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THE CHEMISTRY OF ANESTHETICS[1]

IDIOSYNCRASY has in the past accounted for—serves now to account for—unusual observations in the use of drugs, and perhaps will continue to cover much of our lack of information as to their real therapeutic action, but I am of the opinion that it is a "magic skin."

Sacred, profane and mythological literature abound in incident, fact and fancy, showing that from earliest times man has sought to assuage grief and pain by some means of dulling consciousness. Recourse was had to the inhalation of fumes from various substances, weird incantations, application of drugs, both external and internal, pressure upon important nerves and blood vessels, and the laying on of hands, or animal magnetism. Each has played its part in the mitigation of human ills. It was not until the close of the eighteenth century, however, that modern surgical anesthesia was foreshadowed. Then it was that the discovery of hydrogen, nitrogen, oxygen and nitrous oxide—pneumatic chemistry, as it were—created a field of pneumatic medicine. In 1789, the Pneumatic Institute was founded for the purpose of investigating the "medical powers of factitious airs or gases" and was set up at Clifton by Dr. Beddoes. The immediate idea to be followed out was the treatment of phthisis and other lung troubles by inhalation of various gases. Humphry Davy was assigned the office of superintending the experiments. Davy actually inhaled nitrous oxide, and re-

[1] A lecture delivered at the general meeting of the American Chemical Society, Indianapolis, June 28, 1911.

corded his own sensations and the behavior of others after they had inhaled it.

In 1805, Dr. Warren, of Boston, used "sulphuric ether" on a patient suffering with phthisis, and the year following it was used in attacks of asthma; but Faraday, in 1818, was the first to recognize its value as an anesthetic.

Chloroform was discovered in 1831 independently by Liebig, Soubeiran and Guthrie. It is reported in the *American Journal of Science* for January, 1832, that Dr. Ives, of New Haven, used chloroform in surgery.

In 1828, Girardin read a paper describing surgical anesthesia by means of inhaled gases, but the honor of the discovery of surgical anesthesia has been claimed with more or less acrimonious partizanship for four others, namely, Long, of Jefferson, Ga., who anesthetized a patient with ether in 1841; Wells, of Hartford, Conn., who used nitrous oxide in dentistry in 1844; Morton, a pupil of Wells, used ether instead at the suggestion of Jackson, a chemist, who later claimed to be the real discoverer. Simpson, in 1847, first used ether in midwifery and later chloroform, whose anesthetic properties had been previously described by Flourens. In 1868, Andrews, of Chicago, called attention to the use of oxygen with nitrous oxide to produce a non-asphyxial form of anesthesia. In 1906, Brown, of Cleveland, used a warmed mixture of nitrous oxide and oxygen, followed by ether and chloroform, with great success; and in 1909 Gwathmey, of New York, first used warm moist vapors of pulmonary anesthetics.

I shall not recount the historical data which have to do with other anesthetics, a list of which I have published in the *American Druggist,* as my remarks this morning will be limited to nitrous oxide, ether and chloroform, and these few facts—the results obtained from careful unbiased investigation of the literature and other forms of evidence—are given without elaboration or argument.

The speaker knows of no satisfactory basis of classification of anesthetics, hence those that are to be considered will be taken up in chronological order.

NITROUS OXIDE

In 1772 Priestley first prepared nitrous oxide by reducing NO with moist iron filings. In 1793 Deiman and others prepared the gas by heating NH_4NO_3, essentially the commercial process for its manufacture to-day. It is usually carried out by heating mixed salts, as $NaNO_3$ and $(NH_4)_2SO_4$, $NaNO_3$ and NH_4Cl, etc.[2]

Commercial nitrous oxide is apt to contain these impurities: Cl_2, NO, NO_2, HNO_3, NH_3, HCl, CO_2, O_2, N_2 and rare gases of the air. It is usually purified by passing through solutions of sodium hydroxide, ferrous sulphate and sulphuric acid. Further purification may be accomplished by the formation of a hydrate[3] (N_2O, $6H_2O$) below 0° C. and heating this hydrate, with fractional condensation[4] and subsequent fractional distillation.

Beyond the absence of disturbing impurities, the improved methods of the use of nitrous oxide for anesthetic purposes demand a knowledge of the approximate content of nitrous oxide in the commercial product, as will become apparent later, hence a method for its determination is desirable. Various methods have been proposed, for instance, decomposition into N_2 and O_2, burning with hydrogen, explosion with hydrogen, combustion of

[2] The subject is thoroughly covered in a paper by the speaker and Stevenson, *J. Ind. and Eng. Chem.*, **3**, No. 8.

[3] Villard, *Compt. rend.*, 1894, **118**, 1096.

[4] Stolzenberg, *Ber.*, **43**, 1708.

charcoal with absorption of CO_2 produced, explosion with CO, oxidation of fused mixture of sodium carbonate and Cr_2O_3 and determining the amount of Na_2CrO_4 produced, and absorption in absolute alcohol; and none is satisfactory. There is no good test for N_2O known to me. Dr. Stevenson and the author devised a new method, which gives accurate results in hands skilled in the manipulation of gases. It depends upon passing a definite quantity of the gas over heated copper gauze, after a preliminary treatment to remove oxygen, or compounds which produce copper oxide, from the sample, and then passing hydrogen through the apparatus, absorbing the water formed.

The following table, which is self-explanatory, exhibits the results of our analyses of compressed nitrous oxide as supplied by American manufacturers:

No.	Analysis								
	N_2O	H_2O	CO_2	NH_3	O_2	N_2, etc., by diff.	N_2O by explosion	N_2O by $Cu+CO_2+H_2$	N_2O by $Cu+H_2$
1	99.7	0.13	0	0.006	present	0.16	97.5	99.4	99.7
2	96.6	0.15	0	0.001	present	3.25	95.0	96.2	96.6
3	99.5	0.15	0	0	present	0.35	97.3	99.5	99.5
4	95.9	0.16	present	0	present	3.94	94.1	95.6	95.9

Nitrous oxide which is to be used for anesthesia should contain at least 95 per cent. of N_2O and no solids, liquids, combustible organic matter, chlorine or other oxides of nitrogen. A small amount of carbon dioxide, according to the investigations of Gatch, can have no evil effects. If present, however, the per cent. should be known.

ETHYL ETHER

Experience of expert anesthetists, not accounted for by idiosyncrasy, obtained in the use of ethyl ethers supplied by various manufacturers in numerous surgical cases, furnished one of the motives for my investigations into the chemistry of anesthetics. The standards laid down by the various pharmacopœias of the world are not uniform. In view of that fact alone, a thorough investigation seemed called for. Enquiries addressed to large consumers of the solvent in manufacturing processes adduced further need for satisfactory methods of determining the purity of ethyl ether and of detecting impurities introduced, or proving their absence if eliminated, in the modification of raw products used in its manufacture. The presence of small amounts of substances has oftentimes been the cause of a chemical reaction proceeding in a particular direction by virtue of a so-called "catalytic" or other unknown action. So the presence of even traces of certain substances, as peroxidized compounds, aldehyde, etc., may have caused some reactions to be incorrectly explained, or to follow an unusual, or unaccounted for, route.

Ethyl ether is still made commercially by the historical process of treating alcohol with sulphuric acid, hence the misnomer of "sulphuric ether." Although a number of synthetic processes have been proposed, some of which have been tried out, none has proved a commercial success.[5]

[5] In this connection, reference may be made to the method devised by Fritsche for the preparation of ether free from alcohol. In this method, gas containing ethylene is treated with sulphuric acid (*Z. anal. Chem.*, **36**, 298; U. S. Patent No. 475,640, January 19, 1897), and the ethyl-sulphuric acid so obtained is converted into ether and sulphuric acid by means of water. This process was operated on a commercial scale in this country for some time, but it was reported that the industry was destroyed by the Denatured Alcohol Act (Bull. 92, U. S. Dept. of Commerce and Labor, Bureau of the Census, **1909**, p. 96). It is likely, however, that a similar industry may be revived, as natural gas might serve as a suitable material from which to prepare ether (cf.

The *quality* of ethers on the market depend upon, first, the purity or grade of the alcohol used; and second, secondary reactions which take place not only with impurities in the alcohol, but with ethyl alcohol itself. For example, ethyl ether made from ethyl alcohol denatured with methyl alcohol contained other ethers, as dimethyl oxide or methyl-ethyl ether, not found in the ether made from the old rectified spirit. The liberal interpretation of the Denatured Alcohol Act by our government officials, whereby alcohol denatured by ether itself may now be used, eliminated these substances. Many of the impurities traceable not only to the quality of the raw products used, but the secondary reactions due to their virgin impurities, as variations in temperature, pressure, and other conditions, were removable, and have, in a large measure, been removed or much reduced, by subsequent purification.

The specific gravity of ether intended for anesthesia should not exceed 0.720 at 15° C., providing an ether containing minimum quantities of alcohol and moisture is required; however, an ether which shows a specific gravity of 0.7215 (2 per cent. absolute alcohol), 0.7228 (3 per cent. absolute alcohol), or even 0.724 (4 per cent. absolute alcohol), providing the sole "impurity" is ethyl alcohol, is acceptable for anesthetic purposes according to various pharmacopœias.

In this connection it may be stated that for various reasons a pure ether may be diluted with ethyl alcohol when it is to be used for anesthesia. Impurities then observed may be due in part to the alcohol used in dilution. Practically all ethyl alcohol contains some acetaldehyde.

Ethyl alcohol serves, it is asserted, as a preservative for ether when the latter is properly stored; and small amounts interfere in no way with the application of ether in anesthesia. However, the presence of alcohol is unnecessary except when ether is administered by the "drop method." In this case, the presence of alcohol prevents too rapid volatilization and consequent chilling of the apparatus with which the ether is administered. Some have maintained that pure ethyl ether is unsuitable for anesthesia, but it is a fact that the vapor from ether containing alcohol, when passed through water at 40° C., whereby the alcohol is removed, may be and is being used with great success for anesthesia. The presence of excess moisture should be guarded against in the storage of ether, since ether in contact with water or moist air gives rise to various impurities of an objectionable nature. Thus anesthetic ether of proper grade when prepared may develop impurities to be avoided quite as much as if they had been introduced in the original materials or later produced in the manufacture or added in the preparation for distribution in commerce.

Instances of sophistication have been known, but now they are comparatively rare.

Dr. Davis, of the Johns Hopkins Hospital, has made observations on the temperatures of a number of patients anesthetized with ethyl ether by the "drop method" and by warm vapors of ether. In the former the body temperature dropped 1 to 2° F., and in the latter not more than 0.3° F. in any case.

Ether, when freshly distilled over sodium, possesses a specific gravity of 0.7178 to 0.719 at 15°/4° C.; but if it is not, immediately after its rectification, drawn off into vessels, which are at once sealed and carefully stored, the specific

French Patent 352,687, of 1905, of Lance and Elworthy).

gravity increases in a short time. The purest ether procurable on the market is of 0.718–0.719 specific gravity at 15°, but this absorbs water on exposure to the atmosphere and rises to 0.720–0.721 specific gravity, when it becomes fairly constant.

Since the specific gravity of ether is 0.7178 to 0.719 at 15° C., those requiring ether of 0.720 specific gravity thus allow minimum amounts of water and alcohol. Unless the ether is dried carefully by means of sodium, for example, and is kept constantly dehydrated by storing over such an agent, or great care is taken in storing it after final rectification, it is practically impossible to maintain the specific gravity originally possessed by the ether.

The speaker, assisted by Mr. W. A. Hamor, has conducted an extensive investigation on the changes which occur in ethyl ether during storage, and the experimental data obtained[6] lead to the conclusion that the oxidation of ether in the presence of moisture is productive of a series of complex conversions, initiated, however, by the formation of hydrogen dioxide. The slow combustion of pure ether in the presence of water, and under such conditions as exist when it is improperly stored, would appear to occur in the following stages:

1. The formation of hydrogen dioxide from water and oxygen of the air. This is particularly likely in cases where there is direct exposure to light, and it is more or less activated by contact action.

2. Dissociation of hydrogen dioxide into water and oxygen, which latter then exerts a direct oxidizing action, resulting in the formation of the following: acetic peroxide, acetaldehyde and acetaldehyde peroxide, and eventually acetic acid. The formation of acetic peroxide facilitates a series of oxidations, and by its hydrolysis alone acetic and peracetic acids are formed. The peracetic acid then becomes converted into acetic acid and hydrogen dioxide. Therefore it is reasonable to conclude that a continuous cycle of changes occurs in ether during its oxidation and that such changes result in the simultaneous formation and occurrence of peroxidized compounds, intermediate (aldehyde) and ultimate (acetic acid) resultants.

Our experimental work seems to establish beyond any doubt the fact that ether of anesthetic grade contains peroxidized compounds after exposure to varying temperature conditions and sunlight, in the presence of atmospheric oxygen, for considerable periods of time, especially when it is stored in colorless glass vessels or in badly stoppered tin containers.

Aldehyde is undoubtedly the commonest contaminant of anesthetic ethers, and its presence may account for some of the observations made in practise. It is one of the impurities most likely to be generated by exposing partially filled containers to varying atmospheric conditions for long periods of time. Ether should not be stored in glass vessels for any length of time without being tested for oxidation products before use; and the tin containers should be of such capacity that they need not be opened without being emptied when the ether is employed for anesthetic purposes.

With regard to the acidity of the various anesthetic ethers on the American market, it may be said that none that we have examined contained acids (sulphurous, sulphuric, acetic) in what may be termed injurious amounts, since the amount present never exceeded 0.002 gram of acetic acid per 100 c.c. of the sample in any case. The degree of acidity is liable to vary more or less in both direc-

[6] *J. Ind. and Eng. Chem.*, **3**, Nos. 5 and 6.

tions in short intervals during storage in glass vessels, just as in the case of the oxidation of ether itself. The variations in acidity—theoretical, but not sensible in general—may be due to differences between the rapidity of the oxidation and the saturation of the acids by the bases of the glass. In fact, it should be mentioned here that the nature of the ether container is of vast importance in the light of the oxidation changes which are possible. The extent of the oxidation—or, for that matter, any oxidation at all—is dependent upon the quality of the glass used in bottles for storing ether; and in the case of metallic containers, in view of some recent researches, it is probable that all metals which show anomalous anodic conductivity are likely to develop free hydrogen dioxide in contact with water and oxygen. The presence of such metals should, therefore, be guarded against.

Since it is highly important that ether intended for anesthetic purposes should be carefully manufactured and properly stored, as prolonged exposure to light and air greatly affect the results of etherization, causing coughing, suffocation, and even dangerous after effects, such ether should always be tested for peroxides and aldehyde, and the presence of the latter should be rigorously guarded against, or the ether, if so contaminated, should be administered by a method which eliminates these impurities before it is introduced into the animal system.

We have made an examination as to the value of all proposed tests for the presence of impurities in ethyl ether, and have devised several new and superior ones. A scheme for examination has been worked out and is now available in the literature.[7]

CHLOROFORM

Liebig prepared chloroform from chloral. Soubeiran treated alcohol with "bleaching powder." Schering generated his "bleach" in the presence of alcohol by electrolysis. Then commercial methyl alcohol was used and "methylated spirit," whereby so-called "methylated chloroform" was obtained. Liebig also obtained chloroform by the action of "chloride of lime" upon acetone. Böttger and others used acetates (1848), and then chlorine was liberated in acetone by electrolysis. This process is used extensively in this country now. Methane of natural gas has been burned in chlorine, but this process has not proved successful commercially so far, although "gas chloroform" is spoken of by some in a wise way. Carbon tetrachloride, made by chlorinating carbon disulphide, is being reduced by the process of Smith to produce much chloroform in this country at present. "Chloral chloroform" is imported in small quantities.

From the variety of "Ausgangs-material" and different methods used it is quite evident that crude chloroform may contain a wide range of impurities, which may vary not only with the materials used but also with the conditions of manufacture. Alcohol has been removed from chloroform by washing with water, the chloroform being subsequently dried over calcium chloride. Potassium hydroxide has been used to remove excess chlorine and acids. Manganese dioxide has been employed to remove sulphur dioxide. Chloroform has been shaken with concentrated sulphuric acid until the acid was no longer colored; the vapors of chloroform have been passed through towers of crystallized sodium carbonate after treatment with sulphuric acid, and rectification has followed. To remove special impurities or decomposition products of the chloroform itself, chloroform has been treated with lead dioxide; with potassium permanganate, or

[7] Baskerville and Hamor, *loc. cit.*, **3**, No. 6, p. 395.

with dilute sodium thiosulphate; or it has been distilled over 2 per cent. paraffin or poppy oil. "Chloroform Anschütz" is obtained by distilling from crystals of salicylid-chloroform. "Chloroform Pictet" is made by chilling chloroform to —80° C., filtering off the solids produced, and then lowering the temperature to — 82° C. and drawing off the liquid impurities. The frozen chloroform is then fractioned, the intermediate 80 per cent. of the distillate being taken.

The specific gravity values of chloroform have been determined by different workers as follows:[8]

TABLE I. DETERMINATIONS OF THE SPECIFIC GRAVITY OF CHLOROFORM

0°	11.8°	12°	15°	15.5°	16.5°	17°	18°	18.58°	25°	29°	35.86°	60.8°	61.2°	63°
1.52523	1.5039	1.496	1.485	1.500	1.472	1.491	1.48	1.48978	1.48432	1.49089	1.45695	1.4081	1.40877	1.3954
1.52657		1.512	1.4946			1.507			1.48492					1.4018
			1.4905											1.408114
			1.4976											
			1.5066											
			1.5107											
			1.4989											
			1.4980											
			1.500											
			1.50027											
			1.50085											
			1.49887											

In the course of an investigation on the decomposition of chloroform, we prepared *pure* chloroform.[9] This possessed a density of 1.49887 at 15/4° (average of six determinations), a result in close agreement with the values of Thorpe and Timmermans. This value may be taken as the correct specific gravity at the temperature noted.

The anesthetic chloroform on the American market varies in specific gravity from 1.4730 to 1.4827 at 25/25°, usually in close proximity to 1.476, the minimum density permitted by the pharmacopœia. The samples of chloroform of German manufacture examined varied in specific gravity from 1.487 to 1.492 at 15/15°, although one sample possessed a density of 1.497 at this temperature. Since the correct specific gravity of chloroform is 1.49887 at 15/4°, those officials requiring chloroform of a lower density—that is, anesthetic chloroform—allow the addition of alcohol, and consequently the presence of small amounts of water; the permissible addition usually varies from 0.5 to 1 per cent.

Specific gravity determinations are not to be regarded as criteria of purity beyond indicating the amount of alcohol in chloroform.

The boiling points of chloroform according to different observers are as follows:

BOILING POINT OF CHLOROFORM

Year	Observer	Temperature
1883	Schiff	60.9° at 754.3 mm.
1884	Perkin	62.0° at 760 mm.
1885	Bauer	61.0° at 760 mm.
1889	Thayer	61.6° at 760 mm.
1899	Pettit	61.97° at 760 mm.
1904	Wade and Finnemore	61.15° at 760 mm.
1911	Baskerville & Hamor	61.20° at 760 mm.

In general, it may be said that no specific directions are given for the determination of the boiling point and the influence of the variables (alcohol and water

[8] A discussion of these values is given in an elaborate paper on "Chloroform" by the speaker and W. A. Hamor, which will appear in *J. Ind. and Eng. Chem.*, **3**, No. 10.

[9] Baskerville and Hamor, *loc. cit.*

in particular) has not received enough attention. Opinions are divided as to the value of the determination as a criterion of the purity of anesthetic chloroform. In the speaker's opinion, it is of no value without a knowledge of the content of alcohol and water. In making a careful fractionation of 500 g. of anesthetic chloroform made from acetone, containing 0.5 per cent. alcohol and 0.026 per cent. water, but otherwise pure, the temperature rose at once to + 55.5° C., at which point part of the alcohol and water with some chloroform passed over, the remainder of the alcohol with part of the chloroform going over between + 59.4° and + 61°. The following fractions were obtained:

Temperature	Weight of Fraction
55.5–59.4°	10 g.
59.4–61.0°	177 g.
61.0–61.2°	300 g.
Above 61.2°	13 g.

The influence of alcohol and water, separately or together, on the boiling point of chloroform may be seen from the following table.

BOILING POINTS OF MIXTURES OF CHLOROFORM, ALCOHOL AND WATER

Constituent	Boiling Point	Per Cent. Chloroform
1. Chloroform-alcohol-water	55.5°	92.5
2. Chloroform-water	56.1°	97.5
3. Chloroform-alcohol	59.4°	93.0
4. Chloroform	61.2°	100.0
5. Alcohol-water (95.5 per cent. alcohol)	78.15°	
6. Alcohol	78.3°	
7. Water	100.0°	

There has been not a little variety of opinion among chemists as to the nature and products of the decomposition of chloroform, especially the changes which chloroform undergoes upon exposure to air; in fact, this discordance dates from the introduction of chloroform as an anesthetic and prevails to-day. This condition is ascribable to the many influencing factors occasioned by the degree of purity of the chloroform under examination, the extent and nature of the exposure; but is principally due to the failure to consider, and therefrom to correctly interpret, the rôle of the general variable, alcohol, and with it the accompanying moisture.

The products of the decomposition of "pure" chloroform, according to various investigators, may be thus summarized:

Chlorine; hydrochloric acid	Morson; Maisch; Hager.
Carbonyl chloride	Rump; Regnault.
Carbonyl chloride; hydrochloric acid	Stark; Ramsay; Schoorl and Van den Berg; Dott.
Carbonyl chloride; chlorine	Brown; Schacht and Biltz; Adrian.

The formation of carbonyl chloride is alone definitely agreed upon.

The decomposition of chloroform has been universally conceded to be an oxidation process. It is generally accepted that chloroform is unaffected by light alone, and that light, although it accelerates oxidation, is not a necessary factor in the process; however, several investigators appear to have inclined to the view that light favors decomposition.

With regard to the changes which occur in anesthetic chloroform, that is, chloroform containing alcohol, during exposure to air and light, there also exists a decided diversity of opinion, principally owing to the fact that no examinations were made during the course of the various investigations, so far as we are aware, for the presence of the oxidation products of alcohol in such chloroform. The whole subject required investigation, and accordingly an experimental study of the decomposition of both pure and anesthetic chloroform was carried out. It was also hoped to

throw light on, if not fully explain, the rôle of alcohol[10] and other substances in the so-called preservation of chloroform, a satisfactory explanation of which has been wanting.

Various samples, some twenty-three in all, of both pure chloroform[11] and chloroform containing the usual pharmacopœial amounts of alcohol and water, were exposed, in well-stoppered[12] containers of various sizes, and containing varying amounts of the samples, and of both colorless and anactinic glass, such as are customarily used in the trade, for different periods of time, but at room temperature (20° C.), from September to May, inside of a window having direct southern exposure. The conditions were extreme, but nevertheless were similar to those obtaining in many pharmacies and hospitals.

The anesthetic chloroform used was examined prior to the experiments, and only such chloroform as was found to be free from impurities was used. However, an amount of water equivalent, on the average, to 5.1 per cent. by volume of the alcohol present was permitted.[13] Thus each sample was of pharmacopœial grade.

[10] The amounts of alcohol stated as permissible in the various official chloroforms intended for anesthetic purposes are as follows:

Belgium	1.0 per cent.
Denmark	1.0 per cent.
Sweden	0.5–1.0 per cent.
United States	0.6–1.0 per cent.
France	0.005 part by weight.
Italy	0.5 per cent.
Switzerland	1.0 per cent. absolute.

[11] This chloroform was prepared according to the method of Baskerville and Hamor and was absolutely pure.

[12] No cork stoppers unprotected by metal caps were employed. In the experiments on pure chloroform, glass-stoppered bottles were solely used.

[13] The alcohol content of the anesthetic chloroform used was determined quantitatively by the method of Nicloux.

The tests applied for the detection of the oxidation products of chloroform and alcohol were those previously proved out in our work. Quantitative determinations of the impurities developed were made when possible.

The experimental results warranted the following conclusions:

1. The products of the oxidation of *pure* chloroform are carbonyl chloride and hydrochloric acid, which come about according to these reactions:

$$CHCl_3 + H_2O + O_2 = COCl_2 + HCl + H_2O_2;$$
$$CHCl_3 + H_2O_2 = COCl_2 + HCl + H_2O.$$

We are convinced that oxidation will not occur if water be excluded, and the absolute exclusion of moisture appears to be impossible. Hydrogen dioxide is formed, although we have been unable to detect it in chloroform undergoing oxidation, and therefore conclude that its existence is ephemeral, and oxidation of the chloroform continues throughout the period of exposure. The rôle of the water is that of a true chemical catalyst. The decomposition of pure chloroform is accelerated by light, and carbonyl chloride is formed with increased readiness in the presence of acids.[14]

The extent of the oxidation is dependent upon the nature of the container, the amount of air present, the purity of the sample, and the intensity of the light to which it is exposed.

Free chlorine can only result from the photochemical decomposition of carbonyl chloride:[15]

[14] Cf. Lowry and Magson, *Trans. Chem. Soc.*, **93**, 121, who observed that the formation of carbonyl chloride is evidently accelerated by the presence of acids.

[15] In this connection, see Coehn and Decker, *Ber.*, **43**, 130; and Weigert, *Ann. Physik*, 1907, (4), **24**, 55. The influence of light on the reversible reaction, $CO + Cl_2 \rightleftarrows COCl_2$, is purely catalytic.

$$COCl_2 \rightleftarrows CO + Cl_2.$$

It is likely that in the cases where "chlorine" was identified as an indication of incipient alteration of chloroform, hydrogen dioxide was the cause of the reactions observed. No chlorine was found when containers of anactinic glass were used; and when chlorine is detected, it must be the result of a secondary reaction.

2. The products of the oxidation of anesthetic chloroform are primarily the oxidation products of alcohol, and no decomposition of chloroform itself occurs while the oxidation of alcohol proceeds. When the oxidation of alcohol reaches a maximum, decomposition of the chloroform goes on, as in the case of pure chloroform, with the exception that chlorinated derivatives of the oxidation products of alcohol may result. The decomposition of the chloroform itself is retarded, even prevented, so long as oxidation of the alcohol proceeds, and the retardation is consequently dependent upon the amount of alcohol present.

This leads to the rôle played by ethyl alcohol in the preservation of chloroform, for alcohol does prevent the decomposition of chloroform, as first suggested by Squibb in 1857 and later (1863) by Brown, independently.

Those who have investigated the part played by alcohol in preserving chloroform up to the present time have held that either chloroform decomposes in the presence of alcohol and that the alcohol takes care of the decomposition products or the alcohol acts as a "catalytic retarding agent" (Stadlmayr).

The preservative action of alcohol is due to the combination of the retarder with certain of the reacting substances; and any substance soluble in chloroform and readily oxidizable will exert an inhibitory effect on the oxidation of chloroform itself; for example, sulphur and many other substances.[16] All compounds which have been found to serve as preservatives of chloroform are reducing agents, and the effect is only due to their capacity for oxidation.

Anesthetic chloroform should preferably be furnished in vials or bottles of high-grade anactinic glass,[17] containing about the quantity sufficient for one narcosis, and at the most not more than can be used within several days. If, for any particular reason, chloroform is ordered in a large container, it is advisable, immediately after opening it, to subdivide the entire remaining contents into two-ounce bottles, taking care to fill the small bottles completely. It is important to see that the bottles are completely free from water, and empty bottles should not be refilled without thoroughly cleansing and drying them. In no case should chloroform be gradually withdrawn in small quantities from large bottles or carboys. When it is found necessary to store anesthetic chloroform, it should always be kept in a cool, dark place, in well filled, or, better still, completely filled, tightly stoppered bottles of anactinic glass.

The condition of officinal chloroforms which may be transported across the ocean and continent or kept at sea for variable lengths of time, where they would be subjected to constant agitation, has been investigated. Anesthetic chloroform in unopened, brown glass bottles were subjected

[16] Paper by Baskerville and Hamor, *loc. cit.*

[17] The glass should show no alkaline reaction when the bottle is filled with distilled water containing several drops of phenolphthalein solution and heated at 100° C. for six hours. On the action of alkalies on chloroform, see Berthelot, *Bull. soc. chim.*, (2), **29**, 4; Andre, *Compt. rend.*, **102**, 553; de St. Martin, *ibid.*, **106**, 492; and Mossler, *Monatsh.*, **29**, 573. It appears to be well established that potassium hydroxide in alcoholic solution will slowly decompose chloroform.

to intermittent agitation for over 200 hours in a Spiegelberg shaking apparatus, and it was learned from four samples so treated that it is desirable to prevent the presence of air, *i. e.*, oxygen, being in association with this anesthetic when it is to be shipped in the usual manner. Monneyrat devised a method of displacing air by nitrogen, even making a nitrogen siphon of chloroform.

The keeping qualities of anesthetic chloroform may be seriously affected by the character of containers. The question of keeping anesthetic chloroform in tin containers has been a much agitated one in the Federal War Department, and within the last ten years this department has decided in favor of the tin container.

The opinion of the author is that glass containers are more conducive to purity for several reasons. First, in cleaning the vessels any foreign matters present may be readily observed and the bottles properly cleaned. Second, in the case of tins, some of the flux used in soldering may be introduced and thus impart an acid reaction to the chloroform. Hydrochloric acid accelerates the decomposition of chloroform. The introduction of this flux is also a problem in ether manufacture which requires the utmost care. Third, since it has been stated that spirit containing 95 to 96 per cent. by volume of ethyl alcohol is perfectly indifferent to tin, and tinned metals are absolutely unattacked by 90 per cent. denatured spirit, the tinned metals only being corroded where the tin layer is broken,[18] one would conclude that acid-free chloroform,[19] containing the usual amounts of alcohol and water, would also be without action on tin, providing it is stored in tin containers having no broken or scratched surface, very carefully capped, and with a minimum amount of air. In order to determine this, a five-pound sample of chloroform, containing 0.84 per cent. by volume of absolute alcohol and approximately 0.05 per cent. of water, which had been stored in a tin container, sealed, for sixteen months, was examined for the presence of tin. This sample left a residue non-volatile at 100° C., amounting to 0.0220 g. per liter, but none remained upon ignition and no tin could be detected in the sample. The examination of a sample of anesthetic chloroform which had been kept in a sealed tin for six years also showed that no tin had been dissolved. In both cases, however, oxidation of the alcohol present had occurred, although no decomposition products of chloroform were present.

Fourth, we have been informed by H. H. Dow[20] that he has "demonstrated that moist chloroform in the presence of a metal will slowly form traces of CH_2Cl_2 and probably . . . that it is possible to distil pure, dry chloroform in a metal container and produce a decomposition as shown by the following formula:

$$4CHCl_3 + Cu_2 = C_2Cl_6 + 2CH_2Cl_2 + Cu_2Cl_2.$$

This reaction, however, takes place so slowly that it would never be noticed except in the handling of a material on which superlative efforts have been expended for years in order to get the last extreme of purity." Moreover, "all chloroform contains traces of CH_2Cl_2." In this connection, it should also be mentioned that it is probable that all metals which show anomalous anodic conductivity

[18] Heinzelmann, *Z. Spiritusind.*, **27**, 399. Malmejac, however (*J. Pharm. Chim.*, 1901, **13**, 169), found that a small amount of tin goes into solution in 95° alcohol after six months.

[19] On the action of hydrochloric acid in chloroform on tin, see Patten, *J. Physical Chem.*, **7**, 161, who found that the dry solutions act upon the metal less violently than upon zinc or aluminum, but more violently than on lead.

[20] Private communication.

are likely to develop free hydrogen dioxide in contact with water and oxygen;[21] in the speaker's opinion the presence of such metals should therefore be guarded against in the selection of a container for anesthetic chloroform.[22]

The *Pharmacopœia of the United States* formerly required the use of "glass-stoppered" bottles, but subsequently changed this to "well-stoppered" bottles, thus allowing the use of cork stoppers, a practise which has become general in this country.[23]

The objections which have been urged against the employment of cork stoppers are two in number. First, the chloroform penetrates the cork after some time, especially during the agitation incidental to shipment, causing shrinkage and perhaps consequent leakage.[24]

The second objection is that organic matter is extracted from the cork and the chloroform fails when the sulphuric acid test, a test used for the detection of fusel oil, chlorinated decomposition products, etc., is applied. To obviate these difficulties, certain manufacturers of chloroform have adopted the plan of covering the bottom of corks with tin foil, a procedure which so far has been found to be satisfactory, but which may be open to some of the objections to tin containers. Other manufacturers use a paper or parchment covering, and still others select only the best corks and extract them thoroughly with chloroform before use.

The impurities which anesthetic chloroform brings with it from the manufacturer, the so-called "organic impurities," are traceable to the materials used in the making, method of manufacturing, subsequent purification, and manipulation before marketing; these may be grouped into one class (A). Another class (B) includes those impurities developed during different conditions of storage.

These impurities, even though some may not be of much importance from a physiological standpoint, must still be given attention, since an impure chloroform is more likely to become altered through oxidation during storage, notwithstanding the fact that pure ethyl alcohol has been added. So far as we have been able to learn, the adulteration of anesthetic chloroform is not practised now, and crude chloroform is no longer sold as chloroform of anesthetic grade.

You are spared a discussion of the numerous tests for the various impurities which may be present in anesthetic chloroform, as these will soon be available in one of our papers. Suffice it to say that in our laboratory we have studied every test we have been able to find in the literature and have been forced to devise new ones in some cases, while in others we are unable to make any recommendations at all as

[21] Barnes and Shearer, *J. Physical Chem.*, **12**, 155, 468.

[22] All of the manufacturers of chloroform in this country use brown glass ("anactinic") bottles. Of the eight different makes of German chloroform examined by the speaker, only two were contained in colorless bottles.

[23] In Germany, however, glass stoppered bottles are used by prominent producers of anesthetic chloroform (Kahlbaum; de Haen; Merck; "A.-G. für Anilin-Fabrikation," etc.).

[24] Allain [*J. Pharm. Chim.*, (3), **9**, 571] and Masson [*Ibid.*, (6), **9**, 568] have recommended that when chloroform is kept in cork-stoppered bottles, a lute of "bichromate gelatin" should be used to prevent leakage. This is unnecessary when a proper stopper is used, and the employment of lutings on the stoppers has led to many differences between the manufacturer and consumer in the past. Only one of the many samples of anesthetic chloroform examined by the authors was contained in a bottle having a luted cork stopper, and in this case considerable organic matter had been taken up, and, as a result, the chloroform failed to comply with the important sulphuric acid test or confused its interpretation.

yet. Two illustrations may prove of interest. Paraffin oil, sp. gr. 0.88, may be used to discriminate between 0.08 and 0.09 per cent. of water in chloroform, but it does not show the presence of a smaller amount. We were not aware of any test having been devised to show the presence of less than 0.05 per cent. of water in chloroform until we found that clean crystals of calcium carbide would answer most satisfactorily.

Carbon tetrachloride boils at + 78.1° C. and has a specific gravity of 1.63; chloroform boils at + 61.2° C. and has a specific gravity of 1.4989. A binary mixture containing 7.8 per cent. carbon tetrachloride boils at + 62° C. From what has been said of the presence of the variables, alcohol and water, in anesthetic chloroform and their influence upon the physical properties of chloroform, it will be quite evident that determinations of these physical constants can be of little real value, and their application in general practise, even in well equipped laboratories, is quite out of the question. All our efforts to secure a method applicable on a laboratory scale to detect likely amounts of carbon tetrachloride in chloroform have been unsuccessful. To be sure carbon tetrachloride possesses anesthetic properties, but it must exert its own specific physiological effect and the anesthetist should know the drug he uses.

Among the anesthetic mixtures, the combination of chloroform vapor with oxygen was used shortly after the introduction of chloroform as an anesthetic, and it has recently been reintroduced into practise. Hence it was important to investigate the changes which anesthetic chloroform undergoes when a current of oxygen is conducted through it. Dr. J. T. Gwathmey[25] has recently stated that oxygen increases the value of all inhalation anesthetics as regards life.

Several experiments were carried out in order to determine whether the passage of a current of oxygen through anesthetic chloroform brings about decomposition of the anesthetic. Anesthetic chloroforms containing 0.56 to 1.0 per cent. of alcohol and 0.03 to 0.05 per cent. of water were used. The conditions were such, except that the temperature was about + 20° C., as obtain during administration by the Gwathmey method, his apparatus being used. The oxygen was allowed to flow at such rates through 3½ to 4 ounces of the anesthetic that about one-half remained in the vaporizer after 3½ to 10½ hours. In one experiment the chloroform vapor was passed through water, as is Dr. Gwathmey's practise, and subsequently condensed. The examination of the residue and condensed chloroform showed the following:

Acidity (acetic acid):	
Chloroform used	None.
Residue in container ...	0.00015 g. in 100 c.c.
Condensed chloroform ..	None.
Sulphuric acid test:	
Chloroform used	Negative.
Residue in container ...	Marked reaction.
Condensed chloroform ..	Negative.

Therefore it was concluded that the oxidation products of alcohol are not carried over when the chloroform-oxygen stream is conducted through water, and that these are concentrated in the residue. By this method of administration the patient is protected from the objectionable decomposition products even if they had developed. Furthermore, the vapors of the anesthetic so applied are saturated with water, hence can not exert that desiccating effect upon the mucous membranes they would if not moisture-laden.

[25] The speaker has been collaborating with Dr. Gwathmey, who has directed the clinical observations.

OXYGEN

As animadverted, ninety-four years after the discovery of nitrous oxide and oxygen by Priestley, they were first used in combination for anesthetic purposes. Although Andrews published accounts of several cases, in which, by mixing oxygen with nitrous oxide, he had obtained a more satisfactory form of anesthesia than with nitrous oxide alone, his observations failed to attract the attention they deserved. Ten years later (1878) Paul Bert drew further attention to this form of anesthesia. Hewitt[26] stated previous to the completion of the work reported this morning, that the most recent and best development in modern anesthetics is the combination of oxygen with nitrous oxide whereby a non-asphyxial and safe form of anesthesia may be produced. The results of a long series of experiments with various anesthetics and different mixtures caused Gwathmey to say "Oxygen is indicated with every anesthetic and at all times. The longer the anesthesia, the more urgent is the call for oxygen by the blood." The importance of the quality of the oxygen is apparent.

At the present time, there are the following methods of preparation and manufacture of oxygen:[27] (1) heating chlorates; (2) heating chlorates with various substances; (3) from hypochlorites and reaction of chlorine and water; (4) heating sulphuric acid or sulphates; (5) heating various solids and mixtures (MnO_2, CuB_4O_7, etc.); (6) combustion of solid mixtures (chlorates with combustible material, alkaline peroxides with hydrated salts, etc.); (7) reaction of peroxides (oxone) with water and aqueous solutions; (8) by electrolysis of water; (9) from the air by means of mercury, cuprous chloride, barium dioxide, manganates, plumbates, or living matter, or by dialysis or absorption; and (10) from liquid air.

Oxygen that is to be used in anesthesia should contain at least 95 per cent. O_2 upon the dry basis. We found that the pyrogallate method is the most convenient method to employ and most satisfactory, provided Hempel's[28] precautions to prevent the production of carbon monoxide are taken.[29]

Analyses, by our methods, of oxygen on the American market gave the following results:

No.	Source of Oxygen	O_2	H_2O	CO_2	H_2	Organic Matter	N_2, etc.	All other Impurities
1	$KClO_3+MnO_2$	93.20	0.30	0.11	0	0	6.39	0
2	$KClO_3+MnO_2$	98.31	0.14	present	0	0	1.54	0
3	$KClO_3+MnO_2$	92.82	0.26	trace	0	0	6.92	0
4	$KClO_3+MnO_2$	97.13	0.23	present	0	trace	2.63	0
5	Liquid air	96.10	0.15	0.01	0	0	3.74	0
6	Electrolysis	99.23	0.35	0.03	0.14	0	0.25	0
7	$Na_2O_2+H_2O$	99.20	0.50	trace	0	0	0.30	0

CONCLUSIONS

I realize the danger of a mere chemist making an excursion into the field of medicine, but the extremely venturous one, if he has luck, may be swept by the rocks of which he knows little. I ventured in, as I was unhampered by tradition, and I have done enough in this field to make me take a theoretical plunge.

Modern studies in physiology have unquestionably shown that the animal body exists to a great extent by virtue of the chemical and physical changes going on within it. I know of no valid reason for assuming

[26] "Anæsthetics," The Macmillan Co.

[27] Baskerville and Stevenson, *J. Ind. and Eng. Chem.*, **3**, 471.

[28] Hempel, "Gas Analysis," English translation by Dennis, 1906, p. 149.

[29] Commercial oxygen as supplied in the trade has been quite thoroughly investigated by the speaker and Stevenson, *loc. cit.*

that these changes are essentially different from those we control in the laboratory. If we wish to control a physical or chemical change in the laboratory, we endeavor to become familiar with all the factors and conditions. If we seek to duplicate, we try to duplicate the conditions. I know of only one class of such changes over which we have not as yet secured control, and in that class belongs those processes which we term radioactive. One of the essential factors in controlling a chemical process is the quality of the material with which we are working. I can not, therefore, but regard all published statistics as to the mortality attributed directly to the anesthetic used as more or less worthless, and that a large number of new cases must be observed to secure knowledge of the real physiological effect of the drug when carried into the system by the pulmonary route.

Impure foods, sophisticated intentionally or otherwise, may bring on disease. Impure drugs, concocted or otherwise, fail to produce the full effect planned by the physician in curing disease.

Idiosyncrasy has served to account in large part for untoward after-effects of anesthetics and certain disagreeable consequences, as nausea; and interference with some normal organic functions, as glycosuria and albuminuria, have often been regarded as natural results of anesthesia, and taken for granted. They may now be largely obviated and in many cases entirely avoided by the use of anesthetics that are free from impurities, and by improved methods of administration. These statements are based upon clinical evidence. We now have records of 5,000 cases.

The main objectionable impurity in ether is acetaldehyde. American official ethers call for three to four per cent. of ethyl alcohol in accordance with an old and erroneous theory that alcohol protected the ether. Alcohol is practically never free from water, and in the presence of water and oxygen forms oxidation products. The speeds of the changes depend upon conditions. It has been shown that the administration of moist ether, free from aldehyde, at body temperature, is rarely followed by nausea (less than ten per cent.) and the usual strain upon the kidneys is not observed.

Chloroform was formerly made mainly from alcohol and contained many of the normal impurities of the alcohol used. These were not removed by the methods of purification practised, nor are they totally removable, except by elaborate methods of purification. These impurities doubtless have had much to do with the feeling of uncertainty in administering chloroform. Pure chloroform undergoes decomposition when exposed under certain conditions, such, for example, as the manner in which anesthetic chloroform is dispensed in some drug stores and hospitals. A suitable amount of alcohol prevents this decomposition, shunting the change in composition to itself, hence anesthetic chloroform should contain ethyl alcohol. But the conditions of transportation and keeping of this chloroform should be such as to reduce the change of alcohol to aldehyde and acetic acid to the minimum.

Nitrous oxide, ether and chloroform, each exerts its specific physiologic effect in producing anesthesia without asphyxiation, provided the respiratory and cardiac functions are approximately normal. This may be and is being accomplished by administering these gasified drugs with sufficient oxygen not to interfere seriously with the normal function of the hæmoglobin of carrying oxygen to the capillaries and sustaining cardiac stimulation, and by maintaining the usual concentra-

tion of carbon dioxide in, and providing its regular elimination from, the blood; for it is the respiratory stimulant (Yandall Henderson). Other factors involved are temperature and moisture. The anesthetics are carried into the system at body temperature. This may be and is being accomplished by warming, and, in the case of ether and anesthetic chloroform, by passing the vapor through heated water, which, at body temperature, not only removes the oxidation products, but saturates the gas with moisture (Gwathmey method). The osmotic action of the alveolar cells is thus affected only to the extent of the densities of the gases introduced into the lungs, and not, as normally is the case, by temperature (always lower) and desiccation as well. In other words, by the application of the principles of modern physical chemistry, the numerous variables are so reduced as to secure the real physiological effect of the particular anesthetic drug after it enters the system. Nitrous oxide and oxygen may be used for prolonged anesthesia and successfully for eighty per cent. of surgical cases; furthermore, ether and chloroform may be used with equal safety. The real, and no suppositious, idiosyncrasy of the patient may be met. The expert anesthetist may now not only make it possible for the surgeon to perform even greater miracles, but with more comfort to himself in his work, and with greater happiness and less discomfort to the patient.

Charles Baskerville
College of the City of New York

Cyrus Guernsey Pringle

In 1882 I had the pleasure of accompanying Dr. C. C. Parry and C. G. Pringle on a botanical expedition into Lower California. At this time Mr. Pringle was engaged in forming the Jesup collection of American woods for the American Museum of Natural History, and this was his first trip into Mexican territory, as it was my first.

The personal instruction given me at this time, and many following favors in after years, cemented our friendship. Previous to this time Mr. Pringle was principally known as the originator of the snowflake potato, and of new varieties of wheat and oats, and his labors in this field have added many millions to the profits of the American farmer. To him Luther Burbank owes the first training that he received in originating new varieties of plants, and many others could no doubt testify to the helpfulness of the man, ever above the petty jealousies that beset some lives.

The next twenty years passed without my again meeting the man in person, when we met in Mexico City, and I journeyed with him into many fields of botanical interest—the lava fields near that city, and to the grand barrancas near Guadalajara—replete with discoveries which render his name inseparable from the annals of American botany.

Mr. Pringle carried consideration for others almost to an extreme (were this truly possible), and I have seen him select the heavier burden and give his peon servant the lighter one to carry.

In asking for data concerning his life I received the following reply: "I decided that it was hardly possible for me to comply with your request. It would be too painful to write my autobiography. Shyness has become habitual with me. Besides my aversion to publicity, I am too busy to write much. All my thought and labor goes to the building of a great and superior herbarium."

His choice of a monument is the herbarium of the University of Vermont, which bears his name. His death from pneumonia, on May 26, 1911, aged seventy-three years, was announced in the daily press.

A rich man—who has created millions—not for himself, but for his fellow man.

C. R. Orcutt