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PURE ETHER AND IMPURITIES: A REVIEW*

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GEORGE SANTAYANA has said that "it may be useful to restate old truths in new words, the better to prove their eternal validity." With such an opinion before us, I may be excused the iteration of some results which, although published already, have not been collated in this manner.

PURE ETHER

Ethyl ether has been made pure by three sets of observers independently. In each instance the ether was rendered pure by a separate method. The first occasion was in 1922 in the laboratory of pharmacology of McGill University by Stehle and me (1), the second in 1923 in the department of biochemistry and pharmacology of the National Institute for Medical Research, England, by Dale, Hadfield and King (2), and the third in 1924 in the pharmacotherapeutical institute of the University of Leyden, Holland, by van Leeuwen (3). Briefly, the three methods are respectively as follows:

1. In the first investigation the method consisted in bringing sodium ethylate and ethyl iodide together in alcoholic solution, whereupon the reaction, $C_2H_5ONa + C_2H_5I = C_2H_5OC_2H_5 + NaI$, occurs. The sodium iodide precipitates and the ether is separated from the alcohol by fractional distillation. The possibility of side reactions occurring is not obvious, and the product may be assumed to be quite pure. *A priori*, the possibility of contamination with aldehydes and ketones is practically eliminated because, in preparing the sodium ethylate, the hydrogen generated when the metal was dissolved in the alcohol would have reduced any aldehydes and ketones present to alcohols. In order to serve as a check, however, the ether obtained was analyzed quantita-

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tively for ethylene, while qualitative tests for aldehydes and ketones were performed.

2. In the second set of experiments the starting material was absolute ethyl alcohol, which was fractionated through a 12-bulb, pear-form still-head, the fraction boiling at 78 C. being collected. This was converted into ether by the sulfuric acid process and fractionated through the same column to free from the main bulk of unchanged alcohol. The ether was washed with 3 N-caustic soda, and with successive portions of water. One liter of such ether was boiled gently under reflux with 25 grains of finely-powdered potassium permanganate for eight hours. . . . On the following day 25 grams of powdered caustic potash were added to the mixture, and the boiling continued for eight hours. The wet ether distilled through a 12-bulb, pear-form column between 34.2 and 34.7 C. at 751 mm. The preparation was completely free from aldehydes, ketones, acids, mercaptans, alcohol, and all other known impurities, including ethylene, which is immediately destroyed by alkaline permanganate.

3. In the third investigation ether was made pure in a similar manner to that of the second set of observers, but as it was regarded as theoretically possible that ether contains a small amount of an unknown substance, which also boils at 34.6 C., and as this might be responsible for the narcotic action, it was decided further to purify the ether by mixing it with benzidine, bringing the mixture to boiling point and subsequently cooling. In such manner large crystals of prismatic form are found. Upon the heating of these crystals the ether very easily becomes free, and the residual mass of benzidine may be used several times for the same process. Benzidine possesses the following advantages: It does not decompose ether during the process, but it destroys peroxides, especially ethylperoxide, diethylperoxide and acetyl hyperoxide.

This ether is not only free from any peroxides, but also *it does not form peroxides* if left in the sunlight for a considerable time. When air (freed from aldehyde and acids) was conducted through ether of crystallization in the sunlight for some hours no peroxides were formed.

These three sets of investigation were stimulated by the startling proposition that perfectly pure ether was devoid of anaesthetic properties. This came from two sources, one from Canada and the other from England. Cotton (4), of Toronto, claimed that carbon dioxide may be the active agent in some ethers and reported that he had obtained the best results by the use of ether containing ethylene and possibly another gas of unrecognized nature. According to Wallis and Hewer (5), of London, "certain ketones in the ether were largely responsible for the anaesthetic properties of the ether," and they stated that pure ether was used as a "volatile solvent" for the "mixture of ketones." According to them, ketones are the most important impurities, though they state that the anaesthetic action of ether is enhanced

by treating it with carbon dioxide and ethylene. At the time we considered the lack of chemical details in the papers of Cotton, and of Wallis and Hewer to be unsatisfactory.

The preparations were placed on the market under the names, respectively, of "Cotton Process Ether" and "Ethanesal."

So far it has been shown that, by employing three distinctly different methods, ether was made pure through the efforts of three separate groups of investigators. In each of the three instances the pure ether was found to be most highly satisfactory for the production of anaesthesia in lower animals and in man. In the words of van Leeuwen, "The final conclusion arrived at is that the purest ether which can be obtained is the best narcotic."

At the time of their investigation, Dale, Hadfield and King failed to find any evidence of an anaesthetic potency in their experiments with "ethanesal," as was then supplied commercially, which is not satisfactorily accounted for by that of the purified ether, which was its main constituent. They desired, however, to observe for themselves "the action of the very potently anaesthetic ketones, which, according to Wallis's statement, it should contain. Several samples of 'ethanesal' were accordingly purchased and submitted to fractionation. These investigations failed to reveal the presence of any ketones; the only constituent, apart from ether, present in significant amount was, in the case of all samples examined, normal butyl alcohol." Comment by MacKenzie Wallis disclosed that the "chief ketone had appeared to be methyl-ethyl ketone." This had previously been described as "ketones comprising those in the middle of the series." The analysis of van Leeuwen "entirely agrees with the analysis of Dale, King and Hadfield," that is, concerning "ethanesal," which was bought in England on the open market.

Cotton process ether was examined by van Leeuwen who found little or no carbon dioxide; no acetone or aldehydes, and no peroxides, but ethylene.

Finally, we are all agreed that purest ether possesses to the highest degree the anaesthetic properties which have usually been attributed to it. It is suggested by van Leeuwen that "it would be desirable to add to such an ether a substance which would prevent the formation of peroxides and thus stabilize the ether without interfering with its narcotic action."

EFFECTS OF CERTAIN IMPURITIES WHEN ADDED TO ANAESTHETIC ETHER

Prior to 1926 impurities had for a long time been considered to be injurious even in traces. At that time I (6) conducted a series of experiments in which known quantities of some supposedly noxious compounds which might be expected to occur in ether, and also ketones, were added to pure anaesthetic ether and their effects on respiration,

blood pressure and recovery studied in the dog. The materials used were acetaldehyde, ether peroxide, ethyl mercaptan, ethyl sulfide, acetone, di-ethyl ketone and ethyl-methyl ketone.

ACETALDEHYDE

The acetaldehyde used at first had been in the laboratory for about two years and was doubtless polymerized to a large extent. The percentages employed were 0.25, 0.50, 1 and 5. The length of experimental period was thirty minutes or less. With concentrations up to 0.5 per cent, respiration was not significantly affected and any of the changes noted might frequently be observed in ordinary ether anaesthesia. With 1 per cent or more, the breathing became audibly and visibly embarrassed. In only one instance (that in which 5 per cent was employed) was the blood pressure altered to any appreciable extent. This may have been secondary to the marked disturbance in respiration.

Freshly distilled acetaldehyde was then prepared and various concentrations made up in ether. As in the case of undistilled acetaldehyde, with less than 1 per cent no more change occurs than might be encountered with ether alone. With 1 per cent, the action on respiration is marked, so much so that in general it might be said that there is a definite interference. The blood pressure was not affected significantly even though the mixture was administered for as much as three hours. From these experiments it may be concluded that such percentages as may occur in old or improperly prepared ether, that is, less than 1 per cent, do not affect respiration, blood pressure and recovery to any appreciable extent even when administered for an unusually long time. It may be added that ether containing acetaldehyde in the concentrations here employed has a decided aldehyde odor, especially in the case of the stronger mixtures. What is more, lately (November, 1945) (7) it has been pointed out that acetaldehyde may be considered a volatile anaesthetic.

ETHER PEROXIDE

The ether peroxide used in these experiments was prepared according to the procedure of Wieland and Wingler (8). Various concentrations in ether were made. It was found that with a concentration of 0.5 per cent or greater, definite effects took place in blood pressure and respiration even after short periods of administration. When the anaesthesia was prolonged these were more marked; respiratory embarrassment occurred and a decided fall in blood pressure took place. The effect of ether peroxide in ether to the amount of 0.3 per cent is, in the light of these observations, negligible. With higher concentrations the depression of blood pressure seems to coincide with the results of Mita (9), who found that the direct application of ether peroxide will stop the frog's heart in systole.

SULFUR COMPOUNDS

The usual method of making ethyl ether is that known as the Williamson process which employs sulfuric acid and ethyl alcohol. Side reactions with the production of ethyl sulfide and ethyl mercaptan are conceivable. Both of these substances possess very strong and disagreeable odors which are detectable when very small amounts are contained in ether. This is particularly the case with the mercaptan. The facts concerning their actions on respiration and blood pressure have been published. The preliminary and fortuitous choice of 1 per cent ethyl mercaptan was adhered to throughout because it seemed to do no harm and because it is not at all likely that even the worst ether would contain nearly so much as this. In general, this impurity in 1 per cent concentration does not materially affect the animal. All the animals used made uninterrupted recoveries.

With ethyl sulfide the story is different. When 1 per cent was used the breathing and the blood pressure were both significantly affected. On stopping the anaesthesia, there was evidence of good recovery and yet twelve hours later the dog died after a most severe gastro-enteritis. At necropsy the entire alimentary tract was found to contain only blood-stained mucus. Among other details, the pathologist reported "exudative haemorrhagic gastritis and colitis, suggestive of an excretory activity." One is reminded of the similarity of this action to that produced by ethylene oxide (10). One-tenth of 1 per cent was next used and no changes took place. With 0.3 per cent the alterations encountered were nugatory.

KETONES

Data and tracings were obtained which illustrate the lack of respiratory and blood pressure effects with mixtures containing up to 5 per cent of di-ethyl ketone, ethyl methyl ketone and acetone. That these substances are indifferent, either beneficially or otherwise, was made clear.

It was deemed advisable to try the effects of some of these impurities when administered suddenly during very light anaesthesia as compared with ether alone applied in the same manner. No difference was obtained with the sulfur compounds, but with acetaldehyde greater irritation was evidenced.

So much for a brief recounting of these my arduous endeavors in 1926. Eight years later it was very encouraging to see the results of the investigations carried out by Gold and Gold (11), and it is pleasing to reflect now that the concentration devoted at that time has continued to be fruitful.

Gold and Gold have pointed out that "some manufacturers claim special purity for their anaesthetic ether. They maintain that their ether for anaesthesia contains even less of the foregoing impurities than

is permitted by the Pharmacopeia in anaesthetic ether. Such statements usually appeal to the popular imagination. The purification of drugs to a degree that is unnecessary for practical therapeutics cannot be considered justified if the process entails a marked increase in their cost." They show further that there is "no evidence in the literature to justify the anxiety over the traces of impurities that may be found in ether complying with the U.S.P. requirements for anaesthetic ether, or over the supposed rapid deterioration of ether in metal containers that have been opened, part of the contents used and the remainder stoppered with cork." They "recommended that hospitals buy ordinary U.S.P. ether in large steel drums and that for anesthesia the operating room be supplied with ether in small tin cans filled daily from the drums by the hospital pharmacist." Since my original work, there have been other reports by Hediger and Gold (12) and by Hediger, Chenoweth and Gold (13), all verifying and extenuating the first set of findings. Finally in September 1942 the Council on Pharmacy and Chemistry (14) arranged for the preparation of a report by Dr. Harry Gold, which was published in the same issue of the Journal of the American Medical Association. All anaesthetists ought to be familiar with the details of this report. Suffice it to say that "the Twelfth Revision of the U. S. Pharmacopeia has sanctioned the practice by the revision of the article on ether. According to the new text, official ether for anesthesia may be stored in containers as large as three liters. Furthermore, the Pharmacopeia no longer considers ether unsatisfactory for anesthesia twenty-four hours after the container in which it is supplied is opened; it places no limit on the period of time in which ether remains fit for anesthesia after the container is opened."

And now, it may be seen that at long last several sets of controversy have been broken up by careful investigation. They disappear in *débâcle* and ought to be regarded as nullities. The following quotation from John Dewey's *The Quest for Certainty*, its chapter entitled, *The Supremacy of Method*, seems to be particularly suitable: "Anything that may be called knowledge, or a known object marks a question answered, a difficulty disposed of, a confusion cleared up, an inconsistency reduced to coherence, a perplexity mastered. . . . The scientific attitude may almost be defined as that which is capable of enjoying the doubtful; scientific method is, in one respect, a technique for making a productive use of doubt by converting it into operations of definite inquiry. No one gets far intellectually who does not 'love to think,' and no one loves to think who does not have an interest in problems as such. Being on the alert for problems signifies that mere organic curiosity, the restless disposition to meddle and reach out, has become a truly intellectual curiosity, one that protects a person from hurrying to a conclusion and that induces him to undertake active search for new facts and ideas."

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RESOLUTIONS ON EVIDENCE OF PRACTICE OF MEDICINE, FROM SECTION ON ANESTHESIOLOGY (AMERICAN MEDICAL ASSOCIATION)

Dr. Henry S. Ruth, Section on Anesthesiology, presented the following resolutions and moved their adoption, the motion being seconded by Dr. Lloyd Noland, Alabama:

WHEREAS, The accepted method of notification of the amount of recompense indicated for medical service rendered consists in presentation to the patient or responsible party of a statement or bill for the same; and

WHEREAS, The amount involved has been established over a long period on an individual basis between the physician and the patient; and

WHEREAS, The fee rendered is usually based on the duration of service in time and effort, responsibility involved, material expenditures, the financial status of the patient and the qualifications of the physician; and

WHEREAS, The practice of anesthesiology as well as other specialties has been defined by the American Medical Association as the "practice of medicine"; therefore be it

Resolved, That the presentation of bills and the collection of private fees for medical service rendered by other than recognized physicians be hereby established as evidence of the practice of medicine; and be it further

Resolved, That persons sending such bills shall be liable to the penalties set forth in the medical practice acts and/or laws pertaining to medical education regulating the practice of medicine.

The resolutions were tabled on motion of Dr. Robert E. Schlueter, Missouri, seconded by Dr. Robert H. Hayes, Illinois, and carried.

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