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The Anesthetic : cyclopropane

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THE ANESTHETIC - CYCLOPROPANE

by

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INTRODUCTION

In 1929 a new gas, Cyclopropane was introduced into the armamentarum of the anesthetist, combining in itself speed, both in induction and recovery, high oxygen supply during anesthesia, and power to produce a considerable degree of relaxation, together with a minimum of deleterious effects on the various organs and functions of the body.

In this thesis, I am presenting the results of very comprehensive studies and observations of this gas, comparing it, in a limited degree, with some of the other well known inhalation anesthetics.

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HISTORY

Since the introduction of chloroform, ether and nitrous oxide into the realm of anesthesia, anesthetists have steadily sought for other drugs which would bring about the desired effect unaccompanied by the metabolic changes these produce. Of various substances tried, ethylene appeared the most promising.

Before the advent of ethylene, the surgeon could only to a limited degree choose an anesthetic suitable to the needs of his patients. Chloroform had almost been discarded. If complete and thorough relaxation were desired, it practically meant giving ether. Nitrous oxide, a fair substitute for ether for surface work, did not give the desired relaxation for difficult abdominal surgery.

The introduction of ethylene gave promise of fulfilling a great need. It had the advantages of nitrous oxide in that the induction of anesthesia was short and without either the feeling of suffocation or the excitement stage of ether. The relaxation under ethylene was far superior to that of nitrous oxide, and so nearly approached that of ether as to be sufficient for most abdominal work. Recovery was rapid with little or none of the unpleasant effects of ether. However, because of its explosive tendency, there lurked at the back of the

minds of the surgeon and the anesthetist that an explosion might happen. Induction is rapid but the margin between safe anesthesia and impending death is so narrow that it can be crossed in a few seconds.

Spinal anesthesia was first used in 1885 on frogs and dogs and in 1899 was introduced as an anesthetic in surgery. However, it is only within the past twelve years that spinal anesthesia has been placed upon a sufficiently rational basis to be reasonably safe for the average surgeon. Novocain or spinocain are most frequently used. Preliminary preparation is the same as for a general anesthetic, except that nourishment may be taken up to within an hour or two of the operation.

Pontopon grains 1/3, or morphine grains 1/4 is given one hour before operation. With the patient in an horizontal position a lumbar puncture is done. It makes little difference which lumbar interspace is used, but usually the higher the desired anesthesia, the higher the interspace chosen. Approximately one centigram (or ten milligrams) of the pure crystals is given for each fifteen pounds of body weight, and not to exceed twelve to fifteen centigrams (or one hundred and twenty to one hundred and fifty milligrams). The height of the anesthesia depends upon the drug used, the volume of the

fluid withdrawn, the rapidity of injection, and by the position of the patient.

Within the first ten minutes there is frequently a rather marked fall in the systolic blood pressure. However, this may be combated by the use of either one minim of adrenalin for each ten pounds of body weight or three-fourths grain of ephedrine. The incision may be made as soon as the patient is turned on his back and properly draped. The anesthesia lasts from one to one and one-half hours, and after the first ten minutes the drug becomes fixed to the tissues and the patient may be placed slowly in any position desired (9). It is dangerous to try to obtain anesthesia above the diaphragm.

The alleged advantages of spinal anesthesia are:

1. It removes the dread so many patients have of going to sleep.
2. Freedom from postoperative nausea and vomiting, and strain on the incision.
3. Better relaxation of the abdominal walls and the elimination of the tendency of the bowels to protrude, especially in an emergency abdominal operation where there has been no time for preparation.
4. Freedom from whatever deleterious effect the inhalation anesthetics may have on the various organs.

5. Theoretically, less danger of pulmonary complications especially where the patient has or recently has had a respiratory infection.

6. The anesthetic par excellence for patients with pulmonary tuberculosis.

7. The marked relaxation of the abdominal wall together with the contraction and relative quietness of the intestine makes this anesthetic especially indicated in intestinal obstruction.

The alleged contraindications of spinal anesthesia are:

1. Cases of hypotension where the systolic pressure is below ninety.

2. General sepsis.

3. Marked hypertension.

4. Cases of myocardial degeneration or passive congestion.

5. Involvement of the cerebrospinal system by tumors, syphilis, et cetera, or whenever the spinal fluid is cloudy.

The postoperative care is practically the same as after a general anesthetic, except that the patient must be moved gently and should be kept in a slight Trendelenburg position for at least twenty-four hours to prevent

postoperative headaches.

Propylene, a very closely related substance to ethylene, in laboratory tests was even better than ethylene, but when manufactured and tanked it developed some toxic properties. While looking up the possible sources of the toxicity, Lucas and Henderson (16) suggested that possibly some cyclopropane, an isomere which frequently appears during the preparation of propylene, might have been produced. So it was decided to see whether this gas was the cause of the toxic symptoms or not.

Cyclopropane was first produced by the reduction of trimethylene bromide by zinc dust in the presence of alcohol and traces of water. The gas which was produced by this action did not consist of only cyclopropane but contained a small amount of propylene. The latter was absorbed by potassium permanganate. The residue thus obtained contained from eighty-five to ninety-three per cent cyclopropane and seven to fifteen per cent of an unknown gas. This unknown gas was separated from the cyclopropane by absorption of the latter in sulphuric acid. It was found that the residual gas was not anesthetic even in proportions as high as forty per cent.

The first few experiments with cyclopropane showed that it was not toxic and was a more powerful anesthetic

than propylene.

To measure the effects of the gas on respiration in anesthetic concentrations and the toxic effect in greater concentrations, the apparatus in Figure 1 was connected to the trachea and a manometer was connected to the carotid artery to measure changes in blood pressure.

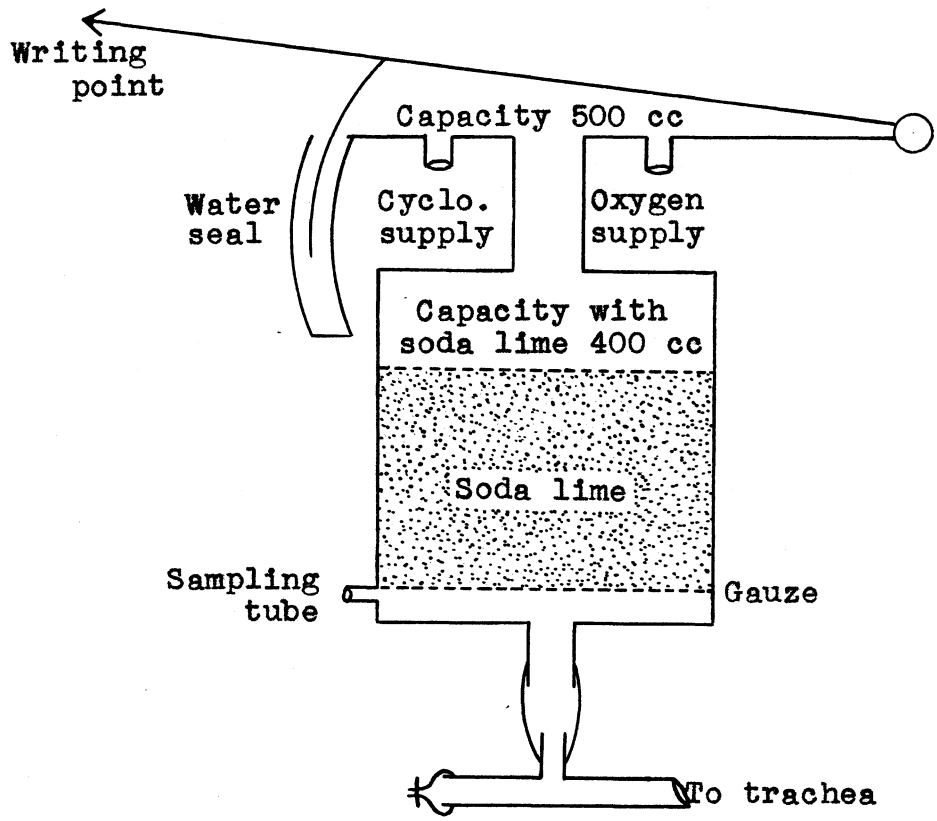


Fig. 1. Apparatus used to demonstrate the effects of various concentrations of cyclopropane on respiration in animals.

The degree of anesthesia was determined by expos-

ing the femoral nerve and stimulating it electrically, also by opening the abdomen and pulling on the intestines. The anesthetization was carried to such a degree that stimulation of the nerve caused but slight or no change in the blood pressure or respiration. The corneal reflex was always absent in this degree and is comparable to deep third stage anesthesia in man. The response to the pulling of the intestines always vanished before that of electrical stimulation. However, even with this degree there was still some flexor tonus in the hind limbs although abdominal musculature was apparently completely relaxed. This is found also to a lesser extent with ether in cats in the surgical stage of anesthesia.

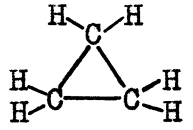
December 3, 1928, Lucas and Henderson (16) performed the original experiments with cyclopropane on cats. It was found that respiratory failure preceded a fall in blood pressure but that there was a wide range between the concentration needed for surgical anesthesia (twelve per cent) and the fatal concentration (twenty-seven to thirty per cent). Other experiments showed that in cats surgical anesthesia could be maintained with ten to eleven per cent of cyclopropane. The percentage required for rabbits was slightly higher, four-

teen to fifteen per cent. The toxic features did not appear rapidly, except with concentrations of eighteen to twenty per cent in cats, although a fall of blood pressure occurred in some cases with sixteen per cent and upwards. The toxic effects were evident either in a fall of blood pressure or more usually in respiration becoming more shallower and slower.

Recovery of cats from doses toxic to respiration was very rapid, two to three minutes; while toxic symptoms of fall of blood pressure caused a slower recovery.

To show the rapid recovery of an animal when not operated upon, Lucas and Henderson (16), using fifteen per cent cyclopropane, deeply anesthetized a cat. After two hours and ten minutes the anesthetic was withdrawn. In one minute the cat winked, and moved its tongue, in three minutes sat up, and walked about, and in five minutes purred when petted.

PHYSICAL AND CHEMICAL PROPERTIES

Cyclopropane, an isomer of propylene, is an inflammable, saturated, gaseous hydrocarbon of cyclic structure,  . This gas was first identified as a chemical entity by Freund (8) in 1882 but it was not until 1929 that Lucas and Henderson (16) reported its anesthetic properties.

The pure cyclopropane has a pungent, sweetish, but not unpleasant odor similar to a mixture of chloroform and ethylene. The pungency is sufficiently marked to cause a laryngospasm if gas of high tension is forced upon an individual even though unconsciousness has been produced with another agent. It is a very inert gas with a molecular weight of 42.05 and density of 1.46 compared with air. It is, therefore, heavier than ethylene, density 0.975, and lighter than ether, density 2.60. Twenty-eight grams or one ounce of cyclopropane is equivalent to approximately sixteen liters or four and one-half gallons of the gas at atmospheric pressure. The gas is liquified at a pressure of seventy-five pounds per square inch and is capable of compression in steel cylinders without polymerization or other known chemical change.

Lucas and Henderson (16) found that 1 cc of olive oil (sp. gr. 0.920) would dissolve 10.35 cc of cyclopro-

pane, while 1 cc of water would dissolve approximately 0.160 cc of cyclopropane. This made an oil to water ratio of 64.4 to 1 at 35° C. For ether, the oil to water ratio is 2.5 to 1; for nitrous oxide, 2.8 to 1; and for ethylene, 13.2 to 1. However, Robbins (21) found that 100 cc of water dissolved 20.8 cc of cyclopropane and explained the difference as probably being due to two factors: First, that the gas used by Lucas and Henderson was not pure, and second, that they may have failed to consider the volume occupied by the water vapor.

Orcutt and Seevers (17) reports the accepted oil-water coefficient at 37.5° C. as being 34.3 to 1 instead of 64.4 as reported by Lucas and Henderson. This characteristic explains the slowness with which complete saturation and stabilization with the gas is obtained in the body.

Cyclopropane in concentrated form causes deterioration of rubber if left in contact with it for any length of time. Therefore, any machine used for the administration of this gas should have all metal valves. This solvent property for rubber is not manifested in the low concentration in which the gas is present in the anesthetic mixture.

Table I represents the explosibility of cyclopropane in oxygen mixtures as found by Stiles, Neff, Rovenstine, and Waters (29).

Explosibility of Cyclopropane in Oxygen Mixtures.

Oxygen	Cyclopropane	Results
20%	80%	No explosion
25	75	No explosion
29	71	Mod. explosive
34	66	Very explosive
73	27	Very explosive
75	25	Mod. explosive
80	20	Mildly explosive
81	19	No explosion

TABLE I. Explosibility of cyclopropane as reported by Stiles, Neff, Rovenstine, and Waters (29).

However, Eversole, Sise, and Woodbridge report the lower limit of explosibility of cyclopropane and oxygen at 2.5 per cent while the upper limit is 50.0 per cent. On the other hand, the lower limit of explosibility of cyclopropane and air is 3.0 per cent

while the upper limit is 8.5 per cent. These latter figures more closely simulate those of others (4). It is evident, therefore, that the average anesthetic mixture (about 15 per cent) is well within the explosive range, but, its explosibility is much less than that of ethylene or of a nitrous oxide-oxygen-ether mixture. When cyclopropane is administered by the closed circuit method the danger of explosion with ordinary precautions is negligible. Griffith (10) does not hesitate to use a cautery or an electric knife at any time. However, as an added precaution, it is generally advised that high potential electrical equipment such as diathermy and X-ray should not be used during the administration of cyclopropane anesthesia.

Lucas and Henderson (16) found that the toxicity of cyclopropane in animals varied with the sample of trimethylene bromide used in its preparation. One sample was water clear and ninety per cent distilled between 161 to 163° C. Another sample was yellowish in color, began to distil at 110° C. and distillation was not complete at 170° C. Only about sixty per cent distilled between 161 to 165° C. Cyclopropane prepared from this source caused the blood pressure to fall more after deep surgical anesthesia and salivation was more marked.

Cyclopropane prepared from a third source of trimethylene bromide required higher percentages to produce anesthesia. Blood pressure was at no time high and tended to fall to half its normal value at deep surgical levels. Also, considerable tracheal mucus was produced, as well as an increased flexor tonus in the hind limbs.

At the present time, 99.5 per cent pure cyclopropane may be obtained which gives uniform results and may by used with safety for long periods of time. However, it is of sufficient toxicity to cause circulatory death, even in the presence of adequate oxygen.

The time required for induction of anesthesia with cyclopropane is usually longer than for ethylene or nitrous oxide, but less than for ether. If the concentration is raised very rapidly, induction can be somewhat hastened. As a rule, a minimum of struggling occurs, and in ordinary concentrations (up to twenty-five to thirty per cent) there does not appear to be much irritation of the upper respiratory tract. There is an increase both of mucus and serous secretion, but less than with ether. During anesthesia with high concentrations of the gas, fibrillary twitchings of the tongue and small muscles of the neck are characteristic. The uniformity of this sign makes it possible to predict

with reasonable certainty that a slight increase in concentration of the gas will result in cardiac irregularities.

EFFECTS ON METABOLISM

Research workers in the field of anesthesia have shown by chemical analysis of the blood and urine before and after anesthesia that there is practically always some metabolic disturbances. The changes which usually occur are increase in acidity of the blood, a decrease in alkali reserve and an increase in blood sugar.

With chloroform and ether these changes are very marked. With ethylene, if adequate oxygen is not administered, there is a marked increase in the acidity and a decrease in the carbon-dioxide-combining power of the blood.

Lucas and Henderson (16) ran blood analyses on cats and rabbits very deeply anesthetized with cyclopropane and found that there was a slight rise in the pH (7.55 to 7.35) and the carbon-dioxide-combining power, with but little change in the blood sugar. These figures were more nearly normal than when other anesthetic agents were used, and they explained the changes as probably being due to the decreased ventilation and the forced breathing of the animal owing to the inertia of the recorder.

Figure 2, (33) shows the average determinations for carbon-dioxide-combining power, sugar, and non-protein nitrogen, before, at the end of, and four hours after

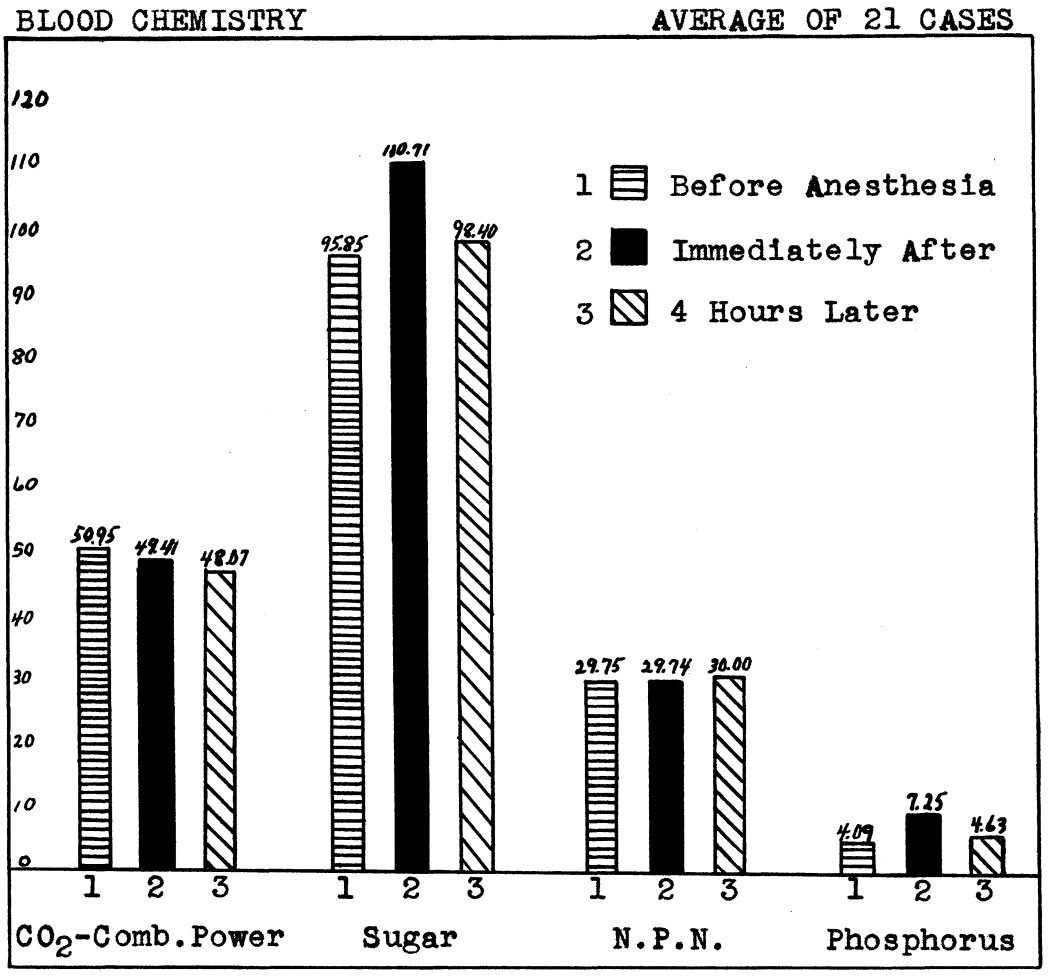


Fig. 2. Average determinations of CO_2-combining power, sugar, N.P.N. and phosphorus in the blood taken from patients before, at the end of, and four hours after operation under cyclopropane anesthesia.

anesthesia in twenty-one cases anesthetized with cyclopropane. Blood phosphorus changes from four cases are also represented, showing a marked increase and a quick return to normal. This compares with the study of phosphorus during anesthesia with other agents and is due to the liberation of phosphorus from the muscles.

Little change in the number of red blood corpuscles is noted before, during, and after cyclopropane anesthesia. However, as with ether and other inhalation agents, a marked leukocytosis occurs, the maximum change being found from the third to the sixth hour after operation. In the average case, this increase is from two to three times the preoperative count. Twenty-four hours postoperatively the white blood count returns to about one-half the maximum, and a normal count is reached on the third or fourth postoperative day. Polymorphonuclear cells are always distinctly increased in the differential count.

Patients under cyclopropane, as with other gas anesthetics, seem, at times, to bleed more profusely. This observation perhaps is partly fallacious because of the bright color of the blood due to an excess of oxygen. Nevertheless, the amount of bleeding from the capillary bed during operation is of interest to the surgeon and is difficult to evaluate. Work has been done showing that other factors such as oxygen and carbon-dioxide content of the blood are more important than the anesthetic agent in influencing wound bleeding. Waters and Schmidt (33) report the reactions of nine surgeons in regard to wound bleeding while using cyclopropane anes-

thesia at the Wisconsin General Hospital. Eight of these surgeons made no comment that more wound bleeding occurs, while one of them was positive that there was increased bleeding. However, on several occasions the comment from the latter source was offered that bleeding was excessive when the agent was ether or nitrous oxide but believed to be cyclopropane. There was no complaint from fifty-four different surgeons using cyclopropane in Griffith's (10) series of three hundred and fifty cases.

Dr. John Urner (11) at the Minneapolis General Hospital kept an accurate record of blood loss in his Obstetrics for the past six years. He found that the percentage of blood loss was about the same with cyclopropane as with ether, ethylene and nitrous oxide.

Observations of coagulation time were made in the twenty-one cases represented in Figure 2 before, during the second one-half hour, and one hour following cyclopropane anesthesia but no significant change was noted. Griffith (10) states that there is more of a tendency to capillary oozing than with ether and explains this as being due, probably, to some effect on the vasomotor control of the arterioles and not caused by any chemical change in the blood or alteration in coagulability.

Respiration during the third stage of cyclopropane anesthesia is remarkably regular. There is no marked diminution in minute volume exchange until intercostal activity is interfered with. The primary effect on the respiration is one of diminished respiratory amplitude rather than rate. The respiratory stimulation during induction with this drug is so much less than with the common inhalation agents that the impression may be gained of severe respiratory depression. After morphine, cyclopropane further diminishes the already slowed rate and decreased amplitude of respiration. When the concentration of the gas is sufficient to produce intercostal paralysis, a very slight increase will effect complete respiratory arrest.

Kidney output is depressed, or an actual suppression occurs during anesthesia with a compensatory increased excretion several hours following anesthesia. This effect, however, is similar to that caused by ether and ethylene and is not more marked.

Raginsky and Bourne (20) studied the effects of cyclopropane on the liver of normal dogs, dogs suffering from chloroform poisoning and starved dogs. Dog number one was a normal dog, anesthetized with cyclopropane for one hour daily for nine days. On the tenth

day the liver was removed and sent to the Pathological Institute of the Royal Victoria Hospital. The following report was received: "Grossly, a normal dog's liver and gall-bladder. The only noteworthy histological changes are circulatory in character. They consist of a moderate dilatation of the intercolumnar capillaries and edema of the parenchyma. This expresses itself as an hydropsical swelling of the hepatic cells, most noticeable about the central veins. There is no cellular exudate. There are no fatty degenerative changes."

They also found that cyclopropane did not interfer with, or impede, the recovery of liver function from chloroform poisoning. Other dogs, after starvation for three to four days consecetively, showed a normal functioning liver twenty-two hours after cyclopropane had been administered for three hours.

Waters and Schmidt (33) report the findings of electrocardiographic tracings obtained before, during induction and every five to twenty minutes throughout five celiotomies of more than one hour duration, using cyclopropane anesthesia. Anesthesia was carried to plane three in three of the cases and to stage four in the other two. Four of these patients showed no electrocardiographic changes from normal other than a mod-

erate slowing of the heart rate. In one case during a two-hour pelvic operation there was evidence of transient heart block in lead II. After one and one-half hours operating and with stage four anesthesia, the tracing showed an inverted diphasic P wave and a shortened PR interval. Ventricular extrasystoles were noted. However, fifteen minutes later the tracings were normal.

Cardiac arhythmias usually begin to manifest themselves just about the time respiration ceases. If artificial respiration is instituted when respiratory paralysis is imminent, the concentration of cyclopropane may be raised to a much higher level before the heart is effected. In dogs under artificial respiration, cardiac arhythmias first began to appear when the cyclopropane concentration reached 26.6 to 72.0 per cent, with an average of 46.8 per cent (27).

The type of early arhythmia is usually nodal rhythm or ventricular extrasystoles, although partial or complete A-V block is not uncommon. Later effects consist in ventricular tachycardia, auricular and ventricular fibrillation. The heart rate under cyclopropane seems generally, if not invariably, to be under the normal resting rate.

Seevers, Meek, Rovenstine, and Stiles (27) think

that irregularities in heart beat with the lower concentrations of cyclopropane may be of vagal origin since they were, in three dogs, abolished by intravenous atropine. Ventricular extrasystoles appeared at a concentration of fifty-six per cent cyclopropane but disappeared with the injection of atropine and did not recur until a concentration of sixty-seven per cent was reached. In another case ventricular rhythm developed with twenty-seven per cent cyclopropane. Following atropine, a concentration of seventy-two per cent was reached without a return of any arhythmia.

Figure 3 (14) represents graphically the relative incidence of extrasystoles of various origins, displaced pacemaker, and sinus arhythmia with respect to the anesthetic agent employed in one-hundred and thirteen surgical anesthesias. The following anesthetic agents were used in making this study: Cyclopropane in forty-one cases, ether in twenty, procaine in thirteen, ethylene in eleven, nitrous oxide in ten, vinyl ether in seven, chloroform in six, and tribrom-ethanol in five. However, the latter three agents are not represented in the graph.

Cyclopropane was the anesthetic of choice in many of the poorer risks which consisted of hypertension or heart lesions. Twenty-three of the forty-one cases

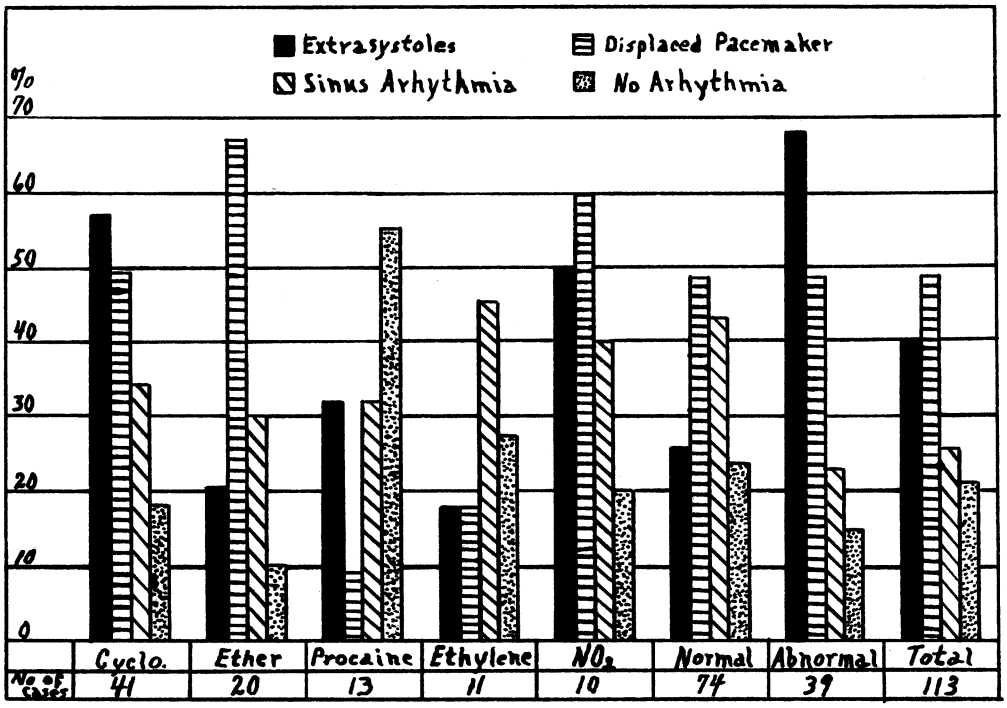


Fig. 3. Percentage incidence of extrasystoles, displaced pacemaker, and sinus arhythmia with respect to various anesthetic agents and presence or absence of heart disease.

operated on under this agent had some form of cardiovascular disease, while the remaining nineteen were apparently normal in this respect. In every instance an electrocardiogram was taken the night before operation, after preoperative medication with morphine and scopolamine, during operation, at the end of the operation as the patient was "coming out", and about ten hours following the operation. Twenty-five to forty-five electrocardiograms were taken during each operation.

The solid black bar indicates the percentage of the

total number of cases under each anesthetic that exhibited any type of extrasystole during the period of anesthesia. Displacement of the pacemaker downward to the auricle, auriculoventricular node or ventricle is designated by the second bar in each case, while the third represents the incidence of sinus arhythmia. The fourth bar indicates the percentage of cases in which no arhythmia occurred during the procedure.

Extrasystoles showed a definite tendency to constitute the predominating form of arhythmia in the patients with abnormal hearts, and this was a factor in the high percentage of the cyclopropane series exhibiting this type of disturbance, since more than half of these had demonstrable cardio-vascular disease. In the other groups, which were predominantly composed of normal hearts, extrasystoles played a less prominent role. The ether cases showed an unusually high incidence of downward displacement of the pacemaker, and in only twenty per cent were extrasystoles found. Displacement of the pacemaker was a prominent feature also of nitrous oxide and cyclopropane but was rarely present under procaine. The preoperative condition of the heart was apparently not a factor in this disturbance, as it occurred with equal frequency in both the normal and the

abnormal hearts. Sinus arhythmia appeared with considerable frequency under all anesthesias, particularly ethylene and nitrous oxide, but showed a definite predilection for the normal as compared with the abnormal hearts.

With the exception of procaine, the proportion of cases in which no arhythmia occurred was below thirty per cent for each anesthetic. Only ten per cent of the ether and eighteen per cent of the cyclopropane cases escaped. The procaine group is conspicuous for its freedom from irregularities, with fifty-four per cent showing no gross changes. In comparing the normal and abnormal hearts, the former fared somewhat better, although the difference was not great. Of the entire series, only about one-fifth of the cases maintained normal rhythm throughout.

ADMINISTRATION

Since anesthetic mixtures with cyclopropane all fall directly in the explosive range, adequate precautions should be taken to prevent explosion. The most important of these is the administration of the anesthetic by an entirely closed system, which of course necessitates the carbon-dioxide absorption technique, (Woodbridge, 36). Extreme care should be taken with each case to insure the absence of any leak in the system.

The maintenance of relative humidity of fifty-five per cent or more in the operating room is a valuable precaution against the danger of ignition by static charges of electricity. High frequency electrical apparatus should not be used in the operating room in which cyclopropane is being administered. This, of course, includes X-ray apparatus as well as electrosurgical units both for cutting and coagulation. On the other hand, however, the low voltage actual cautery is not looked upon as being a source of danger if used at considerable distance from the face of the patient and when a vertical screen is placed between the mask and the field of operation (7).

There are perhaps as many variations in the technique of induction of cyclopropane anesthesia as there

are users of the gas. However, the technique generally employed is as follows: A very rapid flow of oxygen (eight to ten liters per minute) is started into the mask as it is placed on the patient's face and continued until the mask, canister and bag are sufficiently filled to accommodate completely the patient's tidal excursion. At the same time, cyclopropane is introduced at a rate of six hundred to seven hundred cubic centimeters per minute, in average cases, and continued for from thirty seconds to two or three minutes. The addition of cyclopropane is then stopped completely and the oxygen flow set at the metabolic requirement (usually two hundred to four hundred cubic centimeters per minute). The soda-lime is excluded from the breathing circuit until breathing becomes sufficiently stimulated to indicate an accumulation of carbon-dioxide.

An interval of several minutes must intervene before complete distribution to the tissues takes place and maximum narcotic effects result. In certain resistant individuals it may be necessary to give the gas for a few seconds at a more rapid rate, and in some very susceptible ones, or those heavily dosed with pre-operative medication, a slower flow during induction is indicated.

During the period of maintenance an air-tight contact

of the mask on the face simplifies a smooth anesthesia. A constant slow flow of oxygen should be added, approximating as nearly as possible the metabolic demand of the patient, varying usually between two hundred and four hundred cubic centimeters per minute. If physical signs indicate that the degree of narcosis resulting from the mixture originally used to fill the mask, canister and bag is insufficient, the flow of cyclopropane may be resumed for a time sufficient to enrich the mixture properly. If, on the other hand, the degree of narcosis is too profound, a rapid addition of oxygen for a brief period will reduce the potency of the mixture inhaled.

Pharyngeal airways are frequently used for the maintenance of unobstructed respiration. However, lately, the intratracheal method of administration has been introduced (15) and seems to be the most scientific method of administration.

The signs of the depth of anesthesia with cyclopropane are practically the same as with ether. The principal difference noted being a roving eyeball, usually into the second plane of the third stage, and occasionally even into the third plane. Other than this, the signs of anesthesia conform to those noted when other

agents are used.

The disappearance of the lid reflex, used to determine the degree of narcosis below which there is no pain perception, is reliable. In the first plane of the third stage of anesthesia, the patient shows retained extra-ocular muscle activity. As the narcosis deepens and he reaches the second plane, movement of the eyeball ceases, but both the diaphragm and intercostal muscles maintain their normal share of the load of respiration. As the depth of anesthesia increases still further, intercostal activity lessens, is delayed and finally ceases as the patient passes into the third plane, characterized by diaphragmatic breathing only. Diaphragmatic breathing in plane three, however, is not exaggerated during cyclopropane anesthesia as it is with ether. While the patient is passing down through this plane, depression simply increases until complete respiratory paralysis is reached. When respiration ceases, the patient is considered in the fourth stage of narcosis.

Thus, the entire field of anesthesia from a patient awake to a patient in obliterative narcosis, as represented graphically by Romberger (22) in Figure 4, is covered by three phases: Induction (A), moderate anesthesia (B), and deep anesthesia (C).

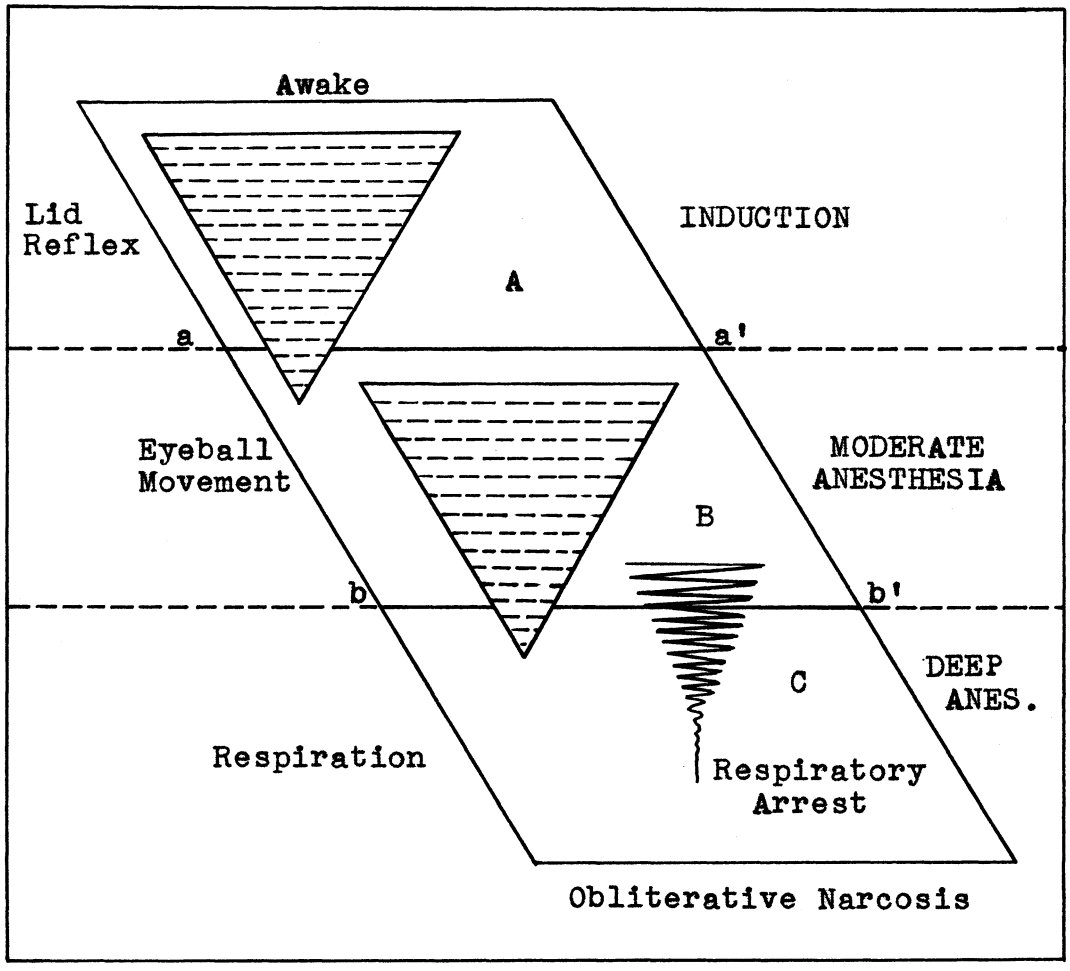


Fig. 4. Signs and Phases of Cyclopropane Anesthesia.

In phase A (induction) watch the activity of the lid reflex. When it slows to the point of absence (a-a'), pain sensation disappears and early (light) anesthesia begins. During phase B (moderate anesthesia) watch the eyeball. As its oscillation becomes less and less, to the point of cessation, central fixation (b-b'), deep anesthesia begins. During phase C (deep anesthesia) it

becomes necessary to observe the respiratory rate and the tidal amplitude. Respiration, regular and machine-like in its rhythmicity, becomes quite shallow, and it continues to become more and more shallow and less and less frequent until it finally ceases. At this point, under a proper technique, the patient is still very pink and the pulse usually unaffected. On lessening the cyclopropane percentage (increasing the oxygen supply) and with slight help by pressure on the breathing bag, respiration is spontaneously resumed.

Cyclopropane possesses two properties that are responsible for differences in physical signs and necessitate different interpretations from those commonly accepted for the older anesthetic agents. First, although a gas like nitrous oxide and ethylene, cyclopropane is of the potency of chloroform and ether, but without their irritant qualities. Consequently, an extremely high concentration can be inhaled without producing laryngospasm, the normal physiologic protection from a sudden and extreme increase in dosage. Lacking this protection, the anesthetist must guard against rushing the patient rapidly from one degree of narcosis to another and not allowing sufficient time for circulatory distribution and maximum effect of one

concentration with full development of the physical signs characteristic of that dose. Second, cyclopropane is not a respiratory stimulant. As commonly administered, ether, nitrous oxide, and ethylene, on the other hand, always tend to produce an initial increase in rate and minute volume respiration. Cyclopropane, if administered with oxygen as a vehicle and without carbon-dioxide excess, may result in no change in respiratory rate or minute volume until depressive doses are reached. The high oxygen concentration used may even result in reduced minute volume in the early stages of administration.

The pupils dilate sluggishly in morphinized patients and the sign is of little value. Color cannot be used as an indication of the degree of narcosis or of danger because an excess of oxygen should be present and the patient decidedly pink at all times. The most valuable signs that the limit of tolerance has been reached are changes in the character of the pulse. Arhythmia, slowing of the rate to fifty or less, or a definite increase in rate demands a reduction in gas concentration. It should be noted, however, that the pulse rate is not usually increased by cyclopropane and that the rate in a normal individual with moderate premedication is between

sixty and seventy per minute. Inflation of the lungs with oxygen is indicated if such pulse changes occur when respiration is decidedly depressed.

The effect of preanesthetic narcotics is to contract or flatten out each phase and to have them blend into each other more quickly. This is especially noted in phases A and C in Figure 4; the patient is surgically asleep markedly quicker, and the respiratory arrest comes on much earlier. However, preliminary morphine and basal narcosis tends to stabilize and render the oncoming signs of cyclopropane anesthesia more readable.

Morphine, grains 1/8 to 1/4, and scopolamine, grains 1/200 to 1/100, are used most frequently for preanesthetic medication. Griffith (10) uses a small rectal dose of avertin (seventy to one hundred milligrams per kilogram of body weight) in combination with cyclopropane for major surgery and finds this combination the nearest approach we have yet made to the "ideal anesthetic". He finds that there is no depressing effects from this drug and that it is especially useful for nervous children.

Narcosis may be produced when cyclopropane is inhaled in a concentration as low as four per cent. It is therefore evident that anesthesia by inhalation of this agent may be effected with air as a vehicle. Insuffla-

tion into the pharynx of cyclopropane at a rate of from two hundred to eight hundred cubic centimeters per minute has maintained satisfactory anesthesia for abdominal surgery. The carbon-dioxide absorption technic, however, has proved more satisfactory.

Waters and Schmidt (33), using 1/8 to 1/4 grain morphine and 1/200 to 1/100 grain scopolamine for preanesthetic medication, administered hypodermically one and one-half hours before induction, showed the concentrations of cyclopropane found by analysis of the mask contents for each degree of narcosis. Figure 5 is a graphic compilation of forty-six cases which were selected in making this study. In the upper circles are shown the maximum percentages found in any one sample, in the middle circles the minimum, and averages for all analyses in the lower circles. It will be seen that the average concentration of cyclopropane for the first plane, third stage anesthesia (roving eyeball) was 7.4 per cent, while the second plane (fixed eyeball, sufficient for the majority of abdominal operations) required an average of 13.1 per cent, and the third plane with intercostal paralysis, required an average of 23.3 per cent. Fourth stage anesthesia, or respiratory arrest, was produced with an average concentration of 42.9 per

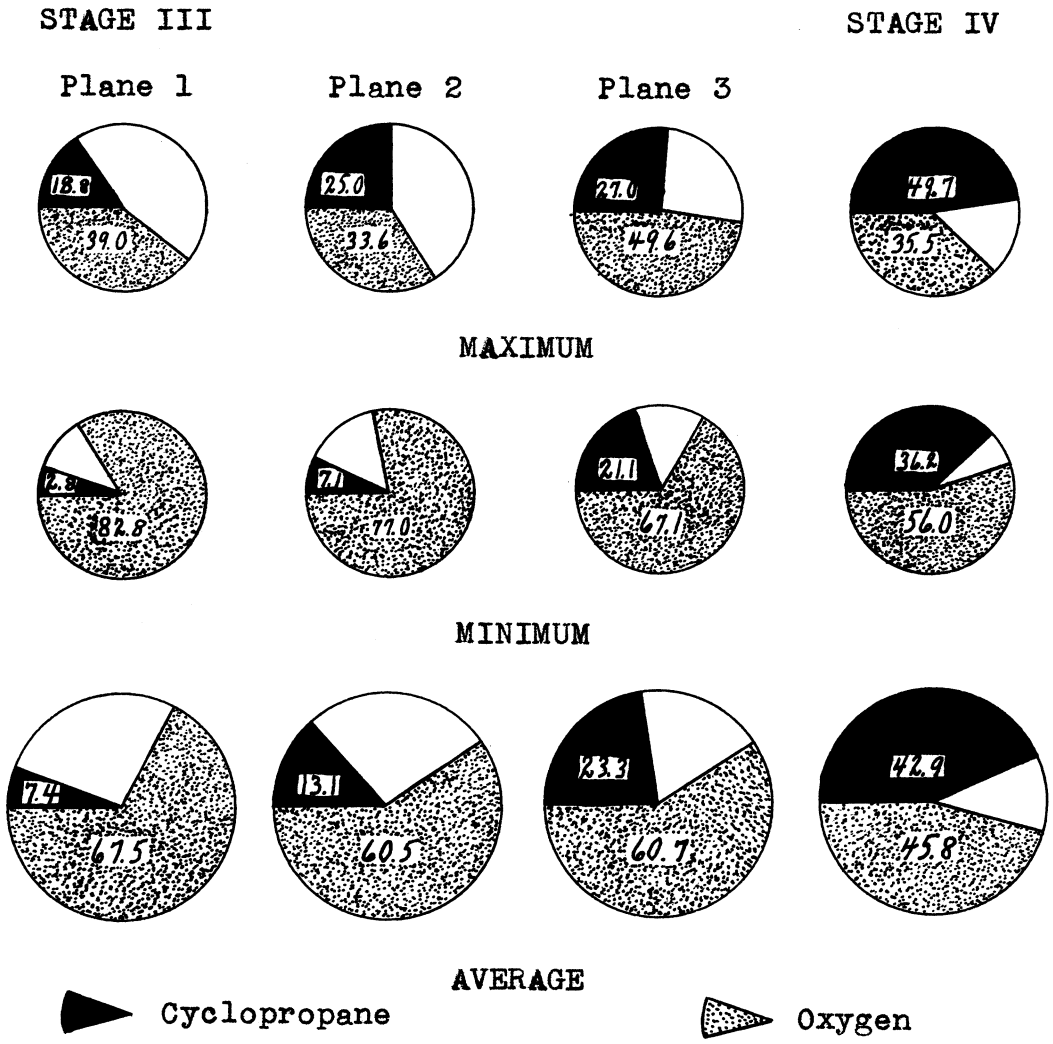


Fig. 5. Gas analyses of mask samples from forty-six cases taken during the various planes of surgical anesthesia and during the fourth stage (respiratory arrest). Upper circles show maximum cyclopropane concentration, middle circles show minimum, and the lower circles show the average percentage for each degree of narcosis.

cent. It will also be noted that the oxygen content always exceeded twenty per cent.

Patients anesthetized with cyclopropane exhibit relaxation comparable to that obtained in all stages of

ether anesthesia. Out of four hundred forty-seven cases reported by Stiles, Neff, Rovenstine and Waters (29) in only two, where relaxation was required, was it impossible to obtain it satisfactorily. In one of these it was obtained with ether only after apnea was reached.

Cyclopropane is more flexible than ether and consequently the depth of anesthesia can be regulated much more quickly. Usually it requires only four to five minutes for a patient in the second plane of surgical anesthesia to fully regain consciousness. Occasionally recovery is even more rapid than this, and in the occasional case may take as long as ten to twelve minutes. Apparently very little of the drug is retained in the body after administration has been discontinued, and the patient once awake remains awake. If the mask is suddenly removed while the patient is inhaling a full anesthetic concentration of cyclopropane, he will sometimes pass through a period of excitation, lasting from a few seconds to three or four minutes, and usually manifest by purposeless movements of the arms and head. This may be avoided by a gradual decrease in the concentration of the gas toward the end of the operation, and in most cases will result in a more nearly normal awakening.

Table II shows the rapidity of elimination of cyclopropane in dogs as found by Robbins (21). In each case the inspired mixture was maintained at twenty-five to thirty per cent.

Time A.M.	Condition of Dog	Milligrams C_3H_6 Per 100 cc Venous Blood		
		Dog 1	Dog 2	Dog 3
10:00	Deep Anesthesia	20.5	20.3	20.0
10:14	" "	23.7	22.3	18.5
10:15	C_3H_6 Stopped			
10:17	Moving Head	6.3	7.1	10.0
10:20	Awake	4.7	4.7	7.9
10:25	"	2.6	4.4	4.7
10:30	"	1.6	2.6	2.9
10:45	"	0.8	1.6	2.1
11:00	"	- -	- -	1.6
11:15	"	0.8	1.3	1.3
11:45	"	- -	1.0	1.0
12:15	"	0.0	0.8	0.5

TABLE II. Rate of elimination of cyclopropane from dogs anesthetized for two to three hours.

Patients who have had both ether and cyclopropane on different occasions usually prefer the latter, in fact they note but little difference between cyclopropane and nitrous oxide or ethylene in so far as induction and recovery are concerned.

Cyclopropane may be used in combination with ether, chloroform, vinethene, ethylene, nitrous oxide, or evipal, without any incompatibilities.

POSTOPERATIVE MORBIDITY

Waters and Schmidt (33) report the postoperative morbidity following six hundred cases each of anesthesia with ether, cyclopropane and ethylene for extra-abdominal surgery, and four hundred cases each of anesthesia with ether and cyclopropane for abdominal surgery as follows:

	Ether	Cyclopropane	Ethylene
Respiratory	8.8%	8.6%	11.0%
Circulatory	5.3	7.7	5.6
Genito-urinary	5.3	5.7	5.8
Gastro-intestinal	5.7	5.9	5.7
Central Nervous system	3.4	4.3	4.3
Nausea and Emesis	40.9	40.3	30.0

TABLE III. Postoperative morbidity following 600 cases each of anesthesia with ether, cyclopropane, and ethylene for extra-abdominal surgery.

	Ether	Cyclopropane
Respiratory	17.5%	9.0%
Circulatory	9.3	12.3
Genito-urinary	23.5	13.3
Gastro-intestinal	34.8	30.3
Central Nervous system	6.3	3.8
Nausea and Emesis	56.3	46.5

TABLE IV. Postoperative morbidity following 400 cases each of anesthesia with ether and cyclopropane for abdominal surgery.

Nausea and emesis following anesthesia with cyclopropane for operations outside the abdominal cavity were similar to that following ether and decidedly more frequent than following ethylene, although distinctly less severe. Following abdominal operations, nausea and

emesis were less frequent and less severe than after ether. Pneumonia did not occur after cyclopropane in the extra-abdominal group, and massive collapse was less frequent. The incidence of pneumonia following abdominal operations under cyclopropane was less than one-third that after ether. Lung collapse was also distinctly less frequent. Tachycardia, a severe drop in blood pressure, or shock occurred distinctly more frequently after cyclopropane than following other agents. However, myocardial degeneration had been recorded preoperatively in more than twice as many of the extra-abdominal cases in which cyclopropane was used as of those in which the other two agents were administered.

Later Schmidt and Waters (25) reported the postoperative morbidity in twenty-two hundred cases anesthetized with cyclopropane as compared with twenty-two hundred cases anesthetized with nitrous oxide, ethylene, or ether.

In Table V is shown the postoperative respiratory morbidity in each group expressed in percentage incidence of each complication. Total percentage complications do not represent the percentage of patients involved, since one patient may have had several complications. In general, it will be seen that there has occurred a slightly

though definitely greater incidence of respiratory damage in the group anesthetized with nitrous oxide, ethylene, or ether.

Respiratory - Postoperative Complications in 4400 Clinical Inhalation Anesthesias

	Cyclopropane	Other Agents
Cases	2200	2200
Complications:		
Pneumonia	0.26%	0.64%
Collapse	0.18	0.58
Laryngitis	2.10	5.13
Cough, slight	4.00	3.60
Cough, severe	0.72	1.90
Hiccough	0.31	0.45
Others	0.31	0.62

TABLE V. Percentage of postoperative respiratory complications in 4400 cases anesthetized by the same technique, expressed in percentages of total cases for each group. One-half of the cases given cyclopropane are compared with the other half who were given nitrous oxide, ethylene, or ether.

In Table VI is shown the comparative postoperative circulatory morbidity. Again total percentage of complications does not refer to patients, and many patients had two or more complications. The figures here show a definite advantage in favor of nitrous oxide, ethylene and ether. This, however, does not show that there is more circulatory damage from the use of cyclopropane than from the nitrous oxide-ethylene-ether group. Be-

cause cyclopropane gives freedom from oxygen deprivation during anesthesia, it was the agent of choice in many cases giving evidence of circulatory handicap before operation.

Circulatory - Postoperative Complications in 4400 Clinical Inhalation Anesthesias

	Cyclopropane	Other Agents
Cases	2200	2200
Complications:		
Tachycardia	4.60%	4.10%
Bradycardia	0.45	0.27
Severe Drop of B.P.	5.20	3.20
Shock	0.54	0.13
Fibrillation	0.09	0.09
Heart Block	0.04	0.04
Others	0.48	0.39

TABLE VI. Percentage of postoperative circulatory complications in 4400 cases anesthetized by the same technique, expressed in percentages of total cases for each group. One-half of the cases given cyclopropane are compared with the other half who were given nitrous oxide, ethylene or ether.

In Table VII is shown the comparative incidence of postoperative nausea and emesis occurring in the two groups. Here the difference is slight, though definitely favorable to cyclopropane. It will be noticed that in the classifications "More than one day, severe" and "After the third day", the advantage is with the cyclopropane group.

Nausea and Emesis - Postoperative Complications in 4400 Clinical Inhalation Anesthesias

	Cyclopropane	Other Agents
Cases	2200	2200
Complications:		
Nausea only	5.80%	4.90%
Nausea and emesis:		
Operative day only	19.50	21.80
1-3 days post oper.	5.65	6.90
After 3rd day	0.63	0.72
1st day severe	0.36	0.36
More than 1 day severe	0.22	0.41
None	68.08	64.90

TABLE VII. Percentage of postoperative nausea and/or emesis in 4400 cases anesthetized by the same technique, expressed in percentages of total cases for each group. Trivial as well as serious morbidity is detailed and compared for the two groups.

In Table VIII is shown an analysis of the deaths occurring in the forty-four hundred cases. This table is self-explanatory except for the deaths from anesthesia. The one death under cyclopropane was a sequel to the aspiration of vomitus during anesthesia in a case of intestinal obstruction. In the other group, the two deaths were due to faulty technique in administering nitrous oxide and ether, and was not due to the anesthetic.

Morgan, Eaman and Griffith (17), in Table IX, show the postoperative complications following cesarean section. They also found that patients anesthetized with

Postoperative Deaths in 4400 Clinical Inhalation Anesthesias

	Cyclopropane	Other Agents
Cases	2200	2200
Total Deaths	94	87
Mortality Per Cent	4.19%	3.99%
Time of Death:		
Day of operation	0	2
1st day postoperatively	6	6
2nd to 3rd day P.O.	20	12
4th to 7th day P.O.	11	22
2nd week	18	14
Later	39	31
Cause of Death:		
Pneumonia	5	14
Other Respiratory	3	6
Hemorrhage	7	2
Other Circulatory	14	9
Toxemia	32	22
Carcinoma	17	15
Shock	3	2
Anesthesia	1	2
Others	12	15

TABLE VIII. Deaths following 4400 operations are analyzed and compared as to cause and time of death in the two groups.

	No. of Cases	Vomiting None	Slight	Severe	Maternal Deaths
Ethylene-Ether	100	58	23	17	2
Cyclopropane	100	89	10	1	0
		Abdominal Distention			
Ethylene-Ether	100	36	38	24*	2
Cyclopropane	100	79	19	2	0

TABLE IX. Postoperative Complications following Cesarean Section using Ethylene-Ether and Cyclopropane Anesthesia. * 7 of these cases progressed to a dynamic ileus.

cyclopropane required an average of three days less hospitalization than those of the ethylene-ether series.

In order to show the effects of prolonged anesthesia, Schackell and Blumenthal (24) subjected a monkey to five uninterrupted anesthesias, over a period of ten days, ranging in duration from 5.2 to 6.7 hours each. The cyclopropane concentrations ranged from 13.7 to 20.0 per cent. Similarly, within a period of twelve days another monkey with advanced pulmonary tuberculosis was subjected to five anesthesias lasting from 6.0 to 6.3 hours each, at cyclopropane concentrations from 15.3 to 19.4 per cent. In each case the heart rate was decreased as the oxygen concentration was increased, and consciousness was regained within one to three minutes after removal of the mask.

In the course of one month, the monkey which was in an advanced stage of pulmonary tuberculosis underwent seven cyclopropane anesthesias of an average duration of 5.8 hours each. For nearly one-fourth of this total time of anesthesia the tension of cyclopropane ranged from sixty to one hundred per cent above that required for surgical anesthesia. In the final one of these anesthesias, the animal died after withstanding for one and one-half hours a cyclopropane tension of thirty-two

per cent. Post-mortem examination revealed that approximately three-fourths of the right lung was consolidated or caseous, and the left lung contained numerous tubercles, but no consolidation. It is interesting to note that the contents of the abdominal cavity were negative.

SPECIAL INDICATIONS

Thoracic surgery: Here the high oxygen supply is a great advantage. These patients almost always have a lowered vital capacity. The position during operation and the release of negative pressure in the chest often put them to a great disadvantage in breathing. The power of the anesthetic is of value in overcoming the marked reflexes which often arise from stimulation of the pleura. The quiet breathing is a help to the surgeon in his work. Reflexes are present at once and the patient ordinarily responds to spoken requests to cough, expectorate, and so forth, in a very few minutes after removing the face mask.

Respiratory obstruction: Here the high oxygen supply is also of value.

Marked anemias: The advantage of the high oxygen supply is evident.

Cardiac cases: Here again the high oxygen supply appears advantageous, especially where decompensation is present. Because of its deleterious action in high concentrations on the heart muscle, cyclopropane might not be so advantageous as some other anesthetic in operations demanding considerable depth of anesthesia. But in all other cases, where marked depth is not necessary, the high oxygen supply, the quiet breathing, and the

comparative lack of stimulation to the pulse and blood pressure more than compensate for the possibility of deleterious action.

States of marked debility and shock: The advantages and qualifications are very similar here to those already discussed for cardiac cases.

Hyperthyroidism: The increased metabolic rate of these patients makes quite obvious the advantage of an anesthetic agent which insures an abundant oxygen supply at all times.

Short procedures where a moderate amount of relaxation is desirable: This would include, for example, pelvic examinations, simple reduction of fractures, and manipulations of joints.

Adjuvant to other general anesthetics: Cyclopropane may supplement either ethylene or nitrous oxide when either of these agents is not sufficiently potent to maintain adequate depth of anesthesia without anoxemia.

Supplement to spinal anesthesia: There are many conditions which may arise during the course of spinal anesthesia in which cyclopropane is of great value. It has proven of value where there is an insufficient sensory effect, insufficient duration, and retching and

vomiting during the course of anesthesia.

Diabetics: In these cases cyclopropane does not increase the conversion of liver glycogen nor hamper the kidney's excretion of sugar, acetone or diacetic acid (11).

Obstetrics: Bourne (3) uses cyclopropane to produce intermittant analgesia as indicated for the more severe labor pains, and maintain anesthesia for delivery procedures. He found that satisfactory analgesia was easily produced when very small quantities of cyclopropane were inhaled with oxygen, that uterine contractions were not inhibited, and that during anesthesia any required degree of muscular relaxation could be obtained without evident harm, and recovery was devoid of untoward effect to mother or child. Uterine tone is well maintained during cyclopropane anesthesia and there has been less post partum bleeding in Griffith's (11) series of one hundred and forty-seven operative deliveries than when any other anesthetic agent was used.

Neurological, severe cardiac, arteriosclerotic, tuberculous and jaundiced patients all seem to do well following cyclopropane administration. It may be used in all ages of patients and has been used on babies ten days old and on patients eighty-five years old.

COST OF ANESTHESIA

Although the cost per gallon of cyclopropane seems quite high, the actual cost per anesthesia is very low. At first the cost of the gas was $1.25 per gallon, however, the cost has since been reduced to about thirty cents per gallon.

In the average adult, if the mask is tight fitting and the closed system does not leak, it is usually possible to produce third stage anesthesia of an hour's duration with approximately a gallon of the gas. In resistant cases, two to three gallons may be necessary. In a number of cases less than one-half gallon has been sufficient. This brings the expense within reasonable limits and well under the cost of gas anesthesia with the older agents, and methods.

Whether cyclopropane will prove to be a distinct contribution or a mere addition to the long list of discarded drugs, only time can tell. At the present time, however, it is generally felt that cyclopropane may become a very valuable adjunct to the anesthetist's armamentarium.

SUMMARY

The toxicity of the cyclopropane varies with the sample of trimethylene bromide used in its preparation.

The gas has no undesirable physical properties, and although explosive, is less so than ethylene.

There is a wide margin of safety between the surgical and lethal tensions of cyclopropane.

Narcosis of surgical depth does not necessarily produce metabolic disturbances and cells of the body do, under deep narcosis, carry on their ordinary metabolism unaffected by the anesthetic.

Blood pressure, pulse and respiratory rates are not altered to any appreciable extent.

Cyclopropane anesthesia does not damage the normal liver of dogs even after repeated administrations, nor after long periods of anesthesia.

It does not impede the usual recovery of the liver of dogs from chloroform poisoning, even when the cyclopropane anesthesia is prolonged.

It does not cause liver impairment in starved dogs even after a three-hour period of anesthesia.

So far there is no evidence that cyclopropane is broken down in the human body and all indications point to its complete and exclusive elimination through the

respiratory system; on this account there would seem to be no contraindications to its use in those patients with insufficient hepatic or renal function.

Respiration invariably fails before the circulation; paralysis occurring at an average concentration of thirty-nine per cent in dogs.

Respiration throughout the third stage is quiet, regular, with little depression of rate.

Minute volume respiration is seriously diminished only when intercostal paralysis occurs.

Arhythmias, conduction disturbances and other electrocardiographic changes are of very common occurrence during surgical operations.

Cardiac arhythmias occur with high concentrations of cyclopropane. The concentration required to produce these irregularities is in the same range as that required to produce respiratory paralysis, which usually occurs a few minutes prior to or following the arhythmia.

The initial cardiac irregularities are probably of vagal origin since they are abolished by atropine, and they are not indicative of permanent cardiac change since a normal rhythm invariably returns as the concentration of cyclopropane diminishes.

Cyclopropane is sufficiently toxic to produce cardiac paralysis even under artificial respiration. These concentrations, however, are far above the anesthetic range, (above 60%)

Surgical anesthesia may be maintained for long periods of time without immediate or late untoward effects.

The gas occupies an intermediate position between ethylene and ether as regards, induction, maintenance, and recovery from anesthesia.

More diligence is required in the use of this gas than with other agents, because the passage through the various stages can be exceedingly rapid.

The gas has been found satisfactory as an anesthetic agent, particularly since adequate muscular relaxation is obtained with concentrations of less than twenty per cent in oxygen. However, for upper abdominal work, cholecystectomy and stomach resections, for instance, noticeable defect in the relaxation has been evident in many cases.

The concentration of the gas to maintain deep surgical anesthesia varies considerably with the individual but averages about twenty-five per cent. Premedication with morphine diminishes by about twelve per cent the

concentration of cyclopropane required to maintain a given level of anesthesia.

Sensations of "ringing in the ears", "fulness in the head" and other unpleasant experiences seem less frequent with cyclopropane than with other agents. This is probably attributed to the complete avoidance of oxygen want from the beginning of inhalation.

Cyclopropane has given satisfaction as a preliminary to ether anesthesia. The induction is pleasant and the tolerance to ether vapor in the presence of a high oxygen content of the inspired gas makes for a smoother and quicker ether induction.

Recovery is somewhat more frequently accompanied by nausea following cyclopropane than with nitrous oxide and ethylene. However, with major surgery the incidence of nausea and emesis is less pronounced with cyclopropane than with the other agents.

Cyclopropane anesthesia is directly indicated in those conditions which are the gravest risks for operation.

In performing thoracoplasty, rib resection for empyema and other operations within or outside the chest, the extremely quiet respiration, ample oxygen supply and quick recovery of the cough reflex have offered ideal conditions for this work.

In obstetrics, cyclopropane is of value because an abundance of oxygen is given with the gas, circulation and respiration are not depressed, anesthesia is produced without appreciable metabolic disturbance, liver function is not impaired, anesthesia is quickly and agreeably induced, satisfactorily maintained at any desired depth with ready flexibility and minimal danger to the mother and child, and recovered from easily and uneventfully.

Cyclopropane is replacing ethylene to the satisfaction of the anesthetist, surgeon and patient. It is chosen in preference to ether in well over seventy-five per cent of the work formerly done with that agent.

In cases in which ether is still used, there seems to be an increasing tendency to choose cyclopropane in preference to nitrous oxide as a means of inducing ether anesthesia.

Because of the small amount of cyclopropane necessary, the actual cost per anesthesia is very low and well under the cost of gas anesthesias with the older agents and methods.

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BIBLIOGRAPHY

1. Bogan, J. B.: A Clinical Evaluation of Cyclopropane: After its Use in 300 Surgical Anesthesias. Anesth. & Analg., 15; 275-280 (Nov.-Dec.) 1936.

2. Bonham, Russell F.: Cyclopropane Anesthesia with Reports of 732 Administrations. Anesth. & Analg., 16; 341-345 (Nov-Dec) 1937.

3. Bourne, Wesley: Cyclopropane Anesthesia in Obstetrics. The Lancet, 20-21, July 7, 1934.

4. Burford, G. E.: Continuous Flow Administration of Cyclopropane. Anesth. & Analg., 15; 254-259 (Sept-Oct) 1936.

5. Duncan, J. W.: Cyclopropane Anesthesia from the Standpoint of the Surgeon. Nebr. S.M.J., 22; 421-425 (Nov) 1937.

6. Eversole, U. H. and Overholt, R. H.: Anesthesia in Thoracic Surgery. J. Thoracic Surg., 5: 510-521 (June) 1936.

7. Eversole, U. H., Sise, L. F. and Woodbridge, P. D.: The Clinical Use of Cyclopropane. Anesth. & Analg., 16; 241-248 (Sept-Oct) 1937.

8. Freund, von August: Uber Trimethylene. Monatshfte f. Chemie; 3, 625-635, 1882.

9. Griffith, F. Webb: The Choice of an Anesthetic. South. Med. & Surg., 92; 501-505 (July) 1930.

10. Griffith, Harold R.: Cyclopropane Anesthesia: A Clinical Record of 350 Administrations. Canad. M. A. J., 31; 157-160 (Aug) 1934.

11. Griffith, Harold R.: Cyclopropane Anesthesia. Anesth. & Analg., 14; 253-256 (Nov-Dec) 1935.

12. Harms, B. H.: Cyclopropane Anesthesia from the Standpoint of an Anesthetist. Nebr. S. M. J., 22; 425-429 (Nov) 1937.

13. Henderson, V. E. and Lucas, G. H. W.: Cyclopropane: A New Anesthetic. Anesth. & Analg., 9; 1-6 (Jan-Feb) 1930.

14. Kurtz, C. M., Bennett, J. H. and Shapiro, H. H.: Electrocardiographic Studies During Surgical Anesthesia. J. A. M. A., 106; 434-441 (Feb 8) 1936.

15. Leech, B. C.: The Pharyngeal Bulb Gasway. Anesth. & Analg., 16; 22-25 (Jan-Feb) 1937.

16. Lucas G. H. W. and Henderson, V. E.: A New Anesthetic Gass:: Cyclopropane. Canad. M. A. J., 21; 173, 1929.

17. Morgan, G. S., Eaman, S. G. and Griffith, H. R.: Cyclopropane Anesthesia for Cesarean Section. Anesth. & Analg., 16; 113-115 (Mar-Apr) 1937.

18. Moffitt, J. A. and Mechling, G. S.: A Comparison of Cyclopropane with Other Anesthetics. Anesth. & Analg., 15; 225-228 (Sept-Oct) 1936.

19. Orcutt, F. S. and Seevers, M. H.: The Solubility Coefficients of Cyclopropane for Water, Oils, and Human Blood. J. Pharm. & Exp. Therap., 59; 206-210 (Feb) 1937.

20. Raginsky, B. B. and Bourne, W.: Effects of Cyclopropane on the Normal and Impaired Liver. Canad. M. A. J., 31; 500-501 (Nov) 1934.

21. Robbins, Benjamin H.: Studies of Cyclopropane. J. Pharm. & Exp. Therap., 58; 243-259 (Nov) 1936.

22. Romberger, F. J.: Signs and Phases of Cyclopropane Anesthesia. J. Indiana M. A., 28; 18-20 (Jan) 1935.

23. Rovenstine, E. A.: Cyclopropane Anesthesia in Thoracic Surgery. Anesth. & Analg., 14; 270-275 (Nov-Dec) 1935.

24. Schackell, L. F. and Blumenthal, R. R.: Gaseous Anesthetics. I. Effects of Cyclopropane on the Healthy and Tubercular Rhesus Monkey. Anesth. & Analg., 13; 133-142 (July-Aug) 1934.

25. Schmidt, E. R. and Waters, R. M.: Cyclopropane Anesthesia, Postoperative Morbidity in 2200 Cases; Anesth. & Analg., 14; 1-3 (Jan-Feb) 1935.

26. Seevers, M. H., Bennett, J. H., Pohle, H. W. and Reinardy, E. W.: The Analgesia Produced by Nitrous Oxide, Ethylene and Cyclopropane in the Normal Human Subject. J. Pharm. & Exp. Therap., 59; 291-300 (Mar) 1937.

27. Seevers, M. H., Meek, W. J., Rovenstine, E. A. and Stiles, J. A.: A study of Cyclopropane Anesthesia with Especial Reference to Gas Concentrations, Respiratory and Electrocardiographic Changes. J. Pharm. & Exp. Therap., 51; 1-17 (May) 1934.

28. Sise, L. F., Woodbridge, P. D. and Eversole, U. H.: Cyclopropane: A New and Valuable Gas Anesthetic. New. Eng. J. Med., 213; 303-308 (Aug 5) 1935.

29. Stiles, J. A., Neff, W. B., Rovenstine, E. A. and Waters, R. M.: Cyclopropane as an Anesthetic Agent: Preliminary Clinical Report. Anesth. & Analg., 13; 56-60 (Mar-Apr) 1934.

30. Tidmore, T. L.: Cyclopropane in General Surgery. South. Med. Jour., 31; 237-240 (Mar) 1938.

31. Tucker, Eldon B.: Observations on the Use of Vinethene and Cyclopropane. Anesth. & Analg., 16; 55-59 (Jan-Feb) 1937.

32. Vollbrechthausen, F.: Observations on 468 Cyclopropane Anesthesias. Anesth. & Analg., 17; 49-53 (Jan-Feb) 1938.

33. Waters, R. M. and Schmidt, E. R.: Cyclopropane Anesthesia. J.A.M.A., 103; 975-983 (Sept 29) 1934.

34. Weinberg, Joseph: A New Era In Anesthesia. Nebr. S. M. Jour., 22; 418-421 (Nov) 1937.

35. Wood, P.: Clinical Use of Cyclopropane and Tribromethanol and Amylene Hydrate. J. A. M. A., 106; 275 (Jan 25) 1936.

36. Woodbridge, P. D.: Better Gas Anesthesia at Less Cost, The Carbon Dioxide Absorption Method. Anesth. & Analg., 12; 161-173 (July-Aug) 1933.