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The Inhalation of Ethyl Alcohol by Man[1]

I. Industrial Hygiene and Medicolegal Aspects
II. Individuals Treated with Tetraethylthiuram Disulfide

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I. Industrial Hygiene and Medicolegal Aspects

THE INHALATION of ethyl alcohol has been investigated in man hitherto only by Loewy and von der Heide (1). These authors, as well as others (2, 3), have also studied the effects of this mode of administration in rats, guinea pigs and dogs. On the basis of their animal experiments together with their data on humans, Loewy and von der Heide concluded that a concentration of 0.1 per cent and certainly no more than 0.25 per cent of alcohol in air was the maximum that could be allowed in workrooms. The fact that the smaller the animal the higher is the rate of ventilation per unit of weight, so that comparisons between man and smaller animals cannot be made unless this factor is taken into account, was overlooked by Loewy and von der Heide. Nevertheless, on the basis of their work, and with this important factor left out of account, the maximum allowable concentration for daily exposures of 8 hours is now set at 0.1 per cent (4, 5).

Examination of the original publication does not reveal any reason

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for accepting this value for the allowable concentration. The human subjects in the study by Loewy and von der Heide were exposed to various concentrations of alcohol in air for up to 2 hours in an 8,000-liter chamber. The concentration of alcohol resulting in the blood after exposure was not determined. In the urine of one subject, collected during a 2-hour exposure, the concentration of alcohol was 0.083 per cent, a value which, on the basis of new experiments to be described here, can only be explained as due to contamination of the urine sample by the atmosphere of the chamber. The symptoms reported by Loewy and von der Heide's subjects, when there were any, included headache, intraocular tension, tiredness, and intense desire to sleep, all of which might have been caused by confinement in the chamber. That they could not have been caused by the small amounts of alcohol absorbed and present in the body will be shown below.

The present investigation was undertaken in view of numerous queries addressed to this Laboratory concerning the possibility of intoxication with alcohol through inhalation. The question has medicolegal interest as well as importance for industrial hygiene and safety, since alcohol is widely used as a solvent in industry. The maximum allowable concentration is accepted at present as 0.1 per cent (1.8 mg. per liter of air). It will be shown later that the rate of lung ventilation would have to be at least 65 liters per minute, at a concentration of 1.8 mg. per liter, for the intake of alcohol to exceed its loss through oxidation and excretion. If all the alcohol taken in by the lungs is not absorbed, the rate of ventilation would have to be greater. Since a concentration of 0.1 per cent seems far below the level which might result in a detectable concentration of alcohol in the blood, it was deemed necessary to study the concentration of alcohol developed in the blood from the inhalation of various concentrations in the air at varying rates of ventilation.

Experimental

Method.—Different concentrations of alcohol in air were obtained by vaporizing 95-per-cent ethyl alcohol at a measured rate (passing it through a rotameter at a constant pressure head) into a long Vycor test tube which was heated by a gas flame. Room air was pumped at the rate of 60 liters per minute through the Vycor tube and the air–alcohol mixture swept out of the tube was cooled by passing through a cooled copper tube. The cool alcohol-in-air mixture was passed into a cylindrical transparent plastic hood (33 cm. in diameter by 23 cm. high), baffled at its entrance, and provided with a cloth skirt. This hood was suspended over the head of the seated subject and the cloth skirt was fitted snugly about the subject's neck. The hood was then lowered maximally to decrease the distance between the inlet of the alcohol–air mixture and the subject's nose and mouth; this also enabled the subject to view his surroundings and to be observed. The air flow was large enough to prevent the subject from breathing any air other than the mixture being fed into the hood.

The concentration of alcohol in the air being respired was analyzed at frequent intervals by obtaining an air sample with a glass syringe whose needle penetrated the upper portion of the plastic hood. Analysis of alcohol in the air and blood was made by a new method (6) which is accurate and has great sensitivity. The concentration of alcohol in the air as determined by analysis was equal to the concentration calculated from the air flow and the rate of alcohol introduced.

In order to maintain effectively constant rates of ventilation above the resting rate, carbon dioxide was allowed to enter the inlet of the pump through a bypass at a constant rate. In this manner the subject respired air–alcohol mixtures containing a constant percentage of carbon dioxide, and the rate of ventilation could be increased above the resting rate to any desired level and kept constant at this level for any desired duration of exposure. This technique eliminated the need for a large chamber where the ventilation could be increased by work. This technique also served to increase the ventilation for long periods without exhausting the subject.

Concentrations Causing Intolerable Irritation

Subjects were placed under the hood in order to observe the local irritant effects of varying concentrations of ethyl alcohol in air. At concentrations from 10 to 20 mg. per liter there was some coughing and smarting of the eyes and nose, but these symptoms disappeared in 5 to 10 minutes. The atmosphere was not satisfactory from the point of view of comfort but could be tolerated easily. At 30 mg. per liter there was continuous lachrymation and marked coughing, but this concentration could be tolerated, although with discomfort. At 40 mg. per liter the atmosphere was just tolerable but the judgment of all subjects was that it would be impossible to remain in it for any prolonged time. Above 40 mg. per liter the atmosphere was intolerable and suffocating; it was impossible to remain in such an atmosphere for even short periods. When the rate of ventilation was increased between two and three times the resting level, the effects were exacerbated so that lower concentrations became less tolerable. In our judgment, the concentration which is just tolerable is about 20 mg. per liter when the ventilation rate is at a point equivalent to hard work, that is, 30 liters per minute. Based on these qualitative observations, all further experimentation was performed at a concentration of approximately 15 mg. per liter.

Percentage of Alcohol Absorbed from Respired Air

The factors concerned with the elimination of alcohol, that is, metabolism and excretion through various avenues, are well known and understood. The factors determining the intake of alcohol are rate of ventilation, concentration respired, time, and percentage absorbed from the respired air; only the latter had to be determined separately. With all of these data at hand it was thought that an equation might be derived on theoretical grounds which would express quantitatively the relations between all the data.

Method.—The percentage of alcohol absorbed from the respired air was determined by filling an 80-liter plastic balloon with a known concentration and volume of alcohol and carbon dioxide. The subject was then placed under the hood and acclimatized for a 10-minute period to the same concentration of alcohol and carbon dioxide as in the balloon. While the subject was still under the hood, a face mask with inlet and outlet valves was attached to him and the air–CO_2–alcohol mixture in the balloon was completely inspired and the expirations were collected in a second plastic balloon. The volume of the second balloon and the concentration of alcohol in it were determined.

TABLE 1.—*Percentage of Alcohol Absorbed from the Respired Air*

Subject No.	*Ventilation Rate* (liters/min.)	*Concentration in Inspired Air* (mg./liter)	*Per Cent Absorbed*
1	8	13.2	72
1	7	14.1	63
1	21	11.0	59
2	22	13.6	60
2	13	15.3	56
2	14	14.0	63
2	25	14.7	61
3	12.5	14.7	64
3	11	19.3	64

With this technique the percentage of alcohol absorbed from the inspired air was determined at rates of ventilation from 7 to 25 liters per minute and at concentrations of alcohol from 11 to 19 mg. per liter. The results are exhibited in Table 1. The average absorption is about 62 per cent and seems to be independent of concentration and rate of ventilation.

Blood Alcohol Concentration from Inhalation of Alcohol

Eight experiments were performed with three male subjects. Blood samples were taken before the start and at hourly intervals after the start of inhalation. The blood samples were taken in a room free of alcohol vapor in order to avoid contamination; this necessitated an absence from the inhalation hood of no more than 1 minute. The concentration of alcohol in the initial blood samples ranged from 0.9 to 2.7 mg. per 100 ml., slightly below the average value of 4 mg. per 100 ml. for human blood found by Gettler, Niederl, and Benedetti-Pichler (7); the preliminary value of the concentrations was subtracted from subsequent values. The concentration of alcohol in the air was determined at about hourly intervals. The rate of ventilation was determined several times during the experimental period with the subject in the hood and provided with a face mask so arranged as to inspire air from the hood and expire it into a Douglas bag, the volume of which was then measured.

In this manner the concentration of alcohol in the blood was determined in all three subjects when the ventilation rate was the resting rate and the exposure was 3 hours, and when the rate of ventilation was increased to 15, 22 and 25 liters per minute with an exposure of 3 hours; and in two of the subjects at 15 and 22 liters per minute when the exposure was for 6 hours. The concentration of alcohol in the inspired air ranged from 13 to 17 mg. per liter.

The reactions to the inhalation of alcohol by the subjects were slight. An initial smarting of the eyes and nose was felt which did not persist for more than 5 to 10 minutes. There was no feeling of weakness, tiredness, intraocular tension, or desire to sleep. The obtained concentrations of alcohol in the blood, with the relevant data, are shown in Figure 1.

Examination of the data reveals that the concentration of alcohol attained in the blood is proportional to the concentration of alcohol in the air and to the rate of ventilation, and inversely proportional to the weight of the subject, a result which is to be expected on theoretical grounds. This may be expressed as:

$$C_B \propto \frac{C_A R}{W}$$

where C_B is the concentration of alcohol in the blood in milligrams per liter, C_A is the concentration of alcohol in the inspired air in milligrams per liter, R is the rate of ventilation in liters per minute, and W is the weight in kilograms. $C_A R/W$ is then the alcohol intake per unit of weight per unit of time, and will be designated α. As the five lower curves in Figure 1 indicate, there are values for α

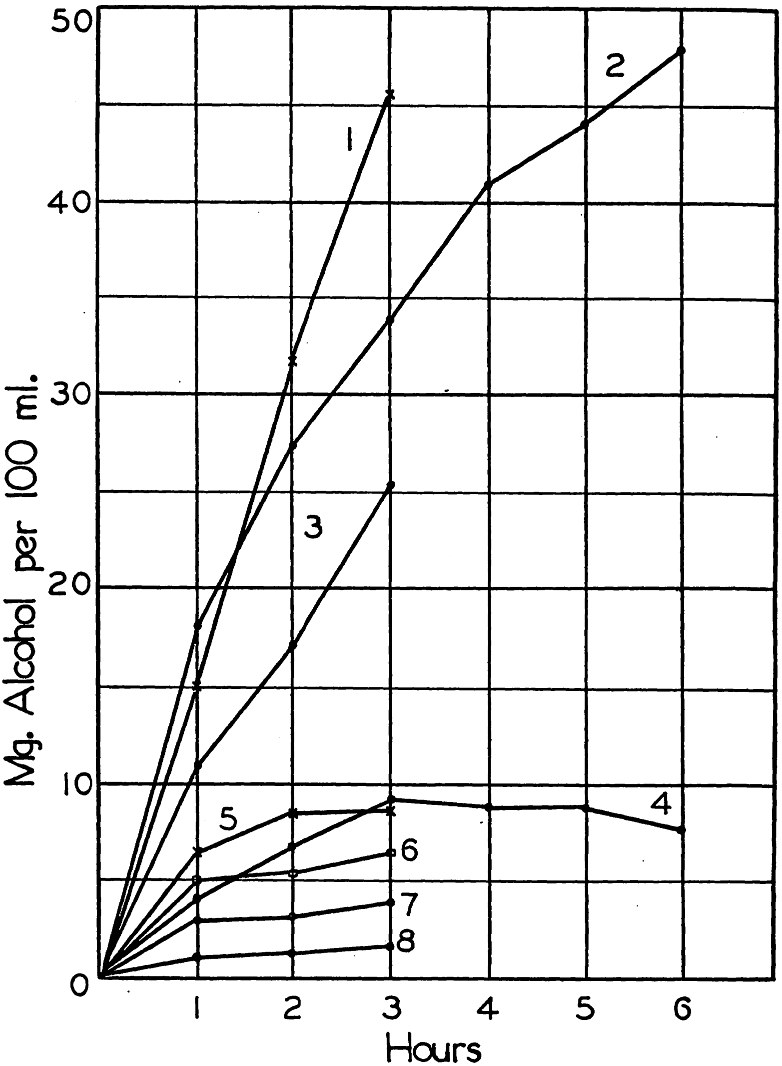

FIGURE 1.—*The Concentration of Alcohol in the Blood from Inhalation of Alcohol.* CURVE 1: Subject 1, 72 kg., 14 mg./L., 25 L./min.; $\alpha = 4.9$. CURVE 2: Subject 2, 82 kg., 16 mg./L., 22 L./min.; $\alpha = 4.3$. CURVE 3: Subject 2, 82 kg., 15 mg./L., 22 L./min.; $\alpha = 4.0$. CURVE 4: Subject 3, 83 kg., 15 mg./L., 15 L./min.; $\alpha = 2.7$. CURVE 5: Subject 3, 83 kg., 15 mg./L., 15 L./min.; $\alpha = 2.7$. CURVE 6: Subject 1, 72 kg., 16 mg./L., 6.7 L./min.; $\alpha = 1.5$. CURVE 7: Subject 3, 83 kg., 16 mg./L., 7.0 L./min.; $\alpha = 1.3$. CURVE 8: Subject 2, 82 kg., 15 mg./L., 8.0 L./min.; $\alpha = 1.5$.

at which the concentration of alcohol in the blood rises slightly but then levels off. It is obvious that at this state of equilibrium the metabolism and intake of alcohol are equal. The complete expression then becomes

$$C_B \propto \frac{C_A R}{W} - M = \alpha - M$$

where M is the rate of alcohol oxidation in milligrams per kilogram, neglecting the small amount of alcohol lost through the urine and the lungs. If the rate of metabolism were a constant quantity then one would expect that at values of α less than or equal to M, no alcohol should be found in the blood. If α exceeded M, then there should be a straight line rise in the concentration of alcohol in the blood, the steepness of the rise being given by α minus M. This is not the case. It would therefore appear that at low concentrations of alcohol in the blood, that is, below 20 to 30 mg. per 100 ml., the rate of oxidation of alcohol may be proportional to the concentration, and above these concentrations the maximal rate of alcohol oxidation is achieved. If this be the case, one would expect to find that at increasing values of α less than or equal to the maximal rate of oxidation various equilibrium levels of alcohol will be obtained in the blood. That this is probably the case is seen from the five lower curves in Figure 1. It follows from this that the maximum equilibrium level that can be reached is between 20 and 30 mg. per 100 ml., since it is at about this concentration that the oxidation of alcohol attains its maximal rate.

An attempt was therefore made to solve the following equation for C_B:

$$\frac{dC_B}{dt} = k\alpha - M$$

where k is a constant involving the percentage of alcohol absorbed from the inspired air (0.62) and the distribution of alcohol in the body.[2] Since M is itself a function of C_B, the equation

$$M = \beta - \beta e^{-\gamma C_B}$$

may be employed, since with proper choice of the constants β and γ, the value of M approaches a maximum rapidly. Other functions of C_B might be employed. The complete solution of the equation involves four cases. The calculations are laborious, and at values of

[2] The assistance of Charles E. Rickart, Department of Mathematics, Yale University, in the derivation and solution is gratefully acknowledged.

C_B where prominent intoxicating effects are to be expected the discrepancies are too large to be useful. The values for C_B calculated from the equations agree with the experimental values in most instances to no better than 20 per cent. The reasons for this lack of agreement seem to lie mainly in the facts that the rate of oxidation of alcohol varies in different individuals and in the same individual at different times, and that the percentage of body weight that is water is also different in different individuals.

It is much simpler to derive an expression which provides a value below which an equilibrium value for C_B will be attained and above which C_B will continue to increase with exposure. Thus if it is assumed that the maximum rate of oxidation of alcohol is represented by 2.67 mg. per liter of blood per minute, a low value chosen with considerations of safety in mind, then $k\alpha = 2.67$ expresses the highest equilibrium value that can be attained. If it is assumed that 70 per cent of the body weight is water, and that 62 per cent of the alcohol inspired is absorbed, then

$$\frac{0.62}{0.7}\alpha = 2.67 \text{ and } \alpha = 3.0.$$

From Figure 1 it is seen that where the value for α is less than 3.0 a steady state is attained, while where the value for α is greater than 3.0 the concentration of alcohol in the blood continues to rise. It is possible to calculate from this expression that for a man weighing 70 kg. and breathing an atmosphere containing 15 mg. of alcohol per liter, a ventilation rate of more than 14 liters per minute is needed in order to obtain a continuous rise in the concentration of alcohol in the blood.

If now the value given in the literature for the maximum allowable concentration is used, i.e., 1.8 mg. per liter, than a man of 70 kg. would have to breathe at a rate greater than 117 liters per minute in order to obtain a continuous rise in the concentration of alcohol in the blood. Since during continuous hard work the rate of ventilation is of the order of 30 liters per minute, a concentration of alcohol in the air not exceeding 7.0 mg. per liter is a more realistic standard for the maximum allowable concentration than the one hitherto accepted. Under working conditions where rates of ventilation less than 30 liters per minute are encountered, and this is the usual case, the concentration of alcohol in the air may be proportionately higher than 7 mg. per liter.

The maximum allowable concentration proposed here can yield concentrations of alcohol in the blood of 20 to 30 mg. per 100 ml. This concentration does not cause sufficient impairment of the faculties to create an industrial hazard, and is well within the universally accepted limit of 50 mg. per 100 ml. below which it is safe to operate a motor vehicle.

For medicolegal purposes, where it is desired to ascertain whether or not an individual might attain a specified concentration of alcohol in the blood from the inhalation of alcohol, an expression has been derived from the present data which gives an estimate of this concentration. The expression is $C_B = 7.4(\alpha - 3.0)T$, where T is time in hours. The calculated value for C_B is in fair agreement with the

TABLE 2.—*Concentration of Alcohol in Blood*

Actual (mg./100 ml.)	*Calculated* (mg./100 ml.)	*Actual* (mg./100 ml.)	*Calculated* (mg./100 ml.)
15	14	41	38
32	28	44	48
46	42	48	58
18	10	11	7
27	19	17	15
34	29	27	22

actual values for C_B (Table 2) for medicolegal purposes, since under ordinary circumstances the concentration of alcohol in the air and the rate of ventilation will not be known precisely. From this equation, at values of α greater than 3.0, it is readily apparent that the intoxicated state is attainable if the exposure is long continued and uninterrupted. At a value of α of about 5.0, an exposure of 6 to 8 hours will result in a concentration of 90 to 120 mg. per 100 ml.

II. INDIVIDUALS TREATED WITH TETD

Patients under treatment with tetraethylthiuram disulfide (TETD) must be on guard against intake of alcohol in any form lest they experience severe reactions. Two instances have been reported to us of patients who claimed to have had reactions as a result of inhaling alcohol. Our clinical observations indicate that an alcohol concentration in the blood of 0.02 to 0.03 per cent can result in severe reactions in an individual pretreated with TETD. It is obvious, therefore, that the maximum allowable concentration of alcohol in the air proposed in the preceding section, which can result in alcohol concentrations of 0.02 to 0.03 per cent in the blood, is not safe for the individual receiving TETD.

Four patients at the Blue Hills Clinic who had been treated with

TETD for periods of 4 to 8 months volunteered to serve as subjects in experiments to determine the allowable concentration of alcohol in air for individuals receiving this drug. The subjects were exposed to various concentrations of alcohol in air for periods of about 2 hours, or until the first signs of a reaction became apparent. The first signs were taken to be flushing of the face or chest and a rise in pulse rate, these having been the first symptoms observed in all reactions in patients tested with alcohol by routes other than inhalation.

The subjects inhaled the alcohol-in-air mixture, through the apparatus described previously, while lying in bed. Alcohol was not admitted into the air until the subject had reached a basal level in pulse rate and blood pressure. The resulting data are collated in Table 3.

TABLE 3.—*Effect of Alcohol Inhalation by TETD-Treated Subjects*

Subject No.	*Experiment*	*Sex*	*Weight* (kg.)	*Alcohol Inspired* (mg./liter)	*Ventilation Rate* (mg./liter)	*Exposure Time* (hours)	*Alcohol in Blood* (mg./100 ml.)	*Reaction*
1	1	M	82	15	7	1.7	6	Yes
2	2	M	75	7.5	7	1.8	3	No
3	3	M	68	7.5	15[1]	1.7	9	No
4	4	F	63	15	15[1]	0.4	7	Yes
4	5	F	63	7.5	7	2.0	8	No

[1] In this experiment 2 per cent carbon dioxide was admitted to raise the ventilation rate.

There is some variation in response, but at 7.5 mg. per liter and 7 liters per minute no reaction was observed in experiments 2 and 5. In experiments 1 and 3, which are equivalent in terms of the amount of alcohol inhaled, only one positive reaction was observed. At 15 mg. per liter and 15 liters per minute the reaction was positive and occurred in less than half an hour.

It seems reasonable to conclude that at an exposure of 7.5 mg. per liter and 7 liters per minute, or the equivalent, no reaction will occur. Since the rate of ventilation may rise to four times the resting rate, it is suggested that the allowable concentration of alcohol in air, for an individual under treatment with TETD, be set at 2 mg. per liter.

In view of this relatively low allowable concentration of alcohol in air, the question arose as to the possible hazard to TETD-treated individuals in commercial and industrial establishments where alcohol vapor may be anticipated. The amount of alcohol encountered may be illustrated by the fact that air samples taken at various places in a brewery gave concentrations of 0.07, 0.09, 0.20, 0.27, 0.78 and 1.42 mg. of alcohol per liter of air. The highest concentration was found above an ale fermenter. Considerable ventilation is used in a brewery to remove carbon dioxide. Inadequate ventilation could result in a double hazard for the TETD-treated individual: a rise in the concentration of carbon dioxide together with a concomitant rise in the concentration of alcohol would increase the amount of alcohol inhaled to a level at which an alcohol reaction would be provoked; carbon dioxide at high concentration is also toxic. Analysis of air samples from three taverns selected on the basis of poor ventilation and crowded conditions gave concentrations of 0.30, 0.30, 0.44, 0.76, 0.80 and 1.18 mg. of alcohol per liter. These concentrations could not provoke a positive alcohol reaction in TETD-treated individuals.

Although the concentrations of alcohol found in the air of the brewery and the taverns are below the maximum allowable concentration of 2 mg. per liter, it is likely that in industrial situations where alcohol is used in the form of a spray, or as a solvent, the concentration may reach a level that would be hazardous for the TETD-treated patient.

Summary

1. A search of the literature pertaining to the inhalation of alcohol by man indicated that the presently accepted value for the maximum allowable concentration in the air was based on vague qualitative observations and that it was erroneous from the standpoint of industrial safety and hygiene and of no value for medicolegal purposes.

2. Qualitative observations were made of the effects of varying concentrations of alcohol in the air at various rates of ventilation. It is concluded that concentrations greater than 40 mg. per liter are intolerably irritating while at concentrations between 10 and 20 mg. per liter work might be carried on, albeit not in comfort.

3. Determinations of the percentage of alcohol absorbed from the inspired air showed that 62 per cent of the alcohol is absorbed.

4. Human subjects were exposed to various concentrations of alcohol in air for periods up to 6 hours, at various rates of ventilation. Determinations of the resulting concentrations of alcohol in the blood indicated a simple relationship for calculating the maximum allowable concentration under various conditions of work.

A maximum allowable concentration of 7 mg. per liter is proposed, which is about 4 times the accepted value.

5. It was shown that intoxication can result from the inhalation of alcohol under certain conditions, and an expression has been given for calculating the concentration which may be expected to develop in the blood provided four facts are known: the concentration of alcohol in the air, the rate of ventilation of the individual, the individual's weight, and the duration of the exposure.

6. Observations on patients under treatment with tetraethylthiuram disulfide showed that the maximum safe concentration for TETD-treated individuals is 2 mg. of alcohol per liter of air.

REFERENCES

1. Loewy, A. and von der Heide, R. Über die Aufnahme des Äthylalkohols durch die Atmung. Biochem. Z. **86**: 125–75, 1918.
2. Gréhant, N. Dosage de l'alcool éthylique dans le sang après l'injection directe dans les veines ou après l'introduction des vapeurs alcooliques dans les poumons. C. R. Acad. Sci., Paris **123**: 192–4, 1896.
3. MacLeod, L. D. The controlled administration of alcohol to experimental animals. Brit. J. Addiction **45**: 112–24, 1948.
4. Drinker, P. and Cook, W. A. Maximum allowable concentrations of atmospheric impurities. J. industr. Hyg. Toxicol. **31**: 51–4, 1949.
5. Jacobs, M. B. The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents; p. 619. New York; Interscience Publishers; 1949.
6. Lester, D. and Greenberg, L. A. The determination of ethyl alcohol. [To be published.]
7. Gettler, A. O., Niederl, J. B. and Benedetti-Pichler, A. A. The isolation of pure, anhydrous ethyl alcohol from non-alcoholic human and animal tissues. J. Amer. chem. Soc. **54**: 1476–85, 1932.