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Anesthesia with inert gases

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I. INTRODUCTION

The use of inert gases as general anesthetics is a relatively recent development. Their use is still in the experimental stage, but from all indications thus far, appear to function as quite satisfactory anesthetic agents. Because of their successful action as anesthetics, these symmetrical, chemically inert gases have served to confound most of the theories of general anesthesia that have so far been propounded.

In this paper, the foremost theories of anesthesia that have evolved through the years will be discussed in some detail. Of course, owing to the voluminous amount of literature devoted to this subject, the review is not meant to be exhaustive. In addition, the concept of the use of inert gases as anesthetics will be traced from its earliest inception up to their present role in anesthesia today. During the relating of this, the extremely interesting story involving the phenomenon of the "bends" encountered by deep sea divers will be described and the part it played in leading to the discovery of the anesthetic properties of the inert gases. It is from this work relating to the effects of high atmospheric pressures on man that much of the knowledge came which led to the realization that inert gases might possess anesthetic properties.

The remaining portion of the paper will deal with the relatively recent work of the actual use of inert gases as general anesthetics.

II. THEORIES OF ANESTHESIA

Before attempting an explanation of anesthesia, perhaps the question of what anesthesia is should be answered.

Anesthesia is derived from the Greek and translated means "lack of sensation". In its simplest form then, anesthesia is the abolition of all sensation and the inhibition of voluntary muscle control. How a drug produces this lack of sensation will be theorized upon in this section. The mechanism underlying the process of anesthesia has as yet never been proven to the satisfaction of all workers, but many and varied theories have been advanced. Some of the more outstanding and acceptable of these theories will be briefly reviewed here after which a discussion of the various theories will be offered.

In general, certain facts are known about general anesthetics and these should be mentioned before proceeding. These general properties are summarized by Collins (1) as:

1. The more potent general anesthetics have a high lipoid solubility.
2. Some water solubility is necessary for the drug to reach the cells.
3. With a high lipoid-water ratio, there is a high potency. This explains the preferential accumulation in nerve tissue. All types

of protoplasm are depressed but there is a special predilection for nerve tissue.

4. The depth of narcosis is dependent on the concentration in the nerve tissue, particularly the brain. The more potent drugs are inert or are slowly destroyed by the cells.
5. When the anesthetic drug is removed there is a reversal of the cells to normal.
6. Inhalation drugs have a high lipoid solubility.
7. Non-volatile drugs may have a high water solubility as well as a high lipoid solubility.
8. Tolerance may be developed to drugs capable of decreasing cellular activity.

The earliest attempted explanation of anesthesia was the lipoid theory. In 1847, von Bibra and Harless (1) brought forth the theory that ether, acetic ether, and ethyl chloride were fat solvents and dissolved out fat-like substances from the brain and thereby caused anesthesia by depositing these substances in the liver. This was subsequently proven to be erroneous, but led to the work of Meyer and Overton in 1899-1901. Their three postulates were (1):

1. All chemically indifferent substances which are soluble in fats and fat-like bodies, must exert a narcotic action on living protoplasm, insofar as they can become distributed in it.
2. The effect must manifest itself first and most markedly in those cells in which fatty or lipoid substances predominate in the chemical structure and presumably in which

they form essential participants of the cell function; viz., in the nerve cells.

3. The relative efficiency of such narcotic agents must be dependent upon their mechanical affinity for lipoid substances.

In 1906, Hans Meyer (2) stated that the determining factor in anesthesia is the distribution coefficient between fatty and watery substances. He was able to prove that a parallel existed between the narcotizing action and the fat/water distribution coefficient. It was his belief that the narcotizing substance entered into a loose physico-chemical combination with the vitally important lipoids of the cell, perhaps with lecithin, and in so doing changed their normal relationship to the other cell constituents, through which an inhibition of the entire cell chemistry resulted. It was also evident that the narcosis immediately disappeared as soon as the loose, reversible combination, dependent on the solution tension, broke up.

In 1926, Winterstein (3) proved that the distribution coefficient increased with increased temperatures in some cases and decreased in others, and the anesthetic effect paralleled these changes. These experiments did much to establish the validity of the lipoid theory and also explained the storage of anesthetics in the fatty tissues of the body.

But there are many difficulties as to the universal applicability of the lipoid theory. A major discrepancy is the fact that many alkaloids and the inorganic ions magnesium and bromide are not fat solvents yet possess anesthetic properties. Then too, there are many fat solvents related to the anesthetic drugs which have no depressant activity on the central nervous system. Also, if anesthetic action depends on the amount of the anesthetic agent dissolved in a lipoid phase, the anesthetic action should vary linearly with the concentration of the anesthetic agent, and not logarithmically, as is the case.

In 1904, Traube (1) attempted to prove a relationship between anesthesia and the ability to lower the surface tension of water. This came to be known as the absorption theory. However, his experiments were based on a liquid-air interface whereas the interface in vivo is a liquid-colloid. He was later forced to conclude that true anesthesia depends more on the presence of lipoids.

The absorption theory later became thought of as relating to cell permeability. In 1907, Hober (1) suggested that the anesthetics which were absorbed decreased the permeability of the cell. His thoughts were that anything making the cell less permeable or

less capable of undergoing electrical polarization, had an inhibiting effect on the cell. He found that anesthetics decreased the normal cell permeability, while stimulants had just the opposite effect. However, many anesthetics have been found which do not regularly decrease cell permeability, nor has there yet been shown what specific metabolic activities are affected.

Claude Bernard in 1875 (4), long before most of the theories of anesthesia were brought forth, insisted that all agents that depress the nerve cell, including asphyxia and heat, do so by producing the same modification in the cell. He proceeded to the far reaching generalization that anesthetics depress every manifestation of life whatsoever. All these phenomena of depression he thought of as resulting from a single mechanism of action, which was produced by a reversible coagulation of cell colloids. More recently, Seifritz (5) has advocated this theory but prefers the term "gelatinization" to "coagulation". The postulates of this theory are:

1. Gelatinization or reversible protein denaturation of cell protoplasm produces or accompanies anesthesia.
2. Anesthetics produce first a decrease in stability of protoplasmic colloids possibly by diminishing or neutralizing the charge upon them. This diminished stability is evidenced as an excitement stage. Dehydration

influences then set in accompanied by diminished permeability and gelatinization occurs. At this point anesthesia occurs. If the quantity of agent exceeds certain values, a third phase may appear in which irreversible gelatinization or coagulation occurs with disappearance of selective semi-permeability. This is death.

3. Recovery from anesthesia is characterized by peptization of the cell protoplasm.

An important aspect of this theory is based on the physical change and this change occurs no matter what the anesthetic may be. Seifritz believes that this change may be due to chemical inactivation of respiratory enzymes. However, he cannot explain whether the anesthetic causes gelatinization which in turn inhibits cellular respiration or the agent causes a reduction in cell respiration followed by gelatinization.

The only other major theory of anesthesia is known as the inhibition of oxidation theory and was advanced in 1912 by Verworn (1). He was the first to suggest that anesthetics act by inhibition of cell oxidation. Various types of anesthetics were found by Warburg (6) to depress oxidation in living cells and the effect was reversible and paralleled the concentration of the agent. Anesthetics accomplished this by occupying catalytic surfaces. Quastel (7) showed that physiological concentrations of anesthetics inhibited oxygen

consumption of the brain reversibly and there was a particular interference with the oxidation of glucose. Other investigators have found depressed oxygen consumption of the brain at clinical anesthetic levels. Jowett (8) stated that the inhibition of oxidation by anesthetics was related to the concentration of the anesthetic and was particularly marked for the pyruvic acid oxidizing system. He specifically indicated a dehydrogenase enzyme factor in the brain which acts as a hydrogen carrier in tissue respiration as the modality highly sensitive to anesthetic agents.

The foregoing, then, are the major theories that have developed through the years to explain the phenomenon of anesthesia. There are objections to each of them. An attempt will now be made to discuss these various theories and evaluate points in their favor and criticisms as to their acceptance.

The first theory of anesthesia was that of Bernard (4), mentioned above. However, many investigators have not entirely accepted Bernard's theory. Meyer (9) limited his concepts to the reversible inhibition of "exotropic irritability of protoplasm". He did not agree with Bernard that such inhibitions must all be attributable to the same mechanism. It was his contention that different drugs may have different primary

points of attack and might bring about the end result of depression through a variety of means. His lipid theory was supposed to be applicable only to the "indifferent narcotics" or the "alcohol group", which was admittedly an ill-defined group of indifferent fat-soluble organic compounds of which ethanol and chloroform were considered to be typical. Magnesium and asphyxial narcosis were specifically excluded from consideration under this theory. The primary weakness of this theory is that it fails to adequately predict in which cases it will be applicable, and not that it fails to claim universal applicability. Perhaps no theory of anesthesia should claim universal applicability, and certainly the concept of one all-inclusive phenomenon of anesthesia does not rest on a particularly tenable and logical basis.

But what then should constitute definite evidence for any theory of anesthesia?

First and foremost, the phenomenon of anesthesia must be considered as being a clinical one. There are only a few drugs that have the characteristics making them safe and convenient for producing anesthesia. And there are also many closely related compounds which possess no anesthetic properties and there is no fundamental pharmacological basis for separating them from

those agents actually used as anesthetics. It may be true that no two drugs give rise to precisely identical patterns of nervous system derangement.

One of the first thoughts concerning the mechanism of anesthesia was that separate structural units play a part, or even that the disruption of a molecule in vivo would liberate fragments that were the effective agents (3). This actually led to the synthesis of some active drugs, such as barbital and urethane. But with the wide diversity in chemical structure of present anesthetics, it is apparent that there is no specific structure necessary for anesthetic activity. The best example of this is that anesthesia can be produced by inert gases such as argon (10), krypton, and xenon (11). These gases are spherical symmetrically arranged atoms without permanent dipoles. Therefore, they furnish a most conclusive demonstration that anesthesia need not depend on the effect of any specific structural grouping. Thus, there is nothing that may be called a general or all-inclusive theory relating structure and activity. But even though there cannot be complete confidence in any prediction, the creation of an anesthetic drug must be based on some sort of tentative hypothesis relating structure and activity.

There are some structural features incompatible

with anesthetic activity (3). Organic compounds which are largely ionized at physiological hydrogen ion concentrations possess no anesthetic activity. Also, compounds having a high solubility in water are rarely anesthetic.

The chemical dissimilarity of compounds producing qualitatively similar effects and the great differences among these compounds with respect to their effective doses are probably the most notable features of the anesthetic group.

A correlation between anesthetic activity and physical properties has long been attempted and a great number of compounds representing a broad range of chemical structures has been examined under various conditions and in different dosages. One of the best known and most extensively investigated correlations is that between anesthetic activity and the distribution coefficient between olive oil and water, the correlation that formed the basis of the lipid theories of Meyer and Overton. Since these determinations are very difficult, it is probable that many of the published values are in error. Olive oil was chosen as simulating the lipids of the brain or of the cell membrane. However, knowledge of the composition of the cell membrane is incomplete and the investigation of these

fat solvent substances is quite difficult.

The distribution of numerous compounds between water and various organic substances was found by Collander (12) to depend both on their polarity and their acidity or basicity. He proved that the lipid molecules in the cell membrane are oriented in layers with the hydrocarbon chains parallel. Thus these layers will be just as hydrophobic as a hydrocarbon and will therefore differ entirely from the same lipids in a bulk phase where there is random orientation.

Although anesthetic activity fails to show anything approaching a perfect correlation with the oil/water distribution coefficient, when the anesthetic doses are multiplied by distribution coefficients, the products do not vary over nearly as wide a range as do the doses themselves.

Lipid solubility has been implicated as the mechanism of the anesthetic effects of the inert gases (10, 11). If this is true and can also be applied to the action of the organic anesthetics, it must be viewed as an important accomplishment. In 1929, Grollman (13) found that the solubility of nitrogen in blood lipoid suspensions is much greater than it is in water. Lannung (14) in 1930 determined that the solubility of helium, neon, and argon is least in water, and in

organic solvents the order of solubilities is about the same for all three gases. Hawkins and Shilling (15) were the first to determine the solubility coefficient of helium in whole blood at atmospheric pressure and it was found to be directly proportional to Henry's Law.

It has been found that at ten atmospheres pressure the total amount of nitrogen in the body is about half that of ether during the light stage of anesthesia, and the nitrogen produces definite depressant effects (16). However, hydrogen has no anesthetic effect at pressures where nitrogen has pronounced effects. Although the fat/water solubility ratio of hydrogen is slightly less than that of nitrogen, the difference is hardly sufficient to account for the difference in anesthetic activity (11). This led Case and Haldane (16) to doubt that lipid solubility is the factor responsible for the anesthetic or depressant effects of nitrogen and the inert gases.

Ferguson (17) has introduced a variant in the study of the physical properties of anesthetics. His reasoning is based on the premise that anesthetic action depends upon a physical mechanism which is governed by the equilibrium existing between the concentration of the drug in the external phase and its concentration in the affected phase. Thus, if an equilibrium exists, the

thermodynamic potential of the drug must be the same in all phases. Therefore, if this potential can be measured in any phase in equilibrium with the affected phase, the potential in the latter is known, even though the site and the nature of this phase is unknown. He thus tried to compare drugs on the basis of their potentials in an accessible phase rather than on the basis of their concentrations there. He used the partial molar free energy, given by the equation,

$$\bar{F} = F_o + RT \ln a,$$

where F_o is the molar free energy in a standard state and a is the activity. The pure substance was chosen as the standard state. Therefore, the activity of the pure substance was defined as unity. In a vapor phase, the activity is approximately the ratio of the partial pressure of the vapor to the saturated vapor pressure of the substance at that temperature. In a solution of a substance of low solubility, the activity is approximately the ratio of the concentration to the concentration of a saturated solution. The activity coefficient of a substance is defined as the ratio of the activity to the molar fraction.

The thermodynamic activities of many drugs at their effective concentrations were calculated. Ferguson found these thermodynamic activities to vary

over a much narrower range than did the effective concentrations of these drugs themselves. He therefore concluded that if a particular pharmacological effect on some one organism depends upon a physical mechanism (which he assumes), the thermodynamic activity of the drug producing this effect will lie in a narrower range, such variations as there are in this range probably being due to secondary effects depending on the chemical structure of the drug.

Another test of the relationship of anesthetic activity to physical properties is the comparison of activities of optical antipodes. It has been found that most of the isomeric enantiomorphs have comparable anesthetic properties. This should be so if anesthesia depends upon physical properties. However, it has been reported that l-arabinose is about twice as active as d-arabinose (18). This is therefore another demonstration that anesthetic activity is not always determined entirely by physical properties, and that no rule relating activity to any physical property or properties whatever can be adequate to predict activity quantitatively.

Another argument is that many compounds having water solubilities and oil/water distribution coefficients in the same range as those of active anesthetics

may have no anesthetic properties, and may in fact be convulsants. For example, gamma-hexachlorocyclohexane, which is a convulsant, does not differ greatly in its solubilities from the delta stereoisomer, which is depressant (19). Also, some derivatives of barbituric acid exhibit both convulsant and anesthetic properties.

It thus cannot be claimed that the anesthetics show any perfect regularity in the relationship of their potency to any physical property. The concept of one all-inclusive theory of anesthesia cannot be accepted without question. The nature of the anesthetic drugs furnishes evidence that similar final effects may result from different mechanisms of action.

It has been a generally accepted fact that an anesthetic enters into no chemical reaction in the body while producing its effect. And even if the anesthetic does undergo some kind of reaction, the only apparent result is the inactivation of the drug. This lack of reactivity in a drug capable of producing anesthesia is typified in xenon, an atom incapable of forming chemical bonds. So the forces operative between the xenon atom and a molecule in the cell must be due to the interaction of a dipole in the molecule with the dipole induced in the xenon atom and the inductive forces due to the rapid variation of charge distribution around

the apparently symmetrical atom (3). Therefore physical forces, rather than chemical, must be responsible for the pharmacological action of xenon. But even if the effect is physical, this physical effect is not yet clear, and the consequence of the primary action that leads to depression of cellular function remains to be described.

Yet lipid solubility is the property of anesthetics that has received most attention from experimenters. The lipids constitute an important structural component of the cell membrane, and lipid solubility has been shown to be a factor in determining the penetration of substances into many varieties of cells (20). Therefore, the property of lipid solubility in anesthetics might be regarded logically as indicating either that the action of the drug is exerted, as postulated by Meyer, within the lipid phase, or that the site of action lies somewhere beyond the lipid phase.

In order that anesthesia be feasible, the anesthetic agent must penetrate to its site of action in a rather short time. Also, it is essential that equilibrium between blood and brain be attained rapidly if anesthesia is to be controllable.

Thus, the physical properties associated with anesthetic activity may have no direct relation to the

actual mechanism of anesthesia, but may rather be the properties essential for the arrival of the drug at its site of action in a time compatible with its recognition as an anesthetic (3). However, this is not to say that a property essential for access to the site of action is not also essential in the final mechanism.

Since the cellular membrane is generally regarded as playing an essential role in the transmission of nervous impulses, it would be logical to suppose that a drug interfering with this process might have its site of action in the membrane. The lipid theory has also served to focus attention on the cellular membrane (3).

Lillie (21) has advanced a theory explaining how modification of the properties of the membrane by drugs might abolish excitability. It is his contention that anesthetic drugs decrease the permeability of the membrane, or at least stabilize the membrane in such a way that it would be incapable of undergoing an increase in permeability under conditions which would normally bring this about. Thus, the increase in permeability that presumably gives rise to the depolarization accompanying a wave of excitation could not occur. In peripheral nerves, it can be demonstrated that impulse transmission can be blocked through a

stabilization of polarization. For example, cocaine (22), procaine (23), and some other anesthetics produce this effect. However, ethyl alcohol and ether (24) cause a depolarization and produce blockage in this way. Holland (25) has recently postulated that the release and subsequent combination of acetyl choline with the receptor protein, cholinesterase, is the process that normally accelerates ion movement across the myocardial membrane. He proved that the magnesium ion, pentobarbital, chloretone, procaine, and cocaine could effectively diminish the transfer of the potassium ion across the cell membrane in auricular tissues of guinea pigs.

Metabolic oxidation being essential for the function of the central nervous system, it is understandable that the question should arise as to whether anesthesia is caused by an interference with this metabolism. Quastel (26, 27) has shown that a number of anesthetics inhibit the consumption of oxygen by brain tissue in vitro. Derivatives of barbituric acid have been studied extensively in this regard. Ethanol (8), ether (26), the magnesium ion (8), and nitrous oxide (26) also have the same effect. This inhibition of oxygen consumption develops rapidly and usually changes very little with time.

In all instances in which the inhibition of oxygen consumption has been investigated, it has been found that oxidation of succinate is not inhibited as is that of glucose, pyruvate, or lactate (26, 28, 29, 30).

McElroy (31) brought forth the theory that some anesthetics act by influencing a reversible equilibrium between native and denatured forms of a protein-enzyme. The anesthetic is supposed to shift the equilibrium toward the denatured form, which is enzymatically inactive and has a larger volume than the active form. However, McElroy could produce no direct evidence that this theory is applicable to the brain.

Still, the inhibition of oxygen consumption has usually been assumed to be due to a direct action of the anesthetic drug upon some enzyme.

Grieg (29) assumes that the anesthetic inhibits oxygen consumption by inactivating some enzyme in the main respiratory pathway. Even though an exact site of anesthetic action has evaded direct identification, progress has been made in the recognition of some separate steps in the oxidative chain that are sufficiently sensitive to the drugs to account for the inhibition of the complete process. He has suggested that the block may be between flavoprotein and cytochrome b.

However, Beecher et al. (32) have recently shown that this inhibition of oxygen consumption is not reflected in the blood since there is no evidence for clinical acidosis associated with ether anesthesia, either by the open drop or the closed system. They determined this since they could demonstrate no increase in fixed acid above normal variations during anesthesia.

Although attempts have been made to demonstrate that concentrations of drugs known to be effective in vivo are sufficient to produce a demonstrable effect in vitro, these attempts have been handicapped by lack of adequate information concerning the concentrations occurring in vivo. Ether, an anesthetic for which there is adequate knowledge of concentrations in vivo, is conceded by Jowett and Quastel (28) not to produce significant effects in vitro at anesthetic concentrations. So from the fragmentary data available, it is evident that there is no very close correspondence between activity in vitro and in vivo.

There have been attempts made to demonstrate in the brain in situ the same effects that are observed in vitro. The vertebral arteries of dogs have been perfused with a pump and it has been possible to show that ether, morphine (33), and pentobarbital (34)

decrease oxygen consumption.

Some investigators have also attempted to demonstrate in vivo a pharmacological antagonism to anesthetics by substances that prevent the oxidative inhibition in vitro. If anesthesia were due to inhibition of oxygen consumption by brain cells, it might be expected that substances preventing the inhibition in vitro would have an antidotal effect in vivo. Thus, the oxidation of succinate not being inhibited by anesthetics as is that of glucose, lactate, and pyruvate, it was suggested by Soskin (35) that anesthetics might be antagonized pharmacologically by succinate. Therefore, sodium succinate was tested as an antidote against pentobarbital and amobarbital in rats and was found to be effective. However, other investigators have not been able to confirm these results so that no decisive conclusions can yet be drawn. If succinate is pharmacologically ineffective as an antidote against anesthetics, this might be merely the result of its failure to reach the brain. So, lack of action would accordingly have no bearing on the theory of anesthesia.

In general, the measurements of oxygen consumption of brain tissue in vitro do not furnish very satisfactory support of the theory of metabolic inhibition. Quastel and Wheatley (26) pointed out that the oxygen

consumption measured is the average for a relatively large mass of tissue. They regarded the unequal influences of anesthetics on different neurological functions as evidence that the drugs are indeed present in unequal concentrations at different centers of the nervous system and accordingly exert unequal metabolic effects at different centers. But the most convincing refutation of the idea of localization of concentration has been furnished in the demonstration that barbital labelled with N^{15} is distributed essentially uniformly throughout the brain (36).

Nevertheless, the fact cannot be disregarded that inhibitions have been produced in vitro and that the oxygen consumption of the brain in the living animal is reduced during anesthesia.

Therefore, despite the fact that numerous attempts have been made to explain the phenomenon of general anesthesia, nothing has as yet emerged that can be called an adequate theory. And as long as the explanation of the synaptic transmission of nerve impulses is a matter of controversy, it is doubtful if a satisfactory explanation for general anesthesia can be given.

III. DISCOVERY OF THE ANESTHETIC ACTION OF INERT GASES

The story of how inert gases came to be recognized as possessing properties of anesthesia is extremely interesting. In order to properly relate how this came about, a discussion of the phenomenon of the "bends" often experienced by deep sea divers must be presented. A great deal of experimental work covering a long period of time has been done to clarify the nature of the "bends" (or, compressed air illness). A brief chronological description of this work will be outlined here.

The first scientific description of the manifestations of the "bends" was be Bert in 1878 (37). He described bubbles in the blood vessels of animals rapidly decompressed after exposure to elevated pressures, and to these bubbles he attributed the symptoms of the "bends", or caisson disease, divers' palsy, or compressed air illness. Upon analysis, these bubbles were found to consist chiefly of nitrogen, the principle inert gas of air, which he believed had come out of solution in the blood and tissues so rapidly as to form gas emboli. Following Berts' work, little advancement in the prevention of compressed air illness was made until 1908.

Boycott et al. (38) discovered that the time in which a man exposed to compressed air becomes saturated with nitrogen varies in different parts of the body and takes from a few minutes to several hours. This follows a logarithmic curve, and the curve of desaturation after decompression is the same type of curve, provided no bubbles have formed. They found that decompression is not safe if the pressure of nitrogen inside the body becomes much more than twice that of atmospheric nitrogen. Consequently, their method of decompression advocated rapidly halving the absolute pressure at first, and subsequently gradually reducing the rate of decompression so that the nitrogen pressure in no part of the body ever becomes more than about twice that of the air.

They found death nearly always due to pulmonary air embolism, and paralysis due to blockage of vessels in the spinal cord by air. Their supposition as to the cause was the presence of bubbles in the synovial fluid of the joints. At post mortem, they found bubbles most freely in the blood, fat, and synovial fluid, and they were not uncommon in the substance of the spinal cord. The method of decompression described by Boycott was used by deep sea divers for many years.

It was not until 1926 that any further contribution

was made to obviate the threat of compressed air illness. In that year, Sayers and Yant (39) found that helium and oxygen mixtures could be breathed by men without apparent discomfort or demonstrable ill effects. They theorized that this mixture would have an advantage over a nitrogen and oxygen mixture due to the fact that helium has a lower coefficient of solubility and a greater diffusibility than nitrogen. Using animals exposed to ten atmospheres of an 80:20 % helium and oxygen mixture for from one to five hours, they found decompression could be accomplished in from one-third to one-fourth the time necessary with a nitrogen and oxygen mixture. They advocated its use in prolonged exposures to increased pressures.

Following the discovery that helium drastically lowered the time necessary for decompression, several investigators began to explore the possibilities of its use as a therapeutic agent. The first report of this nature was by Barach in 1934 (40) who found that a 79:21 % helium and oxygen mixture used on patients with compensated heart disease reduced the total inspiratory and expiratory pressures through a narrow orifice by 20-45%. This of course results in a great saving of pulmonary effort.

Barachs work was followed by many more papers

advocating a helium and oxygen mixture in cases of respiratory obstruction (41, 42), asthma (43, 44), the maintenance of anesthesia without an endotracheal tube (45), and as a method of preventing postoperative pulmonary complications (46, 47).

In 1930, Hershey (48) reported that animals cannot maintain life without the presence of inert gases. Using small animals, he found pure oxygen would not sustain life more than 2-5 days. However, using mixtures of helium and oxygen, argon and oxygen, and nitrogen and oxygen, the animals survived well. But Barach in 1934 (49) was able to maintain life in small animals for 42 days without inert gases, and Orcutt and Waters in 1934 (50) substantiated these findings.

Although alert deep sea divers had often noticed disturbances in motor control and behavior in divers suffering from the "bends", it was not until 1932 (51) that these symptoms were described in the literature. Thereafter for several years, many papers were published delineating the roles of various gases and various conditions in the production of these symptoms.

Shaw et al. (52) in 1934 studied the role of carbon dioxide in producing the symptoms of compressed air illness. They subjected anesthetized dogs to oxygen pressures of 4 atmospheres absolute for periods of time

up to 3 hours. They found significant decreases in blood pressure and convulsive seizures of the head and neck. Recovery was immediate upon reducing the oxygen pressure. Death was caused by either paralysis of the respiratory center or the cardiovascular centers. However, carbon dioxide even at high tensions combined with a normal oxygen pressure produced no symptoms whereas subnormal carbon dioxide tensions together with increased oxygen pressure does produce symptoms. Therefore, they concluded that the oxygen tension is the primary cause of the symptoms.

In 1935, Behnke et al. (53) studied the rate of elimination of dissolved nitrogen in man in relation to the fat and water content of the body. They found that nitrogen elimination follows an exponential type of curve and is a function of the cardiac output. So, the cardiac output can be estimated by dividing the value for nitrogen eliminated during the first minute by the quantity of nitrogen dissolved per liter of blood. It was also proven that the fat and lipoids of the body act as nitrogen absorbents and serve as buffers against bubble formation during the decompression of divers.

Also in 1935 (54), new tables of decompression were reported wherein tissues were divided into classes depending upon how long they took for nitrogen desaturation.

The essential points were that a ratio of 2.8 to 1 atmospheres was allowed for the 20 minute tissues, and a ratio of 2 to 1 atmospheres for the 40 and 75 minute tissues.

The first experimental evidence that increased pressures of air or oxygen produced central nervous system symptoms was reported by Behnke et al. in 1935 (55). These investigators subjected humans to oxygen at 1 to 4 atmospheres for from 45 minutes to four hours. They found a person can breathe pure oxygen at 1 atmosphere for 4 hours, 2 atmospheres for 3 hours, and 3 atmospheres for 2 hours. At 4 atmospheres, two subjects were tested, and one experienced convulsions and the other syncope after 45 minutes. At 1 atmosphere, impaired neuromuscular coordination and the power of attention or an increased effort to maintain these functions occurred after 1-3 hours in 3 out of 4 subjects. In all cases, the blood pressure, respiratory rate, and the minute volume were constant. They ruled out an increased tissue acidity as a factor in the production of convulsions due to the constancy of the respiratory minute volume at 1 to 4 atmospheres.

Also in 1935, Behnke et al. (56) elicited some psychological effects from breathing air at 4 atmospheres pressure. Using 9 humans in pressure chambers, pressures

of 4 atmospheres were introduced for times ranging from 1.5 to 5 hours. These volunteers were doing routine laboratory work. Abnormal reactions were first noted at 3 atmospheres and at 4 atmospheres all were affected similarly but varied in intensity. They found at first a feeling of stimulation and euphoria. Then, there was a slowing up of mental activity. This was apparent by delayed responses to visual, auditory, olfactory, and tactile sensations. There was a tendency to fixation of ideas. Recollection decreased. Accuracy in mathematics declined. In general, a mild stupor developed. There was an impairment of fine movements and defects in co-ordination. These altered responses occurred at the beginning of exposure and did not change after 3 hours. In one test at 10 atmospheres, there was a partial stupefaction and a greatly increased numbness. They believe that a limiting pressure incompatible with human activity would be reached between 10 and 15 atmospheres. That the effect was not due to an increased partial pressure of oxygen was proven by the fact that oxygen was tested alone and there was no euphoria. Therefore, they believe the increased partial pressure of nitrogen is responsible, due to its high coefficient of solubility in lipoid matter.

These above effects and symptoms were well

substantiated by experiments of Case and Haldane in 1941 (16).

In 1937, End (37) again suggested the use of a helium and oxygen mixture in decompressing divers following exposures to increased pressures. In their experiments, they found they could successfully decompress subjects in less than one twenty-third the time required when compressed air is used if a helium and oxygen mixture is used. This they thought was due to the relative insolubility of helium in lipids so that the narcotic effect of nitrogen at high pressures is immunized.

Again in 1937, Behnke (57) suggested a major departure from the previously accepted method of decompression. He proposed a method based on the use of a single curve representing the rate and quantity of nitrogen eliminated from the body as a whole. There should be maintained a constant relative difference of 12 to 19 pounds of air and 10 to 15 pounds of nitrogen between the pressure in the body and the pressure in the lungs.

Behnke and Yarbrough in 1938 (58) determined the solubility coefficients of helium and compared them with nitrogen. They showed that helium was less soluble than nitrogen in fat, and again reiterated the

fact that in a helium and oxygen atmosphere, the narcotic effects of nitrogen at high pressures are largely dispelled. By measuring the inert gas content of the urine they could detect the presence of excess gas held in supersaturation or in bubble form and could often predict the occurrence of the "bends".

In 1939, Behnke and Yarbrough (10) decided to study the effects of an argon and oxygen mixture upon humans in order to determine how it compared with a helium and oxygen mixture. They found that breathing an 80:20 % helium and oxygen mixture at normal pressures is equivalent to breathing air at an altitude of 18,000 feet. Using a 69% argon, 11% nitrogen, and 20% oxygen mixture upon divers, they were told by these divers that they all thought they were lower than they were, since they developed the usual altered mental state. If oxygen were substituted for argon, the diver thought he was being brought to the surface. They thus determined that argon induces greater stupefaction and neuromuscular impairment than nitrogen at increased atmospheric pressures. Therefore, helium elicits negligible mental aberrations in comparison with argon, while the effect of atmospheric nitrogen is intermediate.

Now that Behnke had found that argon produced narcotic effects greater than does nitrogen at increased

pressures, it was of interest to compare the two gases as narcotizing agents in the light of the Meyer-Overton theory of anesthesia. Behnke in 1940 (59) maintained that the absorption of inert gases, such as nitrogen and helium, by the water and lipoid components of body tissues is comparable to the absorption of anesthetic gases. Furthermore, argon and nitrogen, in contrast to helium, induce a narcotic effect at high pressures, and these actions are in accord with the Meyer-Overton hypothesis.

An interesting sidelight is that in more recent years, high altitude fliers have often experienced the "bends" resulting from rapid decreases in atmospheric pressure during ascent, similar to the decrease in pressure which deep sea divers undergo during decompression. In 1946, Lund and Lawrence (60) concluded that these "bends" pains may be caused by collections of gas in the fascial and intermuscular septal planes, which by dissecting to the periosteal insertions of such anatomical layers, cause pain at these insertion points.

It was not until 1946 that Lawrence et al. (11) definitely pointed out the narcotic effects produced by the inhalation of inert gases. Other than the observation by Behnke in 1939 (10) that argon possessed

more narcotic properties than nitrogen at elevated pressures, this was the first indication of the anesthetic effect of the inert gases. These investigators found that in equivalent concentrations, argon has twice the narcotic effect of nitrogen and is twice as soluble in water and in lipoids. However, the fat/water solubility ratio of the two gases is nearly the same. They reasoned from the Meyer-Overton hypothesis that anesthetic effects are relative to the fat/water solubility and concluded that krypton and xenon might show striking narcotic properties. Theoretically, they thought 80% krypton at atmospheric pressure should be as narcotic as 6 atmospheres of air, and xenon under the same conditions should be equivalent to 25 atmospheres of air. Experimentally, they compared various mixtures of krypton and xenon with air upon mice. A 50% krypton, 50% oxygen mixture for 1 hour produced no effects. A 60% xenon, 40% oxygen mixture for 20 minutes produced slight extensor convulsive movements of the head after 2 minutes with developing weakness of the hind legs. A 78% xenon, 22% oxygen mixture for 1 hour produced essentially the same results as in the preceding experiment except that following removal of the gas mixture, the mouse experienced ataxia and unsteadiness with complete recovery in 15 minutes.

Three other experiments utilizing varying concentrations of xenon produced essentially the same results as the preceding experiments. One human volunteer breathed a 50% krypton, 50% oxygen mixture for a few seconds and remarked that it made him feel quite dizzy. Also in this paper were determined the solubilities of various inert gases in water and fats using radioactive isotopes.

IV. THE USE OF INERT GASES AS ANESTHETICS

A. The Use of Inert Gas Anesthesia in Animals

Lawrence et al. (11) were the first to recognize the anesthetic properties of inert gases. Their experiments were described in the previous section, in which the effects of inhalation of mixtures of krypton and oxygen and xenon and oxygen on mice were discovered.

It was not until 1951 when Cullen and Gross (61) resumed studies on the inert gases, that additional experimentation was described of the effects of inert gas anesthesia in animals. Using an 80:20 % mixture of xenon and oxygen, they reported evidence of narcosis in rabbits.

Again in 1951, Cullen and Gross (62) reported on further experimentation with xenon and krypton anesthesia. With the use of an 80:20 % mixture of krypton and oxygen on rabbits, no unequivocal signs of narcosis could be demonstrated. Also, an 80:20 % mixture of xenon and oxygen was administered to rabbits for 15 minute periods. They found minimal narcotic effects, equivalent to the effect of an 80:20 % mixture of nitrous oxide and oxygen. During the inhalation, they demonstrated some loss of the lid reflex, some apparent diminution in response to painful stimuli, a

tendency to remain in induced unnatural postures, and a slowing of the respiration. Recovery was almost immediate with the discontinuance of the inhalation.

Other experiments have been conducted utilizing inert gases as anesthetics upon animals, but have been primarily for the function of determining the mechanism of action of these gases. The results of the work attempting to elucidate the mechanism of inert gas anesthesia will be covered in a later section.

B. The Use of Inert Gas Anesthesia in Humans

Concurrent with experiments on the effect of inert gases on animals were experiments concerning their effects upon humans. Lawrence et al. (11) in 1946 were the first to report upon some of these effects. Exposures to an 80:20 % argon and oxygen mixture produced a progressive narcotic effect. Also, one experimenter breathed a 50:50% mixture of krypton and oxygen for a few seconds and remarked it made him feel quite dizzy.

However, the first experimental research designed to specifically study the effect of inert gas anesthesia was by Cullen and Gross in 1951 (61). Using an 80:20 % mixture of krypton and oxygen on three humans, they found it caused only slight dizziness and discomfort.

Their conclusions were that krypton had no significant narcotic properties at atmospheric pressures. However, with the use of an 50:50 % mixture of xenon and oxygen, there was definite evidence of an anesthetic effect. The pain threshold indicated a fifteen percent increase. Two subjects inhaled a 70:30 % mixture of xenon and oxygen for three minutes and experienced pronounced anesthetic effects with partial loss of consciousness. They concluded that xenon possessed anesthetic properties approximately equivalent to ethylene.

Further studies by Cullen and Gross (62) were undertaken to determine just how effective the inert gases were as anesthetics in humans. Repeating their experiments with an 80:20 % mixture of krypton and oxygen on humans, they demonstrated changes in voice quality, a sensation of wanting to breathe more deeply, a swelling of the head, and an ill-defined but unequivocal dizziness or discomfort. But they did not consider these to be significant anesthetic properties. Using a 50:50 % mixture of xenon and oxygen on six humans, they repeated their findings in demonstrating a fifteen percent increase in the pain threshold. The subjects also reported subjective sensations of dizziness and incipient loss of consciousness. On the basis of these and previous findings, it was decided to use xenon as an

anesthetic for an actual operative procedure on a human. Accordingly, an 81 year old man had an orchidectomy performed using an 80:20 % mixture of xenon and oxygen. Within three minutes from the beginning of the inhalation, consciousness was lost, and within ten minutes the operation was begun. Evidence such as roving eyeballs, active intercostal muscles, and the character of the respirations seemed to indicate that the patient was in the first plane of the third stage of anesthesia. There was enough relaxation of the muscles of the jaw and pharynx to require the insertion of an oropharyngeal airway to overcome obstruction by the tongue. The pulse and blood pressure remained normal, the color was good, and there was no unusual respiratory pattern. When inhalation was discontinued, the patient recovered within two minutes and within five minutes could orient himself clearly. There were no postoperative complications. This is the first report in the literature of an inert gas being used as an anesthetic for an operative procedure in a human being. In the same study, a 38 year old white female was anesthetized with an 80:20 % mixture of xenon and oxygen and a ligation of the Fallopian tubes was done. The vital signs remained normal throughout the procedure and good relaxation was obtained. Recovery was uneventful.

The effects of anesthesia with xenon were again described by Cullen and Gross as being equivalent to that with ethylene.

The next report in the literature of the effects of inert gas anesthesia in humans was by Pittinger et al. in 1953 (63). This study was undertaken to determine the clinicopathologic changes associated with xenon anesthesia in humans. Five patients were used and inguinal hernioplasties were performed on all of them under an 80:20 % mixture of xenon and oxygen. In all cases, consciousness was lost when the concentration of xenon reached 50 percent. A urinalysis, complete blood count, sedimentation rate, bleeding time, clotting time, platelet count, and urea clearance as well as a serum calcium, creatinine, nonprotein nitrogen, phosphorus, potassium, sodium, sugar, and blood urea nitrogen was performed on all five cases both before and during anesthesia. They found a definite downward trend in the platelet counts during anesthesia, the average decrease amounting to about 30 percent. There was also an increase in the number of white cells in the urine, but this and the decreased platelet count were attributed to causes other than the anesthetic. They also found a relative elevation in the segmented cells in the peripheral blood during anesthesia, which is consistent

with that found during anesthesia with ether, nitrous oxide, cyclopropane, ethylene, and chloroform. There was also a slight decrease in serum potassium during xenon anesthesia which the authors thought might be a result of decreased metabolic activity rather than a specific effect of xenon. There was no evidence of respiratory depression, but there was a slight tendency toward a relative bradycardia. The electrocardiographic and oscillographic records revealed no abnormalities of cardiac rhythm. All other determinations were within normal limits. These experimenters therefore conclude that there is a minimal biochemical and physiological disturbance during xenon anesthesia.

The only other report of the use of inert gases as anesthetic agents in humans was by Morris et al. in 1955 (64). An 80:20 % mixture of xenon and oxygen was used on 7 patients. The operative procedures included the insertion of Ra needles for carcinoma of the cervix, a caesarean section, a hernioplasty, a biopsy of the vagina, and three dilatation and curettage procedures. In each case, an electroencephalogram, an electrocardiogram, and blood oxygen and carbon dioxide determinations was done. The electrocardiogram and blood oxygen and carbon dioxide determinations were normal. However, there was a striking difference seen

in the electroencephalographic changes with xenon as compared with those observed with other anesthetics. Xenon does not produce a slow, single rhythmic pattern as is the case with other inhalation anesthetics. Rather, there was a relatively constant course of changes characterized by an initial depression of alpha activity with a low voltage fast pattern followed by a rhythmic 5 to 7 per second pattern mixed with other frequencies. These changes were not as marked as those described for other anesthetics, but were entirely different in character. There was no attempt made for an explanation of this phenomenon.

C. Studies of the Mechanism of Inert Gas Anesthesia

In reference to the mechanism of action of anesthesia by inert gases, about the first report in the literature is by Tobias et al. (65). They studied the uptake and elimination of inert gases by the human body. Using radioactive krypton, they found that it was present in the body primarily in physical solution, chiefly in the body water and fat. Allowing their subjects to inhale a mixture of the radioactive krypton and oxygen, they determined an uptake and desaturation curve, and found that the gas rapidly appeared in the circulation of the extremities. Their results suggest

that these radioactive inert gases might have an application in the study of the circulation to the extremities in the living patient and in numerous problems of gas exchange in normal and pathologic states.

In 1950, Cook (66) undertook the study of the effect of inert gases on the metabolism of insects. He studied the respiratory gas metabolism and visible development. He found that helium and argon alter both the rate of metabolism and the progress of development as seen in metamorphosis of the Drosophila species. Argon in general appears less active than helium although it resembles the latter in its effect on three species studied. Argon does not alter the carbon dioxide production of mice. No hypothesis was offered to account for the experimental findings.

Helium was found by Cook, South, and Young (67) to significantly increase the oxygen consumption and carbon dioxide production of mice. In addition, striated muscle, liver, ventricle, and sarcoma were studied and the oxygen consumption and carbon dioxide production of all tissues was found to be increased by helium.

In 1952, Featherstone et al. (68) reported the distribution of radioactive xenon in dog tissues. Seven dogs were allowed to breathe an 80:20 % mixture of radioactive xenon and oxygen for 20 minutes. They

were then sacrificed and tissues taken for analysis. They found no significant difference in the xenon content of the cerebral parietal cortex, caudate nucleus, thalamus, hypothalamus, or the medulla oblangata. The adrenal gland was shown to contain 155 per cent as much xenon as any of the brain tissues. The kidneys contained about the same amount of xenon as did the brain tissues. Liver and spleen contained approximately 58 per cent as much xenon as did brain tissues, while approximately 28 per cent as much as in brain was found in striated muscle. Their results are in general agreement with calculated theoretical values from the known values for lipid and water content of these organs and the solubilities of the anesthetic gases in water and olive oil.

Young and Cook in 1953 (69) measured the oxygen consumption of mice under the effects of helium. Using an 80:20 % mixture of oxygen and helium, they found the degree of acceleration of oxygen consumption was greater in the heavier mice. They also tested normal mice, mice radiothyroidectomized with I^{131}, and mice fed heavy doses of desiccated thyroid gland. The acceleration of oxygen consumption due to helium was greatest with the slowly metabolizing, intermediate with the normals, and least with the hyperthyroid animals. It was their

conclusion that the effect of helium is inversely proportional to the level of the standard metabolism regardless of the nature of the factors which initially determine that level.

Also in 1953, South and Cook (70) studied the effect of helium on the respiration and glycolysis of mouse liver slices. With an 80:20 % mixture of helium and oxygen, they found an increase in the rate of oxygen consumption and carbon dioxide production to the same degree, the respiratory quotient remaining the same. They also showed a decrease in the magnitude of cyanide inhibition, no effect on the activity of slices which have been poisoned with fluoride when either lactate or pyruvate has been added as a substrate, and a change in the rate of oxygen consumption in liver homogenates which were utilizing pyruvate as a substrate. Therefore, they proved that the citric acid cycle is not subject to the influence of helium in tissue slices, but is altered in homogenates. They postulated that a rearrangement of particulate surfaces may be the significant factors here. In addition, under anaerobic conditions, helium caused a depression of the glycolytic rates in both mouse liver slices and diaphragm, and an increase in the carbon dioxide evolution and lactic acid production of mouse liver homogenates oxidizing either glucose and hexose

diphosphate, or hexose diphosphate alone.

The conclusions reached by these investigators were that:

1. Helium does not alter the substrate utilized by the tissues.
2. Helium interferes in some way with the cyanide-cytochrome oxidase bond, but may not affect cytochrome oxidase in the absence of cyanide.
3. The citric acid cycle is not subject to the influence of helium in tissue slices, but is altered in an unexplained fashion in homogenates. It is postulated that a rearrangement of particulate surfaces may be the significant factor here.
4. The glycolytic cycle is the site of both an inhibitory and an acceleratory effect of helium. The locus of inhibition lies above the aldolase reaction and that of the acceleration between the aldolase and enolase reactions.

Further studies of the above nature were reported by Cook and South in 1953 (71). They confirmed their previous results in showing that helium is capable of increasing the rate of aerobic oxidation in all normal tissues, but not to the same degree. Under anaerobic conditions, helium was found to induce a decrease in the rate of glycolysis of brain slices, liver, and diaphragm. However, helium evoked no response from sarcoma slices under the same conditions. The explanation of these results is that helium indirectly alters the rate of phosphorylation of glucose during anaerobiosis. However, this alteration is dependent on an

undescribed reaction affected by helium.

In 1954, South and Cook (72) studied the effect of argon and xenon on the oxygen consumption and glycolysis in mouse tissue slices. They found the effects to be very similar to those produced by helium. Xenon altered the rate of metabolism in a manner almost identical with that of helium, decreasing the rate of oxygen consumption in brain, liver, and diaphragm mouse tissue slices. It also significantly depressed the rate of anaerobic glycolysis. Argon produced a similar pattern, but of less magnitude. They postulated that although the inert gases may have a specific action on the central nervous system causing narcosis, they may not at the same time alter the rate of intrinsic metabolism of the tissues in the same direction. Even though the total metabolism of the body might be lowered, the metabolic rate of the constituent tissues might be either raised or lowered, depending upon whether the tissues in question were deriving their energy predominantly from aerobic or anaerobic oxidations.

Pittinger et al. in 1954 (73) again investigated the distribution of radioactive xenon in the tissues of the dog. In this experiment, they proved that the thalamus, hypothalamus, caudate nucleus, and medulla oblangata took up xenon faster than did the cerebral

parietal cortex. This contradicted the work by Featherstone (68) and was the first definite evidence that the rate of uptake of inhalation anesthetics is not the same in all parts of the brain.

Experiments designed to determine if the metabolic theory of anesthesia hods true for the inhalation anesthetics, xenon and nitrous oxide, were undertaken by Levy and Featherstone in 1954 (74). Using guinea pig brain homogenates and manometric techniques, they tested the effect of xenon and nitrous oxide with glucose and pyruvate substrates. Their conclusions were that there were no significant differences in the in vitro oxidation of glucose or pyruvate or in oxidative phosphorylation by guinea pig brain tissue when compared with the oxidation in air. They believe, therefore, that the theories of anesthesia involving metabolic inhibition of glucose or pyruvate oxidation or the uncoupling of phosphorylation which are supported by data obtained with barbiturates are not applicable to the gaseous anesthetics xenon and nitrous oxide.

In 1955, Pittinger et al. (75) studied the effects of xenon anesthesia with an electroencephalograph on monkeys. Since it was well known that it was easier to produce anesthesia with xenon in humans than in animals, the investigation was conducted at elevated

pressures. Their findings indicated that profound anesthesia could be obtained with elevated pressures and that hypoxemia is not a concomitant feature of xenon anesthesia if the partial pressure of oxygen is maintained at 200 mm. of mercury. The electroencephalogram indicated a decrease in frequency and a narrowing of the range of frequencies with an increased partial pressure of xenon and the accompanying increased depth of anesthesia. This appreciable rhythmic electroencephalographic activity persisted during profound xenon anesthesia.

V. SUMMARY

The various theories of anesthesia have been described. Much supporting data has been presented in favor of each theory as well as a good deal of theoretical and applied experimentation tending to disprove the validity of each. The only conclusion that can be reached at this time is that there is no one theory that can adequately explain the theory of general anesthesia.

The fascinating story of how inert gases came to be recognized as possessing anesthetic properties was next outlined. This involved delving back into the early literature on the cause and prevention of compressed air illness, common to deep sea divers. The gradual realization of the part that the increased partial pressure of nitrogen played in the etiology of the "bends" naturally led into the investigation of the properties of inert gases. It was not until 1946 that it was definitely proven that krypton, argon, and xenon could produce narcosis.

From here, the discussion led into the actual use of inert gases as anesthetic agents. Although their use as general anesthetics has been quite limited, it has been definitely shown that operative procedures can be undertaken under xenon anesthesia.

The primary deterrant to further experimentation with inert gases is their almost prohibitive cost and difficulty of production. However, recent work has proved that xenon anesthesia is comparable in activity with ethylene. It is used in an 80:20 % mixture with oxygen at atmospheric pressure. Argon and krypton have been shown to possess only negligible anesthetic properties at atmospheric pressures, but are capable of producing narcosis at elevated pressures.

Research designed to elucidate the mechanism of action of inert gas anesthesia has been rather sparse. Even so, it has been determined that inert gases do not function to produce metabolic inhibitions of oxidative reactions. Neither are inert gases taken up by brain tissue in equivalent concentrations in all parts. The electroencephalographic changes during xenon anesthesia are also quite different than those found with other inhalation anesthetics.

In conclusion, it can be said that xenon anesthesia has been found to be practical from a clinical standpoint, but impractical from an economic standpoint. The mechanism by which inert gases function to produce anesthesia has as yet not been explained.

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