average anesthetic mixture is well within the explosive range. (35).

Cyclopropane is a very potent anesthetic agent, producing unconsciousness in 1 to 2 minutes with a ten per cent mixture. It is absorbed rapidly but some 10 or 15 minutes are required before saturation is reached. It is eliminated from the blood by way of the lungs rapidly, consciousness returning in 2 to 10 minutes. The complete elimination from the tissues of the body may require a much longer time.

In too high concentrations it is quite irritating to the respiratory passages, just as ether is, and if breathed in a 50 per cent concentration, may cause laryngospasm (35). It is not a respiratory stimulant (103) and a period of apnea may develop shortly after administration is started. This is especially true if a rather large dose of barbiturates or morphine have been given preoperatively. The effect on res-

piration in deeper anesthesia is similar to the other anesthetics since the respiration ceases before the circulation fails (114).

The most likely site of damage from cyclopropane, however, is the circulatory system and it is this system that gives one of the first warnings during the administration of the gas. Eversole and associates (35) state that any change in the pulse rate, either increase or decrease; any sudden drop in the blood pressure should be interpreted as a danger signal. Continued administration without decreasing the concentration may result in respiratory failure (114)

The explosive property of the gas has been considered and the use of high-frequency electrical apparatus in the room is not safe, since there is no way of being positive such a machine will not spark (35).

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