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THE ALIPHATIC ALCOHOLS: THEIR TOXICITY AND POTENTIAL DANGERS IN RELATION TO THEIR CHEMICAL CONSTITUTION AND THEIR FATE IN METABOLISM

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THE ALIPHATIC ALCOHOLS: THEIR TOXICITY AND POTENTIAL DANGERS IN RELATION TO THEIR CHEMICAL CONSTITUTION AND THEIR FATE IN METABOLISM

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PREPARED BY DIRECTION OF THE SURGEON GENERAL

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INTRODUCTION

The aliphatic alcohols comprise a large number of chemicals which are of industrial importance. They are used as solvents for many different purposes and they are the starting materials in the manufacture of other chemicals, such as esters and ethers, which, in turn, are used as solvents; on the other hand, they may be met with as the result of the decomposition of the same products, especially by hydrolytic cleavage in the organism.

The most common compounds of this type are the monovalent or monohydric alcohols, such as methyl alcohol and its higher homologues. In recent years the bivalent alcohols, ethylene glycol and its homologues and their esters and ethers, have gained in importance as solvents, and recent developments make it most likely that the trivalent alcohol, glycerol, which by itself is used extensively, will become the starting material for a new line of solvents. Alcohols with more than three hydroxylic groups are of no industrial toxicological importance; they have none of the toxicological characteristics of mono- and bivalent alcohols.

In the following, the toxicological action of the various alcohols is discussed and attempts are made to affiliate their toxicity to their physico-chemical properties and their fate in the organism.

A. THE MONOVALENT ALCOHOLS

I. THE SATURATED MONOVALENT ALCOHOLS

The monovalent alcohols are characterized by the chemical formula ROH. They have irritant and narcotic properties which, as will be shown, vary with their chemical configuration and their physico-chemical properties. The lowest member of this series is methyl alcohol.

a. Methyl Alcohol

Chemical characteristics.—Methyl alcohol (methanol, wood alcohol, wood spirit, Columbian spirits), of the formula CH_3OH, has a molecular weight of 32.04[1] and the specific gravity 0.792 at $\frac{20°}{4°}$ C. It solidifies at $-97.8°$ C. and boils at $64.7°$ C.; its refractive index is 1.3288 at 20° C.; it is a colorless fluid with an aromatic odor; and it is miscible in all proportions with water, alcohol, and ether.

According to Coward and Jones (1939) the lower limit of inflammability of methyl alcohol is: with upward propagation of the flame 5.5 to 7.10 percent; with horizontal propagation 6.40 to 7.9 percent; and with downward propagation 6.80 to 8.0 percent; the corresponding values for the upper limit of inflammability being 21.0 to 36.5 percent, 13.5 to 30.5 percent, and 26.5 percent.

The ignition temperature in an atmosphere of air is 470° C. (Thompson, 1929).

Ordinary methyl alcohol, as prepared by distillation of wood, may contain such impurities as acetone, methyl acetate, dimethyl acetate, furfural, allyl alcohol, homologues and condensation products of acetone oily bodies, and other compounds (Baskerville, 1913). Synthetic methyl alcohol is usually of a high degree of purity but may contain traces of formaldehyde, acetone, and amines (Browning, 1937).

According to the biennial census of manufacturers, 1937–I, as published by the United States Department of Commerce, Bureau of the Census, the production of synthetic methyl alcohol increased from 8,793,000 gallons in 1935 to 31,606,320 gallons in 1937, which illustrates the wide industrial use of this material. According to Chemical and Metallurgical Engineering (49: 73, 1942) the production of synthetic methanol in 1941 surpassed that of the preceding year by nearly 25 percent or approximately 10,000,000 gallons.

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[1] Unless otherwise stated the physico-chemical data are quoted from Lange's Handbook of Chemistry, Handbook Publishers, Inc., Sandusky, Ohio, 1941.

Uses.—Large quantities of methyl alcohol are used in the manufacture of formaldehyde and formic acid, in the synthesis of methyl compounds, in the varnish and lacquer industry, and as a solvent for resins, and it may, therefore, be met with in the manufacture of artificial flowers, in the hat and shoe industries, in the varnishing of vats in breweries, and in the polishing of furniture. It is also used as a cleaning agent for many purposes, as an admixture in motor fuel, and as an antifreeze in radiators. It is added to industrial ethyl alcohol as a denaturing agent.

Identification of methanol.—A 5-percent solution of methanol is completely oxidized to carbon dioxide by heating with a solution of 5 gm. of potassium bichromate in 30 cc. of sulfuric acid (1:2) in contrast to the behavior of ethyl alcohol which is oxidized to acetic acid.

Methyl alcohol may best be identified and distinguished from ethyl alcohol by the relation of its refraction to its specific gravity, as pointed out by Gettler (1920) who refers to the publications of Leach and Lythgoe (J. Am. Chem. Soc., 27: 964, 1905 and U. S. Dept. Agri. Bur. Chem. Bull. No. 107, 100, 1907).

It may be identified by the following chemical reactions:

1. Most commonly, methyl alcohol is oxidized to formaldehyde by oxidation with potassium permanganate. The formaldehyde formed is then identified by other reactions. Forty-six such tests were studied by Gettler (1920) who considered seven of these (listed in table 1) as the most reliable and most sensitive, the sensitivity of the first five color reactions being 1:200,000. The last two quoted in the table were more specific but less sensitive.

2. Methyl alcohol may be transformed to methyl iodide by heating with red phosphorus and iodine. The methyl iodide is distilled off and heated with silver nitrite, and the resulting nitromethane, when mixed with ammonia and vanilline, yields a red color (Rosenthaler, 1923).

Table 1.—*Tests for the identification of methyl alcohol*

[Gettler, 1920]

Test	Reference
Phenylhydrazine—ferric chloride—hydrochloric acid.	Vitali, D.: Chem. Zentr., 2: 135, 1898. Meth: Chem. Ztg., 30: 666, 1906. Utz, F.: Chem. Zentr., 1: 602, 1906. Rimini, E.: Chem. Zentr., 1: 1152, 1898.
Phenylhydrazine—sodium nitroprusside—sodium hydroxide.	Same as above and— Aweng, E.: Apoth. Ztg., 17: 159, 1912. Rimini, E. and T. Jona: Chem. Zentr., 1: 1147, 1912. Bono, A.: Chem. Ztg., 36: 1171, 1912.
Apomorphine—sulfuric acid	Wolff, H.: Chem. Ztg., 43: 555, 1919.
Pepton—ferric chloride	Salkowski, E.: Z. Untersuch. Nahrungs. u. Genusmittel, 36: 262, 1918.
Reduced fuchsine—sulfuric acid	Denigès, G.: Compt. rend. acad. sci., 90: 529, 832, 1910; Bull. soc. chim., ser. 4, 7: 951, 1910.
β-naphthol—hydrochloric acid	Mullikan, S. P.: A method for the identification of pure organic compounds. New York and London, 1: 24, 1911.
Hexamethylene—mercuric chloride	Romijn, G.: Chem. Zentr., 2: 257, 1895.

3. Methyl alcohol may also be identified by condensation with certain organic acids (Rosenthaler, 1923).

Treatment of methyl alcohol with sodium hydroxide and brombenzoyl chloride yields crystals of a p-brombenzoic acid methyl ester which have an anise-like odor and melt at 77° to 78° C.

Heating methyl alcohol with anhydrous oxalic acid yields the crystalline oxalic acid methyl ester with a melting point of 54° C.

4. The heating of methyl alcohol with sodium hydroxide and hydroxylamine hydrochloride and subsequent acidulation with sulfuric acid yields hydrocyanic acid which is distilled off and identified by the Prussian blue test or by the ammonium sulfocyanide test. In the opinion of Gettler (1920) this test ranks among the best tests for the identification of methyl alcohol.

5. According to Kollo and Crisan (1932) methyl alcohol may be distinguished from ethyl alcohol by the formation of characteristic compounds of their aldehydes with methone (5,5'-dimethyl-dihydro-resorcinol), these compounds differing with regard to their crystalline structure, melting point, and temperature of sublimation.

Methyl alcohol is usually determined by the procedure of Denigès (1910) which is based on its oxidation by permanganate to formaldehyde and the identification of the latter by Shiff's reagent. He pointed out that this reaction is improved by the presence of ethyl alcohol which results in the formation of formolacetal which reacts very promptly with the fuchsin reagent. This method was modified by Elvove (1917), Chapin (1921), Wright (1927), and Jephcott (1935).

The Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists (1940) gives the following procedure for the determination of methyl alcohol in the presence of ethyl alcohol:

Determination:

Reagents:

> *Solution A.*—Methyl alcohol, 25 percent by volume (±0.1 percent).
> *Solution B.*—Mix 20 ml. of solution A and 95 ml. of absolute ethyl alcohol (or equivalent in dilute alcohol) with H_2O to volume of 2 liters. Make all transfers and dilutions at 20° C.
> *Fuchsin–sulfurous acid.*—Dissolve 0.2 gm. of fuchsin in 120 ml. of hot H_2O, cool solution and add 2 gm. of Na_2SO_3 to 20 ml. of H_2O. Mix, add 2 ml. of HCl and dilute to 200 ml.

a. *Total alcohols.*—Measure at room temperature (20° C.) 25 ml. of sample, add 90 ml. of H_2O, neutralize to litmus with 5 percent NaOH, distill, and dilute volume of distillate to 100 ml. at same temperature as noted when original aliquot was measured. Determine total alcohol (as ethyl alcohol) from the specific gravity of distillate in usual way and estimate percentage of alcohol in original solution by means of proper dilution factor. Test a portion of this distillate by the U. S. P. test for methyl alcohol, taking precaution to determine that HCHO, as such, is not present. If methyl alcohol

is present transfer 10 ml. of distillate to a separator, add 40 ml. of saturated salt solution, shake with 25 ml. of petroleum benzine, and draw off the aqueous salt solution into distilling flask. Wash the petroleum benzine in the separator with two 10 ml. portions of saturated salt solution adding these to the portion already in distilling flask. Distill, receiving distillate in a 50 ml. graduate flask. Calculate quantity of ethyl alcohol to add to this distillate to make a 5 percent solution of total alcohol (assuming it to be all ethyl alcohol) when made up to 50 ml., add this calculated amount, and make up to a volume of 50 ml. Transfer 5 ml. of this distillate to a 200 ml. volumetric flask for color comparison with standards.

b. Color standards.—Transfer to 200 ml. volumetric flasks a series of aliquots, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 ml. of solution B, adding 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5, and 0 ml., respectively, of 5 percent ethyl alcohol. (These amounts of methyl alcohol represent percentages in original unknown solution when unknown is deducted as outlined above.)

c. Methyl alcohol.—To each of the standards and to the unknown add 1 ml. of H_3PO_4 (1+1) and 2 ml. of 3 percent $KMnO_4$ solution and allow mixtures to stand 10 minutes. Add 1 ml. of 10 percent oxalic acid solution and allow mixtures to stand until clear or transparent. Add 5 ml. of H_2SO_4 solution (1+3) and 5 ml. of the freshly prepared fuchsin-sulfurous acid mixture and allow solutions to stand 1½ hours. Dilute to 200 ml., mix thoroughly, and transfer equal quantities to a series of test tubes of uniform color and diameter for color comparison. Compare the unknown with the standard which it most nearly approaches in color intensity, approximating intervals less than 0.5 percent if desired. The value obtained represents the percentage of methyl alcohol in original sample.

In the U. S. Pharmacopoeia XII (1942) the following test for methyl alcohol is given:

To 1 drop of the distillate add 1 drop of dilute phosphoric acid (1 in 20) and 1 drop of potassium permanganate solution (1 in 20). Mix, allow to stand 1 minute, and add sodium bisulfite solution (1 in 20) dropwise until the permanganate color is discharged. If a brown color remains, add 1 drop of the diluted phosphoric acid. To the colorless solution add 5 cc. of freshly prepared chromotropic acid T. S.[2] and heat in a water bath for 10 minutes at 60° C.

In the presence of methyl alcohol a violet color appears.

According to Chapin (1921) carbohydrates, glycerol, formic and acetic acid, formaldehyde, and benzene should be removed prior to the determination of methyl alcohol but amyl alcohol and acetone are said to be less liable to interfere with the determination.

The determination of methyl alcohol in air.—There appears to be no standard method for the determination of methanol in air. Ackerbauer and Lebowich (1942) worked out the following procedure for the determination of methanol and formaldehyde. Five or ten liters of the air is sampled at the rate of 1 liter per 25 minutes by means of an aspirator through a train of 3 wash bottles. The first of these contains a mixture of 75 cc. each of a 1 percent solution of phosphoric acid and of a 2 percent solution of barium chloride to remove sulfur dioxide and formic and acetic acid which may be present in the air. The second wash bottle contains 200 cc. of an alkaline 5 percent solu-

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[2] Chromotropic test solution: Dissolve 50 mg. of chromotropic acid or its sodium salt (1,8-dihydroxynaphthalene-3,6-disulfonic acid) in 100 cc. of 75 percent sulfuric acid.

tion of potassium permanganate which absorbs and oxidizes methanol to formaldehyde. The third wash bottle contains 225 cc. of modified Schiff's reagent. The methanol in the second absorber is determined according to Wright's method (1927) and the formaldehyde in the third absorber according to the method of the same author. A fourth absorber containing 200 cc. of a 2 N sodium bisulfite solution for collection of any formaldehyde which may pass through the third wash bottle may be omitted, because under the conditions outlined only negligible amounts of formaldehyde escape absorption in the third wash bottle. In this solution formaldehyde may be determined by titration with sodium hydroxide, using rosolic acid as indicator. Lockemann and Croner (1914) absorbed the vapors of methyl alcohol and formaldehyde in water and determined first the formaldehyde by means of hydroxylamine hydrochloride and then the methyl alcohol together with the formaldehyde by oxidation with potassium permanganate, decolorization with oxalic acid and titration of the excess of the latter with ½ N potassium permanganate; the difference between these determinations giving the amount of methyl alcohol in the mixture.

The determination of methyl alcohol in blood.—Methyl alcohol in blood may be determined by Widmark's method for the determination of ethyl alcohol with slight modifications, as shown by Neymark (1936). In the determination of methyl alcohol 0.05 N solutions of sodium bichromate should be used for concentrations up to 2.5 per thousand and 0.1 N solutions for concentrations from 2.5 to 5 per thousand. The temperature of the water bath should be raised to 70° C. and the duration of the oxidation should be extended to 2½ hours. It appears, however, questionable to what extent this method can be considered as specific for methanol.

The absorption, distribution, fate, and elimination of methyl alcohol in the organism.—In most poisonings from methyl alcohol the absorption takes place in the gastro-intestinal tract following its ingestion as a beverage. However, it may be absorbed through the lungs in sufficient quantities to cause toxic and even fatal effects, as shown by Loewy and von der Heide (1914) in rats, by Bathem (1927) and Weese (1928) in mice, by Witte (1931) (quoted from Flury and Zernik, 1931) in cats, and by McCord (1931) in different species of animals. Sayers, Yant, Schrenk, Chornyak, Pearce, Patty and Linn (1942) found that with daily exposure to 450 to 500 p. p. m. of methyl alcohol in air the methanol level in the blood of dogs was from 10 to 15 mg. per 100 cc. Lowey and von der Heide (1914) stated that fat animals absorb less methyl alcohol than thin ones in accordance with the low partition coefficient $\frac{oil}{water}$ which for methyl alcohol is $\frac{2.5}{100}$; and they determined in rats the methyl alcohol content of the body after

inhalation of various concentrations of methyl alcohol in air for different periods of time (as illustrated in fig. 1). This figure shows that with inhalation of low concentrations the equilibrium of methyl alcohol in the body is complete within 2 hours, but that with higher concentrations considerable time may elapse before an equilibrium is reached. They found in rats that the percentile amount of methyl alcohol absorbed through the lungs decreases with the concentration f. i., with exposure to concentrations of 0.2 percent aproximately 50 to 80 percent was absorbed, with concentrations of 0.48 percent the absorption was only 30.8 to 42 percent, with 0.83 percent in air it was 24 percent, and with exposure to 2.25 percent it was only 13.3 percent.

ACCUMULATION OF METHANOL IN THE BODY OF RATS
FOLLOWING INHALATION
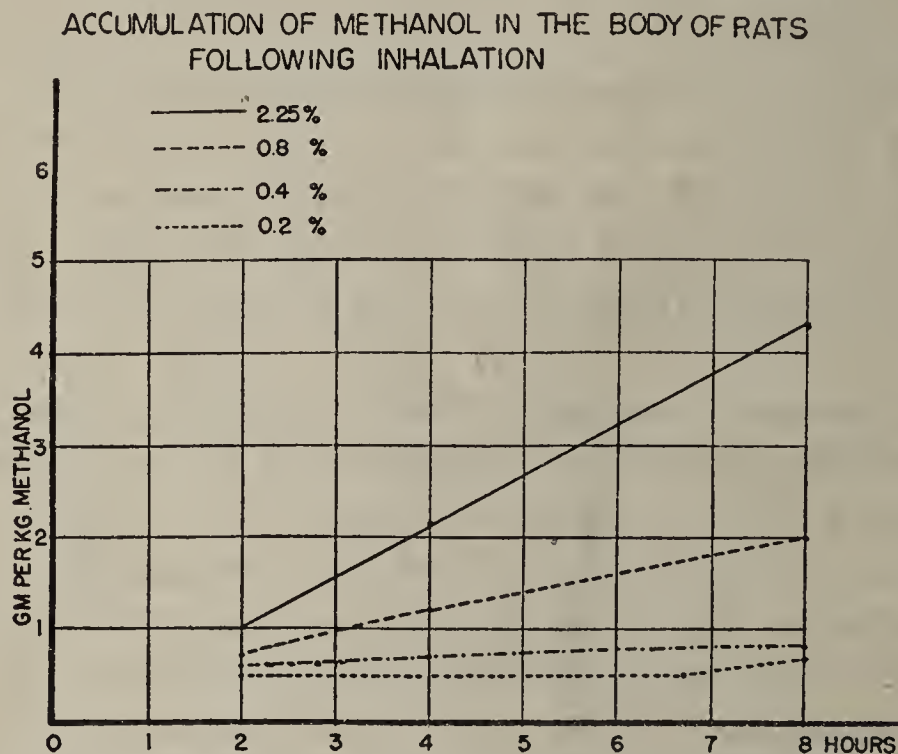
FIGURE 1.—This figure illustrates the accumulation of methyl alcohol in the body of rats following inhalation of various concentrations of methanol in air. (Redrawn from Loewy and von der Heide, 1914.)

Opinions regarding the absorption of methyl alcohol through the skin are quite contradictory. McCord (1931) and Sander (1933) claimed that in animals methyl alcohol is readily absorbed through the skin, and the former stated that for rats, rabbits, and monkeys, 0.5 cc. per kg. body weight may be fatal when applied to the shaven skin under conditions which prevent evaporation. On the other hand, Rost and Braun (1926) saw no toxic effects in rabbits and cats although methyl alcohol was absorbed, as indicated by its presence in the urine.

According to Neymark (1936) the *distribution of methyl alcohol in the organism* follows the same law as that established for ethyl alcohol with the exception that intake of food is less liable to interfere with the concentration in the blood. Yant and Schrenk (1937) stated that following inhalation and oral and subcutaneous administration the distribution of methyl alcohol is very rapid and that the amount in various tissues corresponds closely to their water con-

tent. They found no evidence of selective accumulation, retention, or predilection, and claimed that the methyl alcohol content of the body may be estimated from its concentration in the blood. Nicloux and Placet (1912) determined the methyl and ethyl alcohol content of various organs at the time of death, after the administration of single doses (as given in table 2), and this appears to corroborate the statement of Neymark (1936). This also shows that in comparison with ethyl alcohol the amounts of methyl alcohol isolated 24 and 48 hours after the administration are relatively high, as pointed out by Pohl (1918). Marinesco, Lissievici-Draganesco, Draganesco and Grigoresco (1929) found in 1 experiment, on the twenty-ninth day of continued daily oral administration of 4 cc. per kg. of methyl alcohol in the form of a 10 percent solution, practically identical values in brain and liver (0.539 and 0.524 cc. per 100 gm. tissue), whereas in another experiment the concentration in the liver was slightly lower than that in the brain, being 0.32 as compared with 0.405 cc. per 100 gm. of tissue. It should be pointed out that in both animals the methyl alcohol content of the eyeball was higher than that of the other organs mentioned, and similar results were reported by Yant and Schrenk (1937) who determined the concentration in various organs, as given in table 3.

Table 2.—*Distribution of methyl and ethyl alcohol in various organs of rabbits after intravenous administration*

[Nicloux and Placet, 1912]

	Dose cc./kg.	Cc. in 100 gm. of tissue					
		Blood	Brain	Liver	Kidney	Muscle	Urine
Methyl alcohol	12.8	2.55	3.36	2.86	1.93	0.76	0.50
Ethyl alcohol	7.3	1.8	2.39	1.93	1.6	.44	----------

With regard to the *fate of methyl alcohol in the organism*, most students of the subject (Joffroy and Serveaux, 1896; Bongers, 1895; Völtz and Dietrich, 1912; Nicloux and Placet, 1912; and Flury and Wirth, 1936) agree that methyl alcohol remains in the organism longer than ethyl alcohol, that its oxidation is slower, and that its elimination is delayed. According to Widmark (1933a), methyl alcohol is metabolized about 5 times as slowly as ethyl alcohol, the factor β for rabbits being 0.0008 for methyl alcohol (as determined by Bildsten) and 0.0042 for ethyl alcohol (as determined by Olow). Based on this factor the maximal amount of methyl alcohol metabolized by a man of 70 kg. body weight would amount to only 34 gm., which illustrates the possibility of rapid accumulation and delayed toxic effects. In addition to the slow oxidation the toxicity of methyl alcohol is greater than that of ethyl alcohol because the oxidation products, formaldehyde and formic acid, are both toxic agents.

Table 3.—*Relative distribution of methanol in tissues and fluids of dogs exposed to methanol vapors in air*

Presented on the basis of 100, chosen to represent the amount found in the blood. (Yant and Schrenk, 1937)

Concentration	4,000 p. p. m.	4,000 p. p. m.	15,000 p. p. m.	15,000 p. p. m.
Duration of exposure	12 hours.	5 days.	22 hours.	24 hours.
Killed after exposure	Immediately.	Within 1 hour.	Immediately.	48 hours later.
TISSUE OR FLUID	*Average of 2 dogs*	*Average of 2 dogs*	*Average of 2 dogs*	*Values of 1 dog*
Blood from heart	100.0	100.0	100.0	100.0
Aqueous and vitreous humor	106.5	125.3	------------	134.2
Urine from bladder	[1] 108.2	130.2	83.9	[2] 91.0
Bile	90.2	95.2	[1] 88.4	[2] 146.2
Stomach content	112.1	106.1	70.8	[2] 125.8
Heart muscle	86.6	93.9	77.1	------------
Cerebellum	83.9	88.5	[1] 66.6	88.0
Cerebral hemispheres	92.4	98.3	56.0	88.0
Kidney	90.9	99.4	64.1	71.6
Lungs	83.3	88.7	64.9	89.5
Muscle from leg	84.2	88.7	68.6	71.6
Stomach wall	77.1	86.6	68.4	83.6
Liver	71.8	79.7	73.7	88.3
Spleen	77.5	79.6	64.9	83.6
Brain stem	70.1	76.9	[1] 79.1	59.6
Testicles	------------	------------	67.2	88.0
Eye: Minus aqueous and vitreous humor	61.8	76.5	[1] 42.5	105.8
Pancreas	71.8	78.3	49.3	83.6
Intestinal wall	75.1	79.1	49.2	74.6
Spinal cord	64.6	76.7	[1] 69.1	43.3
Feces from large intestine	[1] 62.9	73.2	51.9	71.6
Adrenal	[1] 40.0	61.6	------------	------------
Bone marrow	39.2	39.4	31.1	46.2
Adipose tissue, intestinal	12.7	11.2	7.0	11.2

[1] Determined in 1 dog only.
[2] Excretory organs.

The statement that the toxicity of methyl alcohol is partly due to the formation of formaldehyde has often been questioned and many investigators, as Scott, Helz, and McCord (1933), were able to isolate methyl alcohol from various organs but failed to detect formaldehyde. This should not be surprising because even after the injection of formaldehyde solutions into tissues formaldehyde can be detected only in the tissue immediately surrounding the site of injection and for a short time after the administration, as was shown by Gianelli (1900) and McGuigan (1914). The main reason for this is that formaldehyde reacts very promptly with proteins, as was shown by Blum (Brunntaler, 1913), Sollmann (1902), and others, and therefore cannot be determined. It is only exceptionally that conditions exist which allow the detection of formaldehyde. Pohl (1893) found in one experiment an indication of formaldehyde formation. But Schrobback (1931), working with Keeser (1931b), showed that in the vitreous humor of calf eyes methyl alcohol is oxidized to formaldehyde, and the latter may be detected with an alkaline solution of phloroglucinol (1 percent phloroglucinol in 10 percent sodium hydroxide). Keeser (1931b) was able to demonstrate free formaldehyde in the abdominal fluid of rabbits during certain phases of methyl alcohol poisoning. In addition, Keeser and Vincke (1940) showed that under the proper conditions horse liver pulp may oxidize methyl alcohol to formaldehyde. Schrobback (1931) showed further that formalde-

hyde formed in the vitreous humor could be condensed with ammonium carbonate to form hexamethylene tetramine.

The formaldehyde formed from methyl alcohol is further oxidized to formic acid. Pohl (1893) showed that, following the administration of methyl alcohol, dogs and rabbits excrete formic acid, the maximal excretion occurring on the fourth day after the administration; and Rost and Braun (1926) noted the maximal formate excretion on the second and third days. Pohl (1893) determined the formic acid content of the blood as 0.4 mg. per 100 cc., of muscle as 0.5 mg. per 100 gm., of the kidney as 34.5 mg. per 25 gm., and of the lungs as 0.44 mg. per 50 gm. This evidently indicates that formates are not stored in the body. The increased excretion of formic acid following administration of methyl alcohol was also demonstrated by Hunt (1902) and

ELIMINATION OF METHYL AND ETHYL ALCOHOL FROM THE BLOOD OF RABBITS
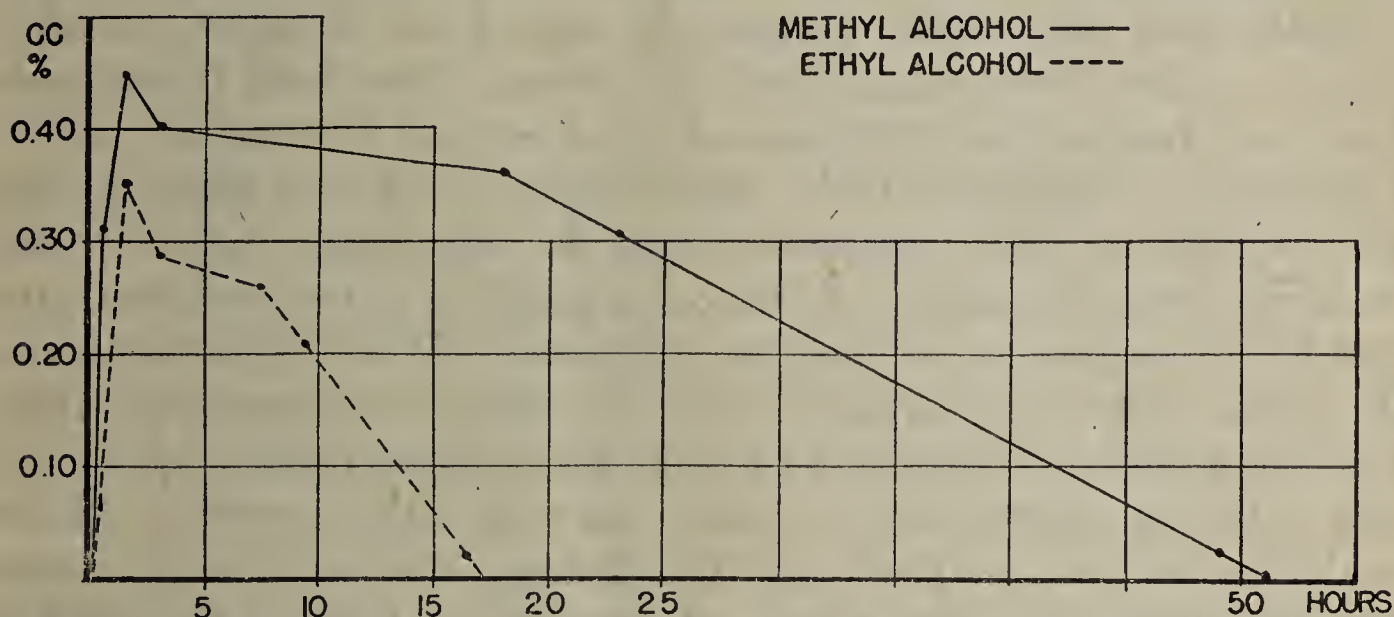
FIGURE 2.—This figure illustrates the elimination of methyl and ethyl alcohol from the blood of rabbits following ingestion of 5 cc. per kg. body weight of these alcohols in 10 percent solution. (Redrawn from Nicloux and Placet, 1912.)

by Kajizuka (1935), and following inhalation of methyl alcohol vapors by Bachem (1927). Klauer (1939) pointed out the importance of formic acid determinations in the urine for the diagnosis of methyl alcohol poisoning, and stated that concentrations of 100 mg. and more per 1500 cc. of urine are indicative of poisoning from methyl alcohol or certain other methyl compounds. Asser (1914) found that in dogs and rabbits the administration of ethyl and amyl acetate and of acetone following administration of methyl alcohol decreased the formation of formic acid in the urine, but he was unable to give an explanation of this phenomenon. According to Leo (1927), with continued administration of methyl alcohol the excretion of formic acid is decreased, but evidently this is not due to a more complete oxidation but is possibly caused by a greater excretion of unoxidized methanol.

As illustrated in figure 2, Nicloux and Placet (1912) showed that the *elimination of methyl alcohol* from the blood stream of rabbits

occurs much more slowly than that of ethyl alcohol, and the same holds true to an even greater extent for dogs, in which 120 hours were required for complete elimination of methyl alcohol from the blood. According to Widmark and Bildsten (1924), following its intravenous injection methyl alcohol disappears from the blood of rabbits at a certain rate which is independent of the concentration. As shown by Neymark (1936) the rate of disappearance of methyl alcohol from the blood is about 10 times as slow as that of ethyl alcohol but this can be speeded up by stimulation of the oxygen metabolism, as by the administration of 1,2,4-dinitrophenol.

Pohl (1908) and Cushny (1910) stated that, following intravenous injection, only traces of methyl alcohol are excreted through the lungs. Völtz and Dietrich (1912) found that after administration of 2 cc. per kg. to dogs, 15.3 percent of the amount given is excreted within 24 hours, 13.8 percent being exhaled and 1.5 percent being excreted with the urine. During the subsequent 24 hours an additional 7 percent was exhaled and 1.5 percent eliminated through the kidneys. During the entire period of 48 hours following the administration, 24.3 percent of the dose administered was excreted and 36.8 percent could be recovered from the organism, so that within 48 hours only 39 percent of the total quantity given had been oxidized in the organism. That the elimination of methyl alcohol with the urine is slow was already found by Joffroy and Serveaux (1896) and more recently confirmed by Rost and Braun (1926) who stated that after administration of single doses to rabbits, methyl alcohol could be detected in the urine for 4 days, the maximal excretion occurring on the second day. According to Völtz and Dietrich (1912) the elimination of methyl alcohol from the body may be speeded up by exercise, increased respiration, increase of body temperature (diaphoresis), and the administration of diuretics.

The general toxicological character of methyl alcohol.—In judging the toxicity of methyl alcohol it has been claimed that toxic reactions observed with certain brands of methyl alcohol should be credited to impurities rather than to the alcohol itself. Ohlemann (1902) believed that its toxic effects on the eye were caused, at least in part, by contamination with furfural, and Igersheimer and Verzár (1913) thought they were partly caused by fusel oils. But Eisenberg (1917) found no appreciable difference between the toxicity of methyl alcohol prepared by distillation of wood and Columbian spirits, and Reif (1923) analyzed samples of methyl alcohol, the ingestion of which had caused severe and fatal poisonings, without finding evidence that impurities, such as allyl alcohol, dimethyl sulfate, and others were responsible for the toxic action. Hunt (1925), Bertarelli (1932), and Alder, Buschke and Gordonoff (1938) showed that wood alcohol and synthetic methyl alcohol are of the

same toxicity. It appears, therefore, that the toxic effects described in the following are inherent properties of methyl alcohol and should not be credited to impurities.

In judging the potential hazards resulting from the absorption of methyl alcohol one has to distinguish between the toxic action which, as will be shown, is largely due to its metabolites, and the narcotic action which is the characteristic effect of alcohols. The narcotic action of methyl alcohol is less than that of its higher homologues, this being possibly explained by its low solubility in oils, fats, and lipoids and by its greater miscibility with water, and for this reason its affinity to and accumulation in certain organs is of a different order than that observed with the higher homologues. The toxicity of methanol is greater than that of ethyl alcohol on account of its less complete and slower oxidation, which results in the formation of more toxic metabolites and the accumulation of methyl alcohol in the organism. For this reason, continued exposure or repeated fractional doses may be more toxic than single doses.

The antiseptic action of methyl alcohol.—The antiseptic action of methyl alcohol is not very marked. Buchner, Fuchs and Megele (1901) found that 10 and 30 percent solutions do not kill brewer's yeast after contact for 1 hour, and 60 and 100 percent solutions were required to kill staphylococcus pyocyaneus aureus, bacillus typhi, and bacillus pyocyaneus. Whitney (1912) found methyl alcohol less toxic than ethyl alcohol as judged by the rate of reproduction of rotifera. Bokorny (1911) found that methyl alcohol may even be utilized by algae and bacteria as a source of carbon.

Methyl alcohol vapors have a more or less marked *irritant effect on the mucous membranes of the eye and of the upper respiratory tract.* Tyson and Schoenberg (1914) noted a copious discharge from the noses and mouths of animals exposed to vapors of methyl alcohol. Flury and Wirth (1934) stated that concentrations of 10 mg. per liter (7,640 p. p. m.) cause only moderate irritation and with concentrations of 90 mg. per liter (68,760 p. p. m.) the irritation is intolerable; and according to Lehmann and Flury (1938) prolonged exposure to concentrations of 65 mg. per liter (50,000 p. p. m.) cannot be tolerated.

The toxicity of methyl alcohol for animals.—In judging the toxicity of methyl alcohol it is generally found that fractional doses are more toxic than single doses but that in contrast to fractional doses, in single doses methyl alcohol is less toxic than ethyl alcohol, as found by Baer (1898), Hunt (1902), Langgaard (1912), Nicloux and Placet (1912), Rost and Braun (1926), Hufferd (1932a), and others. Rost and Braun (1926) claimed that the toxcity of methyl alcohol varies with different species, depending on the development of the central nervous system, and according to Scott, Helz and McCord (1933) rats are very susceptible and rabbits quite resistant.

The minimal fatal doses of methyl alcohol with oral administration has been given by various investigators as follows:

For mice, 10.5–12 cc., Weese (1928).

For rabbits, 8.8 cc./kg., Dujardin-Beaumetz and Audigé (1875).

For rabbits, 14 cc./kg., Langgaard (1913).

For rabbits, 13 cc./kg., Rost and Braun (1926).

For dogs, 8 cc./kg., Haskell, Hileman and Gardner (1921).

With intravenous injection the minimal fatal dose has been stated as:

For frogs, 5.3 cc., Sammartino (1933c).

For rabbits, 20.1 cc./kg., Lehman and Newman (1937b).

For rabbits, 16.1 cc./kg., Nicloux and Placet (1912).

For cats, 5.9 cc./kg. Macht (1920).

The minimal fatal dose for monkeys with absorption through the skin (if all loss by evaporation is prevented) was estimated by McCord (1931) as 0.5 cc. per kg.

The minimal fatal concentration of methyl alcohol vapors in air has been given for mice with exposure for 3 to 4½ hours as 0.4 to 0.6 cc. per liter (242,000 to 363,000 p. p. m.) by Weese (1928), and for rats and rabbits with exposure for an unknown number of hours as 0.0071 mole per liter (176,000 p. p. m.) by Bachem (1927). Witte (1931) (quoted from Flury and Zernik, 1931) found the minimal fatal concentration for cats with 3½ hours' exposure to be 380 mg. per liter (290,000 p. p. m.). With longer exposure the minimal fatal concentration is naturally much lower. Loewy and von der Heide (1914) found that rats die after exposure to concentrations of 41.5 mg. per liter (corresponding to 31,600 p. p. m.) for 10 to 20 hours, and with shorter exposure (6 hours) animals may die after several days, as found by Witte (1931) (quoted from Flury and Zernik, 1931) in cats with exposure to 97.1 and 224.3 mg. per liter (corresponding to 74,000 and 160,000 p. p. m., respectively). Sayers, Yant, Schrenk, Chornyak, Pearce, Patty, and Linn (1942) saw no significant toxic effects in dogs exposed daily for 8 hours for 379 days to concentrations of 450 to 500 p. p. m. of methanol in air.

Féré (1894b) found that the injection of methyl alcohol into fertilized eggs gives a higher incidence of malformation than observed with ethyl alcohol. Sollmann (1920) noted that continued administration of 5 percent methyl alcohol as drinking water to rats caused a considerable decrease of weight and, finally, death. The administration of 2.5 percent solutions was found to inhibit growth, this effect being more marked than that observed with 10 percent solutions of ethyl alcohol. Elhardt (1932) found that the injection of from 0.15 to 0.25 cc. of a 40 percent solution of methyl alcohol into the crop of growing chicks over a period of 2 months had a definitely injurious effect on growth and vigor. Smaller doses than these had a less

marked effect but affected unfavorably the growth of feathers, the development of the comb, and the general disposition of the chicks.

The *effect of methyl alcohol on the central nervous system* of animals was first studied by Poincaré (1878) who noted temporary staggering and attacks of hyperexcitation in animals kept in an atmosphere containing methyl alcohol for 8 to 16 months. Joffroy and Serveaux (1896) observed, in experiments with dogs, motor and sensory disturbances and changes of the body temperature and the respiration. Tyson and Schoenberg (1915) found that exposure of rabbits, dogs, and monkeys to high concentrations of methyl alcohol caused loss of consciousness, loss of pupillary reflexes, slight constriction of the pupils, and death. Macht and Leach (1929) studied the behavior of rats in a maze and found that methyl alcohol causes less severe depression of the central nervous system than ethyl alcohol. According to Lehman and Newman (1937b) the anesthetic dose for rabbits with intravenous injection is 10.5 gm. per kg., methyl alcohol being about one-half as effective as ethyl alcohol. Loewy and von der Heide (1914) studied the narcotic action of methyl alcohol in rats and dogs and found that it is not very marked, as illustrated in table 4. This was confirmed by Flury and Wirth (1934) who found that the narcotic action of methyl alcohol is weaker than that of methyl acetate, and by Mashbitz, Sklianskaya, and Urieva (1936) who found its narcotic action to be inferior to that of acetone. In the experience of Flury and Wirth (1934) concentrations below 170 mg. per liter (130,000 p. p. m.) cause, within 6 hours, only moderate narcosis in cats. Witte (1931) (quoted from Flury and Zernik, 1931) studied in cats the effect of inhalation of various concentrations of methyl alcohol in air, as illustrated in table 5. Comparison of these findings with those of Loewy and von der Heide (1914) appears to indicate that rats are more sensitive than cats and dogs. It should, however, be emphasized that, as pointed out by Flury and Wirth (1934), even concentrations as low as 86 mg. per liter (66,000 p. p. m.) may cause delayed death. Sammartino (1933c) noted in frogs, following intravenous administration of methyl alcohol, clonic-tonic convulsions, opisthotonus and, finally, progressive paralysis. In mammals, convulsions following the repeated administration of doses of 10 cc. of methyl alcohol (in 10 percent solution) to cats were reported as late effects by Rost and Braun (1926) and by Witte (1931) (quoted from Flury and Zernik, 1931) as shown in table 5. According to Gradinesco (1934), in dogs the intravenous injection of small doses of methyl alcohol (1 cc. per kg.) causes an increase of the respiratory amplitude, whereas large doses (10 cc. per kg.) cause a severe depression. Tyson and Schoenberg (1914) noted a marked reduction of the body temperature and a primary stimulation and subsequent depression of the

respiration following inhalation of methyl alcohol vapors, death being due to respiratory arrest.

With regard to the *effect of methyl alcohol on the peripheral nerve structures*, Verzár (1909) found that methyl alcohol causes a primary stimulation of the nerve fiber, being, however, less effective than ethyl alcohol. This was confirmed by Gradinesco and Degan (1934). Bonnet and Lelu (1933) found, with the nerve-muscle preparation of the

Table 4.—*Effect of inhalation of various concentrations of methyl alcohol in air on rats and dogs*

[Loewy and von der Heide, 1914]

Concentration		Duration of exposure in hours	Symptoms
Volume percent	Parts per million		
		Rats	
0. 20–0. 27	2,000–2,700	2–8	No effects.
0. 43–0. 48	4,300–4,800	2–8	With prolonged exposure, moderate depression.
0. 83–0. 88	8,300–8,800	2–8	Moderate depression.
2. 25	22,500	2–8	No effect during first 2 hours; later progressive depression of the central nervous system, passing into light narcosis after more than 4 hours of exposure.
6. 0	60,000	1½	Narcosis after 1 hour.
		Dogs	
1. 0–1. 4	10,000–14,000	2–4	No effect.
0. 15–0. 199	1,500–2,000	24	Do.

Table 5.—*Effect of inhalation of various concentrations of methyl alcohol in air on cats*

[Witte, 1931; quoted from Flury and Zernik, 1931]

Concentration		Duration of exposure in hours	Symptoms
Milligrams per liter	Parts per million		
26. 5	20,000	6	Tolerated without after effects.
48. 2	37,000	6	After 3 to 4 hours, staggering. 1 cat recovered, 1 died after 2 weeks with marked loss of fat.
97. 1	74,000	6	After 4½ hours, toleration of side position. One animal recovered, the other died on the third day, showing marked hyperemia of abdominal organs.
224. 3	160,000	6	After 2½ hours, toleration of side position; after 5 to 5½ hours, deep narcosis; after 4 to 5 hours, clonic convulsions. Death occurred after some days.
380	290,000	3½	After 2¼ hours, toleration of side position; after 3 hours, deep narcosis. Animals died some hours after the exposure.

frog, that 0.5 to 1.0 percent solutions of methyl alcohol first increase and later decrease the chronaxy of nerve and muscle, that of the latter returning to nearly normal values. Higher concentrations (2.0, 3.0, and 5.0 percent) were found to cause sometimes a decrease but more often an increase of the chronaxy. Gradinesco and Degan (1934) found that 5 percent solutions more frequently cause first a decrease and later an increase of chronaxy (hyperexcitability) ending in inexcitability after 6 to 7 hours of immersion. Higher concentrations (15 and 30 percent) were found to have a definite paralyzant effect. This, however, was of a temporary nature since it was reversible by

lavage. The authors pointed out that with concentrations of 5 and 10 percent the results are not uniform and frequently there is first an increase of the chronaxy, as observed by Bonnet and Lelu (1933), which presumably is due to individual differences (seasonal?).

In view of the *deleterious effect on the vision* observed in methyl alcohol poisoning, this effect has been studied very extensively in animal experiments. Holden (1899) fed dogs 50 cc. of methyl alcohol on two occasions, 5 days apart, and noted on the second day thereafter temporary blindness which later gradually subsided. On the eighth day a diffuse turbidity of the cornea without signs of congestion developed. On autopsy he found extensive degenerative changes of the ganglionic cells of the retina and destruction of some medullary sheaths of fibers of the optic nerve, and he assumed that the temporary amblyopia was caused by nutritional disturbances of the ganglionic cells of the retina. Friedenwald (1902) confirmed the destructive effect on the ganglionic cells of the retina in experiments with rabbits which were fed methyl and ethyl alcohol in sufficient doses and for a sufficient period of time to cause, in the case of the latter, cirrhosis of the liver, and he found that these alcohols behaved similarly in this respect. Birch-Hirschfeld (1900) experimented with rabbits and chicks and noted, on the day following the administration, dilatation and rigidity of the pupils, absence of defense reflexes, and inability of the animals to orient themselves in space. Although he noted no ophthalmological changes during life he found at autopsy degenerative changes in the ganglionic cells of the retina and also, in 1 rabbit, of the optic nerve. Later (1901) he expressed the opinion that the retinal changes were the primary manifestations and that the lesions of the optic nerve developed later. Igersheimer and Verzár (1913) repeated the experiments of Birch-Hirschfeld but used more diluted solutions of methyl alcohol in order to prolong the exposure and reduce acute toxic effects. Although they noted a temporary reduction of the light perception they found no degenerative changes in the retina. Kasass (1913) fed increasingly large doses of methyl alcohol to rabbits for 267 days. He noted peripapillary venous hyperemia and, later, constriction of the arteries and bleaching of the papilla which might result in nutritional disturbance in the retina, as had been assumed by Holden (1899). These symptoms disappeared after some weeks. On autopsy he noted vacuolar degeneration in all, but especially in the interior layers of the retina, hemorrhages in the optic nerve and fatty degeneration of the myelin fibers. This assumption appears to be supported by the publication of Goldschmidt (1922) who found that pretreatment of the retina with methyl alcohol prevents, under certain conditions, the reduction of methylene blue to the leucobase by this tissue. This effect increased with the concentration of methyl alcohol used and no reduction of methylene blue was observed by the retina of animals

which had been poisoned with methyl alcohol; it appears, therefore, that the retina of such animals is unable to utilize oxygen. Grignolo (1913) found in dogs that following the administration of methyl alcohol the osmotic pressure of the fluid in the posterior chamber of the eye was increased and there was also an increase of the hydrogen ion concentration which was later confirmed by Tyson and Schoenberg (1914 and 1915) who pointed out that this effect was more marked than the increase of the hydrogen ion concentration in the blood. They explained the greater acidity of the vitreous humor by less complete buffer action as compared with that of the blood. In view of the findings of Keeser (1931b) and Schrobback (1931) the possibility should be considered that more formic acid is formed in this than in other organs because in this medium formaldehyde is less readily bound. Grignolo (1913) found that the increase of the osmotic pressure was paralleled by shrinkage of the ganglionic cells, shrinkage and edema of the granular layers, and atrophy of the optic nerve. Rost and Braun (1926), like Friedenwald (1902), noted similar changes of the eye in dogs, following repeated oral administration of methyl and ethyl alcohol. Whereas some cells of the retina were normal, others were vacuolated, some showed incomplete staining, and shadow cells were seen quite frequently. In addition, the pigment of the retina was destroyed in spots and similar changes were seen in the granular and ganglionic layers, but no changes of the optic disk were noted. Alder, Buschke, and Gordonoff (1938) administered by stomach tube to rabbits 70 percent methyl alcohol (2.5 cc. per kg.) of a high degree of purity on three occasions and killed the animals on the fifth day, when the histological examination of the retina revealed reduction of the ganglionic cells, irregularities of the nuclei, changes and disappearance of Nissl bodies, and loosening of the granular layer. It appears that changes similar to those produced by methyl alcohol may also be seen occasionally in ethyl alcohol poisoning, but it appears to be definitely proved that the injurious effect of methyl alcohol is more marked, presumably on account of its slower and less complete oxidation, as indicated by the observations of Grignolo (1913) and Tyson and Schoenberg (1914 and 1915). Whereas most of these studies on the effect of methyl alcohol on eye and vision were made with oral administration, studies regarding the effects on the eye with inhalation of its vapors are less numerous. Tyson and Schoenberg (1914 and 1915) found that repeated daily inhalation of methyl alcohol vapors for a limited time caused reduction of the vision and, histologically, in one instance, edema of various structures of the eye and early signs of beginning degenerative changes of the ganglionic cells of the retina. McCord (1931) noted atrophy of the optic nerve following inhalation and cutaneous absorption, and Weese (1928) observed in mice, following inhalation of fatal concentrations

of methyl alcohol, degenerative changes in the retina which, however, may possibly have been due to postmortem changes during the preparation of the tissue.

With regard to the *effect of methyl alcohol on the circulation*, Kuno (1913) found that the isolated mammalian *heart* is depressed in $\frac{1}{40}$ to $\frac{1}{50}$ normal concentration (corresponding to 0.8 to 0.6 gm. per liter) and that $\frac{1}{2}$ normal solutions (1.5 gm. per liter) cause complete arrest within a few minutes. According to Fühner (1921) the minimal effective concentration causing depression of the isolated frog heart is 3.740 mole per liter (119.7 gm. per liter); and Wolff (1922) found that a 0.02 percent solution (0.006 mole per liter) has no visible effect, that 1 percent (0.3 mole per liter) causes reduction of the amplitude to about one-fourth of the original, and that concentrations of 3 and 6 mole per liter (96 and 192 gm. per liter) cause diastolic arrest which is completely reversible. Similarly, Simon (1933) stated that the isolated frog heart is reversibly arrested by concentrations of 6.25 mole per liter (200 gm. per liter) of methyl alcohol whereas concentrations of formaldehyde and formic acid of 0.0333 and 0.00434 mole per liter caused irreversible arrest, which illustrates the great toxicity of the oxidation products of methyl alcohol. Similar results were also published by Sammartino (1933a). According to Sklianskaya, Urieva, and Nashbitz (1936), the effect of methyl alcohol on the frog heart is less marked but more lasting than that of acetone.

With regard to the *effect of methyl alcohol on the blood vessels*, Budelmann (1930) noted in perfusion experiments on isolated organs that low concentrations of methyl alcohol caused a peripheral vasoconstriction. Simon (1933) and Sammartino (1933b) found in the Trendlenburg preparation of frogs that concentrations of 1 : 1,000,000 cause vasodilatation, the blood flow being increased by 29 percent. With the same concentration of formic acid or formaldehyde the increase of flow was only 7 and 3 percent, respectively, and, in contrast to methanol, higher concentrations of formic acid and formaldehyde were found to cause vasoconstriction. Therefore, it appears likely that the vasoconstriction observed by Budelmann (1930) may have been due to the formation of these metabolites in the isolated organs.

Miura (1913) studied the *effect of methyl alcohol on the blood*. He found that in dogs and rabbits, following subcutaneous injections of 3.3 cc. per kg., two-fifths of the animals developed an anemia, a reduction of lymphocytes, and a relative increase of the pseudo-eosinophiles and neutrophiles. These animals suffered from hemoglobinuria. Tyson and Schoenberg (1914) noted in dogs, in acute poisonings produced by the inhalation of methyl alcohol vapors, an increase of all cellular elements of the blood with the exception of lymphocytes and an increase of the viscosity. It will be shown that similar findings have been observed in man and it appears that this phe-

nomenon may be explained on the basis of edema formation and dehydration of the blood. There is no evidence to show that methyl alcohol produces abnormal blood pigments. Egg (1927) showed, however, that bivalent iron may form a complex with methyl alcohol and may thus interfere with the catalytic action of hemoglobin. Although the same effect may be observed with ethyl alcohol, this is said to be less significant on account of the more rapid oxidation of the latter. Weese (1928) suggested that the toxic effect of methyl alcohol might be partly explained by an effect on the hemoglobin by impairing the catalytic action of the blood.

With regard to the *effect of methyl alcohol on muscular tissue,* Kuno (1914) found that 0.5 and 1 percent solutions of methyl alcohol in Ringer's solution increase the pendular movements of the isolated intestine without increasing the average tone. Higher concentrations of from 5 to 10 percent cause a short primary stimulation and subsequent depression of the pendular movements and a moderate increase of the average tone. Verzár (1909) found that the depressant effect of methyl alcohol on the striated muscle and the ciliated epithelium is less marked than that of ethyl alcohol, and that with moderate concentrations the depression is preceded by a short stimulation. As pointed out by Bonnet and Lelu (1933), the depressant effect on the muscle structure is less marked than that on the nerve fiber.

With regard to the *effect of methyl alcohol on the metabolism,* Gradinesco and Palmhert (1931) found that methyl alcohol inhibits to a lesser extent than ethyl alcohol the digestive action of natural and artificial gastric juice on solid protein material. Król (1913) showed that in methyl alcohol poisoning there is a considerable increase (100 to 156 percent) of the ammonia excretion, a small fraction of which is neutralized by formic acid. Rewiger (1922) found in experiments with dogs that, in contrast to ethanol, methyl alcohol causes a negative nitrogen balance which could be overcome by an ample intake of proteins. As shown by Höckendorf (1909–10), methyl alcohol increases the sugar excretion of phloridzin diabetic dogs.

Much effort has been devoted to the *question of acidosis in methyl alcohol poisoning.* Schmiedeberg (1912) assumed that the essential feature of methyl alcohol poisoning is the formation of formic acid which, especially in under-nourished individuals and in the absence of sufficient ammonia formation, may lead to acidosis, whereas Harnack (1912) believed that the toxicity of formic acid itself rather than the acidosis produced was the determining factor in methyl alcohol poisoning. Król (1913) assumed that animals poisoned with methyl alcohol were suffering from acidosis caused by the increased excretion of ammonia with the urine. However, according to Loewy and Münzer (1923) this is indicative only of increased acid formation and not of acidosis. Tyson and Schoenberg (1914) showed that in animals

poisoned with methyl alcohol the hydrogen ion concentration of the blood is increased. Haskell, Hileman and Gardner (1921) found in experiments with dogs that, following administration of methyl alcohol, the blood alkali was not always or not sufficiently reduced to cause severe acidosis. They believed that the latter was not the outstanding phenomenon because in their experience the administration of sodium bicarbonate was of limited value. According to Ziegler (1921) the acidosis may be followed by alkalosis which may result from the forced respiration observed in the last stages of methyl alcohol poisoning. Loewy and Münzer (1923) found no evidence of severe acidosis in experimental methyl alcohol poisoning of rabbits and dogs, as indicated by the absence of disturbances of the carbon dioxide binding power of the blood. In contrast to the observations of Haskel, Hileman and Gardner (1921), Leo (1925) found in dogs that the administration of alkali was of distinct value in attenuating the picture of methyl alcohol poisoning. This favorable effect was not seen in mice, rats and rabbits and this may. be explained by the observation of Rewiger (1922) that, in contrast to dogs, even large doses of methyl alcohol do not increase the ammonia excretion of these animals. This observation also supports the assumption of Leo (1925) that the beneficial effect of alkali is directed less towards the acidosis than towards a more rapid elimination of the formic acid as formate. Keeser (1931a) believed that neither acidosis nor the formation of formic acid is as important a feature of methyl alcohol poisoning as is the inhibition of catalytic processes as demonstrated by Egg (1927). It appears, therefore, that in animals the production of acidosis by methyl alcohol poisoning may depend upon the species used, the nutritional status and the time at which the observations were made. In cases of methyl alcohol poisoning in humans acidosis has been observed repeatedly. Harrop and Benedict (1920) reported such a case in which the acidosis was promptly relieved by the intravenous administration of 5 percent sodium bicarbonate. Similar cases were reported by Ustvedt (1936), Merritt and Brown (1941), and others.

With regard to *pathological changes in animals*, Poincaré (1878) noted, in the *central nervous system*, congestion and hemorrhages in the meninges and other signs of inflammatory processes; and similar changes and degenerative processes in brain and spinal cord were reported by Holden (1899), Rühle (1912), Tyson and Schoenberg (1914), Eisenberg (1917), Scott, Helz, and McCord (1933) and others.

Some of the pathological changes found *in the eyes* of animals poisoned with methyl alcohol have been discussed in a previous section where it was shown that the ganglionic cells of the retina are primarily affected and atrophy of the optic nerve has been ob-

served only occasionally, as reported by Scott, Helz and McCord (1933).

Detailed data on *pathological changes in the peripheral nerves* are apparently not available. Only Scott, Helz, and McCord (1933) mention injury of the peripheral nerves.

With respect to *pathological changes in the digestive tract*, Rost and Braun (1926) found, after oral administration of methyl alcohol, scarlet red, dark brown, and black red discoloration of the mucosa of the stomach which was edematous, hemorrhagic and, in spots, corroded. These authors and also Tyson and Schoenberg (1914) reported similar changes of less severe character in the duodenum.

The *liver* may show congestion (as reported by Tyson and Schoenberg, 1914), parenchymatous degeneration, and, in severe cases, focal necroses (as reported by Scott, Helz, and McCord, 1933). In the experience of these investigators the latter is more conspicuous than fatty degeneration which is, in the opinion of Müller (1910), the most common finding and which was also reported by Poincaré (1878), Eisenberg (1917), and Weese (1928).

In the *kidneys* parenchymatous degeneration of the epithelium of the convoluted tubules was reported by Poincaré (1878), Weese (1928), and Scott, Helz and McCord (1933) whereas others such as Tyson and Schoenberg (1914) noted only congestion.

The *heart* muscle may show cloudy swelling and fatty degeneration as observed by Poincaré (1878) and Eisenberg (1917), or granular degeneration with occasional necrosis of fibers as reported by Scott, Helz and McCord (1933).

Following inhalation of methyl alcohol vapors, the *lungs* are usually hyperemic. They may show petechial hemorrhages, as seen by Tyson and Schoenberg (1914), bronchopneumonia (Weese, 1928), and, in milder cases, congestion, edema and desquamation of the alveolar epithelium, as reported by Scott, Helz and McCord (1933).

Methyl alcohol poisoning in man: In man, methyl alcohol poisoning most frequently results from the ingestion of methyl alcohol as a beverage. Baskerville (1913) collected, up to 1913, 720 cases of methyl alcohol poisoning, 390 of which ended fatally, 90 of which developed blindness, and 85 of which suffered impaired vision. Further cases were subsequently reported by Harrop and Benedict (1920), Burhans (1930), Mathewson and Alexander (1932), Neiding, Goldenberg and Blank (1933), Joiris (1935), Kraul (1933), Willemse (1936), Menne (1938), Merritt and Brown (1941) and others. Many single cases result from the ingestion of methanol or alcoholic beverages adulterated with methyl alcohol, and occasionally mass poisonings are observed, as in Hungary in 1909, Berlin in 1911, Hamburg in 1922, and Odessa in 1933. The character and the intensity of the poisoning depends on the quantity of methyl alcohol ingested and the

nutritional status of the individual. In the opinion of Baskerville (1913) who analysed a large number of cases, 55 percent of the cases of methyl alcohol poisoning end fatally, 12 percent suffer permanent blindness, 12 percent have impaired vision, and only 4 percent recover completely.

Whereas injuries resulting from the ingestion of methyl alcohol are, as a rule, not of industrial origin, those caused by inhalation of its vapors do belong in this group. Baskerville (1913) collected from the literature 64 cases of such poisonings, of which 6 ended fatally, 19 suffered permanent blindness, and 33 had impaired vision. More recently, similar cases have been reported only occasionally, as by Robinson (1918) and Schwarzmann (1934), and it appears to be the consensus that only exposure to high concentrations in limited enclosures will cause serious and lasting effects, as also indicated by a study of Loewy (1914). Humperdinck (1941) believed that concentrations of 1,528 to 7,640 p. p. m. are potentially dangerous with regard to possible visual disturbances and that to avoid these the concentration should be kept below 764 p. p. m. (1 mg. per liter).

As pointed out above, the *clinical picture of methyl alcohol poisoning following ingestion of methyl alcohol* varies with the amount of methyl alcohol ingested, the amount of foodstuff in the gastro-intestinal tract, and the nutritional status of the victim.

In light cases of methyl alcohol poisoning the patient may complain about fatigue, headache, a pulling pain in the limbs, nausea, and moderate gastro-intestinal disturbances. Later he may complain of visual disturbances, and there may be a considerable latent period before more serious symptoms become manifest.

In more severe cases the victims suffer from nausea with occasional vomiting and diarrhea. Later they may become cyanotic and restless, their respiration becomes deep and labored, and more or less severe debility may develop. The pupils are usually dilated, their reactivity is reduced, and vision is impaired. If only pupillary symptoms are present the prognosis is usually good (Stadelmann and Magnus-Levy, 1912), but if the patient is dyspneic the prognosis is doubtful and the clinical picture may suddenly become very serious.

In severe methyl alcohol poisoning, nausea, vomiting, and diarrhea are more marked (Król, 1913; Harrop and Benedíct, 1920; and Burhans, 1930), abdominal pain and colic may exist (Schwarzmann, 1934), and the stools may contain blood (Menne, 1938). The patients may be weak, apathetic, and even comatose (Tyson, 1912; Isaacs, 1920; and Burhans, 1930), or they may be excited (Król, 1913) or even maniacal (Neiding, Goldenberg, and Blank, 1933). They may also suffer from visual hallucinations, as reported by Harrop and Benedict (1920). Frequently they complain about more or less severe headache and vertigo. Their reflexes may be increased (Król, 1913; and Schwarzmann, 1934) and they may suffer from convulsions, as re-

ported by Król (1913), Neiding, Goldenberg, and Blank (1933), Bur-
hans (1930) and others. In very severe cases these symptoms may be
associated with opisthotonus (Król, 1913). Later ataxia and periph-
eral neuritis may develop, as seen by Jeliffe (1905), Schwarzmann
(1934) and others. Oppression in the chest and pain in the side
are frequent complaints (Król, 1913; Harrop and Benedict, 1920; and
others). Depending upon the stage of the poisoning, the respiration
may be rapid and shallow (Menne, 1938) or deep and labored as in
diabetic coma (Król, 1913; Harrop and Benedict, 1920; Burhans, 1930;
Ustvedt and Mohn, 1932; Menne, 1938; and others) and the patient
may suffer from more or less severe cyanosis. The circulation may
show varying degrees of failure, the blood pressure may be lowered,
the pulse may be rapid and weak, and the victim may suffer from
collapse associated with lowering of the body temperature (Harrop
and Benedict, 1920; Merritt and Brown, 1941; and others).

In acute cases of methyl alcohol poisoning the cellular elements
and the hemoglobin of the blood may be increased, as observed by
Tyson and Schoenberg (1914) and by Merritt and Brown (1941).
The urine may contain albumen and casts (Burhans, 1930; Joiris,
1935; Merritt and Brown, 1941; and others). The patient may suffer
from more or less severe acidosis (Król, 1913; Harrop and Benedict,
1920; Ustvedt and Mohn, 1932; Ustvedt, 1936; Merritt and Brown,
1941; and others), and lactic and formic acid may be found in the
urine. It has been pointed out above that concentrations of formic
acid of more than 100 mg. per 1,500 cc. may be considered to be
pathognomonic for poisoning from methyl alcohol or other methyl
compounds (Klauer, 1939), and sugar may occasionally be found
in the urine (Joiris, 1935). The blood urea may be considerably
increased, as observed by Joiris (1935) and Merritt and Brown
(1941).

Visual disturbances of varying intensity are the most characteris-
tic phenomena in methyl alcohol poisoning, as reported by MacFar-
lan (1855), Moulton (1901), Hale (1901), Wood and Buller (1904),
Ströhmberg (1904), Hawes (1905), Tyson (1912), Król (1913),
Harrop and Benedict (1920), Ziegler (1921), Burhans (1930),
Mathewson and Alexander (1932), Neiding, Goldenberg and Blank
(1933), Joiris (1935), Willemse (1936), Merritt and Brown (1941)
and many others. DeSchweinitz (1901) and Wood (1912) wrote a
review on this subject. Visual disturbances usually become manifest
about 24 hours after the beginning of the poisoning (deSchweinitz,
1901). The pupils are usually dilated (deSchweinitz, 1901; Tyson,
1912; Ziegler, 1921; and Neiding, Goldenberg, and Blank, 1933);
they may be unresponsive to light but responsive to convergence (de-
Schweinitz, 1901; and Ziegler 1921); or they may be completely
rigid (Tyson, 1912; Ustvedt and Mohn, 1932; Joiris, 1935; Menne,

1938; and others). There may be some scleral congestion (Ziegler 1921), the eyeball may be sensitive to pressure (Ziegler, 1921) and its rotation may cause pain (Tyson, 1912). Occasionally there may be paresis of the muscle, leading to ptosis of the eyelids, as observed by Ziegler (1921). In some cases the first impairment of the vision may show a temporary improvement but later the vision may gradually deteriorate, as observed by deSchweinitz (1901), Harrop and Benedict (1920) and Ziegler (1921). The primary amblyopia may be due to a primary inflammation in the connective tissue of the optic nerve, as assumed by deSchweinitz (1901), or it may be caused by circulatory disturbances in the eye, as assumed by Nagel (1905) and Joiris (1935); and final impairment of the vision may be caused by toxic metabolites, as indicated by the studies of Holden (1899) and Kasass (1913). Ophthalmologically, the edges of the optic disk may be blurred and there may be optic neuritis with exudation into the retina (deSchweinitz, 1901; Wood and Buller, 1904; Tyson, 1912; Harrop and Benedict, 1920; Ziegler, 1921; Ustvedt and Mohn, 1932; and Neiding, Goldenberg, and Blank, 1933). The vessels of the eyeground may be congested, as observed by Ströhmberg (1904), and the veins may be dilated, as reported by Tyson (1912). In the opinion of deSchweinitz (1901) and Ziegler (1921) the final ophthalmoscopic picture is that of retrobulbar neuritis, but it may also end in optic atrophy, as seen by Hale (1901), Wood and Buller (1904), Ustvedt and Mohn (1932) and others. Temporary or permanent scotoma has been observed by Wood and Buller (1904), Tyson (1912), Harrop and Benedict (1920), Ustvedt and Mohn (1932) and Joiris (1935).

As pointed out before and as stated by Stadelmann and Magnus-Levy (1912), in methyl alcohol poisoning the mortality rate is very high. The immediate cause of death appears most frequently to be respiratory failure, as assumed by Stadelmann and Magnus-Levy (1912), Neiding, Goldenberg, and Blank (1933) and Menne (1938), but death may also be caused by cardiac failure, as reported by Burhans (1930). In more protracted cases, injury and dysfunction of the kidney may be the cause of death. Recovery from methyl alcohol poisoning is slow, and marked fatigue, malaise, pain in limbs, and visual disturbances may persist for some time.

Exposure to methyl alcohol vapors may cause *irritation of the mucous membranes* of the respiratory tract and of the eyes, resulting, in severe cases, in tracheitis and bronchitis (Koelsch, 1921) and in blepharospasm (Thies, 1928). Locally, splashes of methyl alcohol may cause chemosis and superficial lesions of the cornea which, however, usually heal promptly and are only exceptionally of serious nature (Thies, 1928). *Systemically*, inhalation of methyl alcohol vapors may cause headache, vertigo, tinnitus, nausea, gastric distrub-

ances, convulsive twitchings, oppression in the chest, visual disturbances, and even amaurosis. Sensory disturbances (paresthesias and anesthesias) appear to be not infrequent but serious cerebral effects appear to be exceptional and, if observed, result only from very severe exposure. Continued exposure to methyl alcohol vapors may lead to anemic conditions, as reported by the Division of Industrial Hygiene of the New York Department of Labor (1917) and by Burhans (1930). Injury of the eyes from the inhalation of vapors was observed quite frequently at the beginning of this century. DeSchweinitz (1901) reported 1 and Wood and Buller (1904) reported 9 cases of blindness resulting from inhalation of high concentrations of methyl alcohol in small enclosures. Baskerville (1913) collected from the literature 64 cases of methyl alcohol poisoning caused by inhalation, of which 5 suffered from temporary and 19 from permanent blindness, and 33 from impaired vision of varying intensity. Cases of this type were also reported by Patillo (1899), Hale (1901), Hawes (1905), Jeliffe (1905), Tyson (1912), Morson (1918), Koelsch (1921) and Schwarzmann 1934). These were characterized by impaired accommodation, restriction of the visual field, and scotoma. It appears that such conditions may improve considerably with discontinuation of the exposure and proper treatment, but complete cures are exceptional (Koelsch, 1921). In addition, individual susceptibility may play a role.

Continued exposure to vapors of methyl alcohol may lead to *chronic poisoning* which is characterized by irritation of the mucous membranes, possibly leading to bronchitis and pulmonary affections which may be associated with headache, tinnitus, tremors, local and multiple neuritides, and more or less severe visual disturbances (Flury and Zernik, 1931).

Contact of methyl alcohol with the skin may lead to irritation and eczema, as observed by Mumford (1925), and to dermatitis, as reported by the Division of Industrial Hygiene of the New York Department of Labor (1917). Occasionally, cases of methyl alcohol poisoning have been reported in which absorption of methyl alcohol through the skin has been credited with causing systemic poisoning. However, in these cases vapors of methyl alcohol had also been inhaled, therefore such toxic effects cannot be associated exclusively with absorption through the skin and one has to agree with Sayers and Yant (1930) that cases of poisoning by absorption through the skin are rare and the evidence for such accidents is inconclusive.

Pathological changes in methyl alcohol poisoning.—In cases of methyl alcohol poisoning the livid spots are said to be reddish but less bright than those seen in carbon monoxide poisoning, the face is frequently cyanotic, and there may be marked rigor mortis (Ströhmberg, 1904). The *respiratory tract* is hyperemic (Ströhmberg, 1904;

and Fraenckel, 1912), the lungs may be congested (Pierce, 1909) or hyperemic and edematous (Ströhmberg, 1904; and Fraenckel, 1912), and there may be bronchitis (Keeser, 1931a). In acute death the *heart* is flabby and dilated and there may be ecchymosis (Ströhmberg, 1904; and Gerbis, 1931). The *digestive tract* is hyperemic (Ströhmberg, 1904; Fraenckel, 1912; and Burhans, 1930), the mucous membranes of the *stomach* may be edematous and may show ecchymosis (Pierce, 1909; and Isaacs, 1920), and with delayed death there may be, in addition, erosion and ulceration (Burhans, 1930; and Menne, 1938). The *liver* has been described as being brownish and friable (Isaacs, 1920), and it may be hyperemic and edematous (Menne, 1938). In acute death there may be diffuse fatty infiltration but no degenerative changes (Fraenckel, 1912; and Gerbis, 1931), but with delayed death there may be fatty degeneration, as reported by Burhans (1930) and Keeser (1931a). In early cases there may be acute hemorrhagic *pancreatitis*, as observed by Burhans (1930). The kidneys are hyperemic and may show hemorrhages (Ströhmberg, 1904; and Keeser, 1931a), cloudy swelling (Isaacs, 1920; and Burhans, 1930), fatty infiltration (Gerbis, 1931) and degenerative changes of the glomerular apparatus (Burhans, 1930). The *meninges* are hyperemic and edematous (Ströhmberg, 1904; and Fraenckel, 1912). The *brain tissue* may also be hyperemic and edematous (Ströhmberg, 1904; Burhans, 1930; and Menne, 1938) and the amount of cerebrospinal fluid may be increased. With regard to pathological changes in the *eye*, Macdonald (1929) found defects of the epithelium of the cornea, optic degeneration of the pigmented epithelial layer of the iris, moderate round cell infiltration of the ciliary body and congestion of the vessels in cases of acute methyl alcohol poisoning. In addition he found cysts and marked degenerative changes of the ganglionic cell layer of the retina. Other investigators (Keeser, 1931a; and Menne, 1938) reported on hyperemia and cloudy swelling of this structure. Macdonald (1929) noted marked distortion and much cellular debris, especially in the region of the optic nerve. The external nuclear layer and the nuclei of the rod and cone layer were irregular; there were many cystic spaces in the reticular layer, and there was engorgement of the choroid vessels. A very similar picture was described by Birch-Hirschfeld (1900) and by Tyson and Schoenberg (1914). Others (Burhans, 1930; and Keeser, 1931a) reported edema and, with longer duration, cloudy swelling and marked degeneration of the optic nerve. Lewin and Guillery (1913) assumed that the pathologic changes of the ganglionic cells are due to a direct toxic action and that changes of the optic nerve are not of secondary, but of primary nature, caused either by a neurotoxic action or by an effect on the blood vessels. In

their opinion it is only in delayed cases that a secondary ascending degeneration may develop atrophy of the optic nerve.

Maximal permissible concentration of methyl alcohol in air.—No definite information is available regarding maximal permissible concentrations of methyl alcohol. Greenburg, Mayers, Goldwater, and Burke (1939) determined the concentration of methyl alcohol and of acetone in "fused collar" operations and found concentrations of 20 to 25 p. p. m. of the former and 40 to 45 p. p. m. of the latter. They noted no abnormalities in workers having this exposure. In the opinion of McCord (1931) and of Scott, Helz, and McCord (1933) the danger threshold of methyl alcohol is well below 1,000 p. p. m.; and prolonged exposure to 4,000 p. p. m. has been found to be fatal to man. At present the consensus is that 200 p. p. m. may be considered as maximal permissible concentration for continued exposure for 8 hours daily.

Dangers from the industrial use of methyl alcohol.—Danger from methyl alcohol poisoning exists in all operations where this material is handled without adequate precautions. This holds true for its manufacture by distillation of wood or by synthetic processes, for its use in the chemical industries, and, especially, for its use in those manufacturing processes such as the making of artificial flowers, straw hats, etc. where methyl alcohol is used as a solvent. At one time there was much discussion as to whether or not the use of methyl alcohol as an antifreeze in automobile radiators involved a hazard to the public, and some Government agencies, such as the Arkansas Legislature (1931), passed a law regulating its use in antifreeze mixtures by requiring the coloring of such solutions, proper labeling, and the keeping of records with regard to its sale. Trumper (1931) was apparently the first to point out the possible danger from the use of methyl alcohol as an antifreeze, but Shumway as well as deSchweinitz (see Trumper, 1931) doubted whether there was any danger from evaporation of methyl alcohol from the radiator. The studies of Sayers and Yant (1930) indicate that there is no danger of poisoning from reasonable handling of methanol as an antifreeze, and Yant, Schrenk, and Sayers (1931) stated that an investigation of many conditions of exposure to vapors and contact with the skin in the manufacturing and handling of methyl alcohol, comparable to the degree of exposure resulting from the handling and use of methyl alcohol as an antifreeze, offered no signs of health hazard.

The prevention of methyl alcohol poisoning.—All operations in which methyl alcohol is handled should have sufficient ventilation so that the concentration of methyl alcohol in air does not exceed 200 p. p. m., and precautions should be taken that the contaminated air does not enter other buildings. If possible, the vapors should be

removed at the site of their liberation by adequate local exhaust ventilation. All vats, barrels, or receptacles of any kind containing methyl alcohol should be kept hermetically closed. In handling methyl alcohol, contact with the skin and contamination of garments should be avoided, and any spilled methyl alcohol should be removed at once. Whenever methyl alcohol is used in an industrial process, printed cautionary signs, calling attention to the danger from exposure to methyl alcohol, should be posted in the workrooms. Enclosures known to contain high concentrations of methyl alcohol vapors should be entered only with adequate protection, such as open air masks and safety lines, and under the supervision of a crew familiar with such exposure.

With regard to other precautionary measures, an agreement should be mentioned between the United States Public Health Service and the manufacturers of methanol, methyl alcohol or wood alcohol which provides that any material containing more than 15 percent of free methanol for use as an antifreeze shall contain sufficient dye to give an intense, permanent, violet color to the solution equivalent to that given by the addition of 0.01 pound of methyl violet 2B to 100 gallons. In addition, all containers shall have prominently displayed a warning sign reading as follows, in prominent, heavy, Gothic capital letters, red on white background:

<div align="center">

(Skull and crossbones)

POISON

CONTAINS OVER _____ PERCENT METHANOL

CAN NOT BE MADE NONPOISONOUS

</div>

In case the methanol is used for purposes other than as antifreeze it should carry the label:

<div align="center">

(Skull and crossbones)

POISON

CONTAINS OVER _____ PERCENT METHANOL

CAN NOT BE MADE NONPOISONOUS

AVOID PROLONGED BREATHING OF VAPOR

</div>

In operations in which methyl alcohol is handled, workers should undergo periodic medical examinations. Subjective complaints, such as burning of the eyes, headache, dizziness and fatigue, and gastrointestinal disturbances, should be considered indicative of harmful exposure. Special attention should be paid to the condition of the eye (conjunctivitis and visual acuity) and to the functioning of the kidneys. The urine should be tested for albumen and casts and the formic acid content should be determined. An increase of the latter above the normal value of 100 mg. per 1,500 cc. should be considered as indicative of excessive exposure.

The treatment of methyl alcohol poisoning.—In poisonings from inhalation of methyl alcohol vapors the patient should be removed from the exposure and given rest, and the elimination should be enhanced by the application of hot packings and diuretics. Special

attention should be paid to visual disturbances and these should be treated by an ophthalmologist.

In cases of poisoning from the ingestion of methyl alcohol the poison should be removed from the stomach by gastric lavage. Mathewson and Alexander (1932) recommended that this be repeated on several days, and Isaacs (1920) suggested that a 1 to 2 percent solution of sodium bicarbonate be used for this purpose and, following this, 100 to 120 cc. of a 50 percent solution of magnesium sulfate (Epsom salt), the latter being left in the stomach to induce catharsis. Saline cathartics should be given in any case unless the patient is in collapse. As suggested by Pohl (1918) these may be preceded by the administration of adsorbent charcoal in order to reduce the absorption of methyl alcohol from the gastro-intestinal tract. The urinary excretion of methyl alcohol and its metabolites should be enhanced by the administration of diuretics and the intake of a large quantity of warm fluids (tea). The elimination may be further increased by diaphoretic measures such as hot baths, hot packings and, if necessary, by pilocarpine (Mathewson and Alexander, 1932). If the patient is cyanotic, inhalation of oxygen may give prompt relief (Merritt and Brown, 1941) and in severe cases venae section and subsequent infusion of saline—in acidosis of 5 percent sodium bicarbonate (300 cc.), repeated if necessary—as suggested by Burhans (1930) and Merritt and Brown (1941) may be very beneficial. As pointed out by Leo (1925) the oral administration of 3 gm. of sodium bicarbonate every 2 hours on 6 occasions during the first day and on 3 occasions during the subsequent days may also prove helpful in the elimination of formates. In severe cases the administration of cardiac stimulants may become necessary and spinal puncture may alleviate the symptoms from the central nervous system and the eye (Mathewson and Alexander, 1932). Visual disturbances may also be improved by the administration of thiamine hydrochloride, as suggested by Simons (1942).

b. Ethyl Alcohol

Chemical characteristics: Ethyl alcohol, ethanol, alcohol, C_2H_5OH, is a colorless liquid of aromatic odor. It has a molecular weight of 46.07 and a specific gravity of 0.789 at $\frac{20°}{4°}$ C. It solidifies at −112° C. and boils at 78.4° C. Its refractive index is 1.3610 at 20.5° C. and it is miscible in all proportions with water, chloroform, and ether. According to Coward and Jones (1939) the lower limit of inflammability with upward propagation of the flame is 3.28 to 5.02 percent, with horizontal propagation, 3.70 to 5.18 percent, and with downward propagation, 3.70 to 5.21 percent. For the upper limit of inflammability the corresponding values are 14.0 to 18.95 percent, 13.80 percent, and 11.50 to 13.65 percent. Its ignition temperature is 425° C. in oxygen and 558° C. in air.

Ordinarily ethyl alcohol is prepared by fermentation of substances containing sugars, such as glucose, levulose, saccharose, and maltose, or by fermentation of amylaceous matters such as starch, dextrin, inulin, and others, after these have first been hydrolysed to sugars. It is separated from the fermented mash by distillation and purified by rectification. Ethyl alcohol can also be prepared synthetically by oxidation of acetylene to acetaldehyde in the presence of mercuric salts and subsequent reduction of the aldehyde by electrolysis or catalytic reduction with nickel. According to Chemical and Metallurgical Engineering, 49: 73, 1942, the annual production of ethyl alcohol in the United States was 337,040,937 proof gallons in 1941.

Uses.—Ethyl alcohol is used extensively as a solvent for fats and oils. It plays an important role in chemical industries, as in the manufacture of ether, artificial vinegar, and fulminate of mercury. It is used extensively in the explosives industry, in the manufacture of artificial silk, in lacquers and varnishes, and as a fuel for combustion engines.

Denatured alcohol.—In order to reduce the high cost of pure alcohol due to taxation, alcohol used in industry is frequently denatured to render it unsuitable for consumption. To fulfill this purpose the denaturing agents must give the alcohol an unpleasant smell or disagreeable taste or cause physiological effects such as vomiting which interfere with the absorption of alcohol. In addition, the denaturing agent must have such physical-chemical characteristics that it is not easily removed from the denatured alcohol. Wiley, Sawyer, Tolman, Bryan, Given, and Berger (1910) gave an extensive discussion on the question of denatured alcohol and the Treasury Department of the United States published in 1932 a pamphlet concerning regulations pertaining to the use and handling of denatured alcohol. The fact that the denaturing agent should not interfere with the industrial uses of denatured alcohol for various purposes must also be considered and this has resulted in the use of a great variety of chemicals for the denaturing of ethyl alcohol. Zangger (1931) discussed in great detail the denaturing technique and the dangers resulting from the indiscriminate use of chemicals for this purpose.[3]

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[3] He enumerates as denaturing agents the following chemicals which in at least one country (Switzerland) are listed as industrial poisons:

Acetone, ether, aniline dyes, acetaldehyde, benzine, benzol, ethyl bromide, methyl bromide, cadmium iodide, chloroform, quinine, chloral hydrate, acetic acid, formaldehyde, ethyl-acetylic ester, amyl acetate, ethyl chloride, iodoform, ethyl iodide, nitrobenzene, methyl-ethyl chloride, nicotine, paraldehyde, phenol, oil of turpentine, carbon tetrachloride, coal tar, pitch, oils, petroleum distillates, and even mercuric chloride and benzyl chloride which have been used tentatively.

Among other chemicals and drugs which have been suggested and sometimes used Zangger (1931) listed:

Agaricin, allyl formate, erythrosin, camphor, ipecacuanha, podophyllin, scammonium, tannin, glucosides, thymol, menthol, pyridine, salicylic acid, salicyl derivatives, varieties of camphor, collodion resin (also toxic resins), phthalic acid esters, acetonitrile, paralyde-hyde, acridine, naphthalene and naphthalene derivatives, dimethyl, ethyl-methyl, and ethyl-phenyl esters of phthalic acid, oxalic acid ethyl ester, nitric acid ethyl ester, dimethyl

This résumé indicates that the indiscriminate use of chemicals as denaturing agents may result in a great variety of toxic effects which have nothing to do with the toxic action of ethyl alcohol itself. It is obvious that a great number of the chemicals listed above should never be used as denaturing agents and it appears advisable to have the denaturing agent stated on the label so that the denatured alcohol may be handled with adequate precautions.

Identification of ethyl alcohol.—In contrast to methyl alcohol, ethyl alcohol is oxidized by potassium bichromate and sulfuric acid only to acetaldehyde and acetic acid. Ethyl alcohol may be identified as follows:

1. When ethyl alcohol is mixed and warmed with an excess of potassium hydroxide and then potassium iodide is added until a permanent yellow color is formed, a crystalline sediment of iodoform is formed upon standing after the addition of a further small amount of potassium hydroxide. This test is said to be sensitive up to concentrations of 1:1,000 and it is only characteristic for ethyl alcohol in the absence of substances with aldehyde and carboxylic acid groups, such as acetone, aldehyde, lactic acid, succinic acid, and others.

2. If ethyl alcohol is mixed with concentrated sulfuric and acetic acid while being cooled and then carefully heated, acetic acid ethyl ester is formed which can be recognized by its characteristic odor.

3. If ethyl alcohol is shaken with benzoyl chloride in a closed vessel and then mixed with sodium hydroxide while shaken until the odor of benzoyl chloride has disappeared, the benzoic acid ethyl ester is formed, which may be identified by its characteristic odor (sensitivity 1 : 1,000).

The determination of ethyl alcohol in alcoholic beverages.—The determination of ethyl alcohol in alcoholic beverages varies with the nature of the materials. The standard procedures for such determinations are given in the Official and Tentative Methods of Anaylsis of the Association of Official Agricultural Chemists. They are based on the distillation of such samples and the determination of the specific gravity of the distillate.

The determination of ethyl alcohol in air.—There appears to be no accepted method for the determination of ethyl alcohol in air. Haggard and Greenberg (1934a) determined it by oxidizing a measured sample of air by means of iodine pentoxide and subsequent titration of the amounts of iodine and hydroiodic acid liberated during this reaction. Greenberg and Keator (1941) described a portable

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sulfide, diethyl sulfide, methyl-ethyl sulfide, methyl rhodanide, thioacetic acid, thiobutyric acid, allyl alcohol, bromo-acetone and chloroacetobenzene.

Finally, as pointed out by Zangger (1931), products of unknown composition, such as acetone oil, aldehyde mixtures, and proprietary mixtures of unknown composition are also used as denaturing agents.

apparatus for the determination of ethyl alcohol in exhaled air which is based on this principle and in which the intensity of the color produced by the liberated iodine in potassium iodide starch solution is measured photoelectrometrically and the resulting values can be read on a scale in mg. percent. It is obvious that this method is not specific and that any volatile organic constituents may be oxidized in the same way and thus cause too high readings. Jetter, Moore and Forrester (1941) determined the alcohol in exhaled air by absorbing the alcohol in magnesium perchlorate and the carbon dioxide content of the same sample in ascarite. The absorbed alcohol is liberated by dissolution of the magnesium perchlorate in water and subsequent steam distillation, and is determined in the distillate by Harger's method.

The determination of ethyl alcohol in biological materials.—The determination of ethyl alcohol in biological materials is of great forensic importance and many methods have been devised for this purpose.

Gettler, Niederl and Benedetti-Pichler (1932) devised an apparatus for the isolation of *pure anhydrous ethyl alcohol* from very dilute solutions.

Alcohol may be determined in blood and other specimens by distilling it and subsequently determining the alcohol in the distillate by means of the interferometer. As pointed out by Kionka and Hirsch (1924), acetone and acetaldehyde interfere with this determination, whereas carbon dioxide, lactic acid, and other fatty acids were said to be eliminated by the distillation. But Hirsch (1928) pointed out that fatty acids may pass into the distillate and suggested that the first distillation be performed after acidulation of the biological material (urine) with phosphoric acid, treating the distillate for 2 hours with lime and redistilling it before making the interferometric determination in the second distillate. Decker (1940) stated that this method is of similar exactness to that of Widmark.

Nicolai (1928) published a specific *microdetermination of ethyl alcohol based on the formation of ethyl iodide* by heating the alcohol distillate with hydroiodic acid and decomposing the ethyl iodide formed with silver nitrate to form silver iodide which can be determined gravimetrically according to the procedure of Stritar (1906). Gettler and Umberger (1942) used a similar procedure but determined the ethyl iodide formed by interaction with bromine, resulting in the formation of iodate which they determined titrimetrically with sodium thiosulfate.

Kluge (1939) published another specific *determination* which is *based on the esterification of ethyl alcohol with dinitrobenzoic acid.* The resulting dinitrobenzoic acid ethyl ester forms well-defined crystals which may be used for qualitative identification. For the quan-

titative determination the ester is hydrolyzed with sodium hydroxide and the alcohol is distilled into an N/15 solution of potassium bichromate in diluted sulfuric acid and the excess of bichromate is determined by titration with sodium thiosulfate.

Haggard and Greenberg (1934a) *determined ethyl alcohol* in air, blood, and urine by oxidation *with iodine pentoxide*, resulting in the formation of iodine and hydroiodic acid which are determined individually and the sum of which yields the total amount of ethyl alcohol.

Werkman and Osborn (1930) showed that *ethyl alcohol can be determined in the presence of other alcohols*, like butyl alcohol, by oxidizing them to the corresponding fatty acids by means of a mixture of potassium dichromate and phosphoric acid. The acids are distilled off and their total amount is determined titrimetrically in the distillate, and the individual acids are determined by the partition method described by Werkman (1930), which is based on their partition between isopropyl ether and water.

Friedemann and Klaas (1936) worked out a method for the *determination* of ethyl alcohol in biological specimens. The alcohol is first removed from the original material by distillation after the addition of lime which binds the commonly occurring volatile substances, then aliquot parts of the distillate are oxidized by heating for 20 minutes in a water bath *with potassium permanganate*, and after it is cooled and acidified the excess of permanganate is determined iodometrically. For the determination of ethyl alcohol in saliva, Friedemann and Brook (1938) worked out a method in which the saliva is first treated with a solution of copper, mercury, and iron sulfate in diluted sulfuric acid, then shaken with calcium hydroxide suspension, filled up to 100 cc. and kept until clear. In 10 cc. of the supernatant fluid the alcohol is then determined as outlined above. Elbel (1938) and Hinsberg and Breutel (1939) showed that this method is more specific than that advocated by Widmark which will be discussed below. Elbel (1938) pointed out that in putrefying blood it is advantageous to precede the distillation from alkaline medium by one in acid medium in order to prevent certain volatile bases from passing into the distillate. It appears that this method is more tedious but more specific than many others, and that it should be preferred in forensic analyses.

A great number of procedures for the *determination of ethyl alcohol* are based on its oxidation to acetic acid *by means of potassium bichromate* in acid solution, but none of these is specific unless the alcohol is first isolated in such a way as to exclude other volatile materials.

Nicloux (1900b) determined ethyl alcohol in blood and milk by separating the former by distillation in vacuo at 60° C. In the distil-

late the alcohol is oxidized by an acid solution of potassium bichromate and the latter is partly reduced to chromium sesquisulfate, the amount of which is proportionate to the quantity of alcohol originally present. The amount of chromium sesquisulfate is measured by the color changes from yellow over green to blue by comparison with standards made up in the same way. Nicloux (1931) modified his original procedure in that the alcohol is oxidized in a closed container with a slight excess of acid chromate of known strength at 80° C., with subsequent determination of the excess of chromic acid by titration with permanganate after the addition of ferrous ammonium sulfate. A further modification was advocated by Nicloux, Le Britton and Dontcheff (1934) by using a more diluted solution for oxidation, by determining the amount of reducing substances in the reagents, and by using smaller containers for the determination.

Heise and Halporn (1932) and Heise (1934) used a modification of Nicloux's method for the determination of alcohol in urine. They mixed 10 cc. of urine with an equal volume of a solution of 10 percent tartaric acid in a half saturated solution of picric acid, distilled the mixture, and collected the first 10 cc. of the distillate. One cc. of this distillate and fractions made up to 1 cc. with water were mixed with 3 cc. of a potassium bichromate reagent made up by dissolving 0.33 percent of potassium bichromate in 50 percent sulfuric acid. After heating the mixtures for 4 minutes in a boiling water bath they were compared colorimetrically. The same procedure can also be utilized for the determination of ethyl alcohol in blood, serum, and plasma by mixing 1 cc. of these with 15 cc. of a 10 percent aqueous solution of tartaric acid containing sufficient picrate to give a definite yellow color and distilling the alcohol from this mixture. Heise and Halporn (1932) believed, by comparison of values obtained by this method and by refractometric determinations, that chloroform, ether, chloral hydrate, salicylates, and acetone did not interfere with this determination since in biological specimens they could not be present in sufficient amounts to cause appreciable reduction of the bichromate reagent. However, Swim, McCawley, and Leake (1940) questioned the specificity of this test and believed that volatile fatty acids, such as lactic and pyruvic acid, and possibly also methyl glyoxal may cause the finding of too high alcohol values.

Gettler and Tiber (1927a) determined ethyl alcohol in the brain by grinding ice cold, weighed portions of the tissues, mixing the pulp with water, tartaric acid, and a small amount of white mineral oil, and distilling this mixture with steam. This distillate is treated with potassium bichromate in concentrated sulfuric acid, mixed, and distilled at a slow rate. After thorough mixing, 50 cc. of the second distillate are titrated against phenolphthalein with an N/20 solution

of sodium hydroxide. The amount of ethyl alcohol per kg. of tissue is obtained by multiplying the number of cc. of sodium hydroxide solution used for this titration, minus the number of cc. used for the blank titration of brain tissue, by 71.8. Russell and Thienes (1932) modified this method by refluxing the first distillate with bichromate and sulfuric acid for 30 minutes prior to the second distillation. They claimed that in this way certain interfering substances, such as methyl alcohol and formaldehyde, are completely oxidized. Abernethy, Russell, and Thienes (1934) showed further that any volatile fatty acids can be removed and a correction for their presence (blank titration of brain tissue) made unnecessary by treating the first distillate with sodium or calcium hydroxide and following this by a second distillation with steam. Kozelka and Hine (1941) removed the interfering substances, such as acetone and formaldehyde, by passing the alcoholic steam distillate through alkaline mercuric chloride into 0.1 normal chromate solution. At the end of the distillation this is mixed with potassium iodide and the liberated iodine is titrated with 0.1 normal sodium thiosulfate, using starch as indicator.

Widmark (1922) described a micromethod for the determination of ethyl alcohol in blood which is also based on the oxidation of ethyl alcohol by chromic acid. The reaction is carried out in a glass-stoppered Erlenmeyer flask with a horizontal glass spoon attached to the stopper. Depending upon the amount of alcohol to be determined, 1 cc. of various concentrations of acid chromate solution are pipetted into the flask. For concentrations of the order of 0.5 percent ethyl alcohol, 0.25 gm. recrystallized potassium bichromate, dissolved in 1 cc. of water and filled up to 100 cc. with concentrated sulfuric acid, are recommended, and for concentrations of less than 0.1 percent of ethyl alcohol 0.05 gm. potassium bichromate dissolved in the same volumes of water and sulfuric acid should be used. The blood sample is withdrawn from a punctured fingertip by means of a glass capillary, the latter is weighed on a torsion balance, its contents is discharged into the glass spoon of the Erlenmeyer, and the empty capillary is weighed again. The well-closed Erlenmeyer is then kept for 2 hours in a water bath at 60° C., during which time the alcohol is distilled from the blood and reacts with the acid chromate solution. After this time the spoon with the dried blood is carefully removed, the acid in the flask is diluted with 25 cc. of distilled water, 0.5 cc. of a 5 percent solution of potassium iodide (free of iodate) are added, and after 1 to 1½ minutes the iodine is titrated with N/10 or N/20 sodium thiosulfate, using starch solution as indicator. The difference between the amount of thiosulfate used for the blank (a) and that used for the titration of the blood distillate (b) is proportional to the amount of alcohol in the blood sample. The results of the thiosulfate determination are too low and 0.01 cc. N/100 thiosulfate solution

corresponds to 1.13 gamma of alcohol (factor f) and the alcohol content of the blood sample (x) can be calculated according to the formula:

$$x = 1.13 \ (b-a)$$

In case N/200 thiosulfate solutions are used for the titration the factor should be 0.57. Mayer (1936a) pointed out that factor f should be 1.15 for complete oxidation of alcohol to acetic acid with an N/100 thiosulfate solution and should be theoretically 0.575 for N/200 thiosulfate solutions, and he quoted the determination of this factor by various investigators as follows:

Widmark	1.13 (1.129) and 0.57 (0.565).
Schmal	1.1228 and 0.568.
Jungmichel	1.129 and 0.565.
Graf and Flake	1.09.

He believed that factor f varies with the amount of sulfuric acid used and that this can be avoided by using phosphoric acid instead of sulfuric acid which is said to give the correct value.

Widmark's method has been widely used for clinical and forensic determinations of alcohol in blood. Stempel (1940) suggested that the use of the viscous acid chromate solution be avoided by placing in the Erlenmeyer flasks 5 cc. of an aqueous chromate solution of proper strength, drying this at 100 to 120° C., and adding, before use, 2 drops of distilled water and 1.5 cc. of sulfuric acid (specific gravity 1.84). Graf and Flake (1932–33) thought that Widmark's method was not as exact as claimed, but Meier and Wyler (1934) showed that it is essential that the proper temperature (60° C. ±0.2) be maintained during the distillation, because at this temperature there is no decomposition of the blood. But they confirmed the observation of Graf and Flake (1932–33) that the bichromate mixtures used in these determinations are sensitive to light and, therefore, should be protected against bright light during the distillation. Nicloux, Le Britton and Dontcheff (1934) cautioned against the use of such high concentrations of sulfuric acid as were used by Widmark and other students of the subject, such as Kluge (1939). Kanitz (1939) pointed out that this method is not specific for ethyl alcohol. Elbel (1938) found that it is less specific than the procedure of Friedemann and Klaas (1936), and this opinion was shared by Hinsberg and Breutel (1939) who pointed out that after ingestion of large doses of ethyl alcohol Widmark's method gives essentially correct values, but with smaller doses the fraction of nonalcoholic volatile constitutents gains in importance, especially when such results are used for further calculation of the amount of alcohol ingested.

Similar methods were used by Janke and Kropacsy (1935) and Newman and Abramson (1942) who described an improvement of this procedure in which the final color determination is made by

means of an electrophotometer, using a filter with maximal transmission at about 480 millimicrons.

Absorption, fate, excretion, and distribution of ethyl alcohol in the organism.—The question as to whether or not *ethyl alcohol is a "normal" constituent of body fluids* and tissues, especially the blood, has been investigated repeatedly and the knowledge of the concentration of alcohol in the blood of abstinent persons is of importance in the interpretation of blood alcohol findings in forensic cases.

Ford (1872) studied the question of whether or not animal tissues in contact with sugar were able to produce alcohol, but since in his experiments the contamination with yeast or bacteria was not excluded, his positive findings are of questionable value. Landsberg (1904) showed that organs of recently killed animals contained only traces of alcohol but gave markedly positive tests when stored without precautions to prevent bacterial infection and growth. He found in organs of freshly killed rabbits quantities of ethyl alcohol of the order of 0.0028 to 0.0083 percent. Maignon (1905), using Nicloux's method, found in various organs of dogs removed by biopsy quantities ranging from 15 to 140 cubic millimeters per kilogram of tissue, 0.0013 to 0.0016 percent in the blood, and 0.0013 to 0.0020 percent in the urine. Reach (1907) used the more specific method of Stritar (1906) and found 0.0017 percent in fresh muscle tissue of rabbits, whereas in older tissues he found values as high as 0.016 percent. In fresh brain tissue he found 0.001 to 0.003 percent and also traces of ethyl esters. Pringsheim (1908) found, in various organs of rats, concentrations of 0.0018 to 0.004 percent. Gettler, Niederl, and Benedetti-Pichler (1932) determined the alcohol content of human, dog, and pig brain as 0.0004, 0.0003 and 0.00007 percent, respectively, and that of human and pig liver as 0.00256 and 0.0007 percent, respectively. With regard to the concentration of "normal" alcohol in the blood, Maignon (1905) determined it as 0.0013 to 0.0016 percent, Schweisheimer (1913) as 0.0036 percent, Kühn (1924) as 0.0006 to 0.0051 percent, Kionka (1928) as 0.001 to 0.006 percent, and Gettler, Niederl, and Benedetti-Pichler (1932) as 0.0013 to 0.004 percent. It appears, therefore, as pointed out by Heise (1934), that the concentration of normal alcohol in the blood is below 0.005 percent, and that this is without medico-legal significance (Heise, 1940).

With regard to the source of the "normal alcohol" found in blood and tisues, Landsberg (1904) assumed that it was formed from carbohydrates, and, similarly, Taylor (1913) believed that it was largely the result of bacterial decomposition of carbohydrates in the gastrointestinal tract but that small quantities may also be formed during the lactic acid metabolism in the muscle. The relation between intake of food and normal alcohol in the blood was demonstrated by Schweisheimer (1913) and Kionka (1928). The former found that blood

taken before meals contained an average of 0.0029 percent, whereas blood taken after meals contained 0.0036 percent; and the latter found that in persons who had been abstinent for 72 hours and then had fasted for 10 hours the blood alcohol level rose after the ingestion of carbohydrates from 0.001 to 0.006 percent to a level of 0.0015 to 0.021 percent. On the other hand, Kühn (1924) found that the intake of single, fairly large doses of carbohydrates had no uniform or distinct effect on the normal blood alcohol level. Kalter and Katzenstein (1932) claimed that during sleep the concentration of normal alcohol in the blood is higher than during waking hours, and they believed that this was connected with the carbohydrate metabolism. Maignon (1905) and Hirsch (1928) showed that in abstinent persons small quantities of ethyl alcohol, similar to those found in the blood, may be eliminated with the urine.

The *absorption of ethyl alcohol* may take place to a moderate extent through the intact skin, as assumed by Filehne (1898) and as shown by Schwenkenbecher (1904). But as demonstrated in mice by Sander (1933) and Bowers, Burleson and Blades (1942) the amount of alcohol absorbed in this way is not sufficient to cause toxic effects.

As shown by Gréhant and Quinquand (1883) (quoted from Kochmann, 1923) ethyl alcohol is readily absorbed through the lungs. Loewy and von der Heide (1918) found in rats that with inhalation of concentrations of less than 5 percent of alcohol in air the absorption is quite rapid, equilibrium being established within $8\frac{1}{4}$ hours. With higher concentrations it takes comparatively more time to reach an equilibrium. It appears that different species may vary in this respect, in that the accumulation is said to be slower in guinea pigs than in rats, and the former are also more resistant and tolerate higher concentrations than the latter.

As pointed out by Kochmann (1923), ethyl alcohol is readily absorbed from the subcutaneous tissue if diluted solutions are injected. High concentrations of 80 to 90 percent precipitate proteins cause local necroses, and their absorption is, therefore, slow and irregular.

As demonstrated by Lallemand, Perrin and Duroy (1861) (quoted from Kionka and Haufe, 1928) and by Gréhant (1899a), ethyl alcohol is readily absorbed from the gastro-intestinal tract, and as shown by Vollmering (1912) the larger portion is absorbed during the first hour after the ingestion. Hanzlik and Collins (1913) showed in dogs and cats that the absorption from the stomach and from the small intestine is of the same order and from the colon about one-fifth higher. They found that the rate of absorption varies with the concentration in which the ethyl alcohol is given, in that 10 percent solutions are more rapidly absorbed than 5 percent or 50 and 90 percent solutions, the maximum being reached after one-half hour. Similarly, Dybing, Rasmussen (1940) found in rats that very little

alcohol is absorbed from the stomach when given in 40 percent solution, and that with the administration of a 5 percent solution the concentration in the blood reaches only one-third of the calculated level. Similar observations were reported by Haggard, Greenberg, and Lolli (1941) who stated that with high concentrations the absorption may be delayed on account of pylorospasm. Harger and Hulpieu (1935) found that, when given on an empty stomach, in concentrations of 25 percent, ethyl alcohol disappears from the gastro-intestinal tract to the extent of 57.7 percent during the first half hour and that after 1 hour 88.5 percent and after 1½ hours 93.4 percent have been absorbed. In the opinion of Jungmichel (1933) the absorption of alcohol from the gastro-intestinal tract is normally completed in 40 to 60 minutes.

As pointed out by Kionka (1928), Widmark (1933a), Haggard, Greenberg, and Lolli (1941) and others, the absorption of ethyl alcohol from the stomach is delayed in the presence of food. Hanzlik and Collins (1913) found that the intravenous injection of ethyl alcohol interferes with the absorption of ethyl alcohol from the stomach, possibly on account of its excretion into the stomach from the blood, but it appears more likely that the rate of absorption of alcohol from the gastro-intestinal tract depends, at least in part, upon the concentration of ethyl alcohol in the blood, that is, on the gradient between the concentration in the intestine and in the blood. In addition, changes in the splanchnic circulation (produced by the intravenous injection of alcohol) may also delay the absorption of alcohol from the gastro-intestinal tract.

With regard to the effect of habituation to ethyl alcohol on the absorption from the gastro-intestinal tract, Miles (1922) believed that habituated persons absorb ethyl alcohol at the same rate as do normal persons. But Faure and Loewe (1923) found that the rate of absorption was more rapid in habituated rabbits than in normal animals. Schweisheimer (1913) and Siegmann (1936) claimed that in chronic alcoholics the absorption is more rapid than in normal persons.

With regard to the effect of various food constituents and drugs on the absorption of alcohol from the stomach, Hanzlik and Collins (1913) found that fats and oils delay the absorption, whereas Haggard, Greenberg and Lolli (1941) believed that it has the opposite effect. Widmark (1933b) claimed that glycine and alanine, when given with ethyl alcohol, delay its absorption by affecting the intestinal epithelium or the liver, or possibly by forming esters in the gastro-intestinal tract. Neymark and Widmark (1936a) found that this effect is absent in dogs fed alcohol on an empty stomach, and irregular when alcohol was mixed with the food. Böhmer (1938) claimed that aspirin and amidopyrine, taken simultaneously with alcohol, cause

delayed and incomplete absorption, whereas quinine has no such effect.

Völtz, Baudrexel and Dietrich (1912) showed that ethyl alcohol is readily absorbed from the urinary bladder. This was confirmed by Nicloux and Nowicka (1913) who believed that alcohol excreted with the urine may be partly reabsorbed from the bladder. But Haggard, Greenberg, Carroll and Miller (1940) claimed that with such concentrations of alcohol as may be eliminated with the urine, its absorption from the bladder is insignificant. Moritz and Jetter (1942) demonstrated that alcohol may diffuse through the wall of the bladder in either direction, depending upon its concentration in the blood and in the urine. They found that in both living and dead animals the passage of alcohol through the mucous membranes of the bladder tends to bring its concentration in blood and urine closer rather than farther from a state of equilibrium.

With regard to the *fate of ethyl alcohol in the organism*, Anstie (1874) found that it is rapidly destroyed in the body. Bodländer (1883) showed that at least 95 percent of the ingested alcohol is oxidized, and according to Strassmann (1891) at least 90 percent is oxidized. Atwater and Benedict (1899) showed that not more than 2 percent of the ingested alcohol is eliminated undecomposed, whereas 98 and even 99 percent are oxidized in the body. Whereas Abelous, Bardier, and Ribaut (1903) claimed that in cold and warm blooded animals alcohol is rapidly and completely oxidized, Nicloux (1931) showed that the rate of oxidation of ethyl alcohol varies with different species. He found that in mice doses of 0.85 cc. per gm. body weight are completely oxidized in 2 hours, that the oxidation is slower in rabbits and very slow in cold blooded animals (frogs), and that in the latter species the oxidation may be increased by raising the temperature. This was confirmed by Newman and Lehman (1937b) who found that birds metabolize alcohol more rapidly than mammals of comparable size, and that smaller mammals oxidize it more rapidly than larger ones.

With regard to the *rate of oxidation of ethyl alcohol in the organism*, Higgins (1916) stated that the oxidation of alcohol begins from 5 to 11 minutes after ingestion, and Mellanby (1919) assumed that the rate of oxidation is constant from the beginning of the absorption until oxidation and elimination are completed. Haggard and Greenberg (1934c) believed that the oxidation of alcohol is not uniform but a function of its concentration in the blood, and Eggleton (1940a) assumed that the metabolic rate of alcohol depends directly upon its concentration in the body and that it is raised by about 30 percent for every 100 mg. percent increase of the concentration of alcohol in the plasma. Neymark and Widmark (1936b) and Keeser and Oelkers (1937) could not confirm the statement of

Haggard and Greenberg (1934c), and Newman and Lehman (1937b) found that the rate of oxidation is constant and independent of the dose, as judged by the disappearance of alcohol from the blood after its intravenous administration. They believed that in rabbits and chickens there is first a rapid initial storage or destruction of a certain amount of alcohol, after which a constant rate of oxidation prevails as with other species of animals. Clark, Morrissey, Fazekas, and Welch (1941) showed, in accordance with Neymark and Widmark (1936b), Keeser and Oelkers (1937) and Newman and Lehman (1937b), that in cats and dogs the rate of oxidation of alcohol is a constant and linear function of the time. Loewy and von der Heide (1918) claimed that with inhalation of alcohol vapors the rate of oxidation of alcohol is 10 to 15 percent higher than that found after oral administration by Völtz and Dietrich (1912).

With regard to the *site of oxidation of ethyl alcohol*, Pringsheim (1908) believed that alcohol is mainly oxidized in the liver. Battelli and Stern (1909) found that the liver of various animals contains an enzyme "alcoholase" which rapidly oxidizes alcohol to acetic acid. They found that the amount of alcoholase varied with different species; horse liver being very rich, followed by beef, sheep, guinea pig, dog, and rabbit liver, the last two containing very little. Masuda (1912) found indications that the oxidation of alcohol in the liver results in the primary formation of acetaldehyde. Hirsch (1916) found that in the presence of air, liver pulp destroys alcohol when incubated at 37° C. and that boiling and ferment poisons destroy this action; and he was able to isolate an enzyme "alcohol-oxidase" as a dry powder. Newman, van Winkel, Kennedy and Morton (1940) showed that alcohol is oxidized by perfused cat liver, and Leloir and Munoz (1938) showed that the aerobic oxidation of alcohol was greater in rat than in pigeon liver and that it could be lowered by fasting the animals. Pringsheim (1908) found that other tissues besides the liver, namely heart muscle and brain, may also oxidize alcohol, and he believed that this was a characteristic of animals habituated to alcohol. Similarly, Rhode and Fischer (1916) (quoted from Kochmann, 1923) found that heart muscle may destroy alcohol. Battelli and Stern (1910) believed, in view of the low alcoholase content of human, dog, and rabbit liver, that alcohol may also be oxidized in other organs. But Messner (1913) found no evidence that organ pulp or blood incubated at 38° C. destroyed measurable amounts of alcohol within 6 hours. Leloir and Munoz (1938) found that in contrast to slices of liver, kidney and muscle, other organs oxidize only very small amounts of alcohol. Binet and Marquis (1938) concluded from experiments with the isolated lung that an appreciable amount of alcohol may be oxidized by this organ. The important role played by the liver in the oxidation of alcohol

is also illustrated by the experiments of Lundsgaard (1938) who compared the destruction of alcohol in the perfused liver with that in the perfused hind leg of cats, the latter being practically nil. He believed that the oxidation of alcohol is a specific function of the liver. With regard to the effect of other organs on the oxidation of alcohol, Mirsky and Nelson (1939) believed that pancreatomy does not cause significant inhibition, whereas Clark, Morrissey, Fazekas, and Welch (1941) believed that the oxidative function of the liver is definitely impaired in pancreatomized animals but that in such animals it may be restored to normal levels by the administration of insulin, the latter increasing the oxidative metabolism of the liver. Mirsky and Nelson (1939) were able to demonstrate a quantitative relation between the percentage of intact liver tissue and the amount of alcohol oxidized, and Clark, Morrissey, Fazekas and Welch (1941) showed that injury of the liver by chloroform definitely reduced the rate of oxidation of alcohol. Lundsgaard (1938), Mirsky and Nelson (1939), and Clark, Morrissey, Fazekas, and Welch (1941) showed that hepatectomy and, to a greater extent, evisceration, abolishes, or at least reduces very materially, the oxidation of alcohol. As shown by Mirsky and Nelson (1939) the oxidative action cannot be restored in eviscreated animals by the administration of glucose and insulin. It appears, therefore, that the liver is the main site for the oxidation of alcohol in the organism.

With regard to the *oxidation products resulting from the destruction of ethyl alcohol*, Atwater and Benedict (1899) found no evidence for the excretion of other metabolites than carbon dioxide and water, especially no indication that acetaldehyde or acetic acid were among the final decomposition products. Battelli and Stern (1910) showed that during the oxidation by alcoholase, acetaldehyde and acetic acid are formed, the amount of the former depending in part upon the alkalinity of the medium. They pointed out that the aldehyde is partly further oxidized to acetic acid and partly bound to the proteins of the tissue, thus escaping the determination. Similarly, Masuda (1912) found in perfusion experiments with the isolated liver, indication of a primary formation of acetaldehyde. In addition, he found small amounts of aceto-acetic acid, presumably formed by aldol-condensation of acetaldehyde with acetic acid. On the other hand, it appears possible, as shown by Embden and Baldes (1912) in the perfused liver, that under certain conditions acetaldehyde may be reduced to alcohol. It has been stated above that, as demonstrated by Leloir and Muñoz (1938) and others, in the liver the oxidation of alcohol is carried up to acetic acid; and it appears, as pointed out by Lundsgaard (1938), that this is further and completely oxidized in other organs, especially in the muscle tissue.

Whereas most students of the subject agree that acetaldehyde is only an intermediate product and Albertoni (1887) was unable to detect its presence in the exhaled air or in the urine after the ingestion of alcohol, it appears that under abnormal conditions or in very severe acute alcohol poisoning small quantities may be detected. Thus Kretschy (1876) found, in several instances, in patients with gastric fistula, that free aldehyde could be detected in the stomach, and Stepp (1920) found, in a severely intoxicated person, small quantities in blood and urine. Several investigators and, more recently, Westerfeld, Stotz, and Berg (1942) who gave an extensive review of the literature on this subject, found that administration of sodium pyruvate materially increases the metabolism of alcohol as indicated by a change in the rate of decrease of blood alcohol from 8.1 mg. percent per hour to 21.1 mg. percent per hour. They showed that during the metabolic destruction of alcohol, pyruvate is more readily utilized. Westerfeld, Stotz, and Berg (1942) assumed that acetaldehyde produced by the primary oxidation of ethyl alcohol may be condensed with pyruvate to form acetoin (methyl acetyl carbinol), thus providing a relationship between the metabolism of alcohol and of carbohydrates. Greenberg (1942) was, however, unable to demonstrate any increase of acetoin in the blood following the administration of pyruvate and alcohol, so it appears that acetoin does not occur as an intermediate product in this reaction and that the increased disappearance of alcohol following the administration of pyruvate cannot be explained on this basis.

With regard to various *factors which may influence the oxidation of ethyl alcohol in the organism,* the effect of *physical exercise* has aroused much interest. Gréhant (1903 b) claimed that in dogs physical exercise favored the disappearance of alcohol from the blood; Völtz and Baudrexel (1911 b) claimed that it favored the pulmonary elimination; and Brechmann (1927) (quoted from Carpenter, 1933) claimed that oxidation was increased during muscular exercise.

Mellanby (1919) claimed that with small doses of alcohol the oxidation was more rapid during exercise than during rest, but after larger doses he was unable to detect any difference. Similarly, Cassinis and Bracaloni (1930) found that in humans muscular exercise prevents to a certain extent the rise of the alcohol level in the blood as compared with its rise during rest, leaving it undecided whether this is due to increased pulmonary excretion or to increased oxidation. Galami (1927) (quoted from Carpenter, 1933) questioned whether exercise favors the oxidation of alcohol, and Carpenter, Lee and Burdett (1933) found in man that muscular exercise has no significant effect on the rate of disappearance of alcohol from the organism. As pointed out by Lundsgaard (1938) similar findings were published by Miles (1924), Nyman and Palmlöv (1934), Rap-

port, Canzanelli, and Guild (1934) and Le Breton (1936). Carpenter (1933) reviewed the subject of the effect of exercise on the destruction of alcohol and came to the conclusion that the information available does not permit a definite conclusion, but Hopkins (1942) stated that there is no evidence that the oxidation of alcohol is more rapid during exercise.

Several *factors which tend to increase the oxygen metabolism* have been studied with regard to the oxidation of alcohol in the organism. Vollmer and Buchholtz (1930) and Preusse (1933) claimed that the feeding of thyroxin and thyroid to mice increased the oxidation of alcohol, but this was not confirmed by Keeser and Oelkers (1937). Widmark (1935) and Le Breton (1936) (both quoted from Lundsgaard, 1938), Harger and Hulpieu (1935) and Ewing (1940) showed that in sufficient doses dinitrophenol increases the oxidation of alcohol in the organs. According to Ewing (1940) this effect is independent of the increased ventilation and the increased body temperature, and its mechanism is apparently not fully understood. Starting from the assumption that irradiation with ultraviolet light increases the oxidative functions of the organism, Riesser and Hadrossek (1930) investigated in mice and rats the effect of ultraviolet irradiation on the toxicity of alcohol and found that it reduces the toxicity of narcotic doses. Their findings were confirmed by Vollmer and Behr (1930) who found that this protective action lasts for ½ to 1½ hours after the last irradiation. Vollmer and Buchholtz (1930) also claimed that for the same reason premedication with methylene blue decreased the toxicity of alcohol.

With regard to the *effect of amino acids* on the oxidation of alcohol, Le Breton (1934c) found in fasting and glucose-fed rabbits that the administration of d-alanine increases the rate of oxidation of alcohol by 40 to 60 percent. This was confirmed with liver slices by Leloir and Muñoz (1938) and in alcohol-habituated animals by Eggleton (1940a) who believed that this was associated with an increase of the total metabolism produced by the oxidation of alanine and not due to a formation of an alanine-ethyl alcohol ester, as postulated *by* Widmark (1933b). Westerfeld, Stotz and Berg (1942) stated that the administration of dl-alanine has an effect on the alcohol metabolism similar to that observed with the administration of sodium pyruvate. Vollmer (1930) found that premedication of white mice with caseosan reduces materially the toxicity of alcohol, presumably by increasing the oxygen metabolism.

Regarding the *effect of carbohydrates on the oxidation of ethyl alcohol,* Vollmer and Buchholtz (1930) showed that premedication of mice with dextrose reduces their susceptibility to alcohol on account of an increase of the oxygen metabolism. Carpenter and Lee (1937c) found that fructose causes more rapid disappearance of alcohol from

the exhaled air than glucose and that it is less rapidly oxidized after the administration of galactose than after the administration of glucose. Clark, Morrissey, and Fazekas (1938) believed that insulin is necessary for the oxidation of alcohol by liver tissue, leaving it undecided whether insulin acts specifically on the oxidation of alcohol or indirectly by affecting the carbohydrate metabolism, possibly by accelerating the oxidation of glucose which in turn may catalyze that of alcohol. In the opinion of Mirsky and Nelson (1939) insulin is apparently not an essential factor for the oxidation of alcohol. Clark, Morrissey, Fazekas, and Welch (1941), however, found in experiments with dogs and cats that the administration of glucose alone has little effect on the oxidation of well-fed dogs, but that of insulin, alone or with glucose, or with glucose and sodium bicarbonate, definitely increased the rate of oxidation of alcohol during the first 2 hours. Lolli and Greenberg (1942) studied the effect of insulin on the disappearance of alcohol from the stomach of rats. They found it ineffective if 50 percent alcohol was given on account of the pylorospasm produced by such high concentrations. With the administration of 25 percent alcohol, insulin caused, however, rapid disappearance from the stomach which may result in a more rapid absorption from the intestine and an increased concentration of alcohol in the blood. Völtz, Baudrexel, and Dietrich (1912) showed in dogs that, when given on an empty stomach, alcohol is oxidized to the extent of 95.8 percent, whereas when given with food 98.4 percent is oxidized. Similarly, Leloir and Muñoz (1938) and Mirsky and Nelson (1939) found that the oxidation of alcohol is reduced by fasting.

With regard to the *effect of fats on the oxidation of alcohol*, Neymark and Widmark (1936a) studied the effect of neutral fat, fatty acids, and glycerol on the alcohol metabolism. They found that fatty acids (oleic acid) prevent the oxidation of a moderate fraction of the alcohol administered. This effect is absent with the administration of glycerol esters of fatty acids (Arachis oil), but the simultaneous administration of a mixture of glycerol and oleic acid increases considerably the effect of the latter. Glycerol alone was found to be ineffective nor did it influence the effect of glycerol and citric acid. Glycerol phosphate was found to have no effect on the alcohol metabolism nor did it influence the action of oleic acid.

The *effect of habituation to ethyl alcohol on its oxidation* has been studied by many investigators. Hunt (1907) found in experiments with mice and guinea pigs that alcohol is more readily oxidized in animals habituated to alcohol than in normal ones. Similar results were reported by Vollmer (1932). Pringsheim (1908) concluded from experiments with rats and rabbits that habituation causes, at least to a certain extent, an increase of the oxidation of alcohol. Völtz and Baudrexel (1911a) found that in habituated dogs the pulmonary

and renal excretion is less than in normal animals. Hansen (1925), Jungmichel (1933), Gettler and Freireich (1931), and others believed that in man habituation to alcohol enhances its oxidation in the organism. In contrast to these statements, Balthazard and Larue (1921) claimed that normal and habituated dogs metabolize alcohol at the same rate, and similar results were reported by Newman and Cutting (1935 and 1936), Faure and Loewe (1923), Keeser and Oelkers (1937), Neymark and Widmark (1938), and others. Hirsch (1916) found that the liver pulp of habituated animals destroys alcohol at the same rate as that of normal animals, and Eggleton (1940b) found that the metabolic rate of alcohol per liver weight of habituated animals was significantly lower than normal, which may perhaps be due to injury of the liver, as reported by Broggi (1935) (quoted from Keeser and Oelkers, 1937).

The *elimination of ethyl alcohol* may take place by various routes. Kochmann (1923) refers to Masing (1854) and Schulinus (1891) as having found that traces of alcohol are excreted through the lungs, and similar statements were made by Perrin and Duroy (1861), Dupré (1872), Schmidt (1875) (all three quoted from Kochmann, 1923), Atwater and Benedict (1902), Pohl (1908), Cushny (1910), and Nicloux (1931). Anstie (1874) found that about one-half as much alcohol is excreted with the exhaled air as with the urine, and Bodländer (1883) found that in dogs 1.946 percent of the alcohol ingested is eliminated through the lungs as compared with 1.596 percent excreted by the kidneys. According to Völtz and Dietrich (1912), 2 to 4 percent is excreted through the lungs and 0.4 to 3.8 percent with the urine during the first 10 to 15 hours after the oral administration of 2 cc. of alcohol per kg. body weight. Nicloux and Nowicka (1913) found that in rabbits 1.5 to 12.9 percent is excreted through the lungs. Völtz and Baudrexel (1911b) found that the pulmonary excretion of alcohol is increased by physical exercise, and according to Völtz, Baudrexel, and Dietrich (1912) it is less when alcohol is given with food. Liljestrand and Linde (1930) determined the distribution of alcohol between air and blood at 37° C. as 0.00063 to 0.00073 and found that at 31° C. 1 cc. of blood contained about as much alcohol as 2 liters of air. They found that alveolar air collected according to Haldane's procedure contained, during the first hours after the ingestion of alcohol, much more than would be expected from its distribution coefficient, due to the admixture of alcohol vapors from the stomach. If this error was avoided, the concentration of alcohol in the exhaled air was lower than expected, presumably because during exhalation part of the alcohol is precipitated onto the mucous membranes of the respiratory tract, so that its concentration corresponds to the partition coefficient determined at 31° C. According to their findings the alcohol content of the exhaled air may

vary with the pulmonary ventilation and with the alcohol content of the blood.

With regard to the *elimination of ethyl alcohol through the kidneys*, Dupré (1872) and Anstie (1874) showed that only a very small fraction of the alcohol ingested is eliminated with the urine; according to Heubach (1875) and Binz (1877) the renal excretion is extremely small in feverish patients; and as shown by Albertoni (1887) the urinary excretion depends upon the amount of alcohol ingested. Bodländer (1883) found that in dogs 1.576 percent of the alcohol ingested was excreted with the urine, about 0.5 percent less than was eliminated through the lungs, and that in man 1.177 percent was eliminated by the kidneys. Similarly, Nicloux and Nowicka (1913) found that the urinary elimination is smaller than the excretion through the lungs. Heffter (1905) and Völtz and Baudrexel (1911b) showed that the urinary excretion of alcohol depends upon the dose ingested. The former pointed out that it is increased when the diuresis is stimulated by the intake of water, and this was confirmed by Kionka and Haufe (1928) and Nicloux and Nowicka (1913) whereas Widmark (1915) believed that it is not affected by the diuresis. According to Haggard, Greenberg and Carroll (1941) the amount of alcohol excreted with the urine depends to a great extent upon the diuretic action of alcohol which may vary greatly with different individuals. Völtz, Baudrexel and Dietrich (1912) showed that the urinary excretion is greater when alcohol is taken on an empty stomach. Carpenter and Lee (1937b) found that the administration of glucose has little effect on the urinary excretion of alcohol. Widmark (1915) showed that the concentration of alcohol in recently voided urine equals that in the blood at the time when the urine was collected, and this was confirmed by Kionka and Haufe (1928). According to Haggard and Greenberg (1934b) alcohol passes from the blood into the urine by diffusion. The ratio of solubility of alcohol (blood=1) was determined by Southgate and Carter (1926) as 1.37, by Carlson, Kleitman, Muehlberger, McLean, Gullicksen and Carlson (1934) as 1.32, by Jetter (1938b) as 1.23, by Bavis (1940) as 1.22, and by Haggard, Greenberg, Carroll and Miller (1940) as 1.31. The latter found that this ratio varies very little with urines of different specific gravity. Following the ingestion of ethyl alcohol, small quantities may be excreted in conjugated form. Neubauer (1901) (quoted from Heffter, 1905) found that in rabbits small quantities, and in dogs even smaller quantities, are excreted in conjugation with glucuronic acid, and according to Pringsheim (1908) it is, to a certain extent, also excreted as ethereal sulfate. However, the amount of alcohol excreted in this way appears to be very small, and in the case

of the ethereal sulfate it may be slightly greater in habituated animals (rats and rabbits).

The excretion of alcohol with the feces is very small or nil, as was demonstrated by Anstie (1874), Bodländer (1883), and Pringsheim (1908).

The excretion of alcohol through the skin is very small (Anstie, 1874; and Nicloux, 1931). According to Bodländer (1883) 0.140 percent of the amount of alcohol ingested is excreted in this way. Nyman and Palmlöv (1936) studied the excretion of alcohol with the sweat and found its concentration to be approximately 80 percent of that of the blood. Since during the collection of the sweat the evaporation of alcohol could not be completely avoided, it appears that the concentration of alcohol in the sweat corresponds to that in the blood and that less than 1 percent of the amount of alcohol administered is excreted with the sweat under normal conditions.

With regard to the *excretion of ethyl alcohol into the stomach*, Gréhant (1903a) found that after the intravenous administration of alcohol, alcohol is excreted into the stomach. This was confirmed by Lukas (1930) following rectal administration and by Newman and Mehrtens (1932) who found that the concentration of alcohol in the gastric juice closely parallels that in the blood.

With regard to *excretion of ethyl alcohol with the saliva*, Linde (1932) found that following the ingestion of alcohol the saliva produced by the parotid gland contained more alcohol than the total saliva, and he assumed that the alcohol passed into the saliva by diffusion, as was also stated by Simonin and Warter (1940); but Friedemann, Motel, and Necheles (1938) believed that, in addition, other factors, perhaps selective action on the salivary cells and possibly also increased blood supply, may play a role, and that under certain conditions alcohol may be actively secreted by the salivary glands. According to Fabre and Kahane (1938) the saliva of normal persons who abstained from alcohol for 48 hours contained only insignificant traces of volatile substances corresponding to 0.030 mg. per cc. Following the ingestion of alcohol there is a close relation between alcohol in the saliva and that in the blood over a period of ½ to 5 hours, the ratio between the alcohol concentration in saliva and blood varying from 0.97 to 1.14. Friedemann, Motel, and Necheles (1938) determined the concentration of alcohol in arterial and venous blood, saliva, and urine of dogs and human beings after the oral administration of alcohol. They found that the maximal concentration of alcohol in saliva coincides with the maximal concentration in the arterial blood, preceding, however, the maximal concentration in the venous blood. As illustrated in figure 3, the concentration of alcohol in the saliva parallels that in the venous blood and is rarely higher than could be accounted for by diffusion.

With regard to the *excretion of ethyl alcohol with the milk*, Nicloux (1899a, b) showed that in human beings and animals alcohol passes readily from the blood into the milk, that the maximal concentration is reached ¾ to 1 hour after the ingestion, and that the concentration in blood and milk are of a similar order. Nicloux (1900a) showed that the concentration in the milk is slightly lower than in the blood and that in severe "intoxication" the concentration of alcohol in the
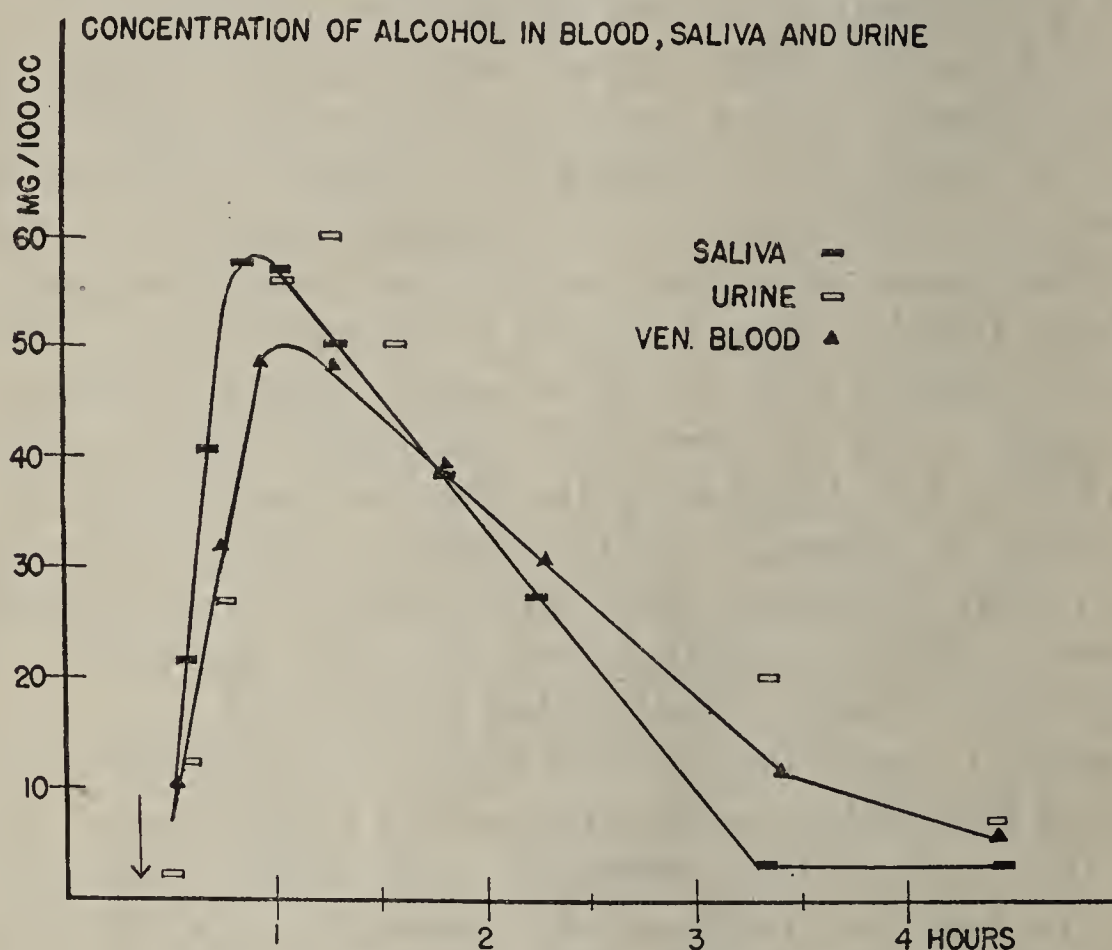
FIGURE 3.—This figure illustrates the concentration of ethyl alcohol in saliva, urine and venous blood in man after ingestion of 300 cc. of 7 percent alcohol (average of 3 human subjects). (Redrawn from Friedemann, Motel and Necheles, 1938.)

milk may be as high as 0.25 percent. Similar results were reported by Völtz and Paechtner (1913) and by Kostick (1921) (quoted from Dervieux, Szumlanski, and Desoille, 1929) who determined the alcohol content of the milk and blood of dogs as follows:

Alcohol content of milk_____	2.0	2.4	3.9	3.9 cc. per kg.
Alcohol content of blood_____	3.1	3.8	4.5	5.4 cc. per kg.

It is obvious that such concentrations may cause severe toxic effects in nurslings fed such milk, as illustrated by the report of Dervieux, Szumlanski and Desoille 1929) who isolated 1.75 cc. of alcohol per liter from the stomach contents of a nursling who had died from alcohol poisoning.

The *distribution of ethyl alcohol in the organism* evidently is based mainly on its diffusion through the tissues. Nicloux (1934) assumed that the amount of water in various tissues controlled the fixation of alcohol in the organism, but, as shown by Nicloux and Gosselin (1934), 14 to 16 percent of the available water does not dissolve or fix alcohol. Le Breton (1934a) showed in rabbits that, following intravenous in-

jection of alcohol, it takes from 20 to 60 minutes, depending on the dose, to establish an equilibrium, and with intraperitoneal injection it takes from 30 to 90 minutes. As shown in experiments with mice and rats, this takes more time with subcutaneous administration and, in addition, larger doses are less readily distributed. When given on an empty stomach the equilibrium may be reached in dogs 1 hour after the administration, but when given on a full stomach it may be considerably delayed. According to Loewy and von der Heide (1918) it takes $8\frac{1}{4}$ hours to establish an equilibrium when concentrations of 0.5 percent of alcohol in air are inhaled, and with higher concentrations it may take even more time.

With regard to the *concentration of alcohol in different organs*, Lallemand, Perrin, and Duroy (1861) found, after oral administration and following intravenous injection, higher concentrations in liver and brain than in blood. Later investigators found that after an equilibrium is reached ethyl alcohol is fairly uniformly distributed among the various organs. Gréhant (1899a) found that in dogs, after oral administration of 5 cc. per kg. body weight, 54.9 cc. of the 58 cc. administered had been absorbed from the gastro-intestinal tract after $3\frac{1}{4}$ hours, and that 100 cc. of blood contained 0.52 cc., 100 gm. of brain contained 0.41 cc., 100 gm. of muscle contained 0.33 cc., 100 gm. of liver contained 0.325 cc., and 100 gm. of kidney contained 0.39 cc. Nicloux (1900c) studied in dogs and guinea pigs, after oral administration, the concentration of alcohol in lymph, saliva, bile, pancreatic fluid, spinal fluid, and amniotic fluid, and found it to be of the same order as, although slightly lower than, that determined in the blood. Alcohol was also found in testes, prostate, ovaries, seminal vessels, and sperm, the content in the testes closely approaching that in the blood. Vollmering (1912) also found a fairly uniform distribution of alcohol in various organs, but he pointed out that until equilibrium is established the blood contains more than other organs, and that in the brain it takes more time to establish equilibrium and to release it than with other organs such as liver and muscle tissue. Similarly, Messner (1913) found in animals killed in alcohol narcosis a fairly uniform concentration in blood, liver, and brain, and slightly less in muscle tissue. Carpenter (1929) found in fowls, following exposure for 2 to 29 hours to vapors of alcohol, the highest concentration in the blood and only a small amount in fat, confirming in this respect similar observations of Vollmering (1912). With higher concentrations the distribution in liver, heart, kidneys, lungs, and spleen was quite uniform. Following continued administration of 4 cc. of alcohol per kg. daily to rabbits, Marinesco, Lissievici-Draganesco, Draganesco, and Grigoresco (1929) found larger concentrations in heart and brain and considerably less in liver and eyeball, the latter containing less ethyl alcohol than found under similar conditions

after the administration of methanol. Nicloux and Redslob (1931) found that, after oral administration, ethyl alcohol passes from the blood into the vitreous humor and that after 3 hours the concentration corresponded to that of the blood, whereas the crystalline humor contained only about one-half this amount. With regard to the distribution of alcohol in the human organism, such data were determined in victims of acute alcohol poisoning; and since the amount of alcohol ingested, the time elapsing between the ingestion and death, and possibly other factors controlling the distribution are not known in such cases, the interpretation of such findings is difficult. Such determinations were made by Pauly and Bonne (1897), Juckenack (1908), Balthazard and Lambert (1921) and Sartori (1930). Whereas Balthazard and Lambert (1921) found a fairly uniform distribution in blood, urine, brain, spleen, liver, kidneys, lungs, heart, and muscle, the values reported by Juckenack (1908) and Sartori (1930) are not uniform as illustrated by table 6.

Table 6.—*Distribution of ethyl alcohol in the human organism in acute fatal alcohol poisoning (in weight percent)*

Author	Blood of large vessels and heart	Heart, lungs, omentum, spleen	Stomach and esophagus contents	Kidneys	Urine	Liver and gall bladder	Brain	Large intestine and contents
Juckenack (1908)_____	0. 53	0. 720	0. 72	0. 37	0. 65	0. 24	0. 42	_____
Sartori (1930)_____	. 40	. 197	. 44	. 32	. 56	. 39	. 26	0. 17

In view of the effect of alcohol on the central nervous system, the concentration of alcohol in the brain has aroused much interest. Kuijper (1883) isolated considerable quantities of alcohol from the brain of a person drowned while intoxicated. Vollmering (1912) showed that the concentration of alcohol in the brain in relation to that in the blood varied at different times after the ingestion. Gettler and Tiber (1927b) determined the "normal alcohol content" of the brain as 0.0025 percent and that in the brains of persons who had ingested various amounts of alcohol as 0.005 to 0.6 percent. They showed that the concentration of alcohol in the brain varied with the intensity of the intoxication, that concentrations below 0.1 percent caused no abnormal psychological effects, and that concentrations of 0.1 to 0.24 percent caused certain disturbances such as increased aggressiveness and carelessness but no disturbance of the equilibrium, and that concentrations of 0.25, 0.4 and 0.6 percent caused the typical picture of intoxication. Gettler and Freireich (1931) claimed that the alcohol content of the brain could be appraised on the basis of the alcohol content of the spinal fluid by dividing this value by the spinal fluid-brain ratio which they determined as being from 1.1 to 1.4. Gettler and St. George (1935) determined the concentration in the

brain of an infant who had died from acute alcohol poisoning as 0.65 percent. Olszycka (1940) studied the distribution of alcohol in various sections of the brain of rats after doses of 2.4 mg. per gram body weight. He found that the concentration in telencephalon, diencephalon, and cerebellum (0.207 to 0.212 gm. percent) was similar to that in the blood (0.231 gm. percent), and that the concentration in the spinal cord and the annular proturberance was slightly lower (0.196 and 0.195 gm. percent). With doses of 3.2 mg. per gram body weight the corresponding values were 0.277 to 0.297 for brain tissue, 0.342 for blood, and 0.269 for the spinal cord.

Nicloux (1899b) showed that alcohol passes from the mother to the fetus and that after equilibrium has been reached the concentration in the maternal and fetal blood are of the same order. Olow (1922) showed that already 12 minutes after the ingestion of alcohol by the mother appreciable quantities may be detected in the fetal blood and that both are of the same order 40 minutes after the ingestion, and that alcohol disappears from both bloods at the same rate.

The *concentration of ethyl alcohol in the blood* varies with the dose of alcohol ingested and the time elapsing between the ingestion and the withdrawal of the blood. Gréhant (1899a,b), Schweisheimer (1913), and Miles (1922) found that following the oral administration of alcohol the alcohol level in the blood increases during the first 1½ to 2 hours and 70 minutes, respectively, and that it remains at an elevated level for a variable length of time and then gradually returns to normal values. Widmark (1915) showed that the rise depends in part upon the amount of food in the stomach, and Olow (1922) and Bornstein and Budelmann (1930) found that when given on an empty stomach the maximal concentration in the blood is reached within 30 minutes, and the former stated that it may return to normal value within 2 and 2½ hours. Haggard and Greenberg (1934b) showed that the concentration of alcohol in the blood drawn from an artery, the jugular vein, the right side of the heart, and the skin capillaries over a period of 6½ hours following the ingestion of alcohol was of very similar order, but that the alcohol level in blood withdrawn from the femoral vein during the period of absorption was much lower and did not correspond to that in the urine or that in the brain. Haggard, Greenberg and Rakieten (1940) showed that before equlibrium is established the concentration of alcohol in the blood drawn from different vessels may show wide differences. Schmidt (1934) found considerable variations (0.04 to 0.08 percent) in the blood of normal subjects after the ingestion of 0.6 cc. of alcohol per kg. body weight in the form of whisky and soda, and he believed this to be mainly due to a different speed of absorption. Gabbe (1917) claimed that, following its intravenous administration, alcohol disappears from the blood rapidly at first and then more slowly. With

the exception of Haggard and Greenberg (1934c) most investigators (Mellanby, 1919; Widmark, 1933a; Neymark and Widmark, 1936b; Newman and Cutting, 1935; and Newman, Lehman, and Cutting, 1937) agree that, following the administration of single doses, alcohol disappears from the blood at a constant rate.

With regard to the distribution of alcohol among the different constituents of the blood, Miles (1922) found that the distribution ratio between red blood cells and plasma is 2:1, Bornstein and Budelmann (1930) noted no difference in the distribution between red blood cells and serum, and Elbel (1935) found the alcohol content of serum greater than that of whole blood. The latter also found that the serum value divided by 1.2 corresponds closely to the amount of alcohol present in whole blood. This was confirmed by Künkele (1936) who determined the ratio also as 1.2 with 1.12 and 1.31 as extremes, and that of the blood clot to that of whole blood as 0.74 with 0.70 and 0.82 as extremes.

With regard to *factors influencing the concentration of ethyl alcohol in the blood*, Miles (1922) showed that this depends in part upon the *concentration* in which the alcohol was given, in that the same dose of alcohol given in more concentrated form results in definitely higher values in the blood. This was confirmed by Turner and Loew (1932) whereas Kionka (1928) claimed that the concentration of the alcohol ingested had no influence on the blood alcohol level, and Rasmussen (1940) found in rats that the blood alcohol level was definitely lower when higher concentrations of alcohol were given. Dybing and Rasmussen (1940) pointed out that this may be partly explained by the histological characteristics of the rat's stomach, two-thirds of which are covered by mucosa containing several layers of glandless cornified epithelium, only one-third being of the ordinary type. On account of its irritant action alcohol also causes pylorospasm and is, therefore, not released into the gut where it would be readily absorbed. In addition, the concentration of alcohol in the blood depends upon the *amount* of alcohol ingested, as demonstrated by many investigators and as will be discussed in a later section.

It has been shown repeatedly that the *amount of food in the stomach affects the alcohol level in the blood*. Widmark (1915 and 1934), Miles (1922), Tuovinen (1930), Turner and Loew (1932), Elbel and Lieck (1936) and others agree that when alcohol is taken on a full stomach the alcohol level in the blood is lower than when alcohol is given on an empty stomach or while the subject is starving. Miles (1922) and Tuovinen (1930) believed that *carbohydrates* ingested with alcohol reduce its concentration in the blood, but Widmark (1934) reported no such effects from carbohydrates and Elbel and Lieck (1936) stated that the quantity of food is more important

than the relative caloric value and the composition with regard to proteins, carbohydrates, and fats. Whereas Tuovinen (1930) and Widmark (1934) stated that the ingestion of *fats* does not interfere with the alcohol level in blood, both believed that *proteins* had definitely an inhibitory effect, in that, as assumed by Widmark (1934), they are precipitated by alcohol and thus delay its absorption. Widmark (1934) and Kanitz (1939) showed that the feeding of *amino acids*, such as glycine, lowers the alcohol level in the blood. Haggard and Greenberg (1940) believed that this effect can be explained best as a prolonged retention of alcohol in the stomach, caused by glycine, resulting in delayed absorption. Widmark (1934) stated that the feeding of *higher fatty acids* and of citric, malic, and tartaric acids as well as primary and secondary phosphates has a moderate lowering effect on the concentration of alcohol in the blood. Kanitz (1939) found that this also holds true for lactic, pyrotartaric, and succinic acids, whereas fumaric and glutamic acids had no or very little effect. The latter also showed that feeding of the ethyl esters of some of these and other acids caused a more or less marked increase of the volatile constituents of the blood, indicating that the use of aromatic, alcoholic beverages for such studies may lead to erroneous results. Allodi and Daprá (1938) showed that serious *damage of the liver* may cause abnormally high alcohol concentrations in the blood. Danopoulos (1938) found that *blocking the reticuloendothelial system* with India ink or with colloidal copper solution increased the alcoholemic curve materially and caused delay of its decline. Similarly, Arima (1941) found that injury of the liver delayed the reduction of the blood alcohol level. Danopoulos (1939a) noted that in patients suffering from scurvy the blood alcohol level was abnormally high without giving an explanation for this phenomenon. Kanitz (1936) showed that in rabbits the administration of 1 gm. of sugar and 1 unit of *insulin* with small doses of alcohol (1.5 cc.) caused, during the resorptive phase, an abnormal increase and later a decrease of the alcohol level in the blood, and that this effect appears to increase within certain limits with the dose of insulin given. Böhmer (1938) stated that large doses of insulin caused lowering of the blood alcohol level during the resorptive phase and an unusual rise during the post resorptive phase which he interpreted as indicative of delayed absorption. According to Arima (1941), injury of the kidney does not affect the blood alcohol curve. In view of the importance of the concentration of alcohol in the blood with regard to medico-legal questions, the *effect of drugs* on the blood alcohol level has aroused much interest. Walter (1938) stated that neither acetyl salicylic acid (aspirin) nor gardan (an amidopyrine preparation) caused a lowering of the blood

alcohol level, the latter causing only a slightly delayed absorption. Similar negative results were reported by Elbel (1938) who found the same to hold true for barbital. Rinkel and Myerson (1941) reported that benzedrine sulfate, paredrine, epinephrine hydrochloride, and atropine sulfate lower the blood alcohol level, decreasing in effectiveness in the order given, and they assumed that this effect was due to delayed absorption, by delaying the emptying of the stomach. McCrea and Taylor (1940) found that the administration of metrazol had no effect on the disappearance of alcohol from the blood of dogs. Siegmund (1938) studied the question as to whether or not *solvents*, such as those used in lacquer spraying, may affect blood alcohol findings, as determined by Widmark's test, but found no evidence of such action at the end of 1 week of spray painting. According to Leschke (1932), Bichler claimed that at *high altitudes* the increase of alcohol in the blood is less rapid, reaches a lower peak, and declines more rapidly than normally, which he thought to be due to the more rapid respiration and greater pulmonary elimination. Schweisheimer (1913) and Fleming and Stotz (1935) claimed that in chronic alcoholism the concentration of alcohol in the blood increases more rapidly, reaches a higher level, and decreases more rapidly than in abstainers, whereas Graf and Flake (1932–33) believed that habituation has no effect on the alcohol level in the blood.

With regard to the *relation of the concentration of ethyl alcohol in blood to that in the urine*, Nicloux (1900c) and Nicloux and Nowicka (1913) claimed that at the moment of secretion the alcohol content of the urine equals that of the blood, and this was confirmed by Widmark (1915), Chabanier and Ibarra-Loring (1916), Gréhant (quoted from Haggard and Greenberg, 1934b) and Schweisheimer (1913). Haggard and Greenberg (1934b) pointed out that alcohol is more soluble in blood than in urine but that the concentrations in blood and urine are of the same order. This was confirmed by Siegmann (1936) who determined the average difference as 0.03 percent. Miles (1922), Southgate and Carter (1926), Bornstein and Budelmann (1930) and Carlson, Kleitman, Muehlberger, McLean, Gullicksen, and Carlson (1934) found that the concentration in the urine parallels that in the blood, being, however, slightly higher. This was interpreted by Bornstein and Budelmann (1930) as indicative of a moderate ability of the kidneys to concentrate alcohol, but it should also be pointed out that the concentration of alcohol in blood samples taken at the time of the collection of urine from the bladder does not represent the concentration of alcohol in the blood at the time of its excretion by the kidneys. The findings of Carlson and his associates (1934) are given in table 7.

Table 7.—*The concentration of alcohol in blood and urine after 2 and after 4 bottles of 3.2 percent beer (in mg. percent)*

[Carlson, Kleitman, Muehlberger, McLean, Gullicksen, and Carlson, 1934]

| | 2 bottles of beer | | | | 4 bottles of beer | | | |
| | Without food | | With food | | Without food | | With food | |
	Urine	Blood	Urine	Blood	Urine	Blood	Urine	Blood
Highest value	0. 61	0. 46	0. 56	0. 39	1. 21	0. 93	1. 06	0. 84
Lowest value	. 21	. 15	. 14	. 15	. 54	. 41	. 56	. 41
Average value	. 39	. 285	. 35	. 254	. 79	. 61	. 76	. 558
Number of subjects	36	36	35	35	33	33	36	36

The relation of the concentration of ethyl alcohol in the blood to that in the saliva was studied by Linde (1932) who found it to be greater in the blood during the absorptive phase, but after an equilibrium had been established the two values were the same. He determined the ratio of the concentration of alcohol in saliva and blood in 26 experiments as 1.21 in the average. Similarly, Vollenbruck (1937) found the same concentration of alcohol in saliva and blood after absorption was complete when the alcohol was taken on an empty stomach or after a light meal but not when taken on a full stomach. Friedemann, Motel, and Necheles (1938) also noted a certain parallelism between the concentrations of alcohol in saliva and blood.

With regard to the *concentration of ethyl alcohol in the spinal fluid*, Nicloux (1900c) showed that alcohol may be detected in the spinal fluid and Schottmüller and Schumm (1912) and Selig (1912) demonstrated its presence in the spinal fluid by means of the iodoform test, which, as demonstrated by Rajewsky (1875) is not sufficiently specific for the detection of alcohol in biological materials. Schumm and Fleischmann (1913), using a specific method for the determination, found, in intoxicated persons, within 2 hours after the ingestion, concentrations between 0.015 and 0.04 percent. They also found that these concentrations decreased when 3 hours had elapsed, and that they were negative after 20 to 24 hours. They found that the concentration in the spinal fluid depends upon the amount of alcohol ingested, and that it increases rapidly during the first hour, remains at a high level for 3 hours, and then decreases rapidly.

Nicloux (1900c) showed that the concentration of alcohol in spinal fluid and blood are of the same order, but according to Schumm and Fleischmann (1913) the increase of the alcohol concentration in the blood is more rapid during the first hour, while in the post absorptive phase the concentration is lower than that in the spinal fluid. This was confirmed by Abramson and Linde (1930) and Mehrtens and Newman (1933), as illustrated in figure 4. They found that the alcohol content of the cisternal fluid rises promptly and

closely approximates that of the blood, and that if the blood alcohol level is kept constant for 4 to 5 hours, the concentrations of alcohol in lumbar and cisternal fluid are equal to or in excess of that in the blood plasma. As indicated by these experiments, alcohol enters the spinal fluid by diffusion, probably largely from the choroid plexus. They suggested that the higher concentration of alcohol in the spinal fluid as compared with that in the blood plasma may be due to a relative impermeability of the absorbing system to alcohol or possibly, but less likely, to an active secretion of alcohol from the choroid plexus. Similar results were reported by Fleming and Stotz (1935).

With regard to the relation between the concentration of ethyl alcohol in the spinal fluid and that in the urine, Lenoble and Daniel
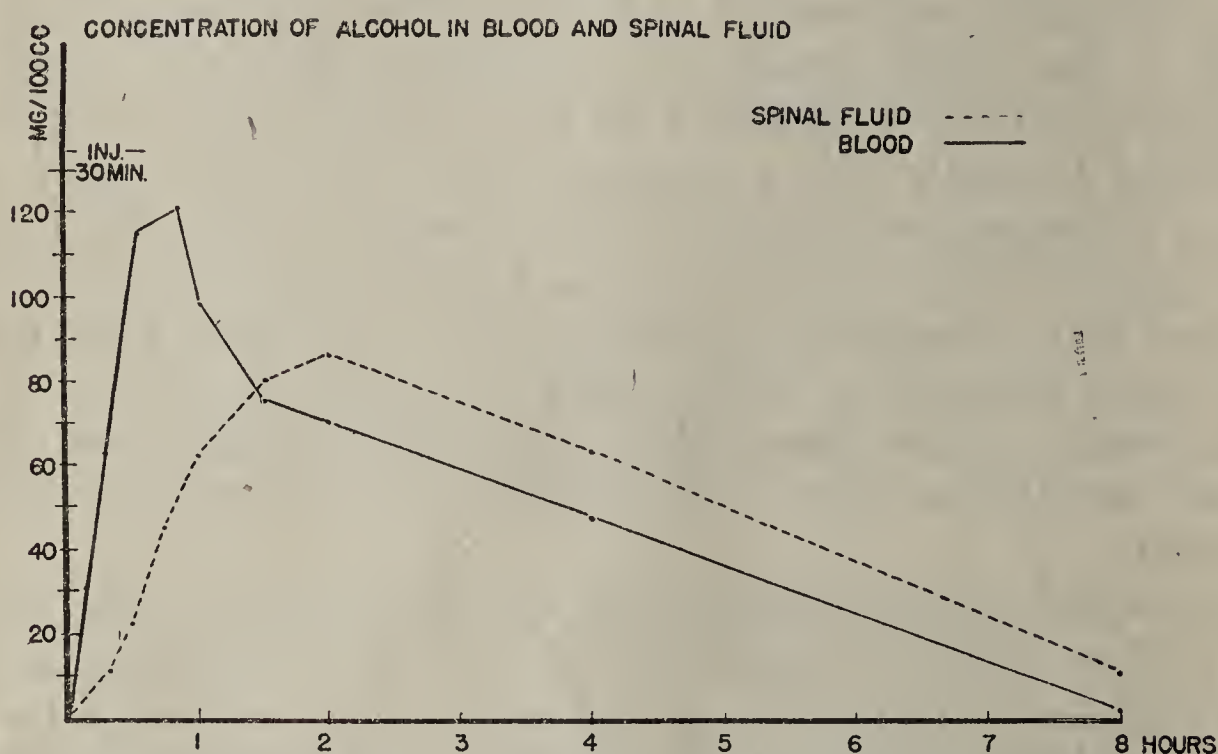
FIGURE 4.—This figure illustrates the concentration of alcohol in blood and spinal fluid in man after a single intravenous injection. (Redrawn from Mehrtens and Newman, 1933.)

(1917) noted that the disappearance of alcohol from the spinal fluid parallels its elimination with the urine but that the concentration in the urine is usually lower than that in the spinal fluid.

Vad and Kulkarni (1929) claimed that alcohol disappears more slowly from the spinal fluid of habitual drinkers than from that of normal persons. Gettler and Freireich (1931) found that the alcohol content of the spinal fluid is usually higher than that of the brain but that after large doses of alcohol this difference becomes less marked.

The antiseptic action of ethyl alcohol.—The antiseptic properties of alcohol had been known before the role of bacteria in the production of infections was recognized. Epstein (1897) showed that absolute alcohol does not kill bacteria when used pure but only when diluted with water in certain proportions, and he found that optimal antiseptic action is obtained with concentrations of 50 percent. Similar findings were reported by Minervini (1898) and Salzwedel and Elsner

(1900). The latter found that concentrations of 50 to 55 percent correspond with regard to their antiseptic action to 3-percent solutions of phenol, but that fresh bacteria may be killed also by absolute alcohol, as was also shown by Buchner, Fuchs, and Megele (1901) for staphylococcus pyrogenes aureus, bacillus typhi, and bacillus pyocyaneus. Tijmstra (1913) gave the optimal antiseptic concentration as 70 percent. Gerschenfeld (1938) found that 95 percent ethyl alcohol did not kill *Bacillus megatherium* and *Bacillus subtilis* until the exposure had lasted about 3 months in the first and 7 to 9 months in the latter case. Christiansen (1918) showed that the antiseptic action of alcohol was due to a twofold mechanism; that it acted by dehydration of the fresh bacteria, as produced by 100 percent alcohol, and by precipitation of the proteins of the plasma. For these reasons dried bacteria, such as used in the silk-thread method and in the glass bead method for testing antisepetics, are not affected to the same extent by absolute alcohol. Christiansen (1918) showed that the penetration of alcohol into the cell varies with the inverse ratio of the surface tension of its solutions which, as shown by Kisch (1912), decreases with the concentration. In addition, an increase of the temperature enhances the penetration of alcohol solutions of a certain surface tension. Within the cell, alcohol precipitates the proteins and therefore kills the organism. This precipitant action depends in part upon the amount of salts within the cells, and this may explain why spores are not killed by alcohol, as was demonstrated by Minervini (1898), Knorr (1932), and others. Since the precipitation of proteins depends also upon the concentration of alcohol, this explains why the optimal antiseptic action of alcohol is bound to certain concentrations.

The effect of alcohol on the central nervous system.—Alcohol depresses the functions of the central nervous system. Albertoni and Lussana (1874) (quoted from Kochmann, 1923) showed that the intravenous and oral administration of proper doses of alcohol causes in birds, motor paralysis, but that loss of sensitivity is produced only by toxic or fatal doses. Baer (1898) studied the effect on rabbits of oral administration of various doses of alcohol. He found that doses of 2.5 to 4.1 gm. per kg. caused moderate poisoning, characterized by primary excitation, subsequent moderate motor depression, and moderate reduction of sensitivity, whereas the corneal, ciliary, and pupillary reflexes were not affected and respiration, pulse rate, and body temperature were not distinctly changed. Doses of 4.45 to 6.15 gm. per kg. caused, after 15 minutes following a slight primary stimulation, complete motor paralysis, marked analgesia, impairment of corneal reflexes, constriction of pupils with sluggish or negative reaction, slowing of the respiration, and reduction of the body temperature, the recovery taking about 10 hours. Doses of 6.25 to 7.44

gm. per kg. caused, within a few minutes, rapid and complete paralysis, reduction of the sensitivity and reflexes, constriction and nonreactivity of the pupils, nystagmus, salivation, occasionally tonic convulsions, marked slowing of the respiration, reduction of the body temperature, and narcosis lasting 36 hours. Turner and Loew (1932) correlated in dogs the concentration of alcohol in the blood with the degree of the depression and found that concentrations of 0.25 percent cause definite intoxication; of 0.30 percent, marked intoxication; and of 0.4 to 0.5 percent, alcoholic stupor. Alexandroff and Talpis (1929) noted in rabbits poisoned with alcohol marked disturbances of the reflexes controlling the posture of the neck, less marked disturbances of the locomotor reactions and the labyrinth reflexes. Versteegh (1922) studied in rabbits the effect of various doses of alcohol on the postural reflexes. He found that oral administration of 3 cc. per kg. caused no disturbances of the reflexes except inhibition of locomotion (lift reaction). Doses of 5 to 6 cc. per kg. abolished the cervical postural reflexes, affecting first the anterior and later the posterior reflexes. Doses of about 8 cc. per kg. abolished the postural reflexes, so that the animals were unable to maintain their normal position. Other reflexes, such as motor eye reflexes, corneal reflexes, patellar reflexes and flexor reflexes, were still positive at a time when the postural reflexes had disappeared. Chauchard, Chauchard and Kijiwara (1930b) studied in dogs the effect of alcohol on the excitability of neurons of the cerebral cortex, especially of those regions which provoke a response in the antagonists. They found that under the influence of alcohol the chronaxy in the cortical neurons becomes stabilized, but that the chronaxy of the cortical zones of antagonists increases at a different speed, thereby creating disturbances which may contribute to the difficulties in coordination observed in acute alcohol intoxication.

With regard to the narcotic dose of alcohol, this varies with the species and with the route of administration, as illustrated by the following reports. Lehman and Newman (1937 b) determined the minimal narcotic dose for rabbits with intravenous injection as 5.6 cc. per kg.; Grilichess (1913), with intramuscular injection, as 8.0 cc. per kg.; Lendle (1928), with intraperitoneal injection in rats, as 4.5 cc. per kg.; and Strauss (1887), with oral administration to rabbits, as 6 to 8 gm. Latven and Molitor (1939) determined the minimal hypnotic dose for mice with subcutaneous administration as 2 cc. per kg., with oral administration as 3 cc. per kg., and with intravenous administration as 0.8 cc. per kg. Flury and Klimmer (quoted from Lehmann and Flury, 1938) determined the narcotic action of alcohol vapors in mice.

The question as to whether or not ethyl alcohol stimulates the respiration has aroused much interest. Wilmanns (1897) and others, such as Binz (1891), Heinz (1890), and Weissenfeld (1898) (the

last three quoted from Kochmann, 1923) showed that the adminis-
tration of moderate doses of alcohol causes a moderate stimulation
of the respiratory center. Wendelstadt (1899) found that small
doses of alcohol cause only a moderate stimulation of the respiration
in normal persons, but that with such doses the effect is much more
marked in fatigued persons; and from observation that highly aro-
matic wine was found to be more effective than pure alcohol it ap-
pears that essential oils may have an additive or perhaps a synergistic
effect. This stimulant effect depends, however, upon the dose of
alcohol administered. Fonteyne (1906) showed that in rabbits the
intravenous injection of 0.16 gm. per kg. stimulates and deepens the
respiration but that doses of 1.44 gm. per kg. cause depression. He
believed that with regard to the depressant action 3 stages can be
distinguished: (1) slight inhibition with deepened respiration; (2)
marked slowing with reduced respiratory volume; and (3) very
marked slowing with shallow respiration. Hooker (1917) perfused
the medulla of dogs with defibrinated blood containing various con-
centrations of alcohol. He found that with an alcohol concentration
in the blood of 0.025 percent there was some stimulation of the respira-
tion, that with 0.1 percent the stimulative response was greater, but
that 0.25 percent caused only a transitory stimulation followed by
prolonged inhibition. Gradinesco (1934) believed that alcohol af-
fects the respiratory center, the first costo-thoracic nerve, and later
also the phrenic nerve. In contrast to these positive findings, Lieb
(1915) found that the oral administration of alcohol to etherized and
decerebrated cats had no stimulant effect on the respiration. Simi-
larly, Hyatt and Jensen (1918) found that in etherized dogs with
sectioned spinal cord to insure loss of sensation in the hind legs
the intravenous injection of alcohol into the desensitized legs caused
only a moderate stimulation of the respiration. Similar results were
reported by Hyatt (1919) with oral administration to dogs whose
spinal cords were sectioned at the height of the eleventh and twelfth
thoracic vertebrae, and he believed that the stimulant effect of alcohol
on the respiration is bound to some local irritation. Hitchcock (1942)
found, however, in humans that small doses of alcohol stimulate the
respiration, at least for a limited period of time; and he believed
this was not due to a reflex mechanism from the gastric mucosa but
was caused by direct stimulation of the respiratory center. Similarly,
experiments of Masserman (1940) indicate that alcohol may have some
stimulant effect on certain structures of the brain. He found that
in cats under light ether anesthesia the intravenous or intraperitoneal
injection of small doses of alcohol may produce a stimulant effect
on the hypothalamus but not on the sigmoid cortex, and that, there-
fore, small doses of alcohol which are easily metabolized may facilitate
the response of the central nervous system, especially that of the lower

diencephalic region. It has been stated before that larger doses of alcohol invariably cause more or less severe depression of the respiration. According to Haggard, Greenberg, and Rakieten (1940), concentrations of 9.3 mg. per cc. of blood in fasting rats will cause respiratory failure, and according to McCrea and Taylor (1940) in dogs the intravenous injection of 3.0 to 7.2 cc. per kg. body weight will cause respiratory arrest which can be overcome temporarily by the administration of metrazol. Gold and Travell (1934) studied in dogs the antagonism between alcohol and strychnine and found that in strychnine poisoning small doses of alcohol may have an antagonistic effect whereas large doses may lead to respiratory depression. This was confirmed by Norris (1937) who claimed that both strychnine and alcohol act somewhat alike on the brain and the spinal cord, causing death by cardiac and respiratory failure, and that alcohol is no antagonist in strychnine poisoning. Reifenstein (1941) studied the antagonism between alcohol and amphetamine sulfate and found that the latter counteracts the narcotic action of moderate doses of alcohol but not that of lethal doses, and that it may even increase the toxic effect of the latter. On the other hand, he found that alcohol may protect rabbits from 1.5 to 2.0 times the minimal fatal dose of amphetamine sulfate.

Attempts have also been made to use alcohol for the production of narcosis in humans. Marin (1929) (quoted from Constantin, 1929) advocated its intravenous administration for this purpose, worked out detailed directions, and claimed that this form of narcosis was simple, comparatively free from post narcotic complications, easily controlled and without untoward effects on the circulation. Constantin (1929) found it satisfactory in two cases, and Fohl (1931) found that pathological organ changes are much less than might be expected, resembling in many respects those seen with other narcotics. However, he believed that there is considerable danger of thrombus formation which may cause embolism. He also found indications of impairment of the circulation and vasomotor mechanism which in his opinion may predispose to certain complications, such as pneumonia, and that the narcosis is not as easily controlled as might be desired.

Much effort has been devoted to the *effect of ethyl alcohol on the functions of the central nervous system of man.* The first experimental studies on this subject were carried out by Kraepelin and his collaborators, by Aschaffenburg (1896), Bergmann (1905), Dodge and Benedict (1915), Benedict (1916), Gyllenswärd (1917), Graf (1932–33), and many others. Jellinek and McFarland (1940) gave an extensive critical review of such psychological tests. They pointed out that different psychological functions are affected by alcohol at different concentrations of alcohol in the blood, or, rather, in the brain. In their opinion it appears to be established that the ingestion of alcohol

impairs the tactile, auditory, and visual sensations and perception, especially in those tests which involve active attention. They showed that most authorities agree that ingestion of alcohol results in an increase of the reaction time, and believed that a critical analysis of data published by earlier investigators throws some doubt on statements that ingestion of alcohol causes a primary reduction of the reaction time, and that such results are partly due to inadequate arrangement of the experiments and partly caused by continuation of the practice effect. The latter effect is not overcome during the first 20 minutes after the ingestion of small doses (10 cc.) of alcohol. It seems to be established that larger doses of alcohol cause an immediate increase of the reaction time the magnitude of which varies with the amount of alcohol ingested and its concentration.

With regard to the effect of ethyl alcohol on muscular strength and coordination, Schnyder (1903) believed that the ingestion of small amounts of alcohol has a favorable effect on the muscular energy only in cases where the energy has been exhausted, that this effect is less marked than that of a nutrient of corresponding caloric value, and that it is unfavorably affected by the depressant effect of alcohol on the central nervous system. He came to the conclusion that in properly nourished persons alcohol has no favorable effect on the muscular energy, but rather impairs it. Jellinek and McFarland (1940) stated that small doses of alcohol (10 to 20 cc.) have been generally found to increase the muscular output above the initial level for at least a short while, that with medium doses (30 to 45 cc.) the increase is less pronounced and that with larger doses (60 to 80 cc.) there is either no change or a deterioration of the performance. They believed that the apparently favorable effect of alcohol on the muscular output can be explained either by a sensory excitation or by a facilitation of the motor impulses. It appears further that impairment produced by medium doses of alcohol is greater in those tasks which require a greater muscular coordination, and that in such experiments it may reach 50 to 60 percent. It is, therefore, evident that alcohol is not suitable for increasing industrial efficiency, but it appears that small doses (10 to 20 cc.) do not necessarily interfere with the efficiency of workers accustomed to alcohol.

With regard to changes in performance of miscellaneous tests of dexterity and skill, Jellinek and McFarland (1940) believed that these are affected by alcohol in proportion to their complexity but that this element may be compensated and even outweighed by familiarity with the task, unless the complexity is of a high degree.

In respect to changes in learning and simple learned performances it appears that these are greatly impaired after the ingestion of alcohol, and animal experiments seem to indicate that this also impairs learned tasks.

Jellinek and McFarland (1940) believed that there is no doubt that the immediate memory is adversely affected by alcohol to a very marked degree and that there is some indication that the impairment increases with the complexity of the memory function, and the same is said to hold true for associative functions, judgment, reasoning, and intelligence.

With regard to the relation between the concentration of alcohol in the blood and its effect on the central nervous system, numerous studies have been made which will be discussed with acute alcohol poisoning. It appears, however, that this relation is not as simple as
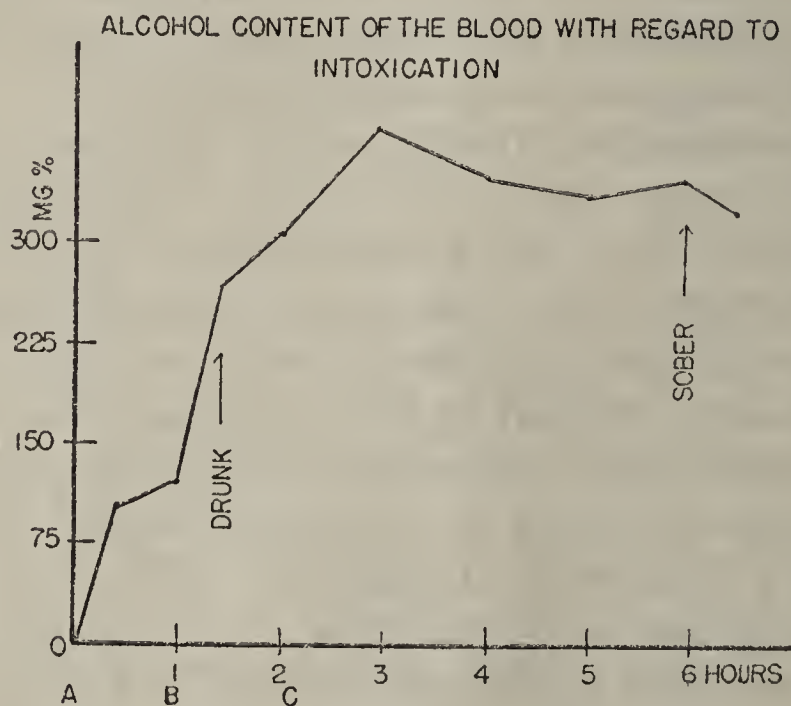
FIGURE 5.—This figure illustrates the concentration of ethyl alcohol in blood subsequent to the ingestion of 1 gm. per kg. body weight of alcohol at A, 0.25 gm. per kg. at B and C, and the beginning of the clinically established drunkenness and the return to soberness. (Redrawn from Mirsky, Piker, Rosenbaum, and Lederer, 1941.)

is usually assumed and that other factors may be involved in this reaction. Mellanby (1919) stated that the effect of alcohol on the central nervous system is greater at a point (A) when the alcohol curve is rising than at a point (B) of the same level when the concentration is falling. This question was studied experimentally in rabbits and man by Mirsky, Piker, Rosenbaum and Lederer (1941). They showed that if in rabbits the blood alcohol level is raised rapidly, within 1 to 2 minutes, to 100 mg. percent the animals show first certain symptoms, such as nystagmus and incoordination, and later, coma. In spite of the fact that this level was maintained by repeated administration of alcohol, the animals came out of the stupor after some time and their behavior was apparently normal. They also showed that with very slow administration of alcohol, higher levels could be reached in the blood before the symptoms described became manifest. Figure 5 illustrates a similar experiment in a human subject who became drunk, as established by Jetter's clinical tests, at around 270 mg. percent alcohol in the blood and sober after about 6 hours, at a time when the blood

alcohol level was still much higher than it was at the time when he was pronounced drunk. Mirsky and his associates assumed that some change or adaptation of the central nervous system may be responsible for this variation in the clinical response to alcohol, but it may also be possible that the narcotic action is bound, to a certain extent, to the gradient between the alcohol concentration in the blood and that in the brain tissue.

With regard to the *effect of ethyl alcohol on the vision*. Hollmann (1905-6), found, in a young man, following acute intoxication, a reduction of the visual field for white and for colors, a reduction of the visual acuity, and, occasionally, negative scotoma, i. e., a scotoma which is not ordinarily perceived but detected only upon examination of the entire visual field. Busch (1910) found that the ingestion of 30 cc. of alcohol causes a distinct decrease of the tachistoscopic perception of visual stimuli but found the visual acuity unimpaired. Schulz (1916 and 1917a, b) demonstrated that, following the ingestion of alcohol, the adaptation to light and dark and, to a lesser extent, to red and green, is affected, and that some persons are more susceptible in this respect than others. But according to Manz (1940) the speed of dark adaptation of the human eye is not changed after the ingestion of alcohol. He found, however, that the realization of depth is distinctly impaired with concentrations of 0.06 to 0.125 percent of alcohol in the blood and that with a blood alcohol level of 0.03 percent there was already some impairment of judgment of depth, mainly characterized by a delay in making the proper estimate. Colson (1940) found, in acute intoxication, no reduction of the visual acuity, the visual field, or the color vision, nor any tendency to hyperphoria. He noted, however, a gradually increasing esophoria which, in two subjects, progressed to convergent strabismus and diplopia in the latter part of the test. One subject had a definite exophoria at the onset of the test and passed through the stage of orthophoria before becoming esophoric. Newman and Fletcher (1941) studied in 50 drivers the effect on vision of approximately 1 ounce of whisky per 30 pounds body weight, to be taken in 15 to 30 minutes. They tested these subjects with regard to visual acuity, depth perception, distance judgment, lateral field of vision, eye coordination, glare resistance, and glare recovery. In every case with a blood alcohol level above 0.115 percent, the result of at least 1 of these tests was changed significantly. The greatest number of changes occurred in the visual acuity, the smallest in the field of vision. They found no definite relation between blood alcohol level and performance, but noted a considerable variation in the tolerance to a given concentration of alcohol in the blood. These few references may suffice to show, as was also pointed out by Jellinek and McFarland (1940), that results of different investigators on the effect of alcohol on the visual acuity are

conflicting, but that some impairment of the visual acuity is indicated.

Alcohol may also have a more injurious effect on the eye, as illustrated by the report of Kaiser (1912) on 1 case of acute alcohol amblyopia, characterized by peripheral restriction of the visual field, loss of sensation to colors and marked reduction of the visual acuity lasting for several days and resulting presumably from a direct toxic effect of alcohol on the nervous structures. Carroll and Goodhart (1938) reported 6 cases of total but temporary blindness lasting usually 24 hours, and they refer to similar cases reported by deSchweinitz (1896) and Schrader (1927). In spite of the blindness, in these patients the pupils reacted normally to light and convergence and there were no abnormalities in the fundi, indicating the functional character of the phenomenon.

With regard to pupillary changes, Stapel (1911) noted in acute alcoholic intoxication the following abnormalities: (1) Bilaterial dilatation, rarely constriction; (2) reduction of the accommodation to light, which may be preceded by a very moderate increase; (3) reduction of the response to sensory and sense stimuli and to psychic reactions; and (4) in maximal intoxication, complete rigidity of the pupils.

The *effect of ethyl alcohol on the static organ* varies with its concentration in the blood. Manz (1940) noted, at a blood alcohol level of 0.03 to 0.04 percent, an increased excitability of the static apparatus and nystagmus, and with concentrations of 0.036 to 0.103 percent he noted that 6 out of 11 test persons showed spontaneous nystagmus.

With regard to the *effect of ethyl alcohol on the spinal apparatus*, Finkelnburg (1904) showed that in dogs the oral administration of ethyl alcohol results, after 12 to 30 minutes, in a slow increase of the cerebrospinal pressure. He concluded from the duration of this phenomenon that this is not due to a circulatory effect but is caused by an increased secretion of cerebrospinal fluid. Lhermitte, de Ajuriaguerra and Garnier (1938) showed that continued administration of alcohol to rabbits does not affect the spinal cord, as claimed by Lhermitte (1935), but that the changes observed by the latter were due to avitaminosis rather than caused by alcohol.

With respect to the *irritant action of ethyl alcohol*, Loewy and von der Heide (1918) stated that only concentrations of 0.1 to 0.25 percent (1,000 to 2,500 p. p. m.) of alcohol in air can be inhaled without discomfort. According to Kochmann (1923) aqueous solutions of 20 percent alcohol cause burning and a feeling of warmth when applied to mucous membranes, solutions of 50 to 60 percent cause pain, and concentrations of 80 to 90 percent may cause similar effects on the intact skin provided that the evaporation of alcohol is prevented.

With regard to the *effect of ethyl alcohol on the peripheral motor nerves*, Kochmann (1923) refers to Biedermann (1881), Mommsen (1881), Efron (1885), Gad (1888), Pietrowski (1893), Breyer (1903),

Waller (1897, 1908, and 1909), Verár (1909) and others as having shown that diluted solutions or low concentrations of alcohol in air may stimulate the excitability of the isolated sciatic nerve of frogs. Gioffredi (1898) (quoted from Kochmann, 1923) showed that this effect is due to an increase of the conductivity. More concentrated solutions cause, however, depression and paralysis of the nerve, the intensity of the depression depending upon the concentration and the duration of the exposure. Bonnet and Lelu (1933) found that 1 percent solutions of alcohol first increase the chronaxy of the isolated sciatic nerve of frogs and later lower it to various extents, and that 2.0 to 3.0 percent cause a moderate decrease and 5 percent a primary increase and subsequent decrease. Gradinesco and Degan (1934) observed, with concentrations of 0.5 to 10 percent, a primary decrease of the chronaxy of varying intensity, depending in degree upon the concentration of alcohol and the duration of the exposure, which was followed by an increase of the chronaxy and paralysis. They found that concentrations of 15 to 30 percent cause complete paralysis which is reversible with lower concentrations but irreversible with higher concentrations. Lapicque and Kajiwara (1930) found in dogs that alcohol affects the chronaxy of antagonistic nerves to a different extent, resulting in a modification of the chronaxy of the extensor and flexor muscles.

With regard to the *effect of ethyl alcohol on the sensory nerves*, it was shown by Horvath (1873) that alcohol paralyzes the peripheral sensory nerve endings after a short primary stimulation and that in this way it may act as a local anesthetic.

The effect of ethyl alcohol on the circulation.—The *effect of ethyl alcohol on the heart* has been studied in cold-blooded and warm-blooded animals. Ringer and Sainsbury (1883) showed in frogs that alcohol depresses the heart muscle and increases moderately the heart rate but not the force of the cardiac contraction. Dreser (1887), working with the isolated frog heart (Williams' arrangement) found that small concentrations of alcohol (0.015 gm. per 45 cc. of blood corresponding to 0.033 percent) have generally no favorable effect and cause only exceptionally a moderate increase of the energy but usually a depression. Using the same procedure Dieballa (1894) found that concentrations of 0.144 to 9.4 percent cause depression of the cardiac action, less vigorous contractions, and a slight effect on the heart rate. These effects were reversible by lavage. Fühner (1921) determined the minimal paralyzant concentration of ethyl alcohol for the heart as 1.206 mole per liter (5.52 per cent). Ransom (1919) stated that 1 percent solutions have only a slight effect on the heart action, 2 percent cause temporary depression followed by recovery, and that 3 and 4 percent solutions cause arrest for 30 minutes. However, after this the heart recovers gradually in spite of continued perfusion with such concen-

tration, although with distinctly toxic concentrations the recovery was never complete. Wolff (1922) found that 2 and 6 normal solutions (9.2 and 27.6 percent) cause cardiac arrest in middle position, and after lavage he noted some increase of the heart rate and more vigorous systolic contraction. A similar observation was reported by Toyoshima (1928). He believed that alcohol always depresses the action of the isolated frog heart, that this effect is not related to the parasympathetic system but is due to a depressant effect on the cardiac muscle, as had been assumed by Ringer and Sainsbury (1883), and that it is also partly caused by an impairment of the conductivity in the venous sinus, the auricles, and probably also the ventricle, whereas Dreser (1887) assumed that the depressant effect of alcohol on the heart was presumably no direct cardiac action and Seliškar (1926) assumed that alcohol affects the contractility more than the conduction. Vernon (1910) found that concentrations of 0.5 per cent of alcohol in saline reduce the beat of the perfused turtle heart to a constant level in about 14 minutes and that no further changes occur over a period of 16 minutes. With higher concentrations the depressant effect was more marked and reached a constant level sooner. He believed that with each concentration a certain amount of alcohol is bound to the contractile substance of the heart muscle. He also noted that, during lavage of the heart with Ringer's solution, there was occasionally a temporary increase of the amplitude of the heart and that this effect was greater during recovery from the effects of higher concentrations of alcohol. These findings were confirmed by Robertson and Clark (1933), who determined the amount of alcohol in the heart muscle and who found that after 5 minutes have elapsed no further alcohol is taken up although the perfusion may be continued for as long as 3 hours.

The effect of ethyl alcohol on the mammalian heart was studied by Martin and Stevens (1895) in the perfused isolated dog heart. They found that under the influence of alcohol the systole is less complete and that in the beginning this effect may be compensated by an increase of the diastole so that the volume of the blood ejected is not decreased, but that later this diastolic compensation fails and the output is reduced. Plumier (1905) stated that alcohol has only a depressant effect on the mammalian heart. In opposition to these findings, Bock (1898) and Loeb (1904) claimed that the mammalian heart is quite resistant to alcohol. Tunicliffe and Rosenheim (1903) found that concentrations of 1:500 (0.2 percent) cause a transient slowing of the isolated mammalian heart and very slight irregularities, but that the heart can be perfused for a relatively long time without causing further alteration. Similarly, Kochmann (1905) found that perfusion with 0.3 percent solutions of alcohol had no distinct effect, 0.4 percent caused reduction of the pulse volume,

0.5 percent caused in addition slowing of the pulse rate, and that 1 percent solutions caused distinct toxic effects but not arrest. Backman (1906) pointed to the great variations in the response of different heart preparations. He found that concentrations of 0.05 to 0.1 percent caused temporary arrhythmia and temporary reduction of the systole in the perfused mammalian heart, these effects being more marked with 0.1 to 0.5 percent solutions. In the opinion of Dixon (1907) concentrations of 0.5 percent have a distinct, depressant effect on the heart action. According to Kuno (1913), 0.077 percent solutions are just sufficient to cause depression of the isolated mammalian heart and concentrations of 2.3 percent cause arrest. Sulzer (1924) found, in experiments with the heart-lung preparation, that concentrations of alcohol in the blood as low as 0.06 percent had only a moderate depressant effect, and that with blood alcohol levels of 0.3 and 0.4 percent the cardiac output was considerably decreased and the venous and pulmonary pressures were markedly increased. These findings were confirmed by Peters, Rea and Grossman (1936). Visscher (1927), working with the heart-lung preparation of the dog, found that even small amounts of alcohol in the circulating blood cause a marked dilatation of the ventricle if the heart is made to perform a constant amount of work, and, because the oxygen consumption is directly proportional to the size of the ventricle, it appears that under the influence of alcohol the mechanical efficiency of the heart is reduced. Brooks (1910) studied in intact unanesthetized animals the effect of alcohol on the heart action with various forms of administration. He found that with oral administration alcohol causes moderate slowing of the heart beat and that this effect is more marked with intravenous administration. This was confirmed by Hyatt (1919), who found that in unanesthetized dogs with transection of the spinal cord at the heights of the eleventh and twelfth thoracic vertebrae the slow intravenous administration of alcohol in the leg thus deprived of central nerve influences causes no stimulation but a slowing of the heart rate. Loeb (1905) claimed that in the perfused isolated cat heart 0.13 to 0.3 percent solutions of alcohol may have a moderate but distinct stimulant effect. Similarly, Wood and Hoyt (1905), Bachem (1906) and Brandini (1908) believed that in proper doses alcohol has a stimulant effect on the mammalian heart. Dixon (1907) thought that in small doses alcohol has little effect on the heart rate but that in large doses it may stimulate the medulla (vagus center), causing slowing of the heart beat. Hooker (1917), however, perfused the medulla of dogs with various concentrations of alcohol in defibrinated blood and found no evidence of such central vagus action. Dixon (1907) claimed that the failing heart is accelerated by alcohol, and that moderate doses of alcohol increase activity and the output of the heart, acting presumably as a nutrient. A similar assumption was made by Hamil (1910), who

found that the concentration of alcohol in the perfusate of the isolated rabbit heart was lower after its passage through the heart but he made no attempts to determine its metabolites in the perfusate. Fischer (1916) reported similar findings but also presented no evidence with regard to the metabolic fate and was unable to find any definite evidence such as claimed by Dixon (1907). Dodge and Benedict (1915) found that in man the ingestion of 30 to 45 cc. of alcohol will cause a moderate increase of the pulse rate which they linked to a decreased response of the vagus or to stimulation of the accelerator nerve. Haggard, Greenberg, Cohen, and Rakieten (1941) determined, in rats kept alive by artificial respiration, the concentration of alcohol in the blood causing cardiac arrest as 0.126 percent with 0.120 and 0.132 percent as extremes. They found that with slow intravenous injection moderate bradycardia develops as soon as the concentration of alcohol in the blood approaches that causing respiratory failure. When the respiration fails, further alterations of the cardiac function are those of hypoxemia characterized by partial or complete heart block and later by ventricular fibrillation. With artificial respiration the heart withstands a concentration of alcohol in the blood until this is approximately 30 percent higher than that causing respiratory arrest. They found that two-thirds of their animals could be revived when artificial respiration was started following respiratory arrest, and this appears to be significant for the treatment of severe acute alcoholic poisoning. In the opinion of Grollman (1942) the summary of the experimental evidence indicates that alcohol is not a cardiac stimulant.

The *effect of ethyl alcohol on the coronary arteries* varies with the concentration. Loeb (1904) stated that perfusion of the isolated mammalian heart with 2 percent alcohol causes no dilatation of the coronary arteries. Similarly, Backman (1906) found no evidence of an increased coronary flow with concentrations of 0.5 to 0.1 percent, but he found that 0.05 percent solutions may cause some, and 0.01 to 0.005 percent a distinct and lasting increase of the coronary flow in spite of the decreased heart action. Brandini (1908) observed dilatation with concentrations of 0.002 to 0.007 percent and constriction with concentrations of 3 percent and more, and Sulzer (1924) found that in the lung-heart preparation concentrations of 0.1 to 0.2 percent in the blood caused constriction of the coronary vessels and a reduction of the coronary flow.

The *effect of ethyl alcohol on the blood vessels* varies with the concentration and also, to a certain extent, with the location of the vessels. Hemmeter (1891) found that the intravenous injection of alcohol causes dilatation of arterioles and capillaries, as judged by an increase of the blood flow through the carotid artery. This was confirmed by Weber (1909) in trepanned dogs by means of the Roy and Sherring-

ton apparatus, and he found that alcohol dilates the cerebral vessels but that the duration of this dilatation is shorter than that in other areas of the body. Stewart (1915) showed that alcoholic beverages such as wine and whisky cause first a diminution and subsequently an increase of the blood flow through the hand. Wood and Hoyt (1905) believed that the vasodilatation was due to depression of the vasomotor center; and a vasodilatory action was also reported by McDowall (1925) and Heide and Schilf (1929), who noted that with intravenous injection of large doses of alcohol this may be followed by a constriction. Cook and Brown (1932) showed that in man the ingestion of 0.5 cc. of alcohol per kg. body weight causes marked vaso-dilatation in the skin, and according to Sjöstrand (1934) the same holds true for the capillaries of the adrenals, the degree of the dilatation depending upon the dose. Dixon (1907) showed that with large doses not only the peripheral blood vessels but also those of the splanchnic region are dilated. This is in contrast to Kochmann (1905), who found that the splanchnic vessels are constricted during the peripheral vasodilatation. Dixon and Ransom (1921) showed that in isolated organs the intra-arterial injection of alcohol causes first vasoconstriction and later dilatation and that a similar twofold effect may be observed in other structures with smooth muscles, such as the bronchioles. Budelmann (1930), working with Starling's heart-lung-kidney preparation, with the perfused hind legs of dogs and the perfused liver, found that small doses of alcohol cause vaso-constriction of the peripheral vessels but not of the splanchnic organs.

The *effect of ethyl alcohol on the blood pressure* is the composite result of its various effects on the heart, the blood vessels, and, to a certain extent, also on the central nervous system. Kochmann (1905) pointed out that in man, with the administration of proper doses, alcohol may produce a rise of the blood pressure, presumably caused by a constriction of the blood vessels in the splanchnic area, which overshadows the vasodilatation in the periphery. John (1908) pointed out that the primary rise of the systolic blood pressure is associated later on with a conspicuous lowering of the diastolic pressure which he attributed to the same mechanism as assumed by Kochmann (1905), and he affiliated the secondary fall of the blood pressure to splanchnic dilatation and congestion in this area, overshadowing the effect of the peripheral secondary constriction. Bachem (1906) reported observations similar to those of Kochmann (1905) but correlated them with an improvement of the heart action, and this assumption was shared by Dixon (1907). The latter found that in man and rabbits the increase of the systolic blood pressure is paralleled by a decrease of the diastolic pressure, resulting in an increase of the pulse pressure, and he believed that with oral administration of alcohol a reflectory mechanism may also be involved, as had also been assumed by Dogiel

(1879) and Gutnikow (1897) (both quoted from Lieb, 1915). Others, such as Zimmerberg (1869) and Rosenfeld (1901) (quoted from Lieb, 1915), did not share this opinion, and Brooks (1910) noted only a transitory rise when alcohol was given by mouth, whereas with intravenous administration he always noted a sharp fall. Lieb (1915) noted in man that the administration of small doses of whisky caused a rise of the blood pressure which was more distinct in persons with hyperactive reflexes than in apathic patients. In accordance with these observations he found that in decerebrated cats the oral administration of 0.5 to 5 cc. of alcohol per kg. body weight had no distinct effect on blood pressure or pulse rate. Similar observations pointing to a reflex mechanism responsible for the primary rise of the blood pressure were reported by Hyatt and Jensen (1918) who found that in contrast to the oral administration the intravenous injection into an anesthetized leg had no such effect. Hooker (1917) showed in perfusion experiments of the medulla of dogs with various concentrations of alcohol that this caused a rise of the blood pressure but not of the pulse rate. Wood and Hoyt (1905) believed that alcohol does not seriously affect the blood pressure and that only toxic doses, leading to central vasomotor paralysis, cause a fall of the blood pressure. Gruber (1923a) pointed out that in susceptible dogs also the oral administration of alcohol may cause a fall of the blood pressure, and McDowall (1925) stated that large doses of alcohol may cause typical shock, associated with excessive dilatation of all vessels and an increase of the venous pressure, without causing direct injury to the heart. In the experience of Milbradt (1932) the intravenous, intramuscular, and oral administration of alcohol causes clinically a lowering of the blood pressure.

With regard to the *effect of ethyl alcohol on the blood*, Burton-Opitz (1904) showed that the intravenous injection, and, more markedly, the administration into the stomach or the duodenum of 10- to 60-percent solutions of alcohol in 0.7-percent sodium chloride solution cause a temporary increase of the viscosity of the blood, the maximal effect being observed after 4 to 10 minutes and lasting for 30 to 45 minutes. Juckuff (1895), Vandevelde (1907) (both quoted from Kochmann, 1923), and Fühner and Neubauer (1907) showed in vitro that alcohol has hemolytic properties. Eiger (1911) showed that this effect is produced by concentrations up to 33.7 percent and that higher concentrations cause increasingly less hemolysis but more and more agglutination, so that with 63.2 percent solutions there is no hemolysis but only agglutination, the corresponding concentrations for methyl alcohol being slightly higher. Schultz (1912) made a detailed study of the alcohol hemolysis and the influence of various factors, and von Fillinger (1912) found that the ingestion of alcohol reduces the resistance of the erythrocytes to various hemolytic agents but that

narcotic doses may have the opposite effect. As pointed out by Koch-
mann (1923), *in vivo*, perhaps with the exception of the intravenous
administration of large doses, hemolysis has never been observed. Mil-
bradt (1932) noted that, following the administration of alcohol, the
coagulation of the blood was increased, the sedimentation slowed and
the surface tension and stability of the plasma decreased, presumably
on account of some changes of the plasma colloids. He noted also
a distinct lowering of the blood sugar and an increase of the amino
acids, the latter resulting possibly from protein changes. Keeser and
Keeser (1927) noted, after the ingestion of 110 cc. of alcohol as 45
percent solution in the course of 2 hours, changes of the physico-
chemical properties of lecithin, its increase in the blood, and disturb-
ances of the normal synthesis and cleavage of phosphatides. He be-
lieved that in acute alcoholic intoxication ferments are generally acti-
vated. This is in contrast to chronic alcoholism where, with the
exception of phosphatase, they are inhibited. Baglioni (1927) studied
the effect of alcohol on the mobility of leucocytes and found that con-
centrations of 0.028 to 1.0 percent have a stimultant effect, whereas
1.12 percent, and, to a greater extent, 2.8 percent affect distinctly the
survival, the latter concentration causing paralysis within a few
hours.

The effect of ethyl alcohol on the striated muscle.—The effect of alco-
hol on the performance of muscular work has been discussed, together
with the effect of alcohol on the central nervous system. Lombard
(1892) showed that although the ingestion of alcohol may increase the
performance of muscular work, it does not increase the response of
the muscle proper to electrical stimuli. Foerster (1912) discussed
the extensive literature on this subject and expressed the opinion that
any improvement of performance is of central origin and not due to
improved muscular contractility, and this appears to be confirmed by
the observations of Vernon and Greenwood (1919). Lee and Salant
(1902) found that oral administration of 0.12 cc. per gram frog in
10-percent solution causes quickening of the muscular contractions
and more rapid relaxation, thus favoring a larger number of con-
tractions and a better performance within a given time, which they
considered as direct muscular effect. Larger doses of 0.2 cc. per
gram in 33.3 percent solution had a definitely unfavorable effect.
Lapicque and Kajiwara (1930) showed that alcohol may affect the
chronaxy of flexor and extensor muscles to a different extent, and
according to Bonnet and Lelu (1933) its effect on the chronaxy of
the muscle is less marked than on that of the nerves. It appears that
local application of alcohol causes first stimulation and later depres-
sion of the striated muscle. With low concentrations the paralysis
may be reversible but with higher concentrations it is permanent on
account of coagulation of tissue proteins.

The effect of ethyl alcohol on the motility of the gastro-intestinal tract.—With regard to the effect of alcohol on the activity of the gastro-intestinal tract, Kuno (1914) showed that 0.2- to 0.5-percent solutions of alcohol in Ringer's solution increase the pendular movements of the isolated intestine without changing its tone, whereas 3- to 5-percent solutions cause a primary stimulation and subsequent depression without permanent loss of tone. Franzen (1928) found that in man the oral administration of alcohol in concentrations of 5 to 7 percent and more delayed the emptying of the stomach, but that lower concentrations had the opposite effect. It should, however, be pointed out that he gave the alcohol in the form of sherry, and that therefore the essential oils may have acted as carminatives. This appears to be supported by the finding of Barlow, Beams, and Goldblatt (1936) who showed that in contrast to pure alcohol, small doses of whisky actually increase the peristaltic activity in some individuals. Beazell and Ivy (1940) reviewed the literature on the effect of alcohol on the digestive tract and they stated that doses of 50 to 100 cc. of 10 percent alcohol inhibit the hunger contractions and that doses of 100 to 200 cc. of 5 to 20 percent and 15 cc. of 42.8 percent alcohol have no consistent effect in dogs and in man, respectively, whereas larger doses delay the evacuation. Haggard, Greenberg and Lolli (1941) and Tennent (1941b) pointed to the frequent occurrence of pylorospasm after the ingestion of alcohol which they explained on the basis of local irritation and possibly also central mechanism. Greenberg, Lolli and Rubin (1942) found that the intravenous administration of 2 cc. per kg. of alcohol as 45 percent solution caused marked delay in the passage of glucose and alcohol from the stomach into the intestine, so that it appears that the delay in the emptying time must be due to a central action of alcohol. Adler, Beazell, Atkinson and Ivy (1941) found that in dogs the intravenous injection of 200 cc. of 20 percent alcohol in saline causes a slight inhibition of the nonpropulsive motility of the colon, whereas the propulsive action was increased whether alcohol was given intravenously or by mouth. In normal persons 250 cc. of 20 percent whisky had no consistent effect on the nonpropulsive activity but tended to stimulate the propulsive action. It appears, therefore, that alcohol may alter the type of colonic motility without altering the amount of motility.

With regard to the *effect of ethyl alcohol on the digestion*, Kretschy (1877) noted in patients with gastric fistula that the ingestion of alcohol slows the digestive action. Chittenden, Mendel and Jackson (1898) found in dogs no favorable influence of alcohol on the digestion. Franzen (1928) claimed that moderate concentrations of alcohol had a favorable effect on the digestive action of pepsin but in the opinion of Gradinesco and Palmhert (1931) the digestive

action of natural and artificial gastric juice for solid proteins is reduced by alcohol. Beazell and Ivy (1940) found that alcohol in concentrations of 5 to 10 percent inhibits the action of digestive enzymes, but they believed this effect to be insignificant because of the fact that such concentrations are only rarely maintained in the stomach and intestine for any considerable length of time. Emiliani and Panza (1940) found that diluted wine (1:3 to 1:10) has no inhibitory effect on the digestive action of pepsin and diminishes only slightly the amylolytic action of ptyalin, the proteolytic action of trypsin and the hydrolytic action (for sucrose) of invertase, and they pointed out that both the alcohol and tannin content may be responsible for this effect. As demonstrated by Chapman (1914) the inhibitory effect of alcohol on the action of enzymes is evidently linked to its precipitant action on proteins.

With regard to the *effect of ethyl alcohol on the secretion of saliva,* Chittenden, Mendel and Jackson (1898) showed that the contact of strong alcohol with the mucous membranes of the mouth causes a temporary increase of the salivary flow which is due to local irritation. Similarly, Beazell and Ivy (1940) believed that alcohol first stimulates and later depresses the sensory nerve endings in the mouth, thus causing the variation in the salivary secretion.

The *effect of ethyl alcohol on the secretion of gastric juice* has been studied by many investigators. Chittenden, Mendel and Jackson (1898) found that alcohol and alcoholic beverages increase markedly the volume and the acid and total solid content of gastric juice when administered into the stomach or into the intestines. This was confirmed by Wallace and Jackson (1902) who showed that this effect disappears after dissection of the nerves supplying the stomach, indicating that it is caused by a reflex mechanism. According to Bickel and Elkeles (1926) the site of this stimulant effect is the parasympathetic intermediate substance of the glandular cells. They found that concentrations up to 10 percent of alcohol increase the secretion of gastric juice without affecting materially the secretion of mucus, whereas higher concentrations favor the secretion of mucus and impair the secretion of gastric juice. Similarly, Beazell and Ivy (1940) found that the administration of 7 percent alcohol stimulates the secretion of gastric juice, the secretion of acid being, however, increased more than that of pepsin, whereas the administration of 10- to 15-percent solutions favors the secretion of mucus. Newman and Mehrtens (1932) showed that a similar stimulation of the gastric secretion can also be produced by the intravenous injection of proper doses of alcohol, that it may be due to a histamine-like action, and that the site of the action is neither the general circulation nor the mucous membranes but somewhere in between these two. Dragstedt,

Gray, Lawton and Ramirez de Arellano (1940) found that the perfusion of lungs with fluids containing alcohol increased the histamine-like action of the perfusate, and they assumed that alcohol has also a "histaminergic" action on the gastric secretion, as was also assumed by Beazell and Ivy (1940). Seymour, Spies, and Payne (1939) claimed that in chronic alcoholics the continued ingestion of strong alcohol causes a diminution of the volume of gastric juice, a diminution of its acidity, an increased evidence of achlorhydria, but little or no change of the peptic activity of the gastric juice.

With regard to the *effect of ethyl alcohol on the excretion of bile*, it appears, as pointed out by Beazell and Ivy (1940), that this needs further study. Dombrowsky (1891) (quoted from Winogradow, 1927) claimed that alcohol does not affect the secretion of bile, whereas Salant (1904) (quoted from Winogradow, 1927) stated that the oral but not the intravenous administration of alcohol caused an increase. Winogradow (1927) found that the administration of 20 to 25 cc. of alcohol in 200 cc. of water by stomach tube has no effect, and that when given with food 20 cc. delays and 20 to 75 cc. generally inhibits the secretion of bile, presumably by some reflectory stimulation from the gastro-intestinal tract. But since this effect is later compensated by an increased secretion of bile, there is no effect on the total output or the composition of bile when collected over a longer period of time. Similarly, Berman, Snapp, Ivy, and Atkinson (1941) showed in dogs with biliary fistula that ingestion of 40 cc. of absolute alcohol with food caused, constantly, a definite depression of the cholic acid output, but only in 2 out of 10 experiments a decrease of the pigment output and in 2 out of 5 dogs a decrease of the secretion of cholesterol.

With respect to the *effect of ethyl alcohol on the pancreatic secretion*, Beazell and Ivy (1940) stated that with any mode of administration of alcohol this is moderately increased.

The *effect of ethyl alcohol on the function of the kidneys* is reflected in functional and histological changes. Januskiewicz (1909) reviewed the older literature and came to the conclusion that the ingestion of 40 to 45 percent alcohol has only a diuretic action lasting only a few hours if taken with considerable quantities of fluid, that neither small nor large quantities stimulate the secretory functions of the kidneys, and that the diuresis observed after the ingestion of large quantities of diluted alcohol is the result of hydremia caused by the increased absorption of water. Bruger, Localio, and Guthrie (1939) came to the same conclusion and pointed out that with ingestion of alcoholic beverages essential oils may play a role in the production of diuresis. Haggard, Greenberg and Carroll (1941) did not share this opinion. They pointed out that there are wide individual variations with regard to the extent of the diuretic action of alcohol, that diuresis is only observed while the concentration of alcohol in the blood is rising,

and that it is absent when the concentration is stationary or falling. Mosonyi and Gömöre (1927) found that, in contrast to distilled water, equal doses of 5 percent solutions of alcohol increase the urinary volume, and correspondingly, the excretion of electrolytes. Kochmann (1923) believed that, in addition, alcohol may have an effect on the secretory function of the kidney but left it open to discussion as to whether the latter is due secondarily to changes of the circulation or caused by a primary effect on the kidney proper. Eggleton (1942) found that, following the ingestion of alcohol, the diuretic effect roughly parallels the amount of alcohol ingested when the volume of ingested fluid and other factors are kept constant. She found that the onset of diuresis starts 20 to 30 minutes after the ingestion, that the intensity of the diuresis is not related in time to the peak of the alcohol level, that it is initiated by the increase of the alcohol in the blood, but that it fails to be maintained if the concentration of alcohol in the blood is kept at a constant level. The alcohol diuresis may be completely inhibited by the administration of pituitary extracts. The effect of alcohol on the diuresis differs from that on the cerebral cortex in that the latter depends largely upon the rate of the increase of the alcohol level in the blood, whereas the diuretic action depends mainly upon the duration of the rise of the blood alcohol. Thus, the diuretic action is more marked with slow absorption than with rapid absorption. Nicholson and Taylor (1938) found that the ingestion of alcohol causes a marked retention of potassium chloride, sodium chloride, nitrogen and water, and they assumed that this was due to a direct action of alcohol on the secretory function of the kidney. They believed that the retention of potassium chloride in the plasma is responsible for some of the after effects of alcoholic intoxication which occur at a time when the blood alcohol level is again low but the potassium chloride level still at its maximum. Murray (1932), on the other hand, found that alcohol may overcome to a certain extent the antidiuretic action of pituitrin and that it has no specific effect on the kidney. Hultgen (1910) found that even the daily consumption of alcohol does not produce irritation of the kidney, and Bruger (1940) in a review of the literature on the irritant action of alcohol on the kidney, came to the conclusion that, with the possible exception of the arterio-sclerotic kidney, there is no evidence that alcohol affects the normal or even the diseased kidney. Bruger, Localio, and Guthrie (1939) found no evidence to show that the ingestion of alcohol aggravates chronic glomerular nephritis and that the transitory effect observed in arterio-sclerotic kidneys may be the result of a transitory deviation of the blood flow from the kidney to the periphery. MacNider (1925) showed that in dogs the oral administration of 10 cc. per kg. of 40 percent alcohol every second day had only a moderate nephrotoxic action which varied with the purity of the alcohol used.

MacNider and Donnelly (1932 a, b) found that such doses given over a period of 6 months to 2 years, caused in some dogs moderate changes in the glomeruli and accumulation of stainable lipoids in the tubular epithelium without a definite increase of the tubular connective tissue. They also noted functional changes characterized by increased urine formation and occasionally by albuminuria and casts. In addition they observed variations in the elimination of phenolsulfonphthalein which may, however, have been influenced by changes of the liver function. Mendel and Hilditch (1910) studied the urinary excretion of urea nitrogen, ammonia nitrogen, creatine nitrogen, creatinine nitrogen, purine nitrogen, and other constituents in dogs and men, under fixed dietary conditions, with and without the intake of alcohol. They found that moderate doses of alcohol exert a moderate protein-saving action which is followed by loss of nitrogen when larger quantities of alcohol are ingested; but even with large doses they found no evidence of a marked disturbance of the protein metabolism. Keller (1889) claimed that the ingestion of alcohol causes a decrease of the urinary nitrogen excretion on the day of the ingestion, followed by a moderate increase; and he noted a significant increase of the chloride excretion, perhaps on account of the diuretic action. Similarly Höckendorf (1909–10) and Salant and Hinkel (1910) found that subacute alcoholic intoxication caused a moderate reduction of the nitrogen excretion and, as found by the latter, also of chlorides and of the total sulfur. They noted a much greater reduction of the total inorganic sulfates and phosphates, whereas the neutral sulfur and ethereal sulfates were increased and indican decreased after the administration of toxic doses of alcohol. With toxic doses the urinary nitrogen may be increased, and according to Mělka (1940) this is presumably not the result of increased destruction of proteins but is caused by an increased excretion of preformed urea from blood and organs since this effect is paralleled by a decrease of the nonprotein values in the blood.

With regard to the *effect of alcohol on other glandular structures*, Sanchez-Calvo (1941) found that the daily administration of 20 cc. of 10 and 50 percent ethyl alcohol caused in rabbits hyperemia of the pituitary gland and hyperfunction of the thyroid.

The effect of ethyl alcohol on the metabolism.—With regard to the effect of ethyl alcohol on the oxygen metabolism, Geppert (1887) showed that the ingestion of 30 to 75 cc. of alcohol diluted with water had no noticeable effect upon the oxygen consumption in man. But Carpenter and Lee (1937a) found that the ingestion of moderate doses of alcohol causes a reduction of the respiratory quotient, and Goldfarb, Bowman, and Wortis (1940) noted that in humans acute intoxication with alcohol may result in a decrease of the oxygen uptake by the brain which returns to normal after recovery from the toxic effect. The latter effect is also indicated by electroenceph-

alographic studies of Davis, Gibbs, Davis, Jetter, and Trowbridge (1941). Since these observations are based on the ratio of the oxygen content of arterial and venous blood entering and leaving the brain it appears to be possible that an increase of the oxygen content of the venous blood does not reflect a decreased oxygen consumption but is the outcome of a more rapid circulation through the brain. Robertson and Stewart (1932) studied in rabbits the effect of alcohol on the oxygen consumption of brain tissue. They noted a primary increase of the oxygen uptake which was greater in the gray matter than in the white, and, subsequently, a reduction to slightly below normal. They suggested tentatively that alcohol might be adsorbed on the oxidizing surfaces of the cells and slowly oxidized, so that the increased oxygen consumption may be due to the oxidation of alcohol. Wortis (1935) found that in deep alcohol narcosis the oxygen metabolism of brain tissue is reduced. Emerson (1935) confirmed the observations of Robertson and Stewart (1932) and of Wortis (1935), and Muñoz (1937) found that in rats small doses of alcohol render the animals less resistant to reduced pressure, becoming, therefore, more susceptible to anoxemia. Newman, van Winkle, Kennedy, and Morton (1940) found, in perfusion experiments, that the oxygen consumption of the perfused liver is reduced by perfusion with alcohol solutions. Warburg (1910) showed that alcohol inhibits the oxygen metabolism of goose erythrocytes, and Ewing (1940) believed that excessive doses of alcohol may be fatal through inhibition of the oxygen metabolism in the tissue.

With regard to the *effect of ethyl alcohol on the carbohydrate metabolism*, Clopatt (1901), Atwater, and Benedict (1902), Tögel, Brezina, and Duriz (1913) and others have shown that the ingestion of alcohol may save carbohydrates. Canzanelli, Guild, and Rapport (1934) pointed out that, although the oxidation of alcohol yields no energy for muscular work, such energy can be utilized for vegetative functions replacing the oxidation of other foodstuffs such as carbohydrates and fats. However, alcohol cannot replace carbohydrates, as indicated by the observation of Higgins, Peabody, and Fitz (1916) that acidosis produced in humans by a carbohydrate-free diet is not relieved by clinical doses of alcohol. Carpenter (1940) reviewed the literature on the effect of alcohol on the metabolism.

The *effect of ethyl alcohol on the fat metabolism* was studied by Clopatt (1901), Atwater and Benedict (1902), Benedict and Török (1906) and others. They found that the ingestion of alcohol may reduce the oxidation of fats. Strassmann (1891) and Mitchell (1935) showed that tissues traceable to alcohol supplementing the food are richer in fat than those produced on the basal diet without alcohol. Carpenter (1940) in his review on this subject stated that, while not

convertible into fat, alcohol may favor deposition of fat in tissues by sparing dietary fats from oxidation.

In contrast to carbohydrates and fats the *effect of ethyl alcohol on the protein metabolism* is very small. Although Hammett (1916) believed otherwise, Miura (1892), Clopatt (1901), and Schaeffer, and Le Breton (1933) (quoted from Le Breton, 1934) agree that the ingestion of alcohol does not save proteins. Atwater and Benedict (1902) found that moderate doses of alcohol increase very slightly the availability of proteins and the same opinion was expressed by Carpenter (1940) in his review on this subject.

Thomas (1898) observed that in acute alcoholic intoxication the carbon dioxide and titratable alkali content of the blood is reduced on account of an increase of fatty acids. Similar observations in dogs and man were reported by Himwich, Nahum, Rakieten, Fazekas, DuBois, and Gilden (1933) who believed that this *acidosis* was probably due to a relative reduction of the carbon dioxide content of the blood and an accumulation of lactic acid, and similar findings, although less marked, were reported by Nicholson and Taylor (1938). Clark and Morrissey (1938) showed that this acidosis can be effectively treated by the administration of sodium citrate and sodium bicarbonate.

Ethyl alcohol as a source of energy.—Riess (1880), Strassmann (1891), and Bjerre (1899) believed that alcohol can be utilized as food and serve as a source of energy. Atwater and Benedict (1902) shared this opinion and claimed that 1 gm. of alcohol is isodynamic with 1.73 gm. of carbohydrates or 0.78 gm. of fat, and a similar statement was made by Rosemann (1903). Mitchell (1935) stated that, in comparison with similar supplements of sugar, the energy of alcohol supplements to basic food is only available for physiologic purposes to the extent of 75 percent and that its growth-promoting power is definitely less. Van Hoogenhuyse and Nieuwenhuyse (1913) (quoted from Carpenter, 1933) came to the conclusion that the ingestion of alcohol liberates, directly or indirectly, energy for muscular work and that such work is also produced more economically. Viale and Gianturco (1921) claimed that, especially in high altitudes, alcohol could be utilized as a source of energy in place of other foods. Sommerkamp (1924) believed that alcohol not only spares carbohydrates and fats but that its energy is also directly available for the performance of muscular work, and similar claims were made by Brechmann (1925 and 1927) (quoted from Carpenter, 1933). Grubbs and Hitchcock (1938) assumed that muscles are able to utiilze alcohol as a source of energy for work, and it has been mentioned that Dixon (1907), Hamill (1910) and others claimed that alcohol may be utilized as a source of energy by the mammalian heart. In contrast to these reports, Hunt (1907) believed that alcohol is no substitute for food,

Höckendorf (1909–10) showed that it does not form glycogen, and Hanzlik (1931) found that the administration of 2 to 4 percent alcohol as drinking water does result in loss of weight, suggesting that the intake of weak alcohol solutions does not act as food. Similarly, Galamini (1927) (quoted from Carpenter, 1933) questioned whether alcohol could be utilized by humans for muscular work, and Terroine and Bonnet (1929) (quoted from Carpenter, 1933) concluded from animal experiments that when production and dissipation of heat are in equilibrium alcohol is oxidized without any benefit to the organism. They believed that at low temperatures alcohol may furnish heat but, as pointed out by Hopkins (1942), the combustion of alcohol is not fast enough to compensate for the greater loss of heat observed under its influence. Le Breton (1934b) showed that alcohol has no specific dynamic action, and Carpenter (1933), in a review of the literature on this subject, concluded that the majority of investigators believe that alcohol is utilized or burned in muscular work and that the work of some of those who are of the opposite opinion may be open to criticism. However, Canzanelli, Guild, and Rapport (1934) showed that in contrast to carbohydrates and fats, alcohol may not be utilized for muscular work, as was also stated by Hopkins (1942). In a more recent review on the food value of alcohol Carpenter (1940) came to the conclusion that the usefulness of alcohol as a source of energy is limited because the initial reaction leading to complete liberation of its energy takes place in the liver which does not respond to the increased demand for energy from the tissue, especially from the working muscle.

The toxicity of ethyl alcohol.—The toxic effects of alcohol are manifold. Moderate intoxication is probably the most common type of poisoning, acute intoxication and chronic alcoholism are frequent, but acute fatal intoxication is comparatively rare. Alexander, Moore, and Leary (1939) stated that in Massachusetts, during the period from 1928 to 1937, alcohol was responsible for 52 percent of the fatalities caused by toxic substances. In addition, alcohol is considered a contributing factor in the fatal outcome of many diseases. This may be illustrated by a recent report on this subject by Schmid (1940). He stated that in 1938, in the United States, 2569 fatalities were attributed to alcoholism, 959 of which were given as alcoholic cirrhosis of the liver. In 1936, 3714 fatalities were attributed to alcoholism, in 4334 fatalities alcohol was considered as a contributing factor, and 802 fatalities were listed as alcoholic cirrhosis of the liver. He pointed out that the contributing influence of alcohol was especially marked in heart attacks (1385 out of 4334 cases), in pneumonia (937 out of 4334 cases), in accidents (613 out of 4334 cases), in nephritis (268 out of 4334 cases) and in cerebral hemorrhages (261 out of 4334 cases).

Table 8.—*Minimal fatal doses of ethyl alcohol for different animal species*

SINGLE DOSES ORALLY

Species	Dose cc./kg.	Time of death	Author
Rabbit	10	Within 24 hours	Langgaard (1913).
Do	12		Barlow, Beams, and Goldblatt (1936).
Do	7.9 to 9.2		Sollmann and Hanzlik (1928).
Dog	7 to 10	Within 12 to 15 hours	Dujardin-Beaumetz and Audigé (1875).
Mouse	7 to 9		Weese (1928).
Do	12 (M. F. D. 50)		Latven and Molitor (1939).

REPEATED DOSES ORALLY

Rabbit	3	After 23 daily doses	Langgaard (1913).

INTRAVENOUS INJECTION

Rabbit	9.4		Lehman and Newman (1937b).
Cat	5		Macht (1920).
Dog	6.8		Hanzlik, Newman, van Winkle, Jr., Lehman, and Kennedy (1939).
Mouse	2.5 (M. F. D. 50)		Latven and Molitor (1939).

INTRAPERITONEAL INJECTION

Cat	8		Sollmann and Hanzlik (1928).
Rabbit	4.4		Barlow, Beams, and Goldblatt (1936).

SUBCUTANEOUS INJECTION

Dog	12	Within 36 to 48 hours	Dujardin-Beaumetz and Audigé (1875).
Mice	6		Vollmer (1931).
Do	10.5 (M. F. D. 50)		Latven and Molitor (1939).

INHALATION

Rabbits and Mice	29,000 p. h. m		Bachem (1927).
Rats	10,000 to 12,500 p. p. m	21 hours	Loewy and von der Heide (1918).
Do	20,000 to 23,000 p. p. m	10 hours	Do.
Do	45,000 p. p. m	6½ hours	Do.
Guinea pigs	45,000 p. p. m	8¾ hours exposure 2 hours later.	Do.

Table 8 gives the summary of the minimal fatal amount of alcohol for various animals as reported by different investigators. It shows that the fatal dose of alcohol for animals varies with the species and the route of administration. Chester, La Belle, and Himwich (1942) showed that newborn rats are more resistant to the lethal effects of alcohol than fetal and adult rats, and they believed this was due to lower metabolic rate of the brain of the newborn animals.

In man the picture of acute alcohol poisoning varies with the quantity of food ingested, the amount of food in the stomach, and the susceptibility and habituation of the individual to alcohol. Children are more susceptible than adults. The *picture of acute alcoholic intoxication* may be summarized as follows: Following the

ingestion of sufficient doses of alcohol the face is flushed, the pulse rate is increased, and there may be some perspiration. The eyes appear first bright, later dull, and the pupils may be dilated or constricted. Motoric unrest, excessive talking, laughing, and joking are characteristic of the early stages of alcoholic intoxication. As the depressant effect becomes more marked these symptoms may be followed by impaired motility, staggering gait, incoordination, lassitude and fatigue. With large doses there may be, in addition, rapid loss of sensitivity, more or less complete impairment of the sensory functions and of the motility, disappearance of reflexes, unconsciousness, and coma. In such advanced cases the conjunctiva is hyperemic, the pupils dilated, the flushing of the face may pass into pallor, the respiration becomes stridulous, slow, and irregular, the skin is cold and clammy, the pulse flat and slow, and there may be vomiting and incontinence of feces and urine. The body temperature is lowered and there may be twitchings and general convulsions. In fatal cases death results from respiratory and circulatory failure. Kaufmann (1925) reported the clinical picture of acute alcohol poisoning resulting from the rectal administration of alcohol. Führner (1930) pointed out the possible additive and synergistic effect of alcohol with other therapeutic agents. Ajtay (1933) reported on a mass poisoning of 33 severe cases of acute alcohol poisoning resulting in 17 fatalities, and Beyreis (1933), Regus (1937), and others reported on fatalities in which the acute intoxication was associated with cerebral hemorrhages. Fatal outcome in acute alcohol poisoning may also result from the aspiration of vomitus resulting in fatal pneumonia, as illustrated by the case reported by Franz (1936). As pointed out above, children are especially sensitive to alcohol, and death may result from the ingestion of comparatively small doses, as reported by Prievara (1941). Severe and fatal poisonings of nurslings from the ingestion of milk from severly intoxicated mothers were reported by Wyckerheld Bisdom (1937) and Dervieux, Szumlanski and Desoille (1929). Severe and fatal alcohol poisonings in children from inhalation of alcohol vapors or its absorption through the skin when applied in the form of alcohol wraps were reported by Kalt (1906), James (1931), Leschke (1932), and Fraenckel (1928). However, it appears questionable whether or not, in the last case mentioned, alcohol was the cause of the fatal outcome. Gettler and St. George (1935) reported on the death of an infant who had received alcohol hypodermically instead of saline.

With regard to the *fatal dose of alcohol for man*, this has been estimated as approximately 6 to 8 gram (8 to 10 cc.) per kg. of body weight (Flury and Klimmer, 1938). With respect to the concentration of alcohol in the blood of victims of acute alcohol poisoning, these values show considerable variations, depending mainly upon the time

elapsed between the ingestion of alcohol and death. Milovanovic (1936) determined the alcohol level in the blood of victims of acute alcohol poisoning as being between 0.519 and 1.332 percent with an average of 0.836 percent. According to this author, Straub found 0.33, Franz 0.41, Jungmichel 0.414, Remund 0.47, Widmark and Schwartz 0.4 to 0.5, Zangger 0.5 to 0.8 and even 1.0, Gelma and Simonin 0.912 and Kohn-Abrest 0.8 to 1.0 percent of ethyl alcohol in the blood of victims of acute alcohol poisoning.

Gettler and St. George (1935) found concentrations of 0.65 percent and it appears, therefore, that in the diagnosis of death due to acute alcohol poisoning the importance of the concentration of alcohol in the blood has to be very carefully evaluated. Villedent (1926) claimed that the concentration of alcohol in the blood of cadavers remains constant for a long time, and Weinig (1936) stated that it is not changed during the first 2 days and that under ordinary conditions it is only between the second and third days that the alcohol values start to increase due to the formation of volatile decomposition products which in septicemic patients may already be interfering during the first day unless more specific analytical methods are used. On the other hand, Wagner (1936) claimed that in cadavers the blood alcohol content is reduced by 5 to 6 percent during the first 2 days and up to 2.0 to 2.5 percent during the third and fourth days, and he pointed out that blood samples taken more than 4 days after death cannot be properly evaluated on account of the progressing decomposition. He also pointed out that the concentration of alcohol in blood samples may vary with different locations in the body, in that blood samples from the cranial cavity and the heart show higher values, blood from the lungs is not suitable, and blood from the heart may give erroneous results on account of the inflow of blood from the lungs. On the other hand, Sjövall and Widmark (quoted from Guldberg, 1938) found that blood from the longitudinal sinuses and from the pulmonary vein gave identical values but differed from that drawn from the iliac vein, and they pointed out the possibility that alcohol may diffuse after death from the stomach into the heart so that the heart blood may yield too high values. This possibility seems to be confirmed by the report of Guldberg (1938) who found, in 4 out of 7 cadavers, the concentration of alcohol in the stomach higher than that in blood and urine. As indicated by the report of Weinig (1936), in the determination of the alcohol content in the blood from cadavers it is of paramount importance that such determinations be made with specific methods which exclude the interference of other volatile constituents, and Scheele (1936) pointed out that Widmark's method is not suitable for this purpose. This was emphasized by Cornish, Draper, and Finn (1938) who demonstrated that alcohol and volatile compounds formed post mortem give very similar reactions

and that the presence of the latter may easily lead to misinterpretation.

With regard to the *toxic doses of ethyl alcohol*, it is impossible to establish a definite relation between the amount of alcohol ingested and the effect on the central nervous system because, as pointed out by Raymondaud (1940), the ingestion of equal quantities of alcohol does not lead to the same concentration in the blood with different individuals because body weight, personal habits, and also other factors which will be discussed below may influence the response to the alcohol ingested. Therefore, it may suffice to quote Truffert and Hausser (1940) who stated that ingestion of doses of less than 0.5 gm. per kg. does not affect the behavior of humans, that doses of 0.5 to 2.0 gm. per kg. cause some disturbance of the behavior, and that doses above 2.0 gm. per kg. cause serious drunkenness.

With regard to toxic concentrations of alcohol in air, Loewy and von der Heide (1918) believed that with continued exposure, concentrations of more than 0.1 percent (1,000 p. p. m.) may cause moderate toxic symptoms. They exposed persons with different degrees of habituation to alcohol to various concentrations of alcohol in air and observed the toxic effects, as illustrated in table 9. This table shows that persons unaccustomed to alcohol are more sensitive to alcohol vapors than those who regularly consume large quantities of alcoholic beverages.

Table 9.—*Toxic effects of inhalation of ethyl alcohol vapors on man*

[Loewy and von der Heide, 1918]

A. PERSONS ACCUSTOMED TO LITTLE ALCOHOL

Average concentration		Duration of exposure in minutes	Symptoms
Percent	P. p. m.		
0.1	1,000	39	No subjective symptoms up to 28 minutes, after 33 minutes moderate frontal headache, after leaving chamber slight drowsiness and pressure around head.
.25	2,500	50	At first feeling of warmth in head, later also of face, trunk and limbs, the latter being preceded by a feeling of cold in hands and feet, nasal irritation, frontal headache and drowsiness, both of which persisted for some time after leaving the chamber.
.88	8,840	64	Alcohol odor first intolerable (feeling of suffocation) but soon tolerable, marked burning of eyes and irritation of nose, marked drowsiness, increasing fatigue and sleepiness, moderate effect on respiration, increasing feeling of heat in head and face, alcohol odor later not noticeable.

B. PERSONS ACCUSTOMED TO ALCOHOL

0.503	5,030	120	After 20 minutes some headache, increasing moderately without becoming severe.
.612	6,120	120	Alcohol odor disagreeably intense, no other effects during exposure except moderate pressure in temporal region, no headache.
.669	6,690	109	Odor nearly intolerable for person A, very intensive but little disagreeable for test person. After 30 minutes pressure above the eyes, stabbing pain in the eyes, feeling of heat. After 90 minutes fatigue and sleepiness. (Urine voided during exposure contained 0.083 percent of alcohol.)

The *diagnosis of alcoholic intoxication* and the *correct appraisal of the degree of the psychic and physical impairment* may be of great importance, and the question of the importance of the clinical observation as compared with the evaluation of the alcohol level in the blood has aroused much comment. Some authors, for example Koller (1936), emphasize the importance of the clinical observation for the proper appraisal of blood alcohol determinations; others, Morgan (1939), believe that the determination of alcohol in blood and urine is the most accurate basis for the diagnosis of alcoholic intoxication for medico-legal purposes. In view of the conflicting views on this subject one has to agree with Helwig (1940) that the diagnosis of drunkenness and, particularly, of the degree of intoxication is subject to many pitfalls, both medical and legal; that there is much disagreement of opinion as to what constitutes alcoholic intoxication; and that many clinical variables have to be considered before a diagnosis is rendered.

With regard to *clinical tests for intoxication*, Southgate and Carter (1926) pointed out the inadequacy of many clinical tests such as standing poised, toeing the line, standing immobile with closed eyes, testing memory, etc. They believe that other signs, such as flushed face, perspiration, dilated pupils, congested eyes, and rapid pulse, are more characteristic and are present in nearly all instances. Schwarz (1927) refers to Fog who emphasized the importance of appearance, attitude, orientation, memory, pronunciation, gait, coordination and steadiness of the hand, pulse, pupils, sensitivity to pain, and odor of breath. He also pointed to the importance of the examination for other affections, such as epilepsy, apoplexy, mental confusion, etc., and to the value of the determination of the concentration of alcohol in the blood for the differential diagnosis. Jetter (1938a) considered as most important signs for the diagnosis of alcoholic intoxication, abnormalities of the gait and inability to walk and the positive outcome of at least 2 of the following tests: Gross abnormalities of the speech, flushed face, dilated pupils, and alcoholic odor of breath. Kniskern (1939) emphasized the importance of careful neurological examination to discover any variations from normal with regard to locomotion, stability, dexterity, and speed of reaction, as indicated by Romberg's test, finger to nose test, writing of signature, ability to button clothes and ability to walk a straight line, turn and come back, and stand on 1 foot. He also advised the performance of tests for orientation, memory and reaction time of thoughts and emotional disturbances. Hegler (1935) recommended as a short cut procedure having the patient dial his telephone number. Most students of the subject agree that any clinical observations should be supplemented by determinations of alcohol in blood, saliva, urine, or exhaled air.

With regard to the *importance of the determination of alcohol in blood* for medicolegal purposes it appears from the work of Rabino-

witsch and Wilen (1939) that the sterilization of the skin and of the hypodermic needle with alcohol does not cause sufficient changes in the blood alcohol values to invalidate distinctly positive findings, although this procedure should be discouraged. It should, however, be pointed out, as stated by Bavis and Arnholt (1939), that all containers should be sealed and labeled before being sent to the laboratory, and that all samples should be run in duplicate or in blood and urine by 2 different methods. Schweisheimer (1913) believed that the psychic condition of an intoxicated person depends upon the concentration of alcohol in his blood. Southgate and Carter (1926) stated that the determination of the alcohol level in blood and urine is a good guide in judging the degree of intoxication, and Bavis and Arnholt (1938) considered it as the best criterion, being definitely related to the degree of intoxication. Truffert and Hausser (1940) believed that the determination of alcohol in the blood is the best, and its determination in the exhaled air the next best criterion for the determination of the degree of intoxication. Friedemann, Motel, and Necheles (1938) recommended the determination of alcohol in the saliva as the most convenient means of measuring the alcohol content of the blood, but Selesnick (1938) believed the determination of alcohol in the blood to be superior to that in urine, saliva, and expired air because it contains only a negligible amount of volatile constituents other than alcohol. Mozes and Katonak (1941) emphasized the importance of chemical tests because they believed that these furnish a far better criterion than even a detailed clinical study, and Ladd and Gibson (1939) gave a very extensive discussion of the legal aspects of blood alcohol determinations with regard to alcoholic intoxication.

The calculation of the amount of alcohol ingested from that determined in the blood.—Widmark (1932 and 1933a) claimed that after ingestion of single doses the amount of alcohol ingested can be calculated from the concentration of alcohol in the blood at a given time after its ingestion by using the formula: $A = pr \ (ct + \beta t)$. In this formula A is the total quantity of alcohol ingested in grams, p is the body weight of the individual in kilograms, and ct is the concentration of alcohol in the blood at the time t calculated in minutes; r is a reduction factor and gives the assumed amount of alcohol at which the concentration of alcohol in the tissue equals everywhere that of the blood, so that pr represents the amount of alcohol in the body. β is another constant which gives the decrease of the concentration of alcohol in the blood per minute in parts per thousand at diffusion equilibrium between the alcohol in blood and tissue.

With regard to the factor r, this is independent of the amount of alcohol ingested and of its concentration, and it has been determined by Widmark and his associates as 0.68 for men and as 0.55 for women with deviations of ± 0.085 and ± 0.055, respectively.

With regard to constant β which gives the metabolic velocity of ethyl alcohol, this also is not affected by the amount of alcohol ingested or by its concentration, and it was determined in a large group of men as 0.0025 ± 0.00056, and for women as 0.0026 ± 0.00037.

Widmark (1932) gave similar formulas which allow the calculation of the amount ingested with continued and intermittent administration. Thürauf (1937) determined the factor β in young, trained soldiers with moderate fat deposits and moderate habituation to alcohol as 0.00217 to 0.00233 and quotes Jungmichel as having found 0.00200. He pointed out that stimulation of the oxygen metabolism, as by dinitrophenol, may increase, and decrease of the oxygen metabolism may lower the factor β. In addition he believed that increased pulmonary excretion of alcohol, as produced by exercise, may impair the results of such calculations. Hecksteden (1938) determined the factor β as 0.0020 and found that this is not reduced in persons suffering from trauma of the skull which has been credited with reducing the oxygen metabolism. Siegmann (1936) determined factors r and β in chronic alcoholics and found higher values than those given by Widmark and Jungmichel. Newman, Lehman, and Cutting (1937) believed that Widmark's formula gives reliable information with regard to the amount of alcohol ingested. Silberstein (1934) and Elbel and Lieck (1936), on the other hand, claimed that, since the absorption of alcohol from the stomach varies with the amount of food in the stomach, any calculation based upon factors r and β may give erroneous results unless this is taken into consideration. Kanitz (1939) pointed out the fact that Widmark's method for determining alcohol is not specific and that volatile materials contained in alcoholic beverages may cause small errors, which, although insignificant by themselves, may become serious if multiplied by the various factors involved in Widmark's formula. Hegler (1935) discussed the usefulness of Widmark's formula and emphasized the need for taking blood samples as early as possible after the ingestion of alcohol, and Mayer (1936a) came to the conclusion that after $1\frac{1}{2}$ hours have elapsed single determinations are not sufficient to permit safe calculation by Widmark's method.

In respect to the appraisal of blood alcohol findings with regard to the determination of the degree of intoxication, Kionka (1928) pointed out that the behavior of different persons and even of the same person at different times may vary considerably with the same alcohol level in the blood, so that the latter cannot be safely considered as an absolute yardstick for the degree of intoxication; and a similar statement was made by Tuovinen (1930). Mirsky, Piker, Rosenbaum, and Lederer (1941) showed, as had been pointed out previously by Mellanby (1919) and Miles (1922), that symptoms of intoxication occur at a lower blood level during the absorptive phase than dur-

ing the post resorptive phase and that during the latter stage a person may appear sober at a blood alcohol level much higher than that at which he became intoxicated. As illustrated in figure 6, Newman and Abramson (1941) found, in a person not accustomed to alcohol, that with ingestion of 0.8 cc. per kg. body weight within 2 hours, the maximal decline of performance and the maximal level of alcohol in blood and saliva is observed after 1 hour and that the performance returned to normal values in 2½ hours even if the concentration of alcohol in the blood was maintained at nearly the maximal level by the ingestion of small quantities of alcohol in milk. In a less susceptible subject the ingestion of 1 cc. and, later, 0.3 cc. per kg. body weight
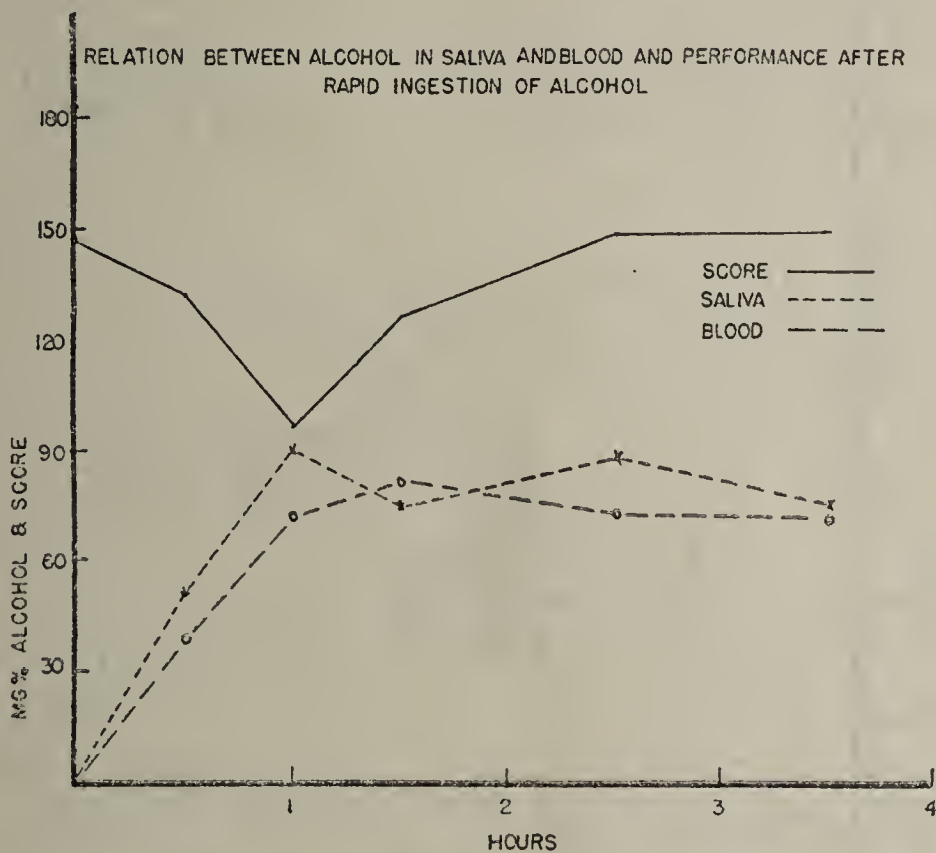
FIGURE 6.—This figure illustrates the relation between the alcohol level in blood and saliva and the performance after the administration of 0.8 cc. per kg. of alcohol and subsequent ingestion of smaller doses sufficient to maintain a fairly constant concentration of alcohol in the blood. (Redrawn from Newman and Abramson, 1941.)

yielded the maximal effect after 30 to 45 minutes, but the performance returned to normal values in spite of the fact that the alcohol level was about 200 mg. percent in the urine and about 160 mg. percent in the saliva. As illustrated in figure 7, with intake of 16 gm. of alcohol in milk every hour there was no appreciable change in performance during a period of 6 hours although the concentration of alcohol gradually rose to nearly 160 mg. percent in the urine and to about 124 mg. percent in the saliva. In another experiment the less susceptible individual ingested 0.5 gm. per kg. body weight and promptly attained concentrations of alcohol in saliva and urine which were insufficient to lower the performance. These alcohol levels were maintained for 4 hours by the hourly ingestion of 8 gm. of alcohol in milk. When after 4 hours another dose of 0.5 gm. per kg. was given, this resulted in a prompt rise of the concentration of alcohol

in saliva and urine of the same order as that which had caused in the first experiment a considerable decrease in the performance within 30 to 45 minutes but which in this experiment had no material effect. These observations appear to indicate that the presence of alcohol in the organism for several hours causes changes in the response of the central nervous system, with the result that concentrations which initially produced drunkenness are no longer capable of producing this effect. It also appears evident that the effect of given concentrations of alcohol in blood, saliva, and urine depends not only upon the abso-

RELATION BETWEEN ALCOHOL IN SALIVA AND URINE AND PERFORMANCE
AFTER SLOW INGESTION OF ALCOHOL
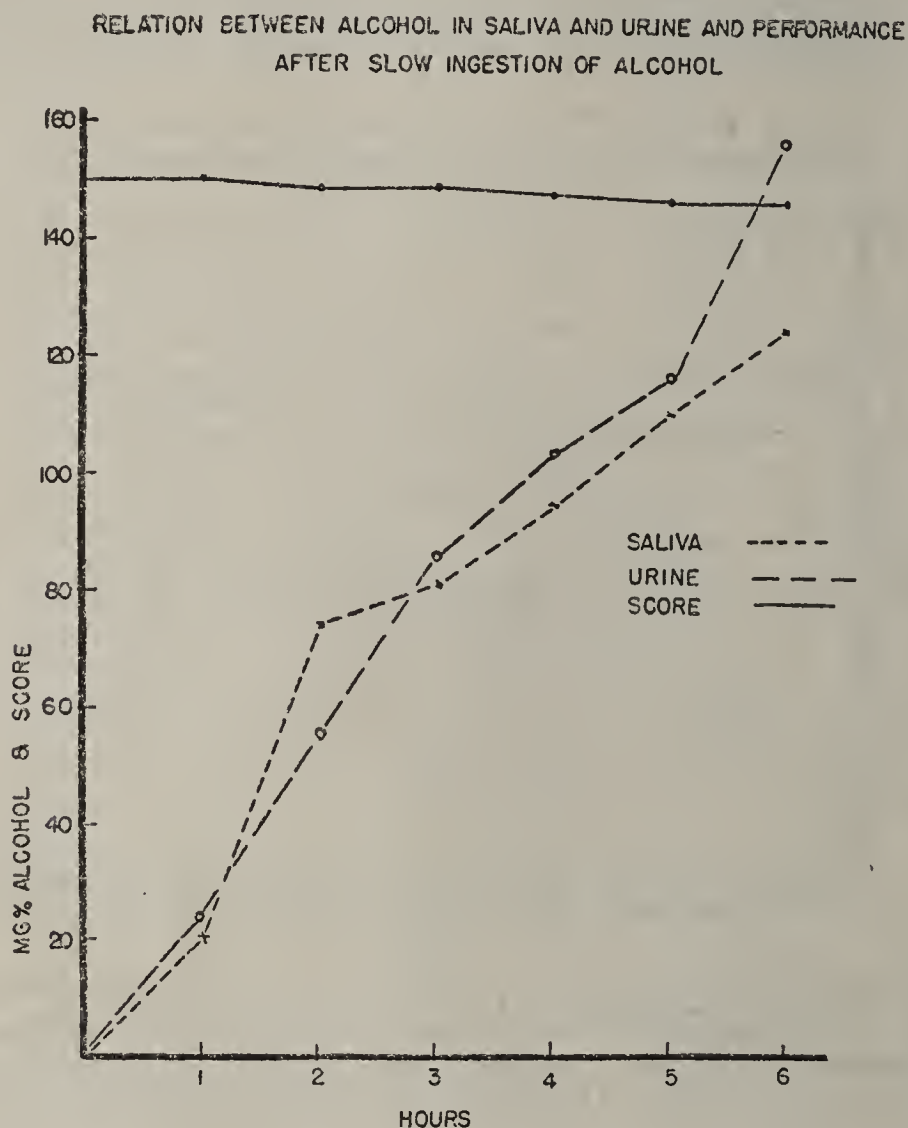
FIGURE 7.—This figure illustrates the relation between performance and concentration of alcohol in urine and saliva during the ingestion of 16 gm. of alcohol in milk every hour. (Redrawn from Newman and Abramson, 1941.)

lute value of such alcohol levels but, among other factors, also upon the time it has been present in the body. Similarly, Eggleton (1941) found that at a given blood alcohol level the nervous disturbance is greater during the absorptive phase than during the post-absorptive phase, that the degree of nervous disturbance at a given blood alcohol concentration increases with the rate at which this concentration is increasing, and that recovery of the central nervous system during the post-absorptive phase is impeded if the rate of disapearance of alcohol from the blood is reduced.

With regard to the *concentration of ethyl alcohol in the blood in relation to the degree of intoxication*, the findings of different investigators are summarized in table 10. This table shows that es-

specially with moderate intoxication there is a considerable spread in the blood alcohol values considered to be characteristic for this condition. This may be due to such factors as discussed above and it may be the result of a different appraisal of the clinical picture as was also pointed out by Jetter (1939). Especially with lower concentrations of alcohol in the blood (below 0.15 percent) the appraisal may become very difficult, and as pointed out by Naville (1928) idiosyncrasy, individual hypersensitivity, and psychic and atypical mental reactions may influence the clinical picture to a considerable extent; and similar statements were made by Kelley and Barrera (1941) and de Crinis (1939). This is also illustrated by the report of Jetter (1938b) who determined the alcohol content of the blood of 20 volunteers after ingestion of 1.0, 1.25, 1.5, and 2.0 cc. of alcohol per kg. body weight.
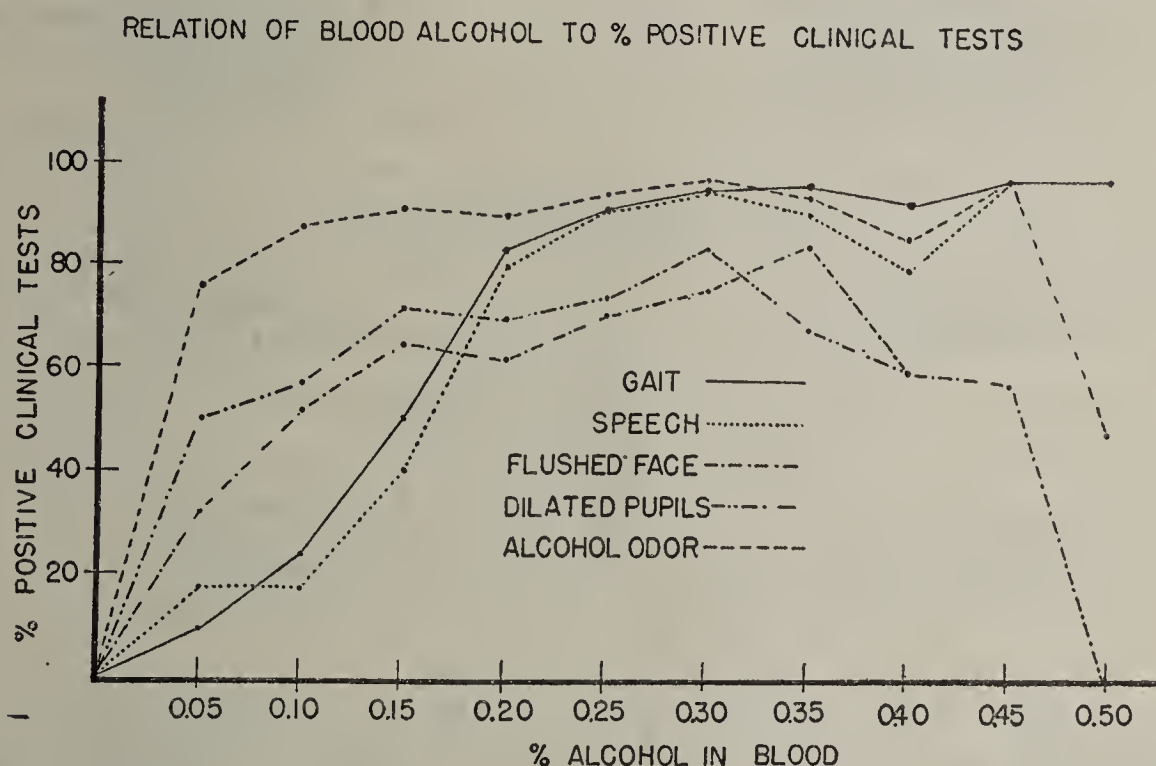
FIGURE 8.—This figure illustrates the percent occurrence of positive clinical tests at various concentrations of alcohol in blood (average of 1,000 cases). (Redrawn from Jetter, 1938b.)

In these experiments the incidence of acute clinical intoxication was 50 percent with blood alcohol levels of 0.015 to 0.125 percent, 57 percent with concentrations in the blood of 0.125 to 1.75 percent, and 100 percent with concentrations of 0.175 to 0.225 percent. A similar study by the same author (1939) shows, in accordance with the findings of Widmark (1932), Schwarz (1927), Bogen (1927), and Harger, Lamb and Hulpieu (1938), that the incidence of the clinical picture of acute alcoholic intoxication rises abruptly with concentrations of 0.1 to 0.20 gm. percent. Jetter (1938a) found that such criteria as abnormalities of gait and speech, flushed face, dilated pupils, and alcoholic odor of breath are related to the concentration of alcohol in blood, as illustrated in figure 8, which indicates that alcoholic odor of breath, dilated pupils, and flushed face become manifest at lower concentrations of alcohol in the blood than abnormalities of gait and speech.

preparations may delay insignificantly the absorption without reducing the maximal level of alcohol in the blood. Böhmer (1938) believed that both aspirin and amidopyrine delayed the absorption without however reducing the blood alcohol curve, whereas he found that insulin (30 units) lowered the resorptive phase but increased the postresorptive heights of the blood alcohol curve. Domenici (1939) showed that strychnine, strophantin, luminal, pantopon, metrazol, vitamin C, coramine, ephedrine, caffeine, camphor, digitalis, and acetyl choline do not influence the concentration of alcohol in the blood. Rakieten (1942) found that in rats doses of 400, 600, and 800 mg. per kg. of acetphenetidine slowed the rate of disappearance of alcohol from the blood, whereas similar doses of aniline, p-aminophenol, and amidopyrine were ineffective. Doses of 1.3 gm. of aspirin, 1.3 gm. of acetphenetidine, and 1.0 gm. of amidopyrine had no effect on the rate of disappearance of alcohol from the blood of human subjects when taken with 120 cc. of 90 proof whisky.

With regard to the *relation of the concentration of alcohol in the urine to the degree of intoxication*, Widmark (1915), Miles (1924) and Southgate and Carter (1926) thought that the alcohol level in the urine was a good gage for the determination of the intensity of the alcoholic intoxication. Bogen (1927) studied the relation between the concentration of alcohol in the urine and the clinical picture of alcoholic intoxication. He found that 50 percent of 35 persons with less than 0.1 percent (1 mg./cc.) of alcohol in the urine had admitted drinking and had alcoholic odor of breath but only a few of these showed flushed face, dilated pupils, abnormalities of gait, or thickened speech whereas many showed lack of inhibition and diminution of self-control. Of 45 patients with 0.1 to 0.2 percent (1 to 2 mg./cc.) alcohol in the urine the majority had a marked odor of alcohol in the breath; more than 50 percent had dilated pupils and flushed face and frequently showed loss of restraint, staggering gait, swaying on standing, confused and blurred speech, and general clumsiness. Of 58 patients with 0.2 to 0.3 percent (2 to 3 mg./cc.) alcohol in the urine, all showed these symptoms to a more marked degree, although 25 percent of these were still able to walk without staggering and to speak clearly, whereas of 64 patients with 0.3 to 0.4 percent (3 to 4 mg./cc.) only 1 could stand without swaying and only 1 could speak clearly. In 35 patients with 0.4 to 0.5 percent (4 to 5 mg./cc.), narcosis and stupor were the rule and the dilation of the pupils gave way to constriction, the flushing of the face to pallor. Thirteen patients with more than 0.5 percent (5 mg./cc.) were all in a state of coma, unable to respond to stimulation, with slow and shallow respiration, cold skin, and general inertness. As the alcoholic level in the urine approaches 0.6 percent (6 mg./cc.) the danger of alcoholic asphyxia becomes imminent. Jetter (1938a) studied the relation between impairment of gait and speech, flushed face

and dilation of pupils, and alcoholic odor of breath and the concentration of alcohol in the urine, as illustrated in figure 9. This figure shows, in accordance with the observations of the same author with regard to the blood alcohol level, that alcoholic odor of breath, flushed face, and dilation of the pupils precede changes of speech and gait. The findings of Bavis (1940) in a similar study substantiate, as was pointed out before, that the individual response to the same concentration of alcohol in the blood is not uniform. With regard to the relation of the concentration of alcohol in the urine to that in the exhaled air, Bogen (1927) found that the concentration in 2,000 cc. of exhaled air was slightly greater than that in 1 cc. of urine, and that the alcohol
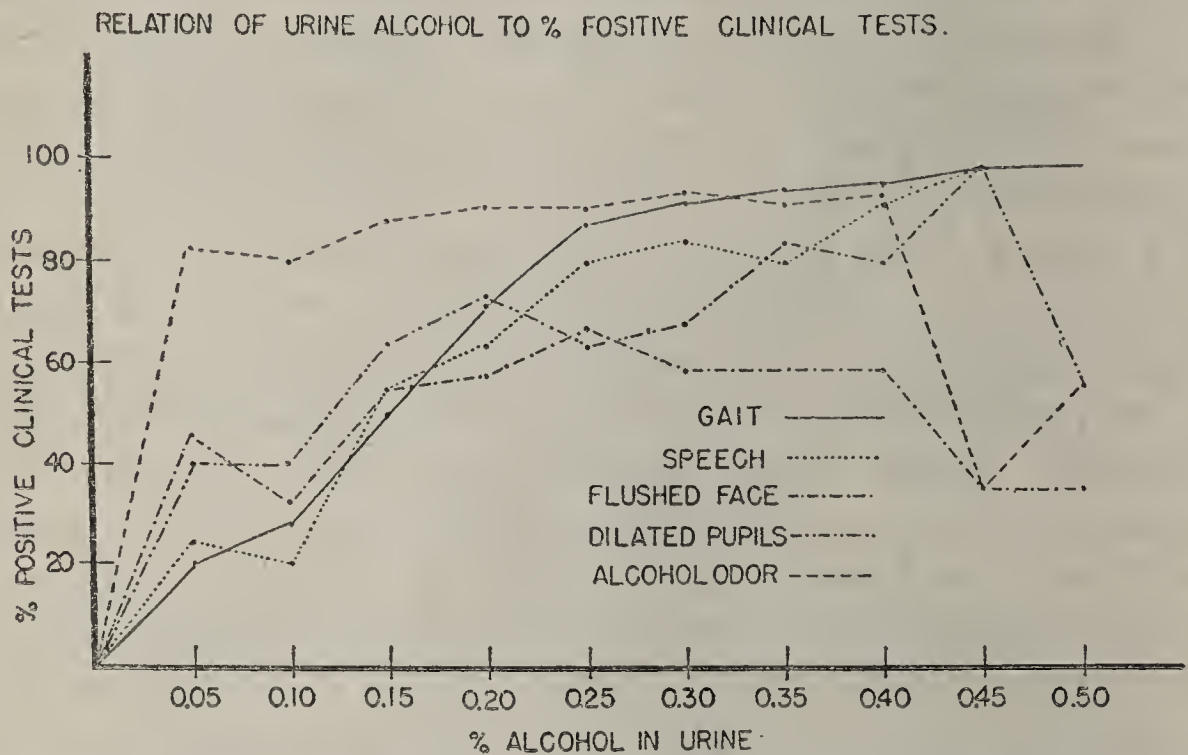
FIGURE 9.—This figure illustrates the percent occurrence of positive clinical tests at various concentrations of alcohol in urine (average of 381 cases). (Redrawn from Jetter, 1938a.)

level in the urine was equal to or slightly lower than that in the blood. According to Mozes and Katonak (1941) the ratio of the concentration of alcohol in 2,000 cc. of exhaled air to that in 1 cc. of urine is 1 : 1.16.

With respect to the *relation between the concentration of alcohol in exhaled air and clinical picture of alcoholic intoxication*, Nelis and van Tiemsche (1937) believed that the determination of alcohol in the breath is a good gage for the degree of intoxication when made within a short time after the ingestion, and that for a positive diagnosis it should be at least 0.04 percent. Harger, Lamb, and Hulpieu (1938) determined the concentration of alcohol in exhaled air and pointed out that the ratio between alcohol and carbon dioxide in the breath may be used for the appraisal of alcohol in the blood. They found that the weight of alcohol excreted with 190 mg. of carbon dioxide is nearly equal to the weight of alcohol in 1 cc. of blood, and that the distribution ratio between alcohol in air and blood is 1 : 2,000. They believed that the determination of alcohol and carbon dioxide

in the exhaled air excludes possible fluctuations in the amount of alveolar air contained in such samples. Haggard, Greenberg, Miller, and Carroll (1941) determined the distribution ratio between the concentration of alcohol in exhaled air and its concentration in blood as 1:1,300, and they believed that the discrepancy between this value and that of Harger, Lamb, and Hulpieu (1938) was largely due to the loss of alcohol in the condensed water vapors within the container used for the collection of the samples. In addition, they pointed out that the concentration of alcohol in the lung air cannot be calculated correctly from the concentration in mixed exhaled air on the basis of the carbon dioxide content of these two types of air because alcohol diffuses more rapidly into the air of the respiratory dead space than does carbon dioxide. They showed that the concentration of alcohol in the alveolar air, the collection of which is rather difficult in untrained persons, corresponds closely to that in "venous" air. The latter is collected by having a person wearing a nose clip rebreathe from a closed glass tube of adequate volume after a deep expiration followed by normal inhalations and exhalations into the tube. They claimed that by this procedure the error involved in the determination of the concentration of alcohol in the exhaled air mentioned above for the appraisal of the blood alcohol level can be avoided. Jetter and Forrester (1941) determined the alcohol and carbon dioxide content of the exhaled air by the method of Jetter, Moore, and Forrester (1941) and calculated the percent concentration of alcohol in blood by multiplying the ratio of mg. alcohol determined in breath over mg. carbon dioxide determined in breath by 0.2. They found no evidence that the absorption of alcohol by water condensed on the walls of the collecting apparatus invalidated the results. Acetone, paraldehyde, esters, aldehydes, and other constituents of beverages and methanol are said to not invalidate the results obtained by this method, but alkalosis and acidosis may give rise to erroneous findings.

With regard to the *relation between the concentration of alcohol in the spinal fluid and the degree of intoxication*, Schumm and Fleischmann (1913) found that the concentration of alcohol in the spinal fluid is approximately proportionate to the amount of alcohol ingested. Bogen (1927) stated that it corresponds closely to that in the urine and, therefore, also to that in the blood. Vad and Kulkarni (1929) claimed that alcohol may be detected in the spinal fluid before a person shows signs of drunkenness or lack of mental control. It was stated in a previous section that Gettler and Tiber (1927b) had developed a method for the calculation of the alcohol content of the brain from that of the spinal fluid, and that they claimed that persons with an alcohol content in the brain of less than 0.1 percent showed no abnormal physiological effects, that 0.1 to 0.25 percent caused such disturbances as increased aggressive-

ness, more or less marked carelessness, but no real intoxication which, however, manifests itself with concentrations of 0.25, 0.4, and 0.6 percent. Helwig (1940) and Gonzales and Gettler (1941) agreed that the determination of alcohol in the spinal fluid and brain gives the most exact and most consistent indication of the degree of intoxication.

It has been pointed out that the degree of alcoholic intoxication, with regard to the concentration of alcohol in the blood, may be greatly influenced by the individual susceptibility. Nagel (1939) developed a *skin test for the determination of the susceptibility or tolerance to alcohol.* He showed that the intradermal injection of 0.3 cc. of approximately 60 percent alcohol into the lateral aspect of the deltoid region, using equal quantities of saline on the other arm as control, causes a cutaneous reaction of a different intensity. He stated that following this injection all persons develop a wheal of 9 mm. diameter but that they differ with regard to the erythema surrounding the wheal which reaches its maximum after 20 to 30 minutes and disappears within approximately 1 hour. By grading the intensity of this erythema he found that of all persons tested, 20 percent were allergic to alcohol and 10 percent belonged to the tolerant or relatively resistant group. As pointed out by Manwaring (1939) these figures substantiate the findings of the Dresden Alcoholic Commission which studied in 1938 the relation between the concentration of alcohol in the blood and the psychological disturbances and found that 20 percent of the test subjects were incapacitated with blood alcohol levels of 0.02 percent, whereas 10 percent were perfectly sober after the alcohol concentration in the blood had increased to 0.12 percent. Manwaring (1939) emphasized, however, that skin allergy and organ allergy do not necessarily run parallel, so that the supposition that skin allergy indicates nervous susceptibility needs further study. Kelley and Barrera (1941) made a study of the relation between Nagel's test, blood alcohol level, and the clinical picture as appraised by criteria similar to those used by Jetter (1938a). They found that different test subjects showed considerable variations in the concentration of alcohol in the blood at the same degree of moderate psychic impairment, and that a number of individuals showed a better relation between the intensity of the skin test and the effect on the mental functions.

A discussion of acute alcoholic intoxication would not be complete without discussion of the *drunken driver*, and numerous studies have been devoted to answering the question of at what concentration of alcohol in the blood a person should be considered as an unsafe driver. The opinions of different investigators of this question are summarized in table 11. It shows that concentrations between 0.1 and 0.2

Table 11.—*The relation between the concentration of alcohol in the blood and impaired driving skill*

Blood alcohol level in gram percent	Impairment of driving skill	Author
0.02	Impairment in some individuals	Straub (1939).
0.05	No significant effect	Holcomb (1938).
0.05	Maximal permissible concentration for safe driving	Straub (1939).
0.06 to 0.08	May result in unsafe driving	deCrinis (1939).
0.1	Some impairment of driving skill in all individuals	Straub (1939).
0.12	Some impairment in all individuals	Bavis (1940).
0.1 to 0.2	Distinct impairment of driving skill	Koller (1936).
0.15	Sufficient impairment to prevent safe driving	Bavis (1940).
0.15	Serious interference with driving skill	deCrinis (1939).
0.30	Unable to drive	Bavis (1940).

percent are most often considered to be sufficient to interfere with safe driving. Lauer (1939) pointed out that a safe driver must be able to meet new situations instantaneously and accurately. He found that slight impairment of the driving skill occurred with concentrations of 0.035 and 0.065 percent of alcohol in the blood and that with such concentrations the judgment was impaired by 25 percent, the motor performance by 23 percent, and the sensory capacity by 14 percent. He found that the drinking of alcohol results in increased variability and inconsistency of performance, decreased tolerance to glare, increased reaction time, poorer observation, and a tendency to speed up and to be less cautious, and that the finer coordination is eliminated first. The Committee for Tests on Intoxication of the National Safety Congress (1939) considered concentrations of 0.15 percent and more as sufficient to indicate inability to drive, and that with concentrations of 0.05 to 0.15 percent, clinical examination should be resorted to in order to decide whether or not the person under investigation is under the influence of alcohol. Berry (1940) believed that drivers with a blood alcohol level of 0.15 percent are 55 times more liable to be involved in traffic accidents than normal persons. Straub (1939) came to the conclusion that the maximal permissible concentration of alcohol in the blood for safe driving is 0.05 percent, and that with blood alcohol values of less than 0.14 percent the degree of intoxication should be established by clinical tests. Cameron (1940) joins McBrath (1939) (quoted from Cameron, 1940) in believing that with concentrations of between 0.03 and 0.2 percent the decision with regard to the degree of intoxication may not be very easy. With regard to the relation between the concentration of alcohol in the urine and the impairment of driving skill, Bavis (1940) believed that 0.15 percent is not sufficient to impair safe driving, 0.20 percent causes unsafe driving, and 0.35 percent causes inability to drive. In judging the impairment of the driving ability many tests have been devised and used, and Newman and Fletcher (1940) came to the conclusion that a performance test in simple steering is a better index than the determination of the concentration of alcohol in blood, urine, or breath.

As reported in an editorial in the Journal of the American Medical Association (1940), the Committee for Tests on Intoxication of the National Safety Council (1939) recommends that chemical tests of body fluids or breath (if properly performed) be used in all cases, criminal or civil, in which the influence of alcohol is suspected. This committee agreed further with the interpretation of chemical tests for alcoholic intoxication recommended by the Committee to Study Problems of Motor Vehicle Accidents of the American Medical Association as adopted by the House of Delegates (1939); namely, that (1) a person with a concentration of less than 0.05 percent by weight in blood or its equivalent in urine, saliva, or breath should not be prosecuted for driving while under the influence of alcoholic beverages; (2) persons with a concentration of above 0.15 percent should be considered to be under such influence; and (3) persons with a concentration of between 0.05 and 0.15 percent should be prosecuted only when circumstances and results of physical examinations give definite confirmation that they are under the influence of alcohol.

Newman, Fletcher, and Abramson (1942) pointed to the considerable variations between the results of aptitude and driving tests of different individuals and their blood alcohol level. These variations may be apparent in the effect of alcohol on the vision, coordination, and the complex activity involved in driving a motor vehicle. They found, however, that with a blood alcohol concentration of 150 mg. per 100 cc. of blood all subjects showed some demonstrable effect of alcohol. On the other hand, they found that not all test subjects with more than 150 mg. of alcohol per 100 cc. of blood were impaired to such a degree that their ability was reduced to below that of the ordinary prudent and cautious driver.

The question as to what extent the *drunken pedestrian* is the cause of traffic accidents has aroused much less comment. Eppel (1940) determined the alcohol content of the blood of pedestrians killed by their own carelessness in 76 traffic accidents and found 0.196 to 0.431 percent of alcohol in 11.4 percent of these cases; 0.096 to 0.165 percent in 10.1 percent; and 0.02 to 0.095 percent in 8.8 percent. Gonzales and Gettler (1941) found that of 2,472 pedestrians killed in highway accidents, 30.7 percent were under the influence of alcohol and 26.2 percent had a brain alcohol content of 0.1 to 0.25 percent or more. This study indicates that in the evaluation of the medicolegal implications of highway accidents the relation of the alcohol content in the blood or brain of the pedestrian should not be ignored, and that negligence on the part of the intoxicated pedestrian may also be an important factor in traffic accidents.

Alcoholic intoxication as an industrial hazard.—It is obvious that the effect of alcohol on the nervous functions and the effect of alcohol on the driving skill, discussed above, also holds true for industrial opera-

tions where reaction time, judgment, and performance are of importance. In addition, it should be emphasized that ingestion of alcoholic beverages increases the susceptibility to many chemical poisons, such as aromatic amino and nitro compounds, carbon tetrachloride, and others. Loewy and von der Heide (1918) stated that in man the inhalation of concentrations of 1,000 to 2,500 p. p. m. of alcohol in air may cause toxic effects, and that with higher concentrations (7,500 p. p. m.) exposure for 45 to 90 minutes may cause somnolence, fatigue, and sleepiness. The question of industrial injuries resulting from the use of denatured alcohol was evidently first discussed by Lewy (1891) who believed that certain denaturing agents, such as pyridine bases and crude wood alcohol, may cause numerous symptoms, such as hoarseness, retching, nausea and vomiting, headache, vertigo, tremors, etc. Such symptoms were observed in workers of different trades handling denatured alcohol in varnishes and lacquers. It appears, however, that these persons worked under very unfavorable conditions (small working places, high temperature, and inadequate ventilation) and a later study by Loewy (1914) on the industrial hazards of denatured alcohol with special reference to methanol, showed that only in a small number of cases could irritation of the eyes and catarrhal affections of the pharnyx and the upper respiratory tract be observed, and these only under especially unfavorable conditions. He pointed out, however, that adequate ventilation and general and personal hygiene are essential in preventing injurious effects from the use of denatured alcohol. With regard to the maximal permissible concentration of ethyl alcohol in air, no definite limits have been established. Several States of the Union have suggested tentatively 250 p. p. m. but it appears that further studies are required before definite standards can be established.

The habituation to ethyl alcohol.—It has been stated repeatedly that there is frequently a difference in the response to alcohol between persons abstaining from the consumption of alcoholic beverages and those who regularly ingest such beverages. Experience with human beings and animal experiments performed by many investigators, particularly Newman and Lehman (1938), have shown that the continued ingestion of alcohol renders persons or animals more tolerant to the effect of alcohol on the central nervous system, so that a better neuromuscular coordination is demonstrated at an equal blood alcohol level than before habituation. Newman and Lehman (1938) believed that after habituation the tolerance of the tissue to alcohol is increased, whereby the cells of the central nervous system acquire the ability to function more effectively at a given alcohol concentration than before habituation. This assumption appears to be supported by the observation of Ahlquist and Dille (1940) that alcohol-tolerant rabbits

are also much more resistant to the depressant effect of other narcotics such as pentobarbital, evipal, and ether.

The clinical picture of the toxic effects of alcohol on the nervous system.—Continued ingestion of excessive amounts of alcohol may result in chronic alcoholism which has been associated with many pathological conditions.

With regard to the *effect of chronic alcoholism on the mentality*, it appears questionable, as pointed out by Allen (1938), whether alcoholism leads to mental instability or whether mental instability leads to alcoholism. Wechsler (1941) studied the I. Q. of chronic alcoholics who did not suffer from other mental diseases and found that their capacity for logical analysis and organization is often affected to a greater degree than the more familiar deterioration of the memory. In his opinion the prolonged use of alcohol impairs the mental functioning of various abilities before there is any evidence of disease of the brain, and there is a relation between the intensity of the impairment and the duration of the alcoholism.

With regard to the relation between chronic alcoholism and certain psychic disturbances, Heron (1912) believed that alcohol is less frequently the cause than the sequela of mental defects, and Fränkel and Benjamin (1933) believed that in many instances of chronic alcoholism excessive drinking is only a secondary symptom, inasmuch as they found that of 458 drinkers examined 25 percent suffered from severe somatic or psychic defects. Bowman and Jellinek (1941), in a review on alcoholic mental disorders, concluded that there seems to be agreement that alcohol addiction is the symptom of many psychoses rather than the primary cause, with the exception of such affections as delirium tremens and Korsakoff's psychosis. Lewis (1941), on the other hand, believed that alcohol as an etiologic factor in mental disease ranks comparatively high, either as an individual cause or as a precipitant agent in certain types of disturbances. The following discussion is largely based on the review of Bowman and Jellinek (1941).

Of the various mental disturbances associated with alcoholism, *pathological intoxication* may be discussed first. As pointed out by Bowman and Jellinek (1941) the outstanding symptoms of this affection are blind rage, confusion, and usually complete amnesia for the condition. The stage of rage may be characterized by anxiety and paranoia. The same authors consider as main neurological reactions, reflex rigidity of pupils, swaying, and weak tendon reflexes which outlast the mental effects. In their opinion its etiologic factor is an existing psychopathic condition and alcoholism is only the eliciting cause. It is not necessarily associated with chronic alcoholism since it may also result from the ingestion of small doses of alcohol and may be observed in hypoglycemic conditions.

One psychosis most commonly associated with chronic alcoholism is

delirium tremens, the clinical picture of which has been discussed recently by Wortis (1940) and Bowman and Jellinek (1941). The onset of delirium tremens is insidious, and the prodromal symptoms may occur days and weeks before the outbreak of the psychosis. They are characterized by anxiety, restlessness, fear, insomnia, nightmares, hypersensitivity of sensory organs, occasional hallucinations, tendency to perspiration, headache, vertigo, and convulsions, and appear predominantly at night. The acute psychosis lasts only from 3 to 4 days, and most symptoms disappear after the so-called terminal sleep. The onset of the acute stage is usually sudden, frequently at night, and is occasionally associated with an epileptic or epileptiform attack. The attack is characterized mainly by visual hallucinations; less frequently by illusions, tactile, auditory and combined hallucinations. There is a marked degree of suggestibility, the learning ability is impaired, the consciousness is dimmed, and the attention and perception are decreased. Orientation for time and space is impaired and there may be motor excitation and hyperactivity. With regard to the physical picture of delirium tremens, this is characterized by a coarse arrhythmic tremor of the tongue, face, fingers, legs, and even of the trunk. The patient may be restless and suffer from insomnia. In the opinion of Bowman and Jellinek (1941) it is questionable whether or not disturbance of the equilibrium should be considered among the cardinal symptoms. Nausea, vomiting, profuse perspiration, constipation, and dehydration may be observed. The body temperature, blood pressure, and pulse rate may be increased. The urinary findings are suggestive of disturbances of the protein metabolism and there are definite indications of impairment of the detoxicating function of the liver and disturbance of the fat and mineral metabolism. In contrast to the older conception, at present delirium tremens is not considered a withdrawal symptom. Delirium tremens is observed only in chronic alcoholism, and injuries or infections, metabolic disturbances of various types, and lack of vitamin B, may be predisposing factors.

Korsakoff (1889) described a symptom complex which he had observed both in alcoholic patients and also as sequelae of infectious conditions and of poisons such as carbon disulfide, carbon monoxide, and others and which has become known as *Korsakoff's psychosis.* Cases of this condition have been reported frequently and more recently by Reifenstein, and Davidoff (1940) and Romano, Michael, and Merritt (1940), and was discussed extensively by Bowman and Jellinek (1941). The onset of this psychosis may be sudden, with delirium, or fairly insidious, with stupor. The patients may show an anterograde amnesia; sometimes impairment of memory, impaired learning ability, disorientation to space and time, confabulation; occasionally illusions, stereotypy of speech, aphasia, and agraphia. They are indifferent to their surroundings or, sometimes, euphoric. The psychosis is often

associated with polyneuritis, as discussed by Jolliffe (1940) and, in contrast to delirium tremens, Korsakoff's syndrome is always associated with degenerative polyneuropathy and brain changes closely resembling those found in chronic alcoholism, and it appears to be possible that the disease may be partly due to lack of vitamin B_1.

Another psychosis, *acute alcoholic hallucinosis*, occurs only in chronic alcoholism and is not a manifestation of acute intoxication. Bowman and Jellinek (1941) considered it as one of the earlier syndromes of chronic alcoholism. The onset of this psychosis is sometimes sudden, but more frequently it is preceded by a prodromal stage characterized by general anxiety, headache, insomnia, and acoustic hypersensitivity. The main symptoms of the psychosis are fear, auditory hallucinations, inclination to anxiety, misinterpretation and systematization with intact orientation and presence of mind. In contrast to delirium tremens, patients suffering from acute hallucinosis are usually well oriented, their perception and attention are not impaired, and generally they are willing to talk. While delirium tremens patients accept their hallucinations and delusions, those suffering from acute hallucinosis seek explanations. The hallucinations of acute hallucinosis have not the coloring of those in delirium tremens; they are less dependent upon the sense of perception and are not altered by perception. In contrast to delirium tremens the motor unrest exists only in the beginning and is less marked. Acute hallucinosis is much less dependent upon the consumption of high-proof spirits than is delirium tremens, and, in contrast to the latter, it is not caused by precipitating factors. It has been stated that in acute hallucinosis, especially in the beginning, there is always leucopenia, and, in contrast, in delirium tremens there is leucocytosis. The duration of the acute hallucinosis is much longer than that of delirium tremens and, in contrast to the latter, patients suffering from the former usually have a high incidence of psychoses, alcoholism, psychopathy, and suicide in their family.

Another type of alcoholic psychosis, *alcoholic paranoid condition*, is recognized by some authorities as an alcoholic mental disorder. In the opinion of Bowman and Jellinek (1941) it cannot be excluded categorically but they believed that it is presumably the late precipitation of a schizophrenic condition.

Chronic alcoholic deterioration, in the opinion of Bowman and Jellinek (1941), is not a clinical entity and has not been classified as an alcoholic psychosis. It is characterized by ethical degeneration, dulling of the finer sentiments, and brutality of the patients. But more important is their lability and the impairment of their memory. Such patients frequently show a dilatation of the facial capillaries, especially of the nose, and myocardial changes; they have a bloated look and their musculature is flabby. In case hard liquors are taken

habitually such patients may suffer from gastritis and possibly also from cirrhosis of the liver. The patients show tremors, sometimes twitchings and choreiform movements, and they may suffer from pain in calves and legs and sometimes from tenderness over the large nerve trunks and peripheral neuritis. Pupillary changes are frequent and their reaction is sometimes sluggish. The physical capacity and stamina of such patients is frequently impaired and their resistance to disease reduced.

With regard to *alcoholic epilepsy* and *dipsomania*, Leary (1938) and Bowman and Jellinek (1941) agree that these are not sequelae but rather causes of alcoholism. The latter pointed out that abnormal drinking is definitely greater among epileptics than in the general population, that there is a high concomitance of alcoholic addicts and epileptics in families with psychopathic heredity, and that there is an acceleration of epileptic seizures in genuine epileptics through alcohol and some indication that alcohol may precipitate latent epilepsy. With respect to dipsomania, as stated by Bowman and Jellinek (1941), it is at present assumed that this belongs to the manic-depressive group of psychoses and that "it still remains a challenging problem."

Another affection of the central nervous system frequently associated with alcoholism is *Wernicke's syndrome* which is characterized by cloudiness of consciousness, varying ophthalmoplegias, and ataxia. According to Jolliffe, Wortis and Stein (1941) it is probably a combination of several nutritional disturbances affecting the nervous system, and the picture need not necessarily be complete in 1 patient. It is frequently preceded by and associated with delirious episodes, and, in those persons who recover, a residual Korsakoff psychosis may be seen. The pathological lesions may extend not only to the cortex but also to the spinal cord and the peripheral nerves. Although usually associated with alcoholism there is evidence that nutritional deficiencies, especially of thiamine hydrochloride, seem to be the most obvious common factor.

Alcoholic polyneuritis is an affection of the peripheral nerves and is frequently associated with alcoholism. Jolliffe (1940) who reviewed the literature on this subject pointed out the difference between polyneuritis and polyneuropathy, the latter being characterized by pathological changes indicating degenerative processes. In the opinion of this author it appears to be established that alcoholic neuropathies are basically caused by nutritional deficiencies, specifically by avitaminoses, predominantly of vitamin B_1, which may be associated with other vitamin deficiencies. In his opinion the idea of a direct causation by alcohol has to be abandoned in view of the identity of alcoholic neuropathy with beriberi, the fact that adequately nourished alcoholics do not develop neuropathy, and that a vitamin B_1 deficient

diet produces experimentally the characteristic symptoms of peripheral neuritis, including the neurasthenic manifestations. Similarly, Wayburn and Guerard (1940) came to the conclusion that avitaminosis B $_1$ as cause of polyneuropathy seems to be established. Laboratory investigations (Evans and Lepkovsky, 1929, 1934 and 1935; Kemmerer and Steenbock, 1933; McHenry, 1937; Salmon and Goodman, 1937; all quoted from Lowry, Sebrell, Daft and Ashburn, 1942) have shown that the vitamin B_1 requirement is influenced by the composition of the diet as well as by the total number of calories. An abundant supply of carbohydrates increases, while substitution of fats for carbohydrates decreases the need for vitamin B_1 and postpones the onset of polyneuropathy. On this basis it was assumed that, like carbohydrates, alcohol increased the need for thiamine. Similarly, Westerfeld, Stotz and Berg (1942) believed that, since the oxidation of alcohol to acetaldehyde requires the nicotinamide coenzyme, and the pyruvate-acetaldehyde condensation requires diphosphothiamine, thus increasing the need for these substances above that required for the metabolism of other foodstuffs, this may be in part responsible for the production of "alcoholic pellagra" and polyneuritis. They believed that on this basis chronic alcoholics maintain a higher requirement for nicotinamide and thiamine and develop more rapidly a deficiency of these vitamins because they actually derive a large part of their daily calories from vitamin-free alcohol. Lowry, Sebrell, Daft and Ashburn (1942) showed, however, in paired feeding experiments with rats on a thiamine-deficient diet, that without exception rats fed water developed neuropathy before the paired litter mates receiving dilute alcohol or whisky instead of drinking water, indicating that alcohol consumption does not increase the thiamine requirement. Wayburn and Guerard (1940) found that a high percentage of peripheral neuropathies occurred in cases of cirrhosis of the liver and that both conditions improved upon therapy with vitamin B_1. Brown (1941), on the other hand, reported less striking results from the administration of thiamine hydrochloride.

The toxic effects of ethyl alcohol on organ functions.—The relation of alcoholism to cardiovascular disease has been much discussed and disputed. Weiss (1940), in an extensive review of this subject, came to the conclusion that among other factors, thiamine deficiency may be a contributing factor; and Leary (1938) also believed that the role of alcoholism as primary cause is at least questionable, and that such sequelae as subarachnoidal hemorrhages, subdural hemorrhages (without contusion or laceration of the brain), and hemorrhages in the mammillary bodies observed in alcoholism may be due to a deficiency of vitamin C in the diet.

The relation of alcoholism to gastritis was discussed by Berry (1941). Seymour, Spies and Payne (1939) studied the gastric secretion in

chronic alcoholics who showed neither clinical evidence of vitamin deficiency nor laboratory evidence of anemia. They found a reduction of the average volume of the gastric juice and the acidity but no impairment of the peptic activity. Beazell and Ivy (1940) came to the conclusion that the ingestion of large amounts of alcohol causes gastritis and achlorhydria from which recovery is relatively rapid. They also believed that dietary deficiencies may be involved in the causation of gastritis. Gray and Schindler (1941) examined 100 chronic alcoholics gastroscopically and found that 55 percent of these showed essentially a normal stomach; that the remaining 45 percent suffered mostly from superficial gastritis, atrophic gastritis or a combination of both; and that 22 percent of the latter showed mucosal hemorrhages. They found no relation between the incidence of gastritis and the duration of the alcoholism, the amount of alcohol ingested, the abuse of nicotine, dental defects, and vitamin deficiency. In a similar study, Berry (1941) found that of 100 persons with unquestionable chronic alcoholism of long standing 30 percent gave no evidence of gastritis; 35 percent suffered from mild superficial gastritis, the gastric mucosa differing only slightly from normal; 35 percent showed distinct chronic gastritis.

The toxic effect of ethyl alcohol on the liver has aroused much comment. Kochmann (1923) in his review on this subject refers to Rosenfeld (1900) who found that the feeding of alcohol resulted in a 10 percent higher incidence of fatty livers in animals thus fed than in the controls. Similarly, Ducceschi (1917–18) found that daily feeding of alcohol to dogs increased the fat content of the liver up to 30 percent and that the cholesterol content was also increased but less markedly. With regard to the effect of alcohol on the liver function, Lamson (1923) (quoted from Rosenthal, 1930) found that doses of 4 cc. per kg. body weight cause inpairment of the liver function on the same or on the following day. Wallace (1927) studied the liver function of 17 patients suffering from acute alcoholic intoxication by determining the bilirubin content of the blood and the urobilinogen excretion in the urine. He found definite evidence of liver injury, proportionate in intensity to the severity of the intoxication, the bilirubin content of the blood and the urobilinogen in the urine, being materially increased immediately following the excess and returning gradually to normal values within 4 to 5 days. Beazell, Berman, Hough and Ivy (1942) found that ingestion of 2 to 3 cc. per kg. in the form of whisky caused no demonstrable ill effects on the hepatic function as indicated by the serum van den Bergh, urine bilirubin, bromsulphthalein clearance, hippuric acid excretion, serum phosphatase, fasting blood sugar, and fructose and glactose tolerance tests. In these subjects the blood alcohol level rose to 150 to 201 mg. per 100 cc. of blood. However, they believed it possible that

with blood alcohol concentrations of 300 to 500 mg. per 100 cc. disturbance of the liver function may be observed. Animal experiments carried out in the same way appear to indicate that dogs are more sensitive than humans to the hepatotoxic action of alcohol. Binswanger (1932) referred to observations of Pohlisch, Büchler, and Boström who found urobilin and urobilinogen in the urine of patients suffering from delirium tremens, but in his experience this does not appear to be the rule. However, this may vary with the time elapsed since the ingestion of alcohol because de Montmollin (1938) observed in the acute stage of various alcoholic psychoses a very marked increase of the urinary urobilin which paralleled the intensity of the psychic disturbance. Using smaller doses (2 cc. per kg.) than Lamson (1923) (quoted from Rosenthal, 1930), Rosenthal (1930) found no evidence of urobilin in the urine or bilirubin in the blood, but he found a slight impairment of the liver function, as indicated by the results of the bromsulphthalein test, which returned to normal within 24 hours. He found, however, that this moderate injury increased materially the susceptibility to other poisons such as chloroform and carbon tetrachloride. Cates (1941b) examined the liver functions of 17 patients suffering from acute alcoholism and found in 4 of them a distinct impairment of the excretion of bromsulphthalein. He believed that in his cases the liver injury was primarily due to lack of proper nourishment; that the retention of the dye is not necessarily related to pathological changes of the liver tissue; and that acute hepatitis may subside completely and only in severe cases lead to Laennec's cirrhosis. This appears to be in accordance with observations made in animals by MacNider (1933). He found that dogs intoxicated for 12 hours with sufficient doses of alcohol to become semianesthetized, developed injury of the liver commencing at the peripheral lobules and consisting essentially of edema of the cells accompanied by accumulation of stainable lipoid material. These changes were paralleled by a retention of phenoltetrachlorphthalein corresponding to the intensity of the injury. Whereas in these animals the function and histology returned to normal within 3 days, it took 12 days with animals which had been intoxicated in the same way for 24 hours. Berman, Snapp, Ivy and Atkinson (1941) administered 40 cc. of alcohol daily to dogs with biliary fistula and found that this caused definite changes of the liver parenchyma which were reflected in the composition of the bile.

Kagawa (1931) studied the mobilization of sugar by alcohol in toads and believed this was due to a reversible narcosis of the liver cells; and Binswanger (1932) believed that in certain alcoholic psychoses the ability of the liver to assimilate sugar is reduced. Connor (1940) believed that ingestion of alcohol with a normal diet causes an abnormal accumulation of sugar in the blood; and Bowman, Wortis, Oren-

stein, and Goldfarb (1939) found, in a group of 18 alcoholics, a marked reduction of the sugar tolerance, presumably on account of malnutrition prior to hospitalization. Tennent (1941a), in a study of the effect of alcohol on the sugar level in the blood, pointed out the variable results obtained by various investigators, as illustrated in table 12. As pointed out by Tennent (1941a) the results of different investigators (Himwich, Nahum, Rakieten, Fazekas, DuBois, and Gilden, 1933; Oppermann, 1913; and Kanai, 1933) show that the effect of alcohol on the blood sugar varies with the dose, in that small doses may cause a decrease and large doses an increase of the blood sugar, and that variable results with regard to the effect of alcohol on the glycogen content of the liver were reported by Kanai (1933) and Salant (1908) (quoted from Tennent, 1941a). Tennent (1941a) showed that rats whose livers were rich in glycogen showed a marked rise of the blood sugar after the administration of 3 grams of alcohol but no rise after 1 gram per kg. body weight, whereas rats whose livers were depleted of glycogen showed no significant rise after the administration of 3 grams per kg. It appears, therefore, that the hyperglucemic action of alcohol depends upon the nutritional status of the test subject and upon the dose administered.

Table 12.—*The effect of alcohol on the blood sugar*

[D. M. Tennent, 1941]

Investigator	Subject	Dose of alcohol	Change in mg. percent	Condition of subject	Route of administration
Himwich et al	Human	1.5 gm./kg	+10	Fasted	Stomach.
Labbe, Nepveux and Chewki.	do	1.0 gm./kg	+12 to 39	do	Do.
Hetenyi	do	16.4 gm	Av. +22	do	Do.
Gavrila and Sparchez	do	0.40 gm./kg		do	Do.
Kolta	do	7.9 gm	Max. +11	do	Do.
Himwich et al	Dog	1.5 gm./kg	+11	do	Do.
	do	7.5 gm./kg	+28	do	Do.
Nitzescu	do	0.5 to 1.0 gm./kg	Av. +6.3	do	Do.
Burdi	do	0.79 to 1.32 gm./kg	−37	do	Do.
Oppermann	do	2.38 gm./kg	−35	do	Do.
		3.95 gm./kg	+11	do	Do.
Blatherwick et al	Rabbit	2.0 to 2.4 gm./kg	Av. −27	do	Do.
Conner	do	3.2 to 8.0 gm./kg	+50	Fed	Do.
Masamme	do		−+	Fasted	Subcutaneous.
Kanai	do	1.19 gm./kg	Av. −19	do	Stomach.
	do	2.37 gm./kg	Av. +20	do	Do.
	do	3.95 gm./kg	Av. +37	do	Do.

With regard to *the relation between alcoholism and liver cirrhosis*, Kochmann (1923) stated that Mertens (1896), Saltykow (1910), Foa (1908), Lissauer (1913), and Grover (1916) were able to produce typical cirrhosis of the liver by inhalation, by intravenous and subcutaneous injection, and by ingestion of alcohol. As stated by Kochmann (1923), Foa (1908) and Lissauer (1913) assumed a primary interstitial growth and secondary degeneration of the liver tissue, whereas Payne (1888) and Kyrle and Schopper (1913) believed that the primary effect was on the parenchyma. Schmid (1940) stated that

in the United States, in 1938, 2,569 fatalities were attributed to alcoholism, 959 of these being reported as cirrhosis of the liver; and he also stated that there appears to be a real or apparent increase of the incidence of this affection. However, it appears that the extent to which alcohol is responsible for the production of cirrhosis of the liver has not been established. Schafir (1913) reviewed the literature on the relation between alcoholism and cirrhosis of the liver and found already at that time a considerable discrepancy of opinion on this subject. He quoted von Hausemann (1904) as stating that cirrhosis of the liver may occur in alcoholism but that the specific effect of alcohol is fatty degeneration of the liver, and he refers to Klopstock (1906), Rösle (1907), von Baumgarten (1907), Fahr (1909), and Kaufmann (1911) who assumed that cirrhosis of the liver as observed in alcoholics is not caused by alcohol itself but that alcohol favors certain toxic factors which by themselves are able to produce cirrhosis of the liver. Schafir (1913) himself was unable to produce experimentally cirrhosis of the liver but only degenerative changes and necroses with fatty infiltration and some interstitial growth not sufficient to be called cirrhosis. Connor (1940) studied the question of the extent to which liver changes in alcoholism were due to inadequate nutrition and came to the conclusion that for the production of cirrhosis of the liver alcoholism has to be associated with starvation, nutritional deficiencies, or certain diseases such as diabetes. Similarly, Beazell and Ivy (1940) were of the opinion that alcohol does not cause cirrhosis of the liver but predisposes to the cirrhogenous effect of other toxic substances and that sometimes it appears to cause cirrhosis in fatty livers produced by a high fat diet. György and Goldblatt (1941) showed that rats on a vitamin deficient diet developed often but not always acute diffuse necrosis of the liver associated with fatty degeneration, and that a diet free of casein and deficient in vitamin B caused necroses with or without cirrhosis within 100 to 150 days. Jolliffe, Wortis, and Stein (1941) reviewed the question of vitamin deficiency and liver cirrhosis in alcoholism.

With regard to the *relation between alcoholism and affections of the pancreas*, Myers and Keefer (1934) stated that alcohol is a predisposing factor in acute pancreatic necrosis because they found that of 21 cases of chronic pancreatitis 7 were associated with alcoholism or with diseases commonly associated with chronic alcoholism. They refer to reports on alcoholic panceratitis by Mondon (1929) and Émile and André (Aron and Jacob) (1930), and to the monograph of Gross and Guleke (1924) who stated that alcoholism, especially in its chronic form, is the cause of pancreatitis characterized by an increase of the intra and interlobular fibrous tissue. The mechanism of this pancreatotoxic effect of alcohol has been explained by a direct toxic effect of alcohol on the pancreas, by obstruction or infection

of the pancreatic duct due to duodenal congestion, and by forcing of duodenal contents or bile into the pancreatic duct as a result of persistent vomiting. The latter explanation has also been accepted by Leary (1938).

With regard to the *relation between alcoholism and disturbances of the kidney function*, Hultgen (1910) found that in dogs the daily intake of alcohol has no irritant effect on the kidney, and he believed that nephritis in alcoholics is probably due to some other factor than alcohol, such as alimentary disorders and exposure to cold or infection. Bruger (1940) reviewed the effect of alcohol on the normal and diseased kidney and came to the conclusion that there is little direct or irrefutable evidence that alcoholism is responsible for Bright's disease and arteriosclerosis because only a negligible amount of alcohol is excreted through the kidney which may account for any slight nephrotoxic action. He believed that with the possible exception of the arteriosclerotic kidney there is no evidence that alcohol affects the normal or even the diseased kidney.

Much attention has been given to the *relation between alcoholism and resistance to infections*. Thomas (1893) (quoted from Kochmann, 1923) showed in rabbits that the administration of alcohol reduced the resistance to cholera infections, and similar results were reported by Abbott (1896) for infections with *Streptococcus pyogenes* and to a lesser extent for those produced by *Bacillus coli* and *Staphylococcus pyogenes aureus*. Valagussa and Ranelletti (1899) noted reduction of the resistance to the toxic action of diphtheria toxin, and reduced resistance was also reported by Laitinen (1900), Goldberg (1901) (quoted from Kochman, 1923) and Pawlowsky (1900). Stillman (1924) found that in mice intoxicated with alcohol, pneumococci persisted in the lungs for longer periods of time than normally, and that a greater incidence of fatal septicemia but less frequently local infections of the lungs occurred. Stillman and Branch (1931) showed that mice previously exposed to pneumococci and then alcoholized and exposed to sprayed cultures developed local lesions of the lungs, either on account of an alteration of the local susceptibility to reinfection or, more likely, because of a limited degree of general immunity. Pickrell (1938) showed that in rabbits severe alcoholic intoxication leading to lasting stupor destroys the resistance to pneumococcus infections, and, in a study of 3,422 cases of lobar pneumonia, Caps and Coleman (1923) found the mortality considerably higher in excessive drinkers than in moderate drinkers, and the rate of fatalities greater among the latter than among abstainers. Pickrell (1940) reported that animals immunized by the injection of antipneumococcus serum are deprived of their resistance by intoxication with alcohol. Similar observations with anthrax and rabies were reported by Deléarde (1897) who assumed that this effect

may be due to an interference of alcohol with phagocytolytic processes. Reich (1915), in a study on the effect of alcohol on the destruction of tubercle bacilli by human leucocytes, found no constant relation although he found some evidence of impairment of the phagocytosis by alcohol. Abbott (1896) assumed that the decreased resistance to infections may possibly be due to starvation or nutritional disturbances associated with alcoholism, and Pickrell (1938) suggested that it may be due to an inhibition of the vascular response by alcohol, interfering with the emigration of leucocytes which would favor an uninterrupted bacterial growth.

With regard to the *effect of alcohol on growth*, Hanzlik (1931) found that in pigeons the administration of 2 and 4 percent solutions as drinking water for 13 to 14 months caused loss of weight, and Barlow, Beams and Goldblatt (1936) found that ingestion of 7.5 percent as drinking water in young rats was without significant effect on the growth rate, whereas in the experience of Sollmann (1920) and Barlow, Beams and Goldblatt (1936) 10 and 15 percent, respectively, had a definite effect.

The relation between alcoholism and the physical and mental condition of offspring has been much discussed, and the literature on this subject is controversial. Schröder (1933) and Koelsch (1936) stated that the available literature does not permit a definite answer as to whether or not alcohol produces genetic changes, but the possibility of such injurious effects has to be considered. The latter assumed, however, that for man it may be considered as established that the ingested alcohol may diffuse into the seminal fluid and that in chronic alcoholism spermatogenesis may be sufficiently damaged to cause azospermia and that an injurious effect on the offspring appears to be likely but is not proved. Statements with regard to the detrimental effect of alcohol are either based on uncritical statistical evidence (Pearson and Elderton, 1910) or on animal experiments. Féré (1896) showed that injection of alcohol into fertilized chicken eggs caused malformation of the embryo. Basset (1910) reported that daily inhalation of alcohol vapors for 1 to 2 months by doves and pigeons caused the yolk to become smaller without affecting the development of the eggs. Stockard (1914) claimed that in guinea pigs the inhalation of alcohol vapors may affect the germ cells of the males, resulting in defective offspring even if mated with normal females, and that an injurious effect may be observed even in the third generation. Similar results were reported by Stockard and Papanicolaou (1918). Arlitt (1919) claimed that mental deficiency produced in rats by continued feeding of alcohol, as demonstrated by their behavior in a maze, was transferred to the offspring equally well by male and female parents, so that animals in the second and third generations were inferior to normal animals. On the other hand,

Rost and Wolf (1925) found in rabbits fed daily doses of 10 to 20 cc. of alcohol for 2½ years, no evidence of a deleterious effect on cell proliferation, duration of gestation, weight, and general condition of the animals, nor was there any evidence of a harmful effect on the embryo or the fetus. Pearson and Elderton (1910) and Elderton and Pearson (1910) refuted the statement that alcoholism of the parent is a cause of degeneration in children. They found a higher death rate among the offspring of alcoholics than among those of sober parents, but this was apparently due more to domestic neglect, accidents, and carelessness than to the toxic effect of alcohol. On the contrary, they found that the general health of children of alcoholics was, on the whole, slightly better than that of children of sober parents, there were fewer delicate children, and epilepsy and tuberculosis were less frequent. In explanation of their findings they suggested that the physically strongest are more inclined towards alcoholic excesses and that there is a survial of the fittest in alcoholic families. They found the relation between parental alcoholism and filial intelligence so slight that it could not be established.

Pathological changes in alcoholism.—With regard to *pathological changes produced by alcohol in the central nervous system* one has to distinguish between the effects of acute intoxication and those of chronic alcoholism. In acute alcoholic intoxication, hyperemia of pia and brain, hemorrhagic diathesis, and edema of the brain have been reported by Regus (1937), Prievara (1941) and Alexander (1941). Kochmann (1923) refers to Berkley (1896), Kremiansky (1868), Neumann (1869) and Lewin (1874) as having produced experimentally hemorrhagic pachymeningitis in dogs. In chronic alcoholism, degenerative changes of various nature may be found. Kochmann (1923) referred to Mairet and Combemale (1892) as having found softening of the brain and the spinal cord, and to Magnan (1869), Vas (1894), Dehio (1895) and Afanassiew (1890) as having reported on degenerative changes of the gray substance of the spinal cord, the ganglionic cells of the anterior horn, and the ganglia. Duchovnikova and Robinson (1929) found, after continued administration of alcohol to rabbits, changes in the parenchyma and mesenchyma and in the ganglionic and glia cells of regressive and progressive type. They reported on toxic degenerative changes, especially of the parenchyma, mainly in the cerebellum, less frequently in the medullary centers and least often in the second and fifth layers of the cortex. Since the nervous damage was much more severe than the vascular injury they believed that these changes were the direct outcome of a toxic action of alcohol on the tissue. Stender and Lüthy (1931) and Lhermitte (1935) described cerebellar changes but it is questionable whether these were caused by alcohol. Stevenson, McGowan and Allen (1941) gave an extensive review of the pathological findings in the brain in alcoholism. They

studied the brains of 44 chronic alcoholics and found relatively slight changes, most of which were presumably due to lack of vitamin B_1 and vitamin B complex. They were unable to confirm the statements of previous authors with regard to the frequent involvement of the optic nerve, frequent severe lesions in the medulla and the blood vessels, severe ependymitis or gliosis, usual or constant marginal localization of the lesions and the presence of important lesions in the cerebellum. With the exception of patients dead from Wernicke's disease there was little relation between the clinical picture and the anatomic distribution of the lesions. Alexander (1941) stated that the brains from chronic alcoholics show atrophy and pseudo-atrophy, especially of the frontal lobe, with a corresponding increase of the fluid in the subarachnoid space, frequently referred to as edema. He pointed out that the shrinkage of the brain may be due to loss of nerve tissue, to dehydration, or to both. In chronic alcoholism, subdural hemorrhages are said to be frequent. In the opinion of Alexander (1941) these are probably due to vitamin C deficiency. In his opinion the histological changes are due either to direct and primary damage of the parenchyma (neuronitis) or to secondary changes of the parenchyma caused by vascular changes (Wernicke's disease). The former is said to be characterized by degenerative changes of the neurons such as swelling, tigrolysis, demineralization, and, finally, shrinking and destruction of the ganglionic cells, irregular swelling, and thinning, and, later, fragmentation of the myelin sheaths. He distinguished 3 types of changes: (1) neuronitis, predominantly of the peripheral nerve fibers; (2) neuronitis, predominantly of the nerve cells; and (3) neuronitis, predominantly of the long nerve tracts within the least vascularized part of the spinal cord. He pointed out that all 3 of these changes can be explained on the basis of an avitaminosis.

With regard to *pathological changes produced by ethyl alcohol in the liver*, Regus (1937) and Prievara (1941) found, in acute alcohol poisoning, hyperemia and some degenerative changes. As shown by MacNider (1933), acute alcoholic intoxication causes in dogs edema and accumulation of stainable lipoid material in the liver cells in the periphery of the liver lobules, these changes being paralleled by a retention of phenol tetrachlorphthalein. Schafir (1913) found in rabbits, after continued administration of alcohol, degenerative changes of the liver cells of variable intensity progressing to necrosis with fatty infiltration which sometimes was associated with very moderate interstitial growth but no cirrhosis of the liver. Similar results were reported by Grover (1916) and Balthazard and Larue (1921). The latter noted definite liver damage, especially of the periportal region, with granular, vacuolar, and fatty degeneration, leucocytic infiltration, and moderate proliferation of the connective tissue. MacNider and Donnelly (1932b) found that continued ad-

ministration of 10 cc. per kg. of 40 percent alcohol solution daily for 6 months to 2 years to dogs on a well balanced diet caused marked injury of the liver involving the peripheral liver lobules and extending inwardly towards the central vein so that two-thirds of the liver lobule may participate in this pathologic process. In these regions the cells were edematous without vacuolization and necrosis, the nuclei were stained faintly, and the cells contained large amounts of stainable lipoid material; the intertubular capillaries were distended with blood, but there were no hemorrhages nor any increase of the connective tissue.

Connor and Chaikoff (1938) showed that cirrhosis of the liver may be produced in dogs by continued administration of alcohol if the liver previously showed fatty infiltration. Connor (1939) in a discussion of various forms of cirrhosis of the liver stated that alcoholism may cause fatty degeneration of the liver which in some cases passes into cirrhosis, and that other factors, especially dietary deficiencies, are evidently involved. Boles and Crew (1940) studied 210 cases of cirrhosis of the liver of all types, 34.4 percent of which had a history of alcoholism, and they believed that alcohol plays an important part in the production of cirrhosis of the liver but that portal cirrhosis may be caused by other factors than alcohol.

With regard to *pathological findings in spleen and kidney*, Prievara (1941) found hyperemia of the spleen in acute alcohol poisoning. Lissauer (1903) and Saltykow (1910) (both quoted from Kochmann, 1923) observed interstitial nephritis and degenerative changes in the kidneys, and similar findings were reported by Honda (1919). Balthazard and Larue (1921) found that continued feeding of alcohol to dogs had comparatively little effect on the kidneys, and Wegelin (1933) believed that alcoholism plays no very important role in the genesis of cirrhosis of the kidney.

In respect to *pathological findings in glandular structures*, Kochmann (1923) referred to Schmiergeld (1909) as having found injury of the inner secretory glands; to Aubertin (1907) as having seen damage of the adrenals; and to Kyrle and Schopper (1913-14) who reported on severe degenerative changes in testes, as was also stated by Arlitt and Wells (1917).

With regard to *pathological changes in heart and blood vessels*, Kochmann (1923) stated that, experimentally, hypertrophy and fatty degeneration of the heart muscle have been reported repeatedly, and Regus (1937) saw degenerative changes in the heart muscle in a case of acute alcohol poisoning. Von Otto (1914) found experimentally that small doses (2 cc. per kg.) caused no pathologic changes, whereas 4 cc. per kg. caused changes in the ganglionic cells without affecting the heart muscle. With larger doses of 6 and 8 cc. per kg. the ganglionic damage and injury of the heart muscle were more

severe, the former being also very marked in chronic alcohol poisoning. In such cases he noted severe degenerative changes of the blood vessels, less severe damage of the muscle fibers, and focal necrosis. He believed that these changes were primarily due to alcohol but were aggravated by an inadequate blood supply caused by the pathological changes in the blood vessels, and he noted that the papillary muscles were especially affected. In the opinion of Kochmann (1923) alcoholism causes first fatty degeneration and subsequently atheromatosis and arteriosclerosis, especially in the large and middle-sized vessels; and Duchovnikova and Robinson (1929) found that in rabbits chronic poisoning causes swelling and desquamation of the endothelium and moderate proliferation of the intima.

With regard to *pathological changes in the lungs*, Regus (1927) and Prievara (1941) found in acute fatal poisonings, bronchopneumonia, subpleural petechia, and edema of the lungs.

The treatment of acute alcohol poisoning.—In the treatment of acute alcohol poisoning any alcohol in the stomach should be removed by gastric lavage and this may even be indicated a considerable time after the ingestion because as shown by Gréhant (1903a), alcohol may be excreted into the stomach. In case the patient is unconscious, chilling should be avoided. This is especially important in cases of acute alcoholic intoxication on account of the heat loss observed in such patients. If the respiration is slow and superficial it may be improved by the inhalation of carbon dioxide, and, as pointed out by van Wulfften Palthe (1926) and Barach (1934), the inhalation of oxygen may have a favorable effect in case the depression of the respiration is not too great; but from experiments reported by Butler (1936) it appears questionable whether in severe poisoning administration of oxygen is of definite value. In severe cases, analeptics and cardiac stimulants may become necessary but these should be used with adequate caution (Reifenstein, 1941).

With regard to the treatment of chronic alcoholism, it has been pointed out that this is frequently superimposed on an existing mental affection and for this reason, and because of its chronic character, it requires the supervision of a psychiatrist.

c. Propyl Alcohol

The higher homologue of ethyl alcohol is propyl alcohol.

Chemical characteristics.—Normal propyl alcohol, propanol 1, $CH_3CH_2CH_2OH$, has the molecular weight 60.09. It is a colorless liquid with a fuel-oil-like odor and of the specific gravity 0.804 at $\frac{20°}{4°}$ C. It solidifies at $-127°$ C., boils at $97.8°$ C., and is miscible in all proportions with water, alcohol, and ether. Its flash point is $+22°$ C.

(Lehmann and Flury, 1938) and its upper limit of inflammability is 2.55 volume percent (Jones, 1938).

Uses.—Propyl alcohol is used as a solvent for gums, resins, oils, and some cellulose ethers, and it may be encountered in the lacquer industry. In the manufacture of alcohol, it is a constituent of fusel oil.

Chemical identification.—Propyl alcohol is oxidized to propionaldehyde and propionic acid. Of its derivatives, phenyl-n-propyl urethane ($C_6H_5NHCOOCH_2CH_2CH_3$) forms needles which melt at 57° to 59° C., α-naphthyl-n-propyl urethane ($C_{10}H_7NHCOOCH_2CH_2CH_3$) forms long tablets melting at 80° C., and n-propyl iodide (C_3H_2I) is a liquid which boils at 102.2° C. There are evidently no accepted methods for the *determination* of propyl alcohol in air or biological specimen.

Absorption, fate, and excretion.—Propyl alcohol is absorbed from the gastrointestinal tract through the lungs, and also through the skin (Christiansen, 1918; and Sander, 1933).

With regard to its *fate in the organism*, Weese (1928) stated that it is apparently completely oxidized. Neymark (1938) showed that in dogs the median velocity of oxidation is 0.003 percent per minute and that propyl alcohol is more readily oxidized than its lower homologues, methyl and ethyl alcohol. Following the administration of comparative doses the concentration in the blood is lower with propyl alcohol than with ethyl alcohol and, as shown by Berggren (1938), it disappears from the blood at a constant rate. After an equilibrium is reached the *distribution* throughout the body is quite uniform.

Antiseptic properties.—Propyl alcohol has antiseptic properties. According to Buchner, Fuchs, and Megele (1901) it is more toxic than ethyl alcohol for brewer's yeast, *Staphylococcus pyogenes aureus, Bacillus typhosus*, and *Bacillus pyocyaneous aureus*. As shown by Christiansen (1918) it is 4 times as effective as ethyl alcohol and also covers a wider range of concentrations. Christiansen (1918) believed that propyl alcohol is more effective as an antiseptic than butyl and amyl alcohol on account of its greater solubility in water.

Effect on the nervous system.—Propyl alcohol depresses the *central nervous system*, causing narcosis. Grilichess (1913) determined the minimal narcotic dose with intravenous injection for rabbits as 0.05 to 0.075 cc. per kg., the corresponding values for methyl and ethyl alcohol being 2.5 and 1.0 cc., respectively. Similarly, Heffter and Juckenack (1919), Rost and Braun (1926), and Lehman and Newman (1937b) agreed that propyl alcohol has more marked narcotic properties than ethyl alcohol, and the latter found it three times as potent, the minimal narcotic dose with intravenous injection for rabbits being 1.71 gm. per kg. body weight. Lendle (1928) showed in rats that the minimal narcotic dose with intraperitoneal injection is 1.5 cc. per

kg. (given as 10 percent solution) and the minimal fatal dose 4.0 cc. per kg., having a margin of safety of 2.66. Baer (1898) found that oral administration of doses of 1.6 to 2.4 gm. per kg. causes in rabbits a moderate reduction of the sensitivity and, in 20 to 30 minutes, a slight paralysis without materially affecting the corneal, ciliary and pupillary reflexes, the respiration, or the pulse rate; doses of 2.58 to 2.96 cc. per kg. cause a moderate primary stimulation, followed in 5 to 10 minutes by incipient paralysis, and in 15 minutes by complete analgesia, reduced reflexes, and depression of respiration and temperature; and doses of 3.0 to 3.46 gm. per kg. rapidly cause paralysis, abolition of sensitivity and reflexes, constriction of the pupils, nystagmus, salivation, lowering of the body temperature, and deep narcosis lasting 36 hours. Weese (1928) studied in mice the narcotic action of the vapor of propyl alcohol and found them to be more potent than the lower homologues, and Starrek (1938) (quoted from Lehmann and Flury, 1938) determined in mice the concentrations causing various degrees of narcosis. He found that concentrations of 8 mg. per liter (3,500 p. p. m.) cause staggering, ataxia, and toleration of side position in $1\frac{1}{2}$ to 2 hours, and that concentrations of 10 mg. per liter (about 4,000 p. p. m.) cause deep narcosis within 4 hours.

The effect of propyl alcohol on the *peripheral nerve structures* was studied by Efron (1885), Breyer (1903) and Bonnet and Lelu (1933). The latter found that 0.5 percent solutions first decrease and later increase the chronaxy of nerve and muscle until the excitability is abolished. In the opinion of Heffter and Juckenack (1919) propyl alcohol is more irritant than ethyl alcohol, and Rost and Braun (1926) showed in dogs that oral administration causes irritation of the stomach, resulting in vomiting.

Effect on the circulatory system.—Like other alcohols, propyl alcohol depresses the function of the isolated heart. Kuno (1913) found that $\frac{1}{200}$ (0.3 gm. per liter) molar concentrations are just sufficient to cause depression and that $\frac{1}{10}$ (6 gm. per liter) molar solutions cause arrest of the isolated mammalian heart within a few seconds. Führner (1921) gave the minimal depressant concentration for the isolated frog heart as 0.369 mole per liter (22.6 gm. per liter).

According to Buchner, Fuchs and Megele (1901), when supplied locally propyl alcohol causes more marked *vasodilation* of the peritoneal vessels than methyl and ethyl alcohol.

Effect on muscle structures.—As shown by Bonnet and Lelu (1933), 0.5 percent solutions of propyl alcohol first decrease, then increase the chronaxy of the *striated muscle*, and with higher concentrations the depressant effect becomes more marked. The *smooth muscle* of the isolated rabbit's intestine is depressed by concentrations of 0.1 to

0.3 percent (Kuno, 1914) and, according to Macht (1920), concentrations of 1:500 cause depression of the isolated pig's ureter.

The toxicity of propyl alcohol.—The toxicity of propyl alcohol, as characterized by the minimal fatal dose for different species and with various types of administration, is summarized in table 13. According to Rost and Braun (1926) propyl alcohol is 1.5 times more toxic than ethyl alcohol, and Lehman and Newman (1937b) considered it twice as toxic as ethyl alcohol. Evidently the toxic effect of propyl alcohol is mainly characterized by depression of the central nervous system, leading with sufficiently large doses, to death by respiratory failure.

Table 13.—*The toxicity of propyl alcohol for different animal species and with various types of administration*

ORAL ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	4.4 to 5.6	Weese (1928).
Dog	3.7 to 4.1	Dujardin-Beaumetz and Audigé (1875).

SUBCUTANEOUS INJECTION

Species	Dose cc./kg.	Author
Mouse	6.2	Starrek (1938) (Lehmann and Flury, 1938).
Dog	5.0 to 5.6	Dujardin-Beaumetz and Audigé (1875).

INTRAPERITONEAL INJECTION

Species	Dose cc./kg.	Author
Rat	4	Lendle (1928).

INTRAVENOUS INJECTION

Species	Dose cc./kg.	Author
Cat	2	Macht (1920).
Rabbit	5	Lehman and Newman (1937b).

Weese (1928) stated that mice tolerate repeated narcosis well; that they recover completely within a short time; and that they show no signs of habituation. However, Elhardt (1932) found that daily administration for 12 weeks of various doses of propyl alcohol into the crop of growing chicks caused a definite impairment of growth, appearance, and disposition.

Pathological changes in propyl alcohol poisoning.—Weese (1928) noted no serious pathological changes in the vital organs of mice following repeated exposure to propyl alcohol vapors. These animals showed only a moderate fatty infiltration of liver, kidney, and heart. Starrek (1938) (quoted from Lehmann and Flury, 1938) saw hyperemia of the lungs in animals which died following the subcutaneous injection of propyl alcohol.

The toxicity of propyl alcohol for man.—There are no reports in the literature regarding the toxic effects of propyl alcohol in man, and evidently no cases of industrial injury have been reported.

d. Isopropyl Alcohol

The only isomeric alcohol of propanol is isopropyl alcohol.

Chemical characteristics.—Isopropyl alcohol, propanol-2, second-ary propyl alcohol, dimethylcarbinol, perspirit, petrohol, avantine, CH_3CH_3CHOH, has the molecular weight 60.09. It is a colorless liquid of the specific gravity 0.789 at $\frac{20°}{4°}$C. It solidifies at $-85.8°$ C., boils at 82.5° C., and is miscible with water, alcohol, and ether. Its flash point is given as $+18°$ C. by Lehmann and Flury (1938) and as 12° C. by Browning (1937), and its upper limit of inflammability is 2.65 volume percent (Jones, 1938).

Uses.—Isopropyl alcohol is manufactured by catalytic reduction of acetone or from olefinic hydrocarbons arising in cracking petroleum (Garlick, 1927). It is a solvent for certain resins such as mastic, colophony, shellac, sandarac, and most copals (Browning, 1937), and it is used in the manufacture of perfumes and cosmetics, in the manu-facture of safety glass (as dehydrating agent) and in the lacquer and varnish industry.

Chemical identification.—Isopropyl alcohol is oxidized to acetone and, further, to acetic and formic acid. The phenyl-iso-propyl-urethane forms needles which melt around 90° C., and the α-naphthyl-iso-propyl-urethane forms long tablets of the melting point 105° to 106° C. Isopropyl-iodide boils at 59.5° C. (corr.).

The determination of isopropyl alcohol.—Rae (1926) determined isopropyl alcohol by oxidation to acetone. The mixture of 10 cc. of the sample with 20 cc. of a 1 percent solution of potassium bichro-mate and 1 cc. of concentrated sulfuric acid is distilled until 3 cc. of the distillate have been collected. This distillate is floated on the surface of a mixture of 2 cc. of a 5 percent solution of sodium nitro-prusside with an equal volume of strong ammonia (sp. gr. 0.880) and approximately 0.3 gm. of ammonium chloride, and kept standing for a few minutes. In the presence of acetone a purple ring is formed at the junction of the 2 layers. Concentrations of 1 cc. of isopropyl alcohol in 100 cc. of water are said to be detectable in this way. A similar procedure was used by Wagner (1934).

Cook and Smith (1929) *determined isopropyl alcohol in urine* by oxidizing it to acetone and estimating the amount of the latter as the mercury sulfate complex of Denigès (1910). In order to differentiate between acetone derived from isopropyl alcohol and the preformed acetone in the urine, a sample of the urine is distilled into a solution of hydroxylamine hydrochloride and the amount of acetone is de-termined by titration of the liberated hydrochloric acid. The differ-ence between the 2 acetone determinations allows the calculation of the amount of isopropyl alcohol present in the urine.

Hahn (1937) *determined isopropyl alcohol in the exhaled air* by absorbing the isopropyl alcohol vapors on a silica gel and subsequently liberating it by distillation with steam. In the steam distillate the alcohol is then determined by the procedure of Knipping and Ponndorf (1926) which is based on the conversion of isopropyl alcohol to isopropyl nitrite, extraction of the latter with carbon tetrachloride, and the determination of the nitrous acid by volumetric determination. The procedure is essentially as follows: Two separatory funnels are arranged, one above the other. Into the lower funnel is placed 50 cc. of a 5 percent solution of sodium bicarbonate and into the upper one is placed a measured quantity of the steam distillate which has been diluted with water to 65 cc. and mixed with 2 gm. sodium nitrite, 40 cc. of carbon tetrachloride, and a mixture of 3 cc. of 25 percent hydrochloric acid and 7 cc. of water. The separatory funnel is then closed with a glass stopper and agitated until the nitrous fumes have disappeared. After separation the carbon tetrachloride layer is drained through the sodium bicarbonate solution in the lower funnel and shaken vigorously, and the carbon tetrachloride layer is then transferred into a 250 cc. volumetric flask containing 20 cc. of distilled water. The extraction with carbon tetrachloride is repeated and the second extract is transferred to the same flask which should contain 20 cc. of water and 90 cc. of chloroform extract. To this is added a measured volume of N/10 solution of potassium permanganate, 1/5 of its volume of a 20 percent solution of manganous sulfate, and 20 cc. of normal sulfuric acid. This mixture is shaken vigorously for 10 minutes and then 1 gm. of potassium iodide is added, the mixture is shaken again, and the liberated iodine is titrated with N/10 solution of sodium thiosulfate, using starch as indicator. One cc. of the potassium permanganate solution used corresponds to 3 mg. of isopropyl alcohol.

Absorption, fate and excretion.—Isopropyl alcohol is *absorbed* from the gastrointestinal tract and through the lungs. According to Macht (1922), massive application to the skin of rats, dogs, and rabbits causes no deleterious effects.

With regard to its *fate in the organism*, it was shown by Albertoni (1887) (quoted from Heffter, 1905) that isopropyl alcohol is partly oxidized to acetone, partly excreted unchanged, and partly excreted as acetone. Neubauer (1901) claimed that isopropyl alcohol is excreted by rabbits, and to a much lesser extent by dogs, in conjugation with glucuronic acid, but this was not confirmed for man by Kemal (1927). According to Cushny (1910) it is, like methyl and ethyl alcohol, partly excreted through the lungs, and according to Pohl (1922) the pulmonary excretion as isopropyl alcohol or as acetone amounts to 12.8 percent of the dose administered orally to rabbits. Kemal (1927) stated that in man the urinary excretion starts 1 hour after the ingestion and,

with sufficiently large doses, may last as long as 48 hours. The pulmonary excretion, however, had already started after 15 minutes. In his experience the urinary excretion, which amounts to only a small part of the total amount ingested, can be increased by diuresis. In a later study, Kemal (1937) found that with administration of 65 to 90 cc. of isopropyl alcohol to dogs, 55 to 71 mg. percent were excreted as acetone, 120 to 134 mg. percent were excreted unchanged with the urine, and 28 to 29 mg. acetone and 63 to 70 mg. isopropyl alcohol were found in the feces. Hahn (1937) found that in man, after the ingestion of 720 mg. in water, 335.94 mg. (46.7 percent) of isopropyl alcohol and 17.08 mg. of acetone were exhaled over a period of 3 hours. According to Neymark (1938) isopropyl alcohol is oxidized in the organism of dogs at the rate of 0.001 percent per minute as compared with 0.003 percent per minute found with propyl alcohol. Since it was found that with the administration of certain amounts of isopropyl alcohol the acetone concentration curve in the blood corresponds to that obtained with the continued administration of actene, it appears that isopropyl alcohol passes quantitatively into acetone. In accordance with its slow rate of oxidation the excretion of isopropyl alcohol is much slower than that of ethyl alcohol (Morris and Lightbody, 1938).

With regard to the *distribution of isopropyl alcohol in various organs*, the findings of Kemal (1937) are summarized in table 14 which shows that 4 hours after the oral administration of isopropyl alcohol the distribution among various organs is not uniform and that their acetone content also shows considerable variation.

Antiseptic properties.—Isopropyl alcohol, like propyl alcohol, has antiseptic properties which, according to Christiansen (1918), are inferior to that of the latter with regard to disinfection of the skin.

Bernhardt (1922), on the other hand, claimed that isopropyl alcohol is a perfect substitute for ethyl alcohol for this purpose, and Grant (1923a) stated that it has more powerful bactericidal and antiseptic properties than ethyl alcohol, the most effective concentration being 30 to 50 percent.

Table 14.—*Organ distribution of isopropyl alcohol in dogs, 4 hours after the oral administration of 90 cc.*

[Kemal, 1937]

Organ	Dog No. 1					Dog No. 2					Dog No. 3				
	Organ weight	Acetone		Isopropyl alcohol		Organ weight	Acetone		Isopropyl alcohol		Organ weight	Acetone		Isopropyl alcohol	
		Mg.	Mg./100 gm.	Mg.	Mg./100 gm.		Mg.	Mg./100 gm.	Mg.	Mg./100 gm.		Mg.	Mg./100 gm.	Mg.	Mg./100 gm.
Blood	620	245	39.5	280	45	680	270	40	300	44	690	190	27.5	211	30.6
Liver	744	22	3	52	7	756	20	2.7	48	6.4	800	26	3.2	60	7.5
Brain	75	38	50.7	80	107	79	31	39	69	88	76	31	40.8	66	86.8
Muscle	100	11.2	11.2	25	25	100	13	13	28	28	100	20	20	38	38
Heart	172	81	47.7	165	97	185	40	22	90	50	160	60	37.5	123	77
Spleen	60	1.8	3	62	103.3	65	22	34	8	12.3	62	13	21	3	4.8
Kidney	115	31	28	65	54	122	29	24	62	52	120	20	16.6	42	35
Abdominal fat	100	3	3	13	13	100	4	4	18	18	100	6	6	25	25
Bladder urine	70	38	54.3	85	121.4	110	40	36	92	83.6	130	50	38.4	112	86

Effect on the nervous system.—With regard to the *effect of isopropyl alcohol on the central nervous system*, Boruttau (1921) showed that in rabbits the oral administration of 1 to 1.5 gm. per kg. causes sleep of several hours duration. Macht (1922) found that with intravenous administration its narcotic action for cats is twice as marked as that of ethyl alcohol and that oral doses of 5 to 5.5 cc. per kg. cause anesthesia lasting from 12 to 24 hours. Rost and Braun (1926) found its narcotic action more marked than that of ethyl alcohol but less marked than that of normal propyl alcohol, and they saw no evidence of a cumulative action; and similar findings were reported by Bijlsma (1928). Starrek (1938) (quoted from Lehmann and Flury, 1938) studied the narcotic action of isopropyl alcohol in mice. He found that concentrations of 8 mg. per liter cause ataxia after 3 hours, toleration of side position after 6 hours, and deep narcosis with loss of reflexes after 7 to 8 hours. Such concentrations, and even exposure for 100 minutes to concentrations of 60 mg. per liter, were found to have no after effects. According to Morris and Lightbody (1938), narcosis produced by isopropyl alcohol is of longer duration than that observed with corresponding doses of ethyl-alcohol.

With regard to the *effect of isopropyl alcohol on the peripheral nerves*, Bonnet and Lelu (1933) found that 1 percent solutions do not affect the excitability of the nerve, 1 to 2 percent increased the chronaxy of nerve and muscle, and concentrations of 3 percent paralyzed the muscle and, later, also the nerve.

With respect to the *irritant action of isopropyl alcohol*, Christiansen (1918) stated that its contact with the skin may cause irritation, but Grant (1939b) claimed that it had no irritant effect on the skin except a slight maceration of the outermost layer of the epidermis and Bijlsma (1928) found that 20 percent solutions caused no irritation of the rabbit's eye, 40 percent caused a slight hyperemia, swelling of the conjunctiva and moderate turbidity of the cornea, these effects being more marked with solutions of 60, 79, and 95 percent.

Effects on the circulatory apparatus.—According to Fühner (1921), isopropyl alcohol depresses the isolated frog heart in concentrations of at least 0.655 mole per liter (39 gm. per liter), and according to Wolff (1922) it causes diastolic tendency and arrest in middle position, the recovery from the depression being less smooth than with ethyl alcohol, in that complete recovery may be preceded by irregularities of the beat and contraction of the heart. Burton-Opitz (1922) showed that in cats the intraperitoneal injection of 3cc. in 10, 25, and 50 percent solutions had no distinct effect on the heart action, but that the injection of pure isopropyl alcohol or 75 percent solutions caused a definite vascular depression of short duration which was slightly more marked than that observed with ethyl alcohol. He noted a fall of the arterial and a rise of the venous pressure, indi-

cating a reduction of the functional energy of the heart (decreased cardiac output) which was paralleled by slowing of the heart rate. Macht (1922) stated that sublethal doses do not affect the blood pressure of cats, and Bijlsma (1928) found that, as compared with ethyl alcohol, it had little effect on the heart action and the blood pressure. Grant (1923b) refers to experiments of W. G. Thompson on human subjects in which the ingestion of 25 cc. of isopropyl alcohol diluted with 125 cc. of water was followed, after ½ hour, by a reduction of the blood pressure of 6 to 20 mm. Hg and, in 4 out of 6 subjects, by an increase of the pulse rate. Fuller and Hunter (1927) reported that in man, intoxication with isopropyl alcohol causes lowering of the blood pressure and the pulse rate.

Toxicity of isopropyl alcohol.—According to Rost and Braun (1926), Bijlsma (1928) and others, isopropyl alcohol is more toxic than ethyl alcohol. The minimal fatal dose for different species and with different forms of administration is summarized in table 15. In contrast to ethyl alcohol, isopropyl alcohol does not cause a primary stimulation but only a depression (Boruttau, 1921). With sufficiently large doses it causes ataxia and narcosis, and, if fatal, paralysis and dyspnea may precede death (Starrek, 1938) (quoted from Lehmann and Flury, 1938). Rost and Braun (1926) and Bijlsma (1928) noted, with repeated administration of isopropyl alcohol, no evidence of a cumulative action; and, similarly, Weese (1928) stated that mice tolerate repeated narcosis without signs of cumulative effects or habituation. Morris and Lightbody (1938), on the other hand, believed that, on account of its slow elimination, isopropyl alcohol may have cumulative effects which may be due to the alcohol itself or to its oxidation product, acetone.

Table 15.—*Toxicity of isopropyl alcohol with various routes of administration for different species of animals*

ORAL ADMINISTRATION

Species	Minimal fatal dose cc./kg.	Author
Rabbit	6.3	Boruttau (1921).
Mouse	6.0 to 7.6	Weese (1928).

SUBCUTANEOUS INJECTION

Species	Minimal fatal dose cc./kg.	Author
Mouse	7.6	Starrek (1938) (Lehmann and Flury, 1938).

INTRAVENOUS INJECTION

Species	Minimal fatal dose cc./kg.	Author
Cat	2.5	Macht (1922).

INHALATION

NOTE.—No fatal concentrations have been reported.

With regard to the *toxic effects of isopropyl alcohol on the human organism*, Grant (1923b) and Morris and Lightbody (1938) referred to experiments of W. G. Thompson who stated that the ingestion of 25 cc. in 125 cc. of water caused in man no exhilaration but dizziness, muscular and nervous disturbances and, after 2 to 3 hours, headache of long duration. Fuller and Hunter (1927) noted, aside from the effects on blood pressure and pulse rate mentioned above, no visual disturbances such as have been reported following ingestion of methanol. There are no reports in the literature with regard to toxic effects from the industrial use of isopropyl alcohol. Donley (1936) reported a case of toxic encephalitis, rhinitis, bronchitis associated with slight anemia, and a moderate lymphocytosis in a patient who had inhaled the vapors of a solvent consisting of 74 percent isopropyl alcohol, 20 percent water, and less than 3 percent each of dimethyl phthalate and methyl cellosolve.

Pathological changes.—Data with regard to pathological changes resulting from the administration of isopropyl alcohol are very scanty. Weese (1928) noted no serious pathological changes except a very moderate reversible fatty infiltration of the liver, kidneys, and heart muscle.

e. n-Butyl Alcohol

The next higher homologue is butyl alcohol which exists in 4 isomeric forms.

Physico-chemical characteristics.—Butyl alcohol, butanol-1, $CH_3-CH_2CH_2CH_2OH$, has a molecular weight of 74.12 and represents a colorless liquid of somewhat pungent odor. It has the specific gravity 0.810 at $\frac{20°}{4°}$C. It solidifies at $-79.9°$ C., boils at $117°$ C., is soluble in 100 parts of water to the extent of 9 parts at $15°$ C., and mixes freely with alcohol and ether. The upper limit of its inflammability is 1.70 percent (Jones, 1938) and its flash point is $+34°$ C. (Lehmann and Flury, 1938).

Butyl alcohol is manufactured by fermentation of maize flour by a special strain of bacillus. It may be synthesized from acetaldehyde, and it is one of the constituents of fusel oil (Browning, 1937).

Uses.—Being a good solvent for many gums and resins and increasing the solvent power of other solvents for cellulose esters or ethers it is extensively used in the lacquer and dye industries and in other industries (shoe industry, manufacture of safety glass, hat and textile industries, etc.) where such solutions are handled (Browning, 1937).

Chemical identification.—Normal butyl alcohol is oxidized to n-butyr-aldehyde and n-butyric acid. The phenyl-n-butyl urethane ($C_6H_5-NHCOO-CH_2-(CH_2)_2-CH_3$) forms needles which melt at

61° C. and the α-naphthyl-n-butyl-urethane ($C_{10}H_7NHCOO-CH_2-(CH_2)_2-CH_3$) forms tablets which soften at 69° C. and melt at 71° to 72° C. N-Butyl iodide (C_4H_9I) boils at 130.4° to 131.4° C. at 754.4 mm. Hg.

Absorption, fate, and excretion.—Normal butyl alcohol is *absorbed* through the lungs, the gastrointestinal tract, and, according to Sander (1933), also through the skin.

Weese (1928) believed that it is completely oxidized in mice, and according to Berggren (1938) the oxidation takes place more rapidly than with ethyl alcohol. It is probably not assimilated as sugar (Höckendorf, 1909–10).

It is evidently not excreted with the urine, at least there are no reports of its excretion in this way.

Effect on the nervous system.—Baer (1898) found that in rabbits the oral administration of 1 to 1.5 gm. per kg. causes a moderate reduction of the sensitivity and within 20 to 30 minutes a slight paralysis without materially affecting the corneal, pupillary, and ciliary reflexes, the pulse rate, and the respiration.   Doses of 1.6 to 2.0 gm. per kg. were found to cause a short primary excitement and then, in 5 to 10 minutes, slight, and after 15 minutes, complete paralysis, analgesia, and impairment of the corneal, pupillary, and ciliary reflexes, and reduction of the respiration and body temperature, followed by recovery after a period of 10 hours. With doses of 2.1 to 2.44 gm. per kg. the paralysis was rapid and complete; the corneal, pupillary, and ciliary reflexes were rapidly reduced; the pupils were constricted; and the animals showed nystagmus, salivation, marked reduction of body temperature and respiration, and deep narcosis which lasted 36 hours. Lendle (1928) determined in rats the minimal narcotic dose with intraperitoneal injection as 0.76 cc. per kg. (given as 1.5 percent solution) and the minimal fatal dose as 1.2 cc. per kg., so that the margin of safety is 1.6; and he found that animals recovered from the narcosis within 54 to 106 minutes. Weese (1928) found that mice tolerate repeated narcosis resulting from the inhalation of vapors of butyl alcohol very well; that they recover completely within a few hours; and that they show neither signs of habituation nor serious organ injury. Starrek (1938) (quoted from Lehmann and Flury, 1938) studied the narcotic action of butyl alcohol vapors in mice. He found that with concentrations of 20 mg. per liter (about 6,600 p. p. m.) mice started to stagger after 1 hour, tolerated side position after 1½ to 2 hours, and became deeply narcotized at the end of 3 hours. Three out of 10 animals anesthetized to deep narcosis died during the following days.

With regard to the effect of normal butyl alcohol on the peripheral nerves, Bonnet and Lelu (1933) found that concentrations of 0.25, 0.35, and 0.50 percent lowered the chronaxy of the nerve, whereas 1 percent solutions rapidly rendered it inexcitable. Cole and Allison

(1930b) found that 0.066 molar concentrations cause irritation of the skin of frogs.

Effect on the circulatory system.—Kuno (1913) found that 1/400 to 1/500 molar solutions (0.19 to 0.15 gm. per liter) of normal butyl alcohol are just sufficient to cause depression of the isolated mammalian heart, whereas 1/15 molar solutions (4.94 gm. per liter) cause cardiac arrest within a few seconds. Similarly, Fühner (1921) determined the minimal effective concentration for the isolated frog heart as 0.109 mole or 8.1 gm. per liter, whereas the corresponding values for normal propyl alcohol were 1/200 and 0.369 molar concentration (0.3 gm. and 22.2 gm. per liter), respectively. Normal butyl alcohol is, therefore, more toxic to the isolated frog heart than the lower isomer.

With regard to the *effect of normal butyl alcohol on the blood vessels*, Buchner, Fuchs, and Megele (1901) found that its application to the peritoneal cavity caused a more marked vasodilatation than that observed with normal propyl alcohol.

With respect to the *effect of normal butyl alcohol on the blood*, Smyth and Smyth (1928) found that 65 exposures to 100 p. p. m. in air caused a reduction of the red blood cells and a relative and absolute lymphocytosis.

Effect on muscle structure.—According to Bonnet and Lelu (1933) the *striated muscle* is affected similarly but to a lesser degree than is the nerve by solutions of normal butyl alcohol. The activity of the isolated intestine of the rabbit is depressed by concentrations of 0.025, 0.03, and 0.05 percent, and concentrations of 0.5 percent cause immediate paralysis and complete loss of tone (Kuno, 1914).

Toxicity of normal butyl alcohol.—The toxicity of normal butyl alcohol, as characterized by its minimal fatal dose for different animal species and with various forms of administration, is illustrated in table 16. Comparison of these data with those presented for other alcohols shows that butyl alcohol is more toxic than the lower homologues, but, in view of its lower volatility, it is less dangerous when inhaled as a vapor (Weese, 1928).

In contrast to the experience with normal propyl alcohol, Elhardt (1932) found that the daily administration of normal butyl alcohol into the crop of growing chicks for a period of 16 weeks had no effect on the growth and appearance of the chicks.

No definite information is available regarding *injurious effects of normal butyl alcohol on the human organism.*—Burger and Stockmann (1932) reported on injury of the liver resulting from exposure to the vapors of a solvent which contained, in addition to butyl alcohol, amyl alcohol, butyl acetate, amyl acetate, and acetone, but it was questionable to what extent butyl alcohol was responsible for the toxic effects observed. Krüger (1932) reported on severe irritation

of the eyes—characterized by burning, lachrymation, sensitivity to light, and fine punctated turbidity of the superficial layer of the cornea—in workers exposed to vapors of a solvent consisting largely of butyl alcohol and butyl acetate with some other solvents.

Table 16.—*The minimal fatal dose of n-butyl alcohol for different species of animals and with various routes of administration*

ORAL ADMINISTRATION

Species	Dose cc./kg.	Author
Dog	2. 2	Dujardin-Beaumetz and Audigé (1875).

SUBCUTANEOUS INJECTION

Species	Dose cc./kg.	Author
Mouse	6. 2	Starrek (1938) (Lehmann and Flury, 1938).
Dog	2. 4 to 2. 8	Dujardin-Beaumetz and Audigé (1875).

INTRAPERITONEAL INJECTION

Species	Dose cc./kg.	Author
Rat	1. 2	Lendle (1928).

INTRAVENOUS INJECTION

Species	Dose cc./kg.	Author
Cat	0. 3	Macht (1920).

Pathological changes.—Little information is available with regard to organic changes resulting from exposure to butyl alcohol. Weese (1928) noted slight reversible fatty infiltration of liver and kidneys following repeated exposure to narcotic concentrations, and similar findings in liver and kidneys were reported by Smyth and Smyth (1928) who, in addition, found in 2 animals hemorrhagic areas in the lungs following repeated exposure to 100 p. p. m.

f. Iso-butyl Alcohol

Physico-chemical characteristics.—Iso-butyl alcohol, 2-methyl-propanol-1, $(CH_3)_2$–CH CH$_2$OH, has a molecular weight of 74.12 and is a colorless liquid with a slightly suffocating odor. Its specific gravity is 0.805 at 17.5° C. and it solidifies at −108° C. and boils at 107° to 108° C. It is soluble in 100 parts of water to the extent of 10 parts at 15° C. and mixes freely with alcohol and ether. Its flash point is +22° C. (Lehmann and Flury, 1938) and its upper limit of inflammability is 1.68 percent (Jones, 1938).

Uses.—The solvent power of iso-butyl alcohol is less marked than that of butyl alcohol and it is of no great industrial importance (Lehmann and Flury, 1938) although it is used to some extent in the lacquer industry (Weber and Koch, 1933).

Chemical identification.—Oxidation with chromic acid yields iso-butyric acid, acetic acid, acetone, and other products. The phenyl-iso-butyl-urethane $(C_6H_5$–NHCOO–CH$_2$–CH–$(CH_3)_2$ forms needles

which melt at 80° C., and the corresponding α-naphthyl derivative $(C_{10}H_7-NHCOO-CH_2-(CH_3)_2$ forms needles of the melting point 103° to 105° C. The iodide (C_4H_9I) boils at 120° C. (corr.)

Absorption, fate, and excretion.—Iso-butyl alcohol is absorbed through the gastrointestinal tract and through the lungs. There is no information as to what extent it may be absorbed through the skin.

According to Neubauer (1901), in rabbits and, to a lesser extent, in dogs, it is partly excreted in conjugation with glucuronic acid, but in the opinion of Weese (1928) it is completely oxidized in mice.

Effect on the nervous system.—According to Rost and Braun (1926) it is more potent as a narcotic with oral administration to rabbits, the minimal narcotic dose being 2.5 cc. per kg. as compared with 5.0 cc. per kg. of normal butyl alcohol. With intravenous injection the minimal narcotic dose for rabbits is 0.9 cc. per kg. (Lehman and Newman, 1937b), this being about 6 times as potent as ethyl alcohol. But with inhalation of the vapors the narcotic action is less marked than that of propyl alcohol and of the same order as that of normal butyl alcohol (Weese, 1928) which indicates that with industrial exposure it is potentially less dangerous than the lower homologues.

According to Bonnet and Lelu (1933) concentrations of 0.35 to 1.0 percent decrease the chronaxy of the isolated nerve and muscle, but later the excitability of the muscle diminishes earlier than that of the nerve.

Effect on the circulatory system.—Little information is available with regard to the effect of iso-butyl alcohol on the ciculatory system. According to Fühner (1921) the minimal depressant concentration for the isolated frog heart is 1.35 mole per liter (100 gm. per liter).

Toxicity.—According to Macht (1920) the minimal fatal dose for cats with intravenous injection is 0.9 cc. per kg., and with slow intravenous administration it is 2.64 gm. per kg. for rabbits (Lehman and Newman, 1937b). There are no reports on the toxic action of iso-butyl alcohol in man.

Pathological changes.—Weese (1928) noted only a slight reversible fatty infiltration of liver and kidneys in mice which had undergone repeated narcosis without any after effects.

g. Secondary Butyl Alcohol

Physico-chemical characteristics.—Secondary butyl alcohol, butanol-2, $CH_3-CH_2-CHOHCH_3$, has a molecular weight of 74.12. Its specific gravity is 0.808 at $\frac{20°}{4°}$ C. and it boils at 99.5° C. It is soluble in 100 parts of water to the extent of 12.5 parts at 20° C. and mixes freely with alcohol and ether. Its flash point is 22° C. (Lehmann and

Flury, 1938). Having 1 asymmetrical hydrocarbon it exists in the form of 2 optical isomers, levo and dextro secondary butyl alcohol.

Uses.—Secondary butyl alcohol is used to a moderate extent in the lacquer industry.

Absorption, fate, and excretion.—Secondary butyl alcohol is absorbed from the gastrointestinal tract and through the lungs. No information is available with regard to its absorption through the skin, its fate in the metabolism and its excretion, with the exception of a statement by Pohl (quoted from Lehmann and Flury, 1938) that 77 percent is excreted through the lungs after intravenous administration.

Systemic effects.—Weese (1928) found in mice that the narcotic action of vapors of secondary butyl alcohol is greater than that of normal or isobutyl alcohol and that it ranks between those of ethyl and propyl alcohol. In his opinion the more marked narcotic action is linked to the higher vapor tension of the secondary butyl alcohol which enhances a more rapid penetration into the blood and the central nervous system. Starrek (1938) (quoted from Lehmann and Flury, 1938) studied its narcotic action in mice. He found that concentrations of 10 mg. per liter as compared to 20 mg. per liter of the normal butyl alcohol caused staggering after 1 to 1½ hours, toleration of side position after 2 to 3 hours, and deep narcosis in 5 hours which was followed by rapid recovery without after effects. Butler and Dickison (1940) determined the narcotic dose for mice with intraperitoneal injection as 1 mg. per gram mouse. Hufferd (1932) found it to be less toxic than normal butyl alcohol for guinea pigs with intraperitoneal injections, the corresponding doses being 0.00093 and 0.00083 mole per 100 gm., respectively. Viditz (1933) noted no measurable difference between the levo and dextro isomers with regard to their narcotic action for tadpoles and fish and their effect on the nerve muscle preparation and the isolated frog heart; and Butler and Dickison (1940) found that the intraperitoneal injection of the 2 optical isomers had the same narcotic action in mice.

There are evidently no reports regarding the toxicity of secondary butyl alcohol for humans.

h. Tertiary Butyl Alcohol

Physico-chemical properties.—Tertiary butyl alcohol, 2-methyl-propanol-2, $(CH_3)_3COH$, has the molecular weight 74.12 and is a colorless liquid or forms rhombic crystals which melt at 25° to 25.5° C. and boil at 82.9° C. It has the specific gravity 0.786 at $\frac{20°}{4°}$ C. and mixes freely with water, alcohol, and ether.

Uses.—The solvent properties of tertiary butyl alcohol are similar

to those of isopropyl alcohol, and it is used on a small scale in the perfume industry (Lehmann and Flury, 1938).

Chemical identification.—Oxidation with chromic acid yields, aside from isobutyric acid, acetone, acetic acid, and other products. The α-naphthyl-tertiary-butyl-urethane, $C_{10}H_7NHCOO-C(CH_3)_3$, forms long tablets which melt at 100° to 101° C., and the tertiary butyl iodide boils at 39° C.

Systemic effects.—Thierfelder and von Mering (1885) found that the administration of 6 cc. to rabbits caused somnolence, whereas the administration of 10 cc. to a medium sized dog had no distinct effects, and they believed that in rabbits but not in dogs and man it is excreted in conjugation with glucuronic acid. Fühner (1921) determined the minimal depressant concentration for the isolated frog heart as 0.637 mole per liter (47.1 gm. per liter), and Weese (1928) found that mice tolerate repeated narcosis well. He found that it is less toxic than isobutyl alcohol but more potent with regard to its narcotic action. Wesse (1928) noted no marked pathological changes except moderate and reversible fatty infiltration of liver, kidneys, and heart. Oettel (1936) reported that when applied to skin tertiary butyl alcohol causes moderate irritation characterized by slight pain, moderate hyperemia, and erythema. Evidently no cases of toxic effects in man have been reported.

i. Amyl Alcohol

Physico-chemical characteristics.—Amyl alcohol, $C_5H_{11}OH$, exists in the form of 8 isomers. Its physico-chemical properties and formulas are summarized in table 17. According to Browning (1937) the amyl alcohol used commercially is obtained from fusel oil and represents a mixture of primary isoamyl alcohol, 2-methyl-butanol-4 (No. 3) an active amyl alcohol, $C_2H_5-CH-CH_3-CH_2OH$ (No. 8). The fusel oil from potatoes and cereals consists essentially of primary isoamyl alcohol (No. 3) and contains only 13 to 22 percent of active amyl alcohol. There are several grades of commercial amyl alcohol which are characterized by their boiling point and specific gravity. Amyl alcohol has a pungent and penetrating odor.

According to Browning (1937) amyl alcohol may also be manufactured from petroleum distillates and is marketed under the name of Pentasol. It represents a mixture of 5 of the 8 insomeric alcohols.

Whereas commercial amyl alcohol is a good solvent for many gums and resins and, to a lesser degree, for ethyl cellulose, copal ester, mastic and coumarone, Pentasol is said to be no solvent for cellulose esters or coumarone (Browning, 1937).

Uses.—Amyl alcohol is used as a solvent in the lacquer industry and in the chemical and explosives industries, and it may be encountered in many industries such as textiles, shoe, and hat industries where such lacquers are used.

Table 17.—*Physico-chemical properties of amyl alcohol*

Name	Formula	Molecular weight	Specific gravity	Melting point °C.	Boiling point °C.	Solubility in 100 parts of—			Flash point °C.	Upper limit of inflammability vol.%	Form and color
						Water	Alcohol	Ether			
Normal amyl alcohol, pentanol-1.	CH₃—(CH₂)₃CH₂OH	88.15	0.817 $\frac{20°}{20°}$ C.	---	137.8 to 137.9	2.7 (22° C.)	Miscible	Miscible	---	11.19	Colorless liquid.
Secondary amyl alcohol, pentanol-2.	C₂H₅—CHOH—CH₃	88.15	.810 $\frac{20°}{20°}$ C.	---	118.5 to 119.5	16.6	do	do	---	---	Do.
Primary isoamyl alcohol, 2-methyl-butanol-4.	(CH₃)₂—CH—CH₂—CH₂OH	88.15	.813 $\frac{15°}{4°}$ C.	−117.2	132.0	2 (14° C.)	do	do	[2]46° C.	11.20	Do.
Secondary isoamyl alcohol, 2-methyl-butanol-3.	(CH₃)₂—CH—CHOH—CH₃	88.15	.819 $\frac{19°}{00°}$ C.	---	113 to 114	Slightly soluble	do	do	---	---	Do.
Amyl alcohol, pentanol-3.	(C₂H₅)₂CHOH	88.15	.815 $\frac{25°}{4°}$ C.	---	115.6	do	Soluble	Soluble	---	---	Do.
Tertiary amyl alcohol, 2-methyl-butanol-2 (amylene hydrate).	(CH₃)₂—COH—C₂H₅	88.15	.809 $\frac{20°}{4°}$ C.	−11.9	102	do	do	do	---	---	Do.
Tertiary amyl alcohol, 2,2-dimethyl-propanol-1.	(CH₃)₃—C—CH₂OH	88.15	---	52 to 53	113 to 114	do	Miscible	Miscible	---	---	Crystalline.
Active amyl alcohol [3]	C₂H₅—CH—CH₃—CH₂OH	88.15	.816 $\frac{20°}{4°}$ C.	---	128	do	do	do	---	---	Colorless liquid.

[1] Jones (1938).
[2] Lehmann and Flury (1938).
[3] The natural active amyl alcohol is levorotatory (α)D=5.9°.

Chemical identification.—The primary isobutyl carbinol (No. 3) may be oxidized with potassium permanganate (1:1000) with the formation of iso-valerianic acid aldehyde and iso-valerianic acid iso-amyl esters which may be identified by their odor. If heated with sulfuric and acetic acid it yields iso-amylacetate. According to Holländer (1910) this can be identified by adding 1 drop of phenyl-hydrazine and boiling. After cooling, the mixture is underlaid with concentrated hydrochloric acid. In the presence of amyl acetate a green color is formed at the zone of contact of the 2 layers. The phenyl-iso-amyl-urethane ($C_6H_5HNCOOC_5H_{11}$) melts at 57° to 58° C. and the corresponding α-naphthyl compound ($C_{10}H_7HNCOOC_5H_{11}$) forms leaflets which melt at 67° to 68° C. The iso-amyl-iodide boils at 152° C. (Rosenthaler, 1923).

Upon oxidation, the active d-amyl alcohol (No. 8) yields d-methyl-ethyl-acetic acid. The phenyl urethane derivative melts at 30° C. whereas the α-naphthyl-urethane compound forms fine needles which melt at 82° C. (Rosenthaler, 1923).

The *tertiary amyl alcohol*, amylene hydrate (No. 6) yields a ruby red color with ½ cc. of a 1 percent solution of vanilline and 10 cc. of sulfuric acid, and upon oxidation it yields acetone, acetic acid, and carbon dioxide. The α-naphthyl-urethane derivative forms coarse needles which melt at 70° to 72° C.

For the *detection of tertiary amyl alcohol in the presence of secondary amyl alcohol*, Michael and Zeidler (1911) (quoted from Rosenthaler, 1923) heated the mixture with 3N hydrobromic acid in a sealed tube in a boiling water bath for 5 minutes, resulting in the formation of trimethyl ethylene from tertiary amyl alcohol. If after the separation of this hydrocarbon sufficient hydrobromic acid is added to the remaining alcohol to bring its concentration up to 4.5N and it is heated again in the same way for 1½ hours, the secondary amyl alcohol is also changed to trimethyl ethylene.

For the *detection of secondary isoamyl alcohol in the presence of the primary isoamyl alcohol*, the same authors dissolved the alcohol mixture in 30 parts of 4.5N hydrobromic acid and heated it as above for 1 hour. The presence of the secondary isoamyl alcohol is indicated by the formation of trimethyl ethylene.

Determination.—Basset (1910) determined amyl alcohol (fusel oil) in liquids by the pink or red color produced with furfural and sulfuric acid. Korenman (1932) utilized the same reaction for the determination of amyl alcohol in air. In this procedure the air is collected in a dry flask of known volume. Twenty cc. of ethyl alcohol and the same amount of water are added and shaken for 2 or 3 hours. To 1 cc. of this solution 0.1 cc. of a 1 percent alcoholic solution of furfural and, while cooling, 1.5 cc. concentrated sulfuric acid are added, heated for 3 minutes in boiling water, and, after cooling, the pink to

red color is matched against standards of known strength prepared in the same way.

Absorption, fate, and excretion.—Amyl alcohol is absorbed through the gastro-intestinal tract, the lungs, and the skin (Schwenkenbecher, 1904, and Sander, 1933).

Neubauer (1901) claimed that a small fraction of the amount of amyl alcohol administered is excreted in conjugation with glucuronic acid, and he refers to Binz, Bodländer, and Strassmann as having found that only 5 to 10 percent of the total dose administered is excreted through the lungs and kidneys, the rest being completely oxidized in the body. According to Höckendorf (1909–10) amyl alcohol increases the sugar and decreases the nitrogen excretion in phloridzin diabetic dogs. This may indicate that amyl alcohol may be utilized as sugar. Pohl (1908) claimed that only traces of isoamyl alcohol are excreted through the lungs.

Effect on the nervous system.—Strauss (1887) found that in rabbits doses of 5 to 6 gm. given orally cause, within a few minutes, deep coma and loss of corneal reflexes lasting for 5 to 6 hours. Lendle (1928) determined in rats, with intraperitoneal injection, the minimal narcotic dose as 0.36 cc. per kg. (given in 10 percent solution), recovery following after 35 to 50 minutes, and the minimal fatal dose as 0.6 cc. per kg., so that the margin of safety is 1.7. As pointed out by Lendle (1928), both doses are probably 25 percent smaller since the amyl alcohol was in 33 percent ethyl alcoholic solution. Hufferd (1932) gave the narcotic dose with oral administration for guinea pigs as 0.00067 mole per 100 gm. (0.72 cc. per kg.) body weight.

Isoamyl alcohol causes narcosis in rats with intraperitoneal injection of 0.5 cc. per kg., according to Lendle (1928), and since the minimal fatal dose was determined as 1.0 cc. per kg. the margin of safety is 2.0. According to Lehman and Newman (1937b) the minimal narcotic dose for rabbits with intravenous injection is 0.85 gm. per kg., isoamyl alcohol being, therefore, 6.5 times as potent as ethylalcohol. Hufferd (1932) determined the narcotic dose for guinea pigs with oral administration as 0.00063 mole per 100 gm. body weight (0.69 gm. per kg.).

The *secondary amyl alcohol* causes narcosis in rats with intraperitoneal injection of 0.65 cc. per kg., the minimal fatal dose being 1.0 cc. per kg. and the margin of safety 1.5 (Lendle, 1928). With oral administration to guinea pigs, narcosis is produced by doses of 0.00052 mole per 100 gm. body weight (0.56 gm. kg.) (Hufferd, 1932).

With regard to the irritant action of amyl alcohol, Cole and Allison (1930b) found that concentrations of 0.022 mole per liter cause irritation of the skin of frogs, and, according to Müller-Lobeck (1935), concentrations of 2.7 mg. per liter cause neither turbidity of the cornea

nor irritation of the conjunctiva of rabbits as observed with comparable concentrations of amyl acetate.

Effect on the circulatory system.—Salant (1909) found that the intravenous injection of amyl alcohol in 2 percent solution causes a more severe and more lasting fall of the blood pressure than observed with corresponding doses of ethyl alcohol. Heide and Schilf (1929) found that in dogs anesthetized with morphine, chloroform, or ether, even small doses of isoamyl alcohol (less than 0.5 cc. of a 2 percent solution) cause a considerable fall of the blood pressure and moderate vasodilatation. Kuno (1913) determined the minimal depressant concentration for the isolated mammalian heart as 1/1500 to 1/2000 mole (0.059 to 0.044 gm.) per liter and the paralyzant concentration as 1/50 mole (1.76 gm.) per liter. Fühner (1921) determined the minimal depressant concentration for isoamyl alcohol as 0.039 mole (3.4 gm.) per liter.

Buchner, Fuchs, and Megele (1901) found that the vasodilatation produced by direct application to the peritoneum is more marked than that observed with propyl and butyl alcohol.

Effect on other organs.—Kuno (1914) found that concentrations of 0.0125, 0.015, and 0.02 percent cause a moderate depression of the pendular movements of the isolated intestine and that 0.2 to 0.25 percent solutions rapidly cause complete paralysis. Macht (1920) stated that amyl alcohol causes depression of the isolated ureter of the pig.

The toxicity of amyl alcohol.—According to Salant (1909) the minimal fatal dose for frogs is 1/8 to 1/7 that of ethyl alcohol, and for rabbits it is from 2 to 4 times as toxic as the latter. Baer (1898) found that in rabbits the oral administration of 0.83 to 1.08 gm. per kg. causes a moderate reduction of the sensitivity; within 20 to 30 minutes it causes slight paralysis without distinct impairment of the corneal, pupillary, and ciliary reflexes and of the pulse rate and respiration. Doses of 1.25 to 1.66 gm. per kg. were found to cause, after 5 to 10 minutes, slight and, after 15 minutes, deep narcosis with impairment of the corneal, ciliary, and pupillary reflexes, reduction of the body temperature, and reduction of the respiration. With administration of 1.7 to 1.95 gm. per kg. the paralysis was rapid and complete, the pupillary, ciliary, and corneal reflexes became rapidly weaker, the pupils were constricted, and body temperature and narcosis were materially lowered. Starrek (1938))(quoted from Lehmann and Flury, 1938) found that in mice the subcutaneous injection of 5 mg. per gram of normal amyl alcohol caused staggering, toleration of side position, dyspnea, motoric irritation, and finally deep narcosis. Isoamyl alcohol in doses of 6 mg. per gram body weight causes staggering, toleration of side position in 20 minutes, and narcosis in

30 minutes. Table 18 gives a summary of the minimal fatal doses as determined by various investigators in different species.

With regard to *pathological changes* resulting from the absorption of amyl alcohol, Strauss (1887) found that the repeated oral administration of amyl alcohol to rabbits caused organ damage, especially of the liver.

Table 18.—*Toxicity of amyl alcohol for different animal species with different routes of administration*

ORAL ADMINISTRATION

Type of amyl alcohol	Species	Minimal fatal dose cc./kg.	Author
	Dog_____	1. 7 to 1. 9	Dujardin-Beaumetz and Audigé (1875).
	Rabbit_____	2..0 to 2, 4	Sollmann and Hanzlik (1928).

SUBCUTANEOUS INJECTION

Normal_____	Dog_____	2. 2 to 2. 8	Dujardin-Beaumetz and Audigá (1875).
Iso_____	Mouse_____	13	Starrek (1938) (Lehmann and Flury, 1938).
	Mouse_____	9. 2	Starrek (1938) (Lehmann and Flury, 1938).

INTRAPERITONEAL INJECTION

Normal_____	Rat_____	0. 6	Lendle (1928).
Iso_____	Rat_____	1. 0	Lendle (1928).

INTRAVENOUS INJECTION

Normal_____	Cat_____	0. 15	Macht (1920).
Iso_____	Cat_____	0. 26	Macht (1920).
Iso_____	Rabbit_____	1. 9	Lehman and Newman (1937b).

With regard to *toxic effects from industrial exposure* there is very little definite information. According to Lewin (1927) ingestion of 0.5 gm. of fusel oil causes somnolence, headache, and irritation of the throat of several hours duration. He refers to a publication of Hilbert (1899) in which the exposure to the vapors of fermenting mash which contained, among other constituents, amyl alcohol caused excitement, insomnia, and colored vision. Eyquem (1905) observed in workers in an explosives plant who were exposed to the vapors of amyl alcohol and ether, irritation of the mucous membranes of the eyes and of the respiratory tract, digestive disturbances, loss of appetite, anemia, muscular weakness, and nervous disturbances. Several cases of fatal amyl alcohol poisoning in an explosives plant were reported by Robert (1907), as stated by Rambousek (1911). The victims suffered from nausea, vomiting, headache, vertigo and, in the more severe cases, the patients developed twitchings, loss of consciousness and delirium before death. Other industrial poisonings in which amyl alcohol was one of the constituents to which the victims were exposed were reported by Burger and Stockmann (1932)

and by Baader (1933). Two other fatalities reported by Zangger (1933) may have had exposure to tetrachlorethane in addition to amyl alcohol.

The *tertiary amyl alcohol*, amylene hydrate, is of little industrial importance but it has been used as a hypnotic.

With regard to its *absorption, fate, and excretion*, it is mainly absorbed from the gastrointestinal tract, having a boiling point of 102° C. According to Pohl (1908) appreciable quantities are excreted through the lungs following its intravenous administration to dogs. It is questionable whether it is excreted in conjugation with glucuronic acid (Thierfelder and von Mering, 1885) and is said to be partly excreted unchanged (Fränkel, 1927).

With respect to its effect on the nervous system, Thierfelder and von Mering (1885) found it more effective than the tertiary butyl alcohol, doses of 3 cc. given orally causing in a large rabbit, in 10 to 15 minutes, deep sleep lasting for 12 to 24 hours. Lendle (1928) determined the minimal narcotic dose with intraperitoneal injection in rats as 0.9 cc. per kg. and the minimal fatal dose as 1.6 cc. per kg., so that the margin of safety is 1.8.

According to Fühner (1921) the minimal depressant concentration for the isolated frog heart is 0.184 mole (16.2 gm.) per liter. Bock (1898) found in the isolated mammalian heart that tertiary amyl alcohol had little effect on the output and the rate, and he assumed that the reduction of the blood pressure observed by earlier investigators was due to peripheral vasodilatation.

With regard to its toxic action, Flury and Zangger (1928) stated that with sufficiently large doses it may cause circulatory disturbances characterized by vasodilatation and small and slow pulse. Jacobi and Speer (1920) published a case of medicinal poisoning resulting from the rectal administration of 35 gm. or as pointed out by Loewe (quoted from Jacobi and Speer, 1920) probably more correctly 28 to 29 gm. of amylene hydrate. This resulted in deep sleep, loss of reflexes, collapse, and circulatory failure. Since the patient showed signs of improvement during the first 24 hours after the poisoning, and because he was found to have also suffered from pneumonia, it appears questionable whether death resulted from amylene hydrate poisoning. A similar case of amylene hydrate poisoning was reported by Anker (1892) resulting from the ingestion of 27 gm. of amylene hydrate. In this patient unconsciousness lasted 24 hours, somnolence persisted for 6 days, and for several weeks there was an excessive secretion of mucus from the respiratory tract. During the first 24 hours after ingestion, the respiration was impaired and the heart action weak. Large therapeutic doses (4 gm. in water) may cause sleep readily, but are liable to cause also headache, nausea, and impairment of circulation and respiration more readily than observed with paraldehyde.

j. Higher Aliphatic Alcohols

The higher aliphatic alcohols—hexyl, heptyl, octyl, nonyl, decyl, undecyl, and cetyl alcohol (hexadecanol)—are of very limited practical importance. Some of these have been studied in serial experiments covering a number of alcohols with a limited objective, and these experiments will be discussed in another chapter dealing with the relation between the chemical structure and the physiological action of alcohols.

Of the higher aliphatic alcohols, only *octyl alcohol* (capryl alcohol) is of any practical importance. This is used as an antifoaming agent, as a dehydrating agent for lubricating oils, in the printing of textiles, in air conditioning, in the manufacture of paper, in photographic work, and in insecticide sprays.

Macht and Leach (1930) studied the toxic action of 23 of the 89 possible isomers of octyl alcohol on goldfish. They found that they caused paralysis of the respiratory center and the neuromuscular apparatus, the primary alcohols being more toxic than the secondary alcohols, and these, in turn, being more effective than the tertiary alcohols. In some instances these workers also determined toxicity in cats with intravenous injection of 0.1 percent solutions. Such injections caused depression of the respiratory center, but no definite relation between their toxicity and their chemical structure could be established. Schroeder and Macht (1930) found that nearly all primary octyl alcohols show some local anesthetic action in concentrations of 1:1000. With the tertiary alcohols this anesthetic action is of shorter duration and requires higher concentrations.

With regard to the *effect of octyl alcohol on the circulation*, Clerc, Paris, and Sterne (1932) found that in rabbits and dogs it produces a lowering of the blood pressure and the surface tension of the blood which is of fairly long duration, and they suggested its use for the treatment of certain forms of hypertension in man. Similarly, Paris (1937) found that in rabbits, doses of 2 to 4 mg. per kg. cause a marked fall of the blood pressure, paralleled by lowering of the surface tension of the blood, increased clotting time, increased viscosity of the blood, and an increase of the red blood cells. According to Cavalli (1940) octyl alcohol causes no vasodilatation nor vasoconstriction; however, it lowers the surface tension in concentrations of 0.000087 gm. percent and more. McLain (1940) found that caprylic alcohol causes hemolysis and that in this respect it is 50 times as effective as ethyl alcohol and 200 times as effective as distilled water.

Cavalli (1940) found that concentrations of 0.5 mg. per 80 cc. Ringer's solution cause, in the isolated intestine, immediate loss of tone and inhibition of the contractions, whereas concentrations one-tenth as strong have no constant effect. Similarly, Macht and Leach (1930) found that octyl alcohols depress smooth muscle structures

such as the vas deferens of the rat and the isolated uterus of the guinea pig, but they were unable to establish a relation between the intensity of this action and the chemical structure of the different isomeric alcohols.

Paris (1937) stated that octyl alcohol has distinct diuretic properties.

According to Clerc, Paris, and Sterne (1932), pure octyl alcohol is toxic for rabbits in doses of 2 cc. in contrast to a saturated aqueous solution which is only slightly toxic.

No information appears to be available with regard to the toxicity of the vapors of octyl alcohol aside from the fact that they cause irritation of the mucous membranes of the eyes and the upper respiratory tract.

II. THE UNSATURATED MONOVALENT ALCOHOLS

The lowest member of the unsaturated alcohols is *allyl alcohol* propene-1-ol-3, $CH_2=CH-CH_2OH$, which has the molecular weight 58.08. It is a colorless liquid of the specific gravity 0.854 at $\frac{20°}{4°}$ C. which solidifies at $-129°$ C., boils at $96.6°$ C., and is miscible with water, alcohol, and ether. According to Jones (1938) the upper limit of its inflammability is 2.40 percent.

It is prepared by heating glycerol and oxalic acid to 200° C., and may be obtained from crude wood alcohol by fractional distillation (Flury and Zernik, 1931).

Allyl alcohol is absorbed through the gastro-intestinal tract, the lungs, and, according to Sander (1933), readily through the skin of mice. Evidently nothing is known with regard to its fate in the organism or in respect to its excretion.

Miessner (1891) found that, in rabbits, doses of 0.15 to 0.1 cc. are slowly fatal, and doses of 0.2 cc. rapidly prove fatal, causing marked irritation of the mucous membranes, marked vasodilatation, lowering of the blood pressure, and considerable irritation of the kidneys as indicated by the presence of albumen in the urine. Piazza (1915) noted lowering of the body temperature, diarrhea, irritation of the kidneys, fibrillary twitchings, and paresis. According to Carlier (1911) the intravenous injection of saline saturated with allyl alcohol causes a primary rise and a subsequent fall of the blood pressure, first shallow and later dyspneic respiration, and, finally, convulsions. Similarly, Atkinson (1925) noted in dogs, vomiting, marked irritation of the gastric mucosa, convulsive movements, and coma; and in 1 dog he noted, following the administration of a sublethal dose, temporary opacity of the cornea and blindness.

Miessner (1891) noted irritation of the mucous membranes, reddening of the skin, increasing dyspnea, paralysis of the hind legs, and irritation of the kidneys in mice exposed to vapors of allyl alcohol. McCord (1932) exposed rabbits, rats, and 1 monkey to concentrations of 50, 200, and 1,000 p. p. m. of allyl alcohol in air. The monkey, which was exposed to 1,000 p. p. m., showed vomiting, diarrhea, and severe pain, and died after 4 hours of exposure. At autopsy the intestinal tract was markedly inflamed and showed petechial hemorrhages which were also found in kidneys and spleen, and similar inflammatory reactions were also seen in the brain and the meninges. Of 2 rabbits exposed to the same concentration, 1 died 3½ hours after the beginning of the exposure and the other died after 3¼ hours. Both developed severe dyspnea and discharged an exudate from nose and mouth. Rats exposed to this concentration died after 3 hours.

Three rabbits and 4 rats exposed to 200 p. p. m. showed, after 1 hour, obvious discomfort, noisy respiration, and discharge from nose and mouth, but tolerated from 3 to 18 exposures for 7 hours each.

Of 2 rabbits and 5 rats exposed for 7 hours daily to 50 p. p. m. in air, each 1 of the former died or was killed after either the 14th or the 28th exposure, whereas the rats died after an average of 30 exposures.

These experiments show that allyl alcohol causes considerable irritation, characterized by pulmonary edema, hemorrhages, gastroenteritis, diarrhea, and nephritis with hematuria, and that the dangerous concentration of allyl alcohol in air may be well below 50 p. p. m.; and, according to McCord (1932), even 5 p. p. m. will cause some irritation.

According to Lewin and Guillery (1913), exposure to vapors of allyl alcohol may not only cause lacrimation, irritation of the conjunctiva, and pain in the eyes, but also disturbances of accommodation. Oettel (1936) stated that direct contact of allyl alcohol with the skin will cause, after 70 minutes, moderately sharp pain, and moderate erythema and hyperemia. According to Miessner (1891), allyl alcohol is 50 times more toxic than propyl alcohol, and Atkinson (1925) considers it to be 150 times more toxic than methanol.

With regard to cases of human poisoning from exposure to allyl alcohol vapors, Flury and Zernik (1931) refer to the case of a chemist who suffered from irritation of the mucous membranes of nose and eyes, pain in eyes and head, difficult respiration, general malaise, and disturbances of accommodation as a result of exposure to this material.

The corresponding alcohol with a triple bond is *propargylic alcohol*, propin-1-ol-3, $CH \quad C - CH_2OH$. It has the molecular weight 56.06, and is a colorless liquid of the specific gravity 0.972 at $\frac{20°}{4°}$ C. which solidifies at $-17°$ C. and boils at 114° to 115° C. It is soluble in water, and it mixes freely with alcohol and ether.

Tietze (1926) found that in rabbits the subcutaneous injection of 0.2 cc. per kg. diluted with 10 cc. of saline causes, at first, light narcosis, diarrhea, and paresis; after 2 hours, lowering of the body temperature and slowing of the respiration; later, increasing depression of the respiration; and, finally, death due to respiratory paralysis. In another rabbit twice this dose (0.4 cc. per kg. diluted with 20 cc.) caused no distinct effect in 3 hours, but when 0.8 cc. per kg. was given on the next day the animal died in 6 hours.

Of the higher homologues of propargylic alcohol, diethyl-ethenyl-carbinol, $(C_2H_5)_2 - C - (C \equiv CH)OH$, was studied by Bock (1930) who found, in dogs, that doses of 0.2 gm. per kg. cause sleep and narcosis from which the animals do not recover, but smaller doses of 0.16 gm. per kg. have no effect.

According to the same author, the methyl-tertiary-butyl-ethenyl-carbinol, $(CH_3)_3 - C - C - CH_3(C \equiv CH)OH$, in doses of 0.25 gm. per kg. causes sleep.

III. ACETONE SUBSTITUTED ALIPHATIC ALCOHOLS

Diacetone alcohol, dimethyl-acetonyl-carbinol, pyranton A, $(CH_3)_2$-$COHCH_2 - COCH_3$, is a colorless liquid of the molecular weight 116.16 and the specific gravity 0.931 at 25° C., which boils at 165° to 166° C., and which is miscible with water, alcohol, and ether. Its flash point is 45° to 46° C. (Lehmann and Flury, 1938).

According to Browning (1937) diacetone alcohol is a good solvent for nitrocellulose, cellulose acetate, cellulose ethers, and many resins, and it is, therefore, met with in the lacquer industry, in the textile and dyeing industries, and in the manufacture of quick-drying ink.

According to Walton, Kehr and Loevenhart (1928), the intravenous injection causes, in rabbits, fall of the blood pressure, depression and narcosis, the onset, depth, and duration of the latter varying with the dose. The fall of the blood pressure is said to be due to reduction of the cardiac output and not to vasodilatation, and it is not affected by dissection of the vagus. In rats the intravenous injection of even relatively small doses is said to produce sleep. With intravenous injection in rabbits the narcotic dose ranges from 1.0 to 1.5 cc. per kg. body weight, whereas the minimal fatal dose is 3.25 cc. per kg. With intramuscular injection the minimal fatal dose is slightly higher, namely 3 to 4 cc. per kg, and the somniferous doses 2.0 cc. per kg., whereas with oral administration the minimal fatal dose is 5 cc. per kg. and the narcotic dose is 2.4 to 4 cc. per kg. These data indicate that diacetone alcohol is about twice as toxic as acetone, for which the corresponding minimal fatal doses were determined as 6 to 8 cc. per kg., 5.0 cc. per kg., and 10 cc. per kg. According to Gros (quoted from Lehmann and Flury, 1938) the repeated subcutaneous injection of 0.08 cc. causes in rats somnolence followed by recovery. In rabbits, oral doses of 2 cc. given 12 times daily caused moderate narcosis, injury of the kidney—as indicated by the presence of albumen and sugar in the urine—and death in three-fourths of the animals. Inhalation of concentrations of 10 mg. per liter (2,100 p. p. m.) caused, in mice, rats, rabbits, and cats, restlessness, irritation of the mucous membranes, excitement and, later, somnolence. In rabbits kidney injury was observed. Keith (1932) noted temporary changes of the liver following the oral administration of 2 cc. per kg. to rats. These developed 6 hours after the administration, reached their maximum after 24 hours, but were, after this, retrogressive. These animals showed also a temporary reduction of the red blood cells and of the hemoglobin.

There appear to be no records with regard to toxic effects observed with industrial exposure, but the results from animal experiments indicate that diacetone alcohol is about twice as toxic as acetone and that it may cause injury of the kidney, liver, and blood.

IV. PHENYL SUBSTITUTED ALIPHATIC ALCOHOLS

Among the phenyl substituted aliphatic alcohols, *benzyl alcohol*, phenyl carbinol, $C_6H_5CH_2OH$, is of some importance. It is a colorless liquid of the molecular weight 108.13 and the specific gravity 1.043 at $\frac{20°}{4°}$ C. which solidifies at $-15.3°$ C. and boils at 204.7° C. It is soluble in 100 parts of water to the extent of 4 parts at 12° C. and mixes freely with alcohol and ether. Its flash point is, according to Lehmann and Flury (1938), 96° C.

Benzyl alcohol is used in the manufacture of carbon paper, as dope in the airplane industry, and in the perfume industry.

With regard to the *absorption, fate and excretion* of benzyl alcohol in the organism, Battelli and Stern (1909) refer to Jaquet as having found that liver and kidneys oxidize benzyl alcohol to benzoic acid. The latter is conjugated with glycine and excreted as hippuric acid (Macht, 1918). Diack and Lewis (1928) found that after the oral administration of benzyl alcohol the excretion of hippuric acid is only slightly less prompt than after the administration of sodium benzoate, illustrating the rapidity of the oxidation to benzoic acid.

The *effect of benzyl alcohol on the central nervous system* is not very marked. Macht (1918) found that in rabbits and dogs intravenous doses of 5 to 10 cc. per kg. of a 1 percent solution may have some sedative effect without affecting the respiration or the respiratory center; large doses may, however, cause paralysis of the respiration. Starrek (1938) (quoted from Lehmann and Flury, 1938) found that in mice the subcutaneous injection of 3 mg. per gram body weight causes, in 8 minutes, toleration of side position, and, in 20 minutes, deep narcosis, labored respiration and paralysis of the hind legs.

As shown by Macht (1918), benzyl alcohol has local anesthetic properties. When applied to the tongue it causes first, slight irritation, and, later, numbness. One percent solutions cause complete anesthesia of the frog's skin and of the cornea of rabbits and dogs, preceded by a slight irritation. According to Sollmann (1919) it is a fairly efficient local anesthetic for mucous membranes, being, in this respect, superior to procaine but somewhat less effective than holocaine and cocaine, especially with regard to the duration of the anesthesia. He pointed out that even 1 percent solutions of benzyl alcohol cause considerable smarting. As shown by Macht (1918), 1 percent solutions of benzyl alcohol may cause complete paralysis of the isolated sciatic nerve of the frog.

With regard to the *effect of benzyl alcohol on the circulation*, Macht (1918) found that the intravenous injection of 5 to 10 cc. per kg. of a 10 percent solution causes, in rabbits and dogs, a fall of the blood pressure which is due to vasodilation and not to a direct toxic effect on the heart. As stated by Gruber (1923a), Mason and Pick, and Nelson and Higgins noted lowering of the blood pressure following parenteral administration of benzyl alcohol, but Gruber (1923a) did not see any such effect after the oral administration. He stated that the intravenous injection of large doses may paralyze the heart muscle prior to the respiratory center.

As shown by Macht (1918), benzyl alcohol depresses smooth muscle structures, and Gruber (1924) showed that it has some diuretic action.

The minimal fatal dose of benzyl alcohol is: For mice, 1 cc. per kg.; for rats, 1 to 3 cc. per kg.; for guinea pigs, 1 to 2.5 cc. per kg.; and for rabbits, 2 cc. per kg. (Macht, 1918). Lehmann and Flury (1938) quote Starrek (1938) as having determined the minimal fatal dose with subcutaneous injection for mice as 2 mg. per gram body weight, and stated that in this species benzyl alcohol is twice as toxic as butyl alcohol and 3 times as toxic as isopropyl and amyl alcohol. It has evidently not given rise to industrial poisoning.

Macht (1918) showed that benzyl alcohol has antiseptic properties, 0.5 percent solutions killing bacillus Friedländer in 19 hours, bacillus pyocyaneous in 24 hours, and bacillus coli in 72 hours. Macht and Hill (1923) showed that its solutions in oil also have distinct bactericidal action.

Of the higher homologues of benzyl alcohol only *tolyl-methyl-carbinol*,

$$H_3C \diagup \diagdown - \underset{H}{\overset{OH}{C}} - CH_3,$$

has been studied, and according to Schoene (1938) it has cholagogic properties. It is a constituent of the ethereal oil from curcuma domestica and has no industrial importance.

V. RELATION BETWEEN THE CHEMICAL STRUCTURE AND THE PHYSIOLOGICAL ACTION OF MONOVALENT ALCOHOLS

Table 19 gives a résumé of the physico-chemical data of some of the aliphatic alcohols.

It shows that with normal alcohols the specific gravity increases with the molecular weight, and that the specific gravity of the iso compounds and, evidently to a greater degree, the specific gravity of the secondary and tertiary compounds is lower than that of the normal alcohols.

Similarly, the boiling point increases with the molecular weight of the normal alcohols, and the boiling point of the iso, secondary, and tertiary alcohols is lower.

Corresponding to the changes of the boiling point, the vapor pressure at a given temperature decreases with the molecular weight. But it should be pointed out that the vapor pressure of isopropyl and isobutyl alcohol is greater than that of the corresponding normal alcohols and that the vapor pressure of the secondary and, especially, the tertiary alcohols (tertiary butyl alcohol) is considerably higher.

The flash point increases with the molecular weight, and the lower limit of inflammability decreases with the molecular weight.

The available data indicate that the surface tension of normal alcohols increases with the molecular weight and the surface tension of the iso, secondary, and tertiary alcohols is lower than that of the normal compounds.

Whereas the solubility in water decreases with the molecular weight, the solubility in oil increases so that the partition coefficient oil/water increases with the increase of molecular weight. The available data do not show whether or not, or to what extent, the iso, secondary, and tertiary alcohols differ from the normal compounds.

The toxicological properties of aliphatic alcohols increase with the molecular weight, as was already shown by Richardson (1869), and it has generally been found that the iso compounds are less effective than the normal alcohols. It has been shown by several investigators, such as Fühner (1904 and 1905) on sea urchin eggs, by Fühner and Neubauer (1907) with the hemolytic action on red blood cells, by Fühner (1921) in the isolated frog heart, by Kamm (1921) in paramecia, and by Morgan and Cooper (1912) and Tilley and Schaffer (1926) on bacteria, that the effectiveness of the various normal alcohols from one member to the next higher homologue increases approximately 3.3 times. According to Tilley and Schaffer (1926) for secondary alcohols this ratio is slightly lower, namely, 3.0, and for tertiary alcohols it is 2.7.

In contrast to these findings with comparatively primitive test ob-

Alcohol		Solubility in 100 parts of—			Partition coefficient oil/water
		Water	Ether	Alcohol	
Methyl	C.)	~	~	~	
Ethyl	C.)	~	~		[8] 0. 03
Normal propyl (propan	C.)	~	~	~	[8] .13
Isopropyl (propanol-2)	C.)	~	~	~	
Normal butyl (butanol	C.)	9 15° C	~	~	
Secondary butyl (butar	C.)	12. 5 20° C	~	~	
Isobutyl (2-methyl-pro 1).	C.)	10 15° C	~	~	
Tertiary butyl (2-meth panol-2).	C.)	~	~	~	[8] .18
Normal amyl (pentanol		2. 7 22° C	~	~	
Secondary normal amy tanol-2).		16. 6	~	~	
Primary isoamyl (2-n butanol-4).	C.)	2 14° C	~	~	[9] .47
Secondary isoamyl (2-m butanol-3).		Slightly soluble	~	~	
Amyl (pentanol-3)		do	Soluble	Soluble	
Tertiary amyl (2-meth tanol-2).		do	do	do	
Tertiary amyl (2,2-din propanol-1).		do	~	~	[9] 1. 0
Active amyl		do	~	~	
Normal hexyl (hexanol		0.59 20° C. Slightly soluble.	~	~	
Normal hexyl (hexanol		Slightly soluble	~	~	
Normal hexyl (hexanol		do	~	~	
Normal heptyl (heptan		0. 1 18° C. Very slightly soluble.	~	~	
Normal octyl (octanol-1		Slightly soluble	Soluble	Soluble	
Octyl (octanol-2; capry	C.)	0. 13 25° C	do	do	
Normal nonyl (nonano		Insoluble	~	~	
Normal nonyl (nonano		do	Soluble	Soluble	
Normal nonyl (nonano		do	Very soluble	Very soluble	
Normal primary decy anol-1).				Soluble	
Normal undecyl (undec		Insoluble		do	
Normal undecyl (undec		do		do	
Normal dodecyl (dodec				do	

[1] Doolittle (1935).
[2] Weese (1928).
[3] Landolt and Börnst

isoamyl alcohol, international critical tables.

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Table 19.—*Physico-chemical properties of aliphatic monovalent alcohols*

Alcohol	Formula	Molecular weight	State	Specific gravity	Melting point °C.	Boiling point °C.	Vapor pressure At 30° C.[1] mm. Hg.	Vapor pressure At 20° C.[2]	Flash point[4]	Inflammability (in percent) Upper limit[5]	Inflammability (in percent) Lower limit[5]	Surface tension	Solubility Water	Solubility Ether	Solubility Alcohol	Partition coefficient oil/water
Methyl	CH_3OH	32.04	Colorless liquid	0.792 20°/4° C.	−97.8	64.7	160	96	{ 1 to 32 (52) }	36.50	6.72	22.61 (20° C.)	~	~	~	----
Ethyl	CH_3-CH_2-OH	46.07	...do...	.789 20°/4° C.	−112	78.4	78	44	{ 9.0 to 32.0 (65) }	18.95	3.28	22.27 (20° C.)	~	~	----	[8]0.03
Normal propyl (propanol-1)	$C_2H_5CH_2OH$	60.09	...do...	.804 20°/4° C.	−127	97.8	29.4	15.2	22.5 to 45.5	--------	2.55	23.8 (20° C.)	~	~	~	[8].13
Isopropyl (propanol-2)	$(CH_3)_2CHOH$	60.09	...do...	.789 20°/4° C.	−85.8	82.5	60	{ 19.2 332.4 }	{ 11.75 to 14.5 (67) }	--------	2.65	21.7 (20° C.)	~	~	~	----
Normal butyl (butanol-1)	$C_2H_5CH_2CH_2OH$	74.12	...do...	.810 20°/4° C.	−79.9	117	11	5	35 to 35.5	--------	1.70	24.6 (20° C.)	9 15° C	----	~	----
Secondary butyl (butanol-2)	$CH_3CHOHC_2H_5$	74.12	...do...	.808 20°/4° C.	----	99.5	26	16.6	(88)	--------	----	[6]23.5 (10° C.)	12.5 20° C	~	~	----
Isobutyl (2-methyl-propanol-1)	$(CH_3)_2CHCH_2OH$	74.12	...do...	.805 17.5°C.	−108	107 to 108	17	8.6	{ 27.5 (111) }	1.68	----	22.8 (20° C.)	10 15° C	~	~	----
Tertiary butyl (2-methyl-propanol-2)	$(CH_3)_3COH$	74.12	...do...	.786 20°/4° C.	25.0 to 25.5	82.9	56.9	{ 40.6 330.6 }	--------	----	----	20.7 (20° C.)	~	~	~	[8].18
Normal amyl (pentanol-1)	$CH_3(CH_2)_3CH_2OH$	88.15	...do...	.817 20°/20° C.	----	137.8 to 137.9	5.54	2.77	--------	--------	1.19	----	2.7 22° C	~	~	----
Secondary normal amyl (pentanol-2)	$C_2H_5CH_2CHOHCH_3$	88.15	...do...	.810 20°/20° C.	----	118.5 to 119.5	12	--------	(110)	--------	----	----	16.6	~	~	----
Primary isoamyl (2-methyl-butanol-4)	$(CH_3)_2CHCH_2CH_2OH$	88.15	...do...	.813 15°/4° C.	−117.2	132.0	4.9	2.3	40 to 42	--------	1.20	[7]23.8 (20° C.)	2 14° C	~	~	[9].47
Secondary isoamyl (2-methyl-butanol-3)	$(CH_3)_2CHOHCH_3$	88.15	...do...	.819 19° C.	----	113 to 114	--------	--------	--------	--------	----	----	Slightly soluble	~	~	----
Amyl (pentanol-3)	$(C_2H_5)_2CHOH$	88.15	...do...	.815 25°/4° C.	----	115.6	--------	--------	--------	--------	----	----	...do...	Soluble	Soluble	----
Tertiary amyl (2-methyl-butanol-2)	$(CH_3)_2COHC_2H_5$	88.15	...do...	.809 20°/4° C.	−11.9	102	--------	--------	--------	--------	----	----	...do...	...do...	...do...	----
Tertiary amyl (2,2-dimethyl-propanol-1)	$(CH_3)_3CCH_2OH$	88.15	Crystalline	----	52 to 53	113 to 114	--------	--------	--------	--------	----	----	...do...	~	~	[8]1.0
Active amyl	$C_2H_5CH(CH_3)CH_2OH$	88.15	Colorless liquid	.816 20°/4° C.	----	128	--------	--------	--------	--------	----	----	...do...	~	~	----
Normal hexyl (hexanol-1)	$CH_3(CH_2)_4CH_2OH$	102.17	...do...	.820 20°/20° C.	−51.6	155.2 to 155.7	--------	--------	--------	--------	----	----	0.59 20° C. Slightly soluble.	~	~	----
Normal hexyl (hexanol-2)	$CH_3CHOH(CH_2)_2C_2H_5$	102.17	...do...	.818 16.8°/4° C.	----	137 to 138	--------	--------	--------	--------	----	----	Slightly soluble	~	~	----
Normal hexyl (hexanol-3)	C_2H_5-$CHOHCH_2C_2H_5$	102.17	...do...	.818 20°/4° C.	----	135	--------	--------	--------	--------	----	----	...do...	~	~	----
Normal heptyl (heptanol-1)	$CH_3(CH_2)_5CH_2OH$	116.20	...do...	.824 20°/4° C.	−34.6	175 756 mm.	--------	--------	--------	--------	----	----	0.1 18° C. Very slightly soluble.	~	~	----
Normal octyl (octanol-1)	$CH_3(CH_2)_6CH_2OH$	130.22	...do...	.827 20°/4° C.	−16	194 to 195	--------	--------	--------	--------	----	----	Slightly soluble	Soluble	Soluble	----
Octyl (octanol-2; capryl)	$CH_3(CH_2)_5CHOHCH_3$	130.22	Liquid	.822 20°/4° C.	−38.6	179 to 180	--------	--------	--------	--------	----	27.53 (20° C.)	0.13 25° C	...do...	...do...	----
Normal nonyl (nonanol-1)	$CH_3(CH_2)_7CH_2OH$	144.25	...do...	.828 20°/4° C.	−5	213.5	--------	--------	--------	--------	----	----	Insoluble	~	----	----
Normal nonyl (nonanol-2)	$CH_3(CH_2)_6CHOHCH_3$	144.25	...do...	.823 20°/4° C.	−35	193 to 194	--------	--------	--------	--------	----	----	...do...	Soluble	Soluble	----
Normal nonyl (nonanol-3)	$C_2H_5CHOHC_6H_{13}$	144.25	...do...	.825 20°/4° C.	−22	194.5 750 mm.	--------	--------	--------	--------	----	----	...do...	Very soluble	Very soluble	----
Normal primary decyl (decanol-1)	$CH_3(CH_2)_8CH_2OH$	158.28	Colorless oil	.830 20°/4° C.	7	231	--------	--------	--------	--------	----	----	----	----	Soluble	----
Normal undecyl (undecanol-1)	$CH_3(CH_2)_9CH_2OH$	172.30	Liquid	.833	19	131 15 mm.	--------	--------	--------	--------	----	----	Insoluble	~	...do...	----
Normal undecyl (undecanol-2)	$CH_3(CH_2)_8CHOHCH_3$	172.30	...do...	.827 20°/4° C.	12	228 to 229	--------	--------	--------	--------	----	----	...do...	~	...do...	----
Normal dodecyl (dodecanol-1)	$CH_3(CH_2)_{10}CH_2OH$	186.33	Leaflets	.831 20°/4° C.	24	255 to 259	--------	--------	--------	--------	----	----	----	----	...do...	----

[1] Doolittle (1935).
[2] Weese (1928).
[3] Landolt and Börnstein (1905).
[4] Doolittle (1935) in ° F., International critical tables.
[5] Jones (1938).
[6] Results probably 3 to 4 percent low.
[7] Presumably isoamyl alcohol, international critical tables.
[8] Meyer (1899).
[9] Seidell (1919).

jects, comparative studies in higher animals gave a lower ratio of the increase of the toxic action of normal alcohols. Joffroy and Serveaux (1895a, b) and Baer (1898) found in dogs; Macht (1920), in cats; Rost and Braun (1926), in guinea pigs and rabbits; and Weese (1928), in mice, a rational increase of less than 3.0 whereas Fühner (1912a) found in frogs an increase of 3.99 between adjoining homologues.

It appears, therefore, that, whereas certain toxicological properties may be affiliated quite readily to certain physico-chemical characteristics, their systemic effects are the result of a combination of a number of factors, the appraisal of which shall be attempted in the following synopsis.

It has been pointed out that aliphatic alcohols have more or less marked *antiseptic properties.* Wirgin (1904) found that this increases from methyl alcohol to amyl alcohol so that the latter is 10 times as effective as the former, and Morgan and Cooper (1912) and Christiansen (1918) found propyl alcohol more effective than ethyl and methyl alcohol. Tilley and Schaffer (1926) studied the germicidal action of alcohols by means of a modified Rideal-Walker test with *Bacillus typhosus* and *Staphylococcus aureus.* They determined the phenol coefficient and the molecular coefficient, the latter being the molecular weight of the alcohol tested divided by the molecular weight of phenol and multiplied by the phenol coefficient. Their results are summarized in table 20 which shows that the disinfectant action

Table 20.—*The germicidal action of various alcohols on different organisms*

[Tilley and Schaffer, 1926]

Alcohol	Bacillus typhosus		Staphylococcus aureus		Ratio	
	Phenol coefficient	Molecular coefficient	Phenol coefficient	Molecular coefficient	Bacillus typhosus	Staphylococcus aureus
Methyl	0.026	0.009	0.030	0.010		
Ethyl	.040	.020	.039	.019	2.2	1.9
Propyl	.102	.065	.082	.053	3.25	2.8
Butyl	.273	.215	.22	.175	3.30	3.30
Amyl	.780	.73	.63	.59	3.39	3.37
Hexyl	2.3	2.5			3.38	
Heptyl	6.8	8.4			3.46	
Octyl	21.0	29.0				
Secondary propyl	.064	.041	.054	.034		
Secondary butyl	.152	.120	.131	.103	2.9	3.0
Secondary amyl	.38	.36	.32	.30	3.0	2.9
Secondary hexyl	1.00	1.09			3.0	
Tertiary butyl	.081	.064	.064	.050		
Tertiary amyl	.182	.170	.142	.133	2.7	2.7
Tertiary hexyl	.45	.49			2.9	

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increases with the molecular weight in the normal series from methyl to ethyl, propyl, butyl, amyl, hexyl, heptyl, to octyl alcohol; that the secondary alcohols are less active than the normal alcohols, as illustrated by the comparison of secondary propyl, butyl, amyl, and hexyl alcohol with the corresponding normal compounds; and that the tertiary alcohols are even less effective than the latter. Similar findings with *Bacillus coli* and *Staphylococcus aureus* were published by Kokko (1939). As illustrated by figure 10 which gives the antiseptic concentration of various alcohols which
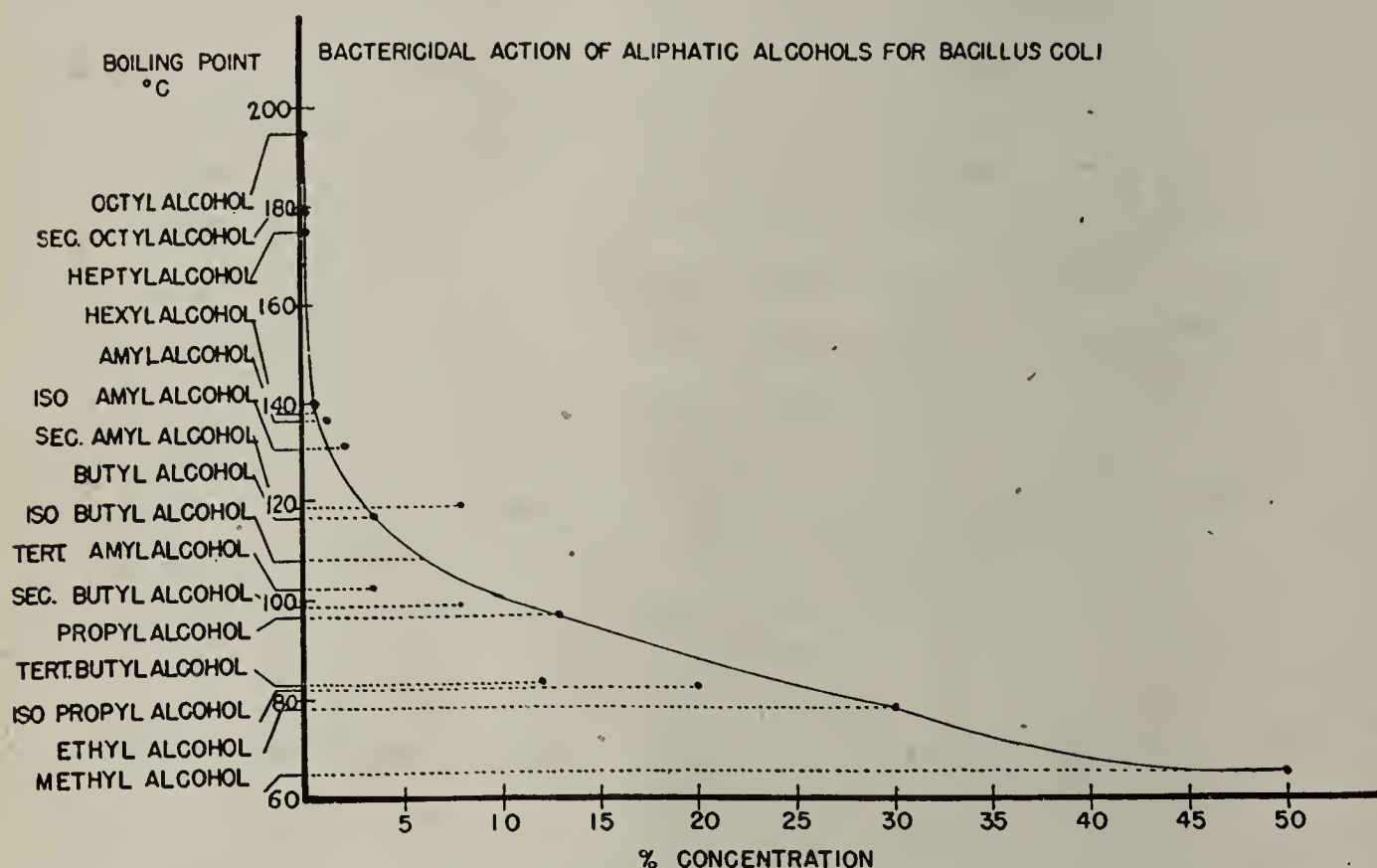
FIGURE 10.—This figure illustrates the relation between the boiling point of primary, secondary, and tertiary alcohols and their antiseptic action against *Bacillus coli.* (Redrawn from the data of Kokko, 1939.)

kill *Bacillus coli* within a certain period of time, the germicidal action of the normal alcohols increases with the boiling point, whereas the secondary and tertiary alcohols are less potent. Löckemann, Bär, and Totzeck (1941) studied the bactericidal properties of methyl, ethyl, propyl, and isopropyl alcohol in various dilutions with different bacteria. They found that the maximal bactericidal action was produced by 60 to 90 percent methyl alcohol, 50 to 90 percent ethyl alcohol, 20 to 90 percent propyl alcohol, and 30 to 80 percent isopropyl alcohol. It appears, therefore, that the range of the bactericidal action increases with the molecular weight and that the iso compounds are less effective than alcohols with an equal number of carbons in a straight chain. In table 21, some physico-chemical properties of these alcohols are summarized, together with their germicidal action as determined by Tilley and Schaffer (1926). It shows that, according to the available data, the antiseptic action in the normal series increases in the same direction as the surface tension, the partition

Table 21.—*The relation between the physico-chemical properties of aliphatic alcohols and their antiseptic action against Bacillus typhosus*

Alcohol	Formula	Molecular coeficient	Boiling point ° C.	Surface tension	Solubility in water	Partition coefficient oil/water[2][3]
Methyl	CH_3OH	0.009	54.7	22.61	Miscible	
Ethyl	CH_3CH_2OH	.020	78.4	22.27	___do___	0.03
Normal propyl	$CH_3(CH_2)_2OH$	.065	97.8	23.8	___do___	.13
Normal butyl	$CH_3(CH_2)_3OH$	.215	117	24.6	9 [15]°	
Normal amyl	$CH_3(CH_2)_4OH$	.73	137.8 to 137.9		2.7 [22]°	
Normal hexyl	$CH_3(CH_2)_5OH$	2.5	155.2 to 155.7		Slightly soluble	
Normal heptyl	$CH_3(CH_2)_6OH$	8.4	175 at 756 mm.		Very slightly soluble.	
Normal octyl	$CH_3(CH_2)_7OH$	29.0		27.53		
Secondary propyl	$(CH_3)_2CHOH$	.041	82.5	21.7	Miscible	
Secondary butyl	$CH_3CHOHC_2H_5$	.120	99.5	23.5(?)	12.5 [20]°	
Secondary amyl	$C_2H_5CHOHCH_3$	.36	118.5 to 119.5		16.6	
Secondary hexyl		1.09				
Tertiary butyl	$(CH_3)_3CH_2CHOHCH_3$	.064	82.9	20.7	Miscible	.18
Tertiary amyl	$(CH_3)_2COHC_2H_5$	.170	102		Slightly soluble	1.0
Tertiary hexyl		.49				

[1] Tilley and Schaffer (1926).
[2] Baum (1899).
[3] Meyer and Gottleib-Billroth (1920).

coefficient oil/water, and the decrease in solubility in water. In a comparative study of the antiseptic action of methyl, ethyl, and propyl alcohol, Christiansen (1918) found that the antiseptic action and the precipitant effect of these alcohols on proteins were not strictly parallel, as illuustrated by the fact that the molar concentrations of the 3 alcohols (17.5, 9.0 and 4.3 mole per liter, respectively) which cause complete precipitation of globulin free serum albumin differ in their antiseptic action inasmuch as propyl alcohol in 4.3 molar concentration kills bacteria much more rapidly than methyl and ethyl alcohol in 17.5 and 9.0 molar solutions, respectively. Neither was there a definite relation between the surface tension and the antiseptic action of these alcohols, as illustrated in table 20 which shows that the increase in surface tension is of an entirely different order than the increase of the molecular coefficient. Quite different from the changes of the surface tension of the alcohols themselves are the changes of the surface tension of their aqueous solutions with different concentrations. Kisch (1912) determined the surface tension of various concentrations of a number of alcohols by means of the capillary manometer, as illustrated in figure 11. This figure shows that the surface tension of 0.5, this being one-half the surface tension of water/air, is obtained with 44 percent methyl alcohol, 28 percent ethyl alcohol, 9 percent propyl alcohol, 5 percent isobutyl and 1.5 percent isoamyl alcohol. He found that the minimal inhibiting concentrations of methyl, ethyl, isobutyl, and isoamyl alcohol on the germination of yeast cells were 45, 28, 6, and 2 percent which caused a reduction of the surface tension of 0.4725 to 0.5058, 0.4823, 0.4339, and 0.4941, respectively from that of water/air. If the ratio of the concentrations of the alcohols, required to reduce the surface tension

of water/air to 0.5 of the original value, is compared with the ratio of the phenol coefficients established by Tilley and Schaffer (1926), a good agreement is found. As shown in table 20, methyl, ethyl, and propyl alcohol are miscible with water, whereas the higher homologues become increasingly less soluble. On the other hand, the precipitant action of the higher homologues on proteins increases, with the molecular weight, from methyl to butyl alcohol. Neither of these functions offers an adequate explanation for their antiseptic action. It appears, however, that as soon as the alcohol concentration in the medium reaches a point sufficient to lower the surface tension to approximately 0.4 of that of water over air, it may readily penetrate into the cells (Christiansen, 1918). This may explain, to

EFFECT OF ALCOHOLS ON THE SURFACE TENSION OF WATER
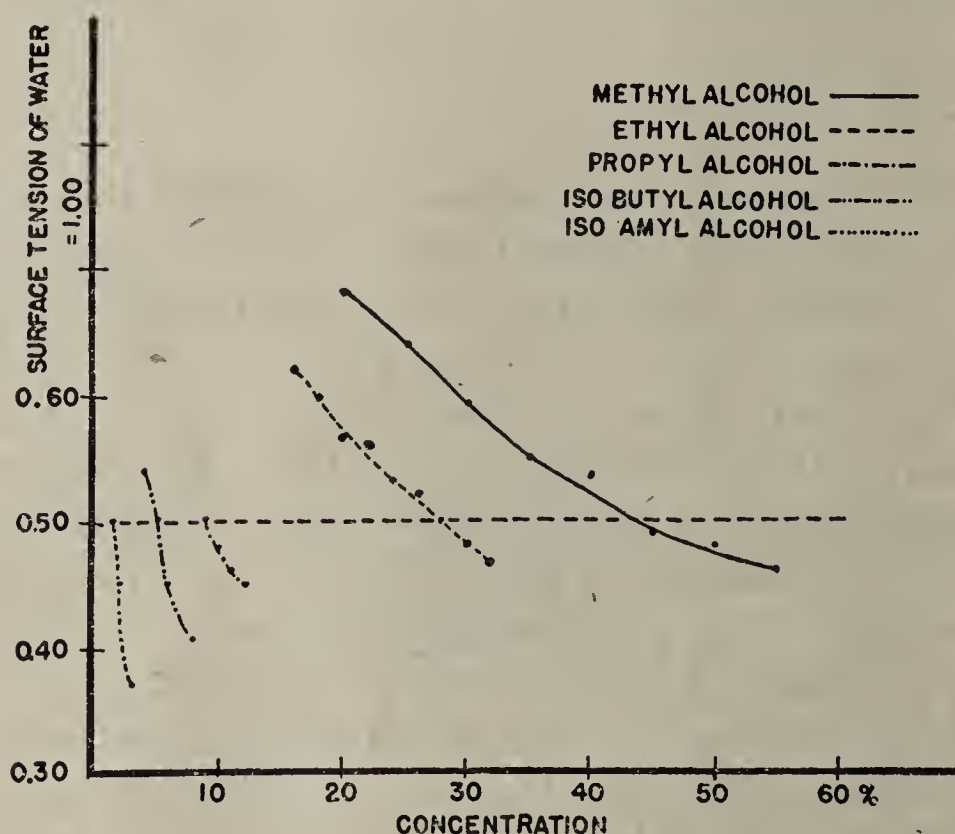
FIGURE 11.—This figure illustrates the reduction of the surface tension of water ($=1.00$) by various concentrations of aliphatic alcohols. (Drawn from data of Kisch, 1912.)

a large extent, the superiority of higher alcohols as antiseptics. The rate of penetration at the same surface tension is further increased by elevation of the temperature. After their penetration into the cell, the alcohols will precipitate the proteins. With the lower homologues this may be largely caused by dehydration because of their great solubility in water, and with the higher homologues other factors may play a role. Of the studies on the effect of aliphatic alcohols on other simple organisms, those of Loeb (1912) with sea urchin eggs should be mentioned. He found that the permeability of the oval membrane of fundulus eggs is equally increased by 2 molar solutions of methyl alcohol, molar solutions of ethyl alcohol and 8 molar solutions of butyl alcohol, and that $\frac{1}{4}$ molar concentrations of the latter correspond in their effectiveness to a $\frac{1}{16}$ molar solution of amyl al-

cohol. Comparison of these data with the concentration of the various alcohols which cause a 50 percent reduction of the surface tension, as illustrated in figure 11, shows the close relationship between this and the effect on the permeability of cell membranes. Singer and Hoder (1929) studied the effect of different alcohols on spleen tissue cultures of guinea pigs with regard to inhibition of emigration of leucocytic and lymphocytic elements, inhibition of growth of fibroblasts, and the stimulant effect on growth and the intensity of growth, as illustrated in table 22. It also shows that in this respect the toxicity of

Table 22.—*Effect of aliphatic alcohols on tissue cultures (spleen of guinea pigs)*

[Singer and Hoder, 1929]

Alcohol	Concentrations, in percent, which cause		
	Death	Inhibition	Stimulation
	Percent	*Percent*	*Percent*
Methyl	>2	1	0.1
Ethyl	2	1	.01 to .001
Normal propyl	1	0.1	(?)
Isopropyl	1	.1	.01(?)
Normal butyl	0.1	.1 to .01	(?)
Secondary butyl	1	.1	.01
Tertiary butyl	1	.1	.1

alcohols increases with the molecular weight, but the available data do not allow a more detailed analysis of these results. Similar results were reported by Kirihara (1932) with fibroblast cultures.

With regard to the *fate in the metabolism* of the various aliphatic alcohols, it appears that the primary alcohols are generally oxidized over the corresponding aldehydes to carboxylic acids, and, further, to carbon dioxide and water, depending upon the stability of the acid radicle towards oxidative processes. Thus, methyl alcohol is oxidized to formaldehyde and formic acid; ethyl alcohol to acetaldehyde and acetic acid, and, further, to carbon dioxide and water; and normal propyl alcohol to propionic acid, which, in turn, is oxidized to carbon dioxide and water. According to Weese (1928), normal butyl alcohol is also completely oxidized in metabolism.

The secondary alcohols, on the other hand, are oxidized to ketones. Thus, isopropyl alcohol is oxidized to acetone. According to Neubauer(1901), secondary alcohols are excreted also, partly in conjugation with glucuronic acid.

Tertiary alcohols are resistant to oxidation and they are excreted in conjugation with glucuronic acid (Neubauer, 1901; and Fränkel, 1911).

The pulmonary excretion varies with different alcohols. According to Pohl (1908), after their intravenous administration to dogs, methyl, ethyl, and amyl alcohol are excreted only in small quantities through the lungs, whereas isopropyl alcohol and tertiary amyl alco-

hol are excreted to a considerable extent. With regard to methyl, ethyl, and isopropyl alcohol, Cushny (1910) believed that their pulmonary excretion is comparable to their evaporation from aqueous solutions; that it depends not so much on their volatility, as determined by their boiling point, as on their miscibility with water; and that the pulmonary excretion decreases with their solubility in water. Aside from their different fate in the organism, the speed of oxidation and elimination of the different alcohols varies considerably and, therefore, also, the duration of their action which may be an important factor in their toxicity.

With regard to the *effect of aliphatic alcohols on the central nervous system*, Richardson (1869) showed that the depressant effect of alcohols on the central nervous system, body temperature, heart action, and respiration increases with the molecular weight, as indicated by a comparison of the effect of methyl, ethyl, propyl, butyl, and caprylic alcohol. Meyer (1899) and Overton (1901) showed, with a number of alcohols, that the increase of the narcotic action, as determined in tadpoles, increased with their partition coefficient oil/water, as will be discussed in a later section. Munch and Schwartze (1925) determined, in rabbits, the minimal narcotic and the minimal lethal doses of a greater number of alcohols with oral administration, as illustrated in table 23. This table confirms Richardson's law, in that the toxicity

Table 23.—*Minimal narcotic and certain lethal doses of alcohols as determined by oral administration to rabbits*

[According to Munch and Schwartze, 1925]

Alcohol	Average cc/kg.		Mole/kg.		Ratio (ethyl alcohol=1)	
	Minimal narcotic dose	Certain lethal dose	Minimal narcotic dose	Certain lethal dose	Minimal narcotic dose	Certain lethal dose
Methyl	7.5	18.0	0.1875	0.4500	0.5	0.48
Ethyl	5.5	12.5	.0945	.2150	1.0	1.00
Normal propyl	1.75	3.5	.0236	.0472	4.0	4.6
Isopropyl	2.85	10.0	.0380	.1333	2.5	1.6
Normal butyl	1.05	4.5	.0115	.0465	8.2	4.6
Isobutyl	1.75	3.75	.0191	.0410	4.9	5.2
Secondary butyl	1.25	6.00	.0137	.0655	6.9	3.3
Tertiary butyl	1.80	4.5	.0191	.0480	4.9	4.5
Isoamyl	0.875	4.25	.0080	.0391	11.8	5.5
Secondary amyl	.50	3.5	.0046	.0322	20.5	6.7
Tertiary amyl	.75	2.5	.0069	.0230	13.7	8.6

increases in the normal series with the molecular weight. It also shows that, with this form of administration, the iso compounds are less effective than the normal alcohols, the secondary and tertiary alcohols ranking in between. Lehman and Newman (1937b) determined the minimal anesthetic dose with intravenous injection in rabbits for methyl, ethyl, n-propyl, isobutyl and isoamyl alcohol as 10.5, 5.6, 1.71, 0.93 and 0.85 gm., respectively. The results of a similar study by Lendle (1928), with intraperitoneal injection in rats,

is given in table 24 which shows that, whereas the toxicity and narcotic action of alcohols increases with the molecular weight, the

Table 24.—*Minimal narcotic and minimal fatal doses of alcohols with intraperitoneal injection in rats*

[Lendle, 1928]

Alcohol	Narcotic dose cc./kg.	Lethal dose cc./kg.	Margin of safety	Median time of recovery from narcosis in minutes
Ethyl	4. 5	8. 0	1. 8	210 to 360.
Normal propyl	1. 5	4. 0	2. 66	90 to 200 (approximate).
Normal butyl	. 76	1. 2	1. 6	54 to 106.
Normal amyl	[1]. 36 (0. 45)	[1]. 6 (0. 75)	1. 7	35 to 80.
Isoamyl	. 5	1. 0	2. 0	49 to 51.
Secondary amyl	. 65	1. 0	1. 5	93 to 180.
Tertiary amyl	. 90	1. 6	1. 8	10 to 13 hours.

[1] Corrected value because normal amyl alcohol was given in dilute ethyl alcoholic solution.

median time of recovery from the narcosis decreases. Comparison of the narcotic action of isoamyl alcohol, secondary amyl alcohol, and tertiary amyl alcohol with that of normal amyl alcohol shows that the narcotic, and, less markedly, the minimal fatal doses and the time required for the recovery from the narcosis increases with the branching out of the side chains. As stated by Lendle (1928), the onset of death resulting from the administration of fatal doses of normal butyl and normal amyl alcohol occurs earlier than with the lower homologues. This observation and the much more rapid recovery from the narcosis mentioned seem to indicate: (1) that these alcohols diffuse more rapidly into and out of the tissue than the lower homologues; and (2) that, if the latter is correct, they must disappear more rapidly from the circulation, as indicated by the findings of Neymark (1938) and Berggren (1938) who found that the rate of oxidation of methyl, ethyl, propyl, and butyl alcohol increases with the molecular weight. Schneegans and von Mering (1892) had found, in rabbits, with administration of aqueous solutions of various alcohols by stomach tube, that the narcotic action of primary alcohols is less marked than that of the secondary and tertiary alcohols, and they had assumed that with tertiary alcohols the narcotic action depends upon the type of alkyl radicle linked to the tertiary carbon atom, in that the narcotic action, as determined by their procedure, was relatively poor when a methyl radicle was substituted, was better when this was replaced by an ethyl radicle, and increased with the number of ethyl radicles linked to the tertiary carbon atom. Similarly, Macht, Bryan, and Grumbein (1938), in a comparative study of the narcotic actions of (1) 2,2-dimethyl-propanol, (2) 2,2-dimethyl-butanol, (3) 2-ethyl-2-methyl-butanol, and (4) 2,2-diethyl-butanol, found the alcohol with the largest number of ethyl radicles most effective. It should, however, be pointed out that this alcohol (4) had a much higher molecular weight than the lowest member of this series (1).

As shown above, the findings of Schneegans and von Mering (1892) are not in accordance with those reported by other investigators. Kochmann (1923) thought that the limited solubility of alcohol in water resulted in a delayed absorption of normal amyl alcohol from the stomach, but Lendle (1928) pointed out that Schneegans and von Mering (1892) did not determine the toxicity by establishing the minimal fatal dose in cc. per kg. but by measuring the duration of the effects caused by the same doses, and that, in this way, the rate of elimination may influence the duration of the effect. The same holds true for the extensive study of Hufferd (1932), as illustrated in table 25. He studied the narcotic action of alcohols in guinea pigs with administration by stomach tube, and used the following criteria: (1) sluggishness or drowsiness, (2) loss of control of hind legs, (3) loss of control of hind and fore legs, sufficient to make locomotion impossible, (4) narcosis from which the animal cannot be aroused by holding it by the hind legs and shaking it violently, and (5) narcosis, so that no reaction is produced by pinching the skin. Choosing criterion 3, as illustrated in table 25, for comparison of the narcotic action, it is evident that the effectiveness of normal alcohols increases, with their molecular weight, from methyl to normal amyl alcohol, and that, with the higher homo-

Table 25.—*The narcotic action of alcohols with oral administration to guinea pigs*

[Hufferd, 1932]

Alcohol	Mole per 100 gm. body weight					
	0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Methyl (acetone free)		0.099	0.0136	0.0173	0.0357	
Methyl (synthetic)			.0129	.0148	.0208	
Ethyl (100 percent)		.0070	.0071	.0084	.0093	0.0133
Ethyl (96 percent)		.0045	.0052	.0070	.0070	
Normal propyl		.00205	.00295	.00322	.00322	
Isopropyl		.00249	.00302	.00393	.00434	
Normal butyl		.00082	.00073	.00089	.00102	
Isobutyl		.00087	.00099	.00108	.00114	
Secondary butyl		.00077	.00096	.00093	.00114	
Tertiary butyl		.00096	.00126	.00176	.00182	
Normal amyl		.00062	.00067	.00067	.00069	
Isoamyl		.00060	.00060	.00063	.00067	
Secondary amyl		.00034	.00049	.00052	.00045	
Tertiary amyl		.00037	.00046	.00046	.00051	
Normal hexyl		.00074			.00076	.00075
Secondary hexyl				.00039	.00043	
Tertiary hexyl				.00025	.00028	.00025
Normal heptyl		.00085			.00106	
Secondary heptyl				.00046	.00040	
Normal octyl	0.0005 to .0016					
Normal nonyl	.0005 to .0014					

logues, the effect is too-irregular to allow definite conclusions. Isopropyl and isobutyl alcohol have more marked narcotic action than the normal alcohols, whereas the secondary butyl alcohol and the secondary amyl alcohol are more potent than the corresponding iso

alcohols, and the tertiary butyl alcohol and the tertiary amyl alcohol are more toxic than the corresponding secondary alcohols. Genuit (1940) studied the antipyretic action of methyl, ethyl, propyl, and amyl alcohol in rabbits rendered hyperpyretic by the subcutaneous injection of coli toxin and found that this increases with the molecular weight, but that the effect of amyl alcohol and fusel oil was not as great as might have been expected.

Weese (1928) studied, in mice, the narcotic action and toxicity of vapors of aliphatic alcohols, using as a criterion the period of exposure to a certain concentration which is required to produce deep narcosis (toleration of back position) or which is required to cause death after termination of the exposure, as illustrated in figures 12 and 13.

FIGURE 12.—This figure illustrates the narcotic concentrations of vapors of aliphatic alcohols in mole per liter, as measured in mice by the period of time, in minutes, required to produce narcosis (toleration of back position) with exposure to certain concentrations. The asterisks indicate the saturation point of the various alcohols at 20° C. The curve for secondary butyl alcohol is identical with that of the tertiary butyl alcohol. (Redrawn from Weese, 1928.)

These curves start with the smallest amount of alcohol expressed in moles, the vapors of which, in 5 liters of air at 20° C., may cause narcosis (figure 12) or death (figure 13). Corresponding to the slower action of lower vapor tensions, the curves first decline steeply and then, in the region of the saturation point, they turn sharply and run nearly parallel to the abcissa, indicating the time required to produce the desired effect at vapor saturation at 20° C. As pointed out by Weese (1928), it will be noted that in many instances the calculated saturation point does not coincide with the bent of the curve, as indicated on figure 12 by stars. This may indicate that the vapor air mixture is not uniformly distributed within the exposure chamber (narcosis bottle) or it may be caused by differences in the temperature

in the immediate neighborhood of the animal and the rest of the narcosis bottle. The different position of the curves above the ab-

FATAL CONCENTRATIONS OF ALIPHATIC ALCOHOLS FOR MICE IN MOLE PER LITER
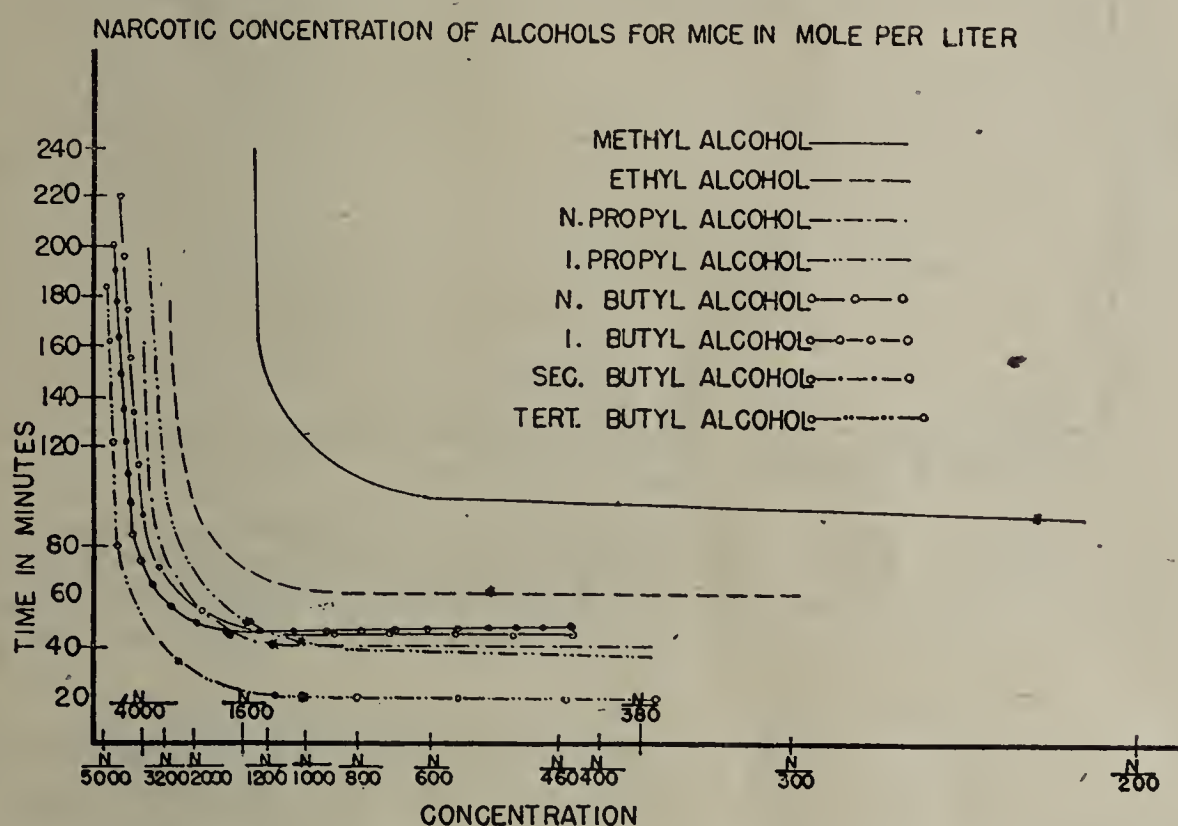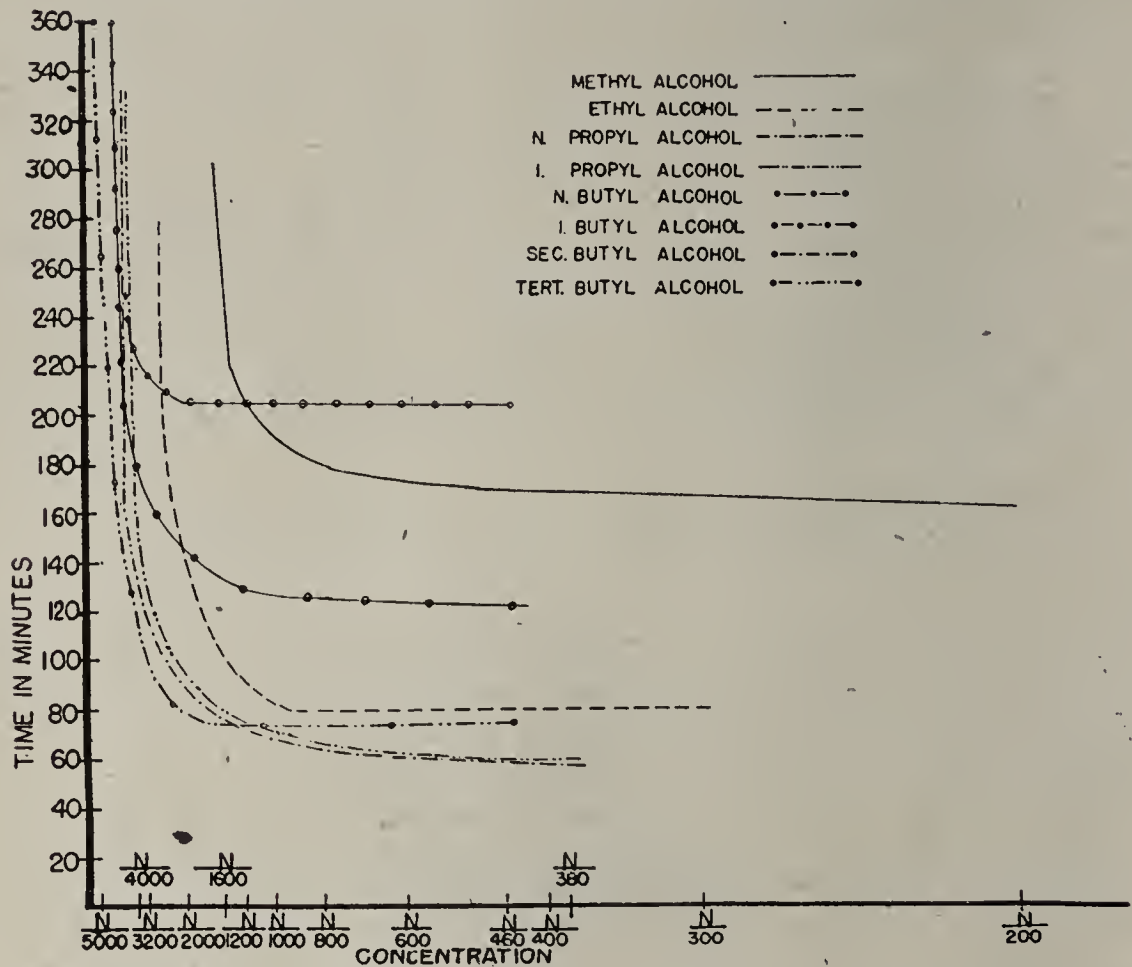

FIGURE 13.—This figure illustrates the fatal concentrations of aliphatic alcohols, in mole per liter, as measured by the shortest period of exposure required, with certain concentrations, to cause death after discontinuation of the exposure. (The curve of secondary butyl alcohol is identical with that of tertiary butyl alcohol.) (Redrawn from Weese, 1928.)

cissa, i. e., with vapors resulting from equimolecular quantities of the alcohols, is the outcome of three factors: (1) the vapor tension, (2) the resorbability, and (3) the specific toxicity of the alcohols.

Table 26.—*Vapor tension of alphatic alcohols*

[Weese, 1928]

Alcohol	Satura-tion pres-sure at 20° C. in mm. Hg.	Minimal quantity of liquid caus-ing satura-tion pressure at 20° C. in cc.	Alcohol	Satura-tion pres-sure at 20° C. in mm. Hg.	Minimal quantity of liquid caus-ing satura-tion pressure at 20° C. in cc.
Methyl	96	1.1	Normal butyl	5	0.13
Ethyl	44	.7	Isobutyl	8.6	.22
Normal propyl	15.2	.3	Secondary butyl	16.6	.42
Isopropyl	19.2	.4	Tertiary butyl	40.6	1.1

Table 26 gives the vapor pressures of the alcohols used in this study at 20° C. It shows that the vapor tension of normal alcohols decreases from methyl to butyl alcohol; that the vapor tension of the iso alcohols is greater than that of the normal compounds; and that the same holds true to a more marked degree for the secondary, and to an even greater degree for the tertiary alcohols. As shown in

figures 12 and 13, the narcotic and the toxic actions increase with the molecular weight in the range of unsaturated vapors, that is, as long as the vapor tension of equimolecular concentrations of the normal alcohols is uniform. The iso compounds are less effective than the normal alcohols but the secondary and tertiary butyl alcohols are more potent than the normal butyl alcohol. In the range of saturated vapors, however, an additional factor becomes manifest which influences considerably the effectiveness of the different alcohols. With methyl, ethyl and propyl alcohol the narcotic and toxic action increases with the molecular weight in spite of a decreasing saturation pressure of the three isomers. Butyl alcohol differs from the three lower homologues. Although the specific toxicity of butyl and isobutyl alcohol is greater than that of methyl, ethyl and propyl alcohol, their vapor tension, which controls their availability to blood and nervous system, is so low that the narcotic effects are less than with propyl alcohol. With the secondary and tertiary butyl alcohols, on the other hand, the saturation pressure is so much higher that, in spite of their lower specific toxicity, their narcotic effect is greater. As shown in figure 13, their toxic action is lower, ranging between ethyl and propyl alcohol, because, as shown by Pohl (1908), both are eliminated through the lungs within 6 hours to the extent of 77 and 65 percent, respectively.

This synopsis shows that the systemic delayed effects in many instances do not follow the same pattern as the findings with microorganisms, tadpoles, and isolated organs, with which the toxicity of alcohols increases with the molecular weight, the iso compounds are less effective than the normal alcohols, and secondary and tertiary alcohols are also less toxic.

With regard to the *effect of aliphatic alcohols on the peripheral nerves*, Efron (1885) studied their effect on the nerve fiber with the nerve muscle preparation of the frog by using various aqueous solutions. He found that these cause, first, stimulation and, subsequently, depression of the nerve. With methyl alcohol the primary stimulation was less marked than with ethyl alcohol, and normal propyl alcohol caused only depression, whereas isopropyl alcohol caused a marked primary stimulation. He found the depressant action of isobutyl alcohol more marked than that of the tertiary isomer, and amyl alcohol more effective than any of the other alcohols tested. In the same way, Breyer (1903) determined the stimulant concentrations of various alcohols and determined the maximal concentrations producing this effect as follows:

Methyl alcohol_____	2 molar =	8.02 percent
Ethyl alcohol _____	2 molar =	11.28 percent
Propyl alcohol_____	1/20 molar =	0.37 percent
Butyl alcohol_____	1/20 molar =	0.46 percent
Amyl alcohol_____	1/40 molar =	0.27 percent

Bonnet and Lelu (1933), in studying the effect of alcohols on the nerve-muscle preparation of the frog, found that the depressant effect on the nerve fiber increases from methyl to butyl alcohol (see table 27),

Table 27.—*Effect of alcohols on the nerve-muscle preparation*

[Bonnet and Lelu, 1933]

Alcohol	Concentration in mole per liter	Time of onset of paralysis (in minutes)		Alcohol	Concentration in mole per liter	Time of onset of paralysis (in minutes)	
		Of muscle	Of nerve			Of muscle	Of nerve
Methyl	0.0248	88	103	Isopropyl	0.0131	(1)	(1)
Ethyl	.0171	90	100	Normal butyl	.0109	10	30
Normal propyl	.0134	90	90	Isobutyl	.0108	10	10

1 No effect after 130 minutes.

isopropyl being less toxic than normal propyl alcohol but isobutyl alcohol being slightly more effective than the normal compound because, as they assumed, the former is a secondary and the latter a primary alcohol. Since it has been shown above that changes of the permeability of cell membrane are closely paralleled by the effect of alcohols on the reduction of the surface tension, it appears quite possible that similar changes regulate the effect of alcohols on nerve structures, but the available data are not sufficient to establish this possibility.

Raether (1905) studied the effect of alcohols on various nerve structures, as summarized in table 28, which shows that the effect on the

Table 28.—*The effect of aliphatic alcohols on various nerve structures*

[Raether, 1905]

Alcohol	Paralysis of the sciatic nerve of the frog		Irritation of the cornea of the frog		Irritation of the skin of the frog		Irritation of the human tongue	
	Concentration	Concentration	Concentration	Concentration	Concentration	Concentration	Concentration	Concentration
	Percent	*mole/liter*	*Percent*	*mole/liter*	*Percent*	*mole/liter*	*Percent*	*mole/liter*
Methyl	24.00	7.5	12.0	3.8	40.1	12.5	12.0	3.8
Ethyl	11.24	2.44	5.6	1.22	28.1	8.0	5.6	1.22
Propyl	2.5	0.42	0.8	0.13	14.98	2.5	0.75	0.125
Butyl	1.5	.2	.33	.044	4.6	0.62	.38	.05
Amyl	0.54	.06	.14	.016	2.16	.25	.14	.016

different functions studied increases with the molecular weight of the alcohols. A similar study with regard to the effect of alcohols on the perception of taste was published by Hallenberg (1914), as illustrated in table 29. Macht and Davis (1933) studied the depressant effect of aliphatic alcohols on the sensory nerve endings in the rabbit's cornea and the skin of the frog. They found that neither propyl, butyl, primary, secondary or tertiary amyl alcohol, nor the higher alcohols with from 13 to 18 carbons had local anesthetic properties, but

Table 29.—*Effect of alcohols on the perception of taste*

[Hallenberg, 1914]

| Alcohol | Minimal effective concentrations | | | | | |
| | Nauseous taste | | Bitter taste | | Burning taste | |
	Volume percent	Molar solution	Volume percent	Molar solution	Volume percent	Molar solution
Methyl	0.1	0.025	6.5	1.62	11.5	2.87
Ethyl	.009	.0016	2.6	0.45	5.0	0.86
Propyl	.003	.0004	1.2	.16		
Butyl	.0004	.00004	0.6	.07		

that heptyl and nonyl alcohol had some and octyl alcohol had distinct local anesthetic properties. The physico-chemical data on these higher alcohols reported in the literature are too incomplete to allow an attempt to offer an explanation for these findings.

With regard to the *effect of aliphatic alcohols on the circulatory apparatus*, Ringer and Sainsbury (1883) found, in the isolated frog heart, that the same degree of depression is produced by 12.1 cc. methyl alcohol, 6.73 cc. ethyl alcohol, 3.5 cc. propyl alcohol, 1 cc. butyl alcohol and 0.4 cc. amyl alcohol, and Dold (1906) found a very similar relation, the respective toxicities being: methyl alcohol, 1; ethyl alcohol, 1.75; propyl alcohol, 2; butyl alcohol, 6; and amyl alcohol, 35. Similar studies reported by Fühner (1921), Pickford (1927) and Clark (1930) are summarized in table 30. These studies show that

Table 30.—*Depressant effect of aliphatic alcohols on the isolated frog heart*

| Alcohol | Depressant concentration in mole per liter | | | Effect on surface tension | | Solubility in water mole/liter Fühner (1921) |
	[1] Fühner (1921)	[2] Pickford (1927)	[3] Clark (1930)	Number of drops water=39	Molecular concentration reducing surface tension of water to 63 dynes/cc. Clark (1930)	
Methyl	3.740	0.9	1.6	50½	1.5	Miscible
Ethyl	1.206	.35	.65	51¼	.5	Miscible
Normal propyl	.369		.17	51½	.14	Miscible
Normal butyl	.109	.03	.05	51½	.043	0.919
Normal amyl			.02		.018	
Normal heptyl	.003		.0007	51¼	.0024	.008
Normal octyl		.0003	.0002		.0006	
Normal decyl			.00003		.000094	
Normal dodecyl			.000006			
Normal tetradecyl			.0001			
Isopropyl	.655			54		Miscible
Isobutyl	.135			53½		1.351
Isoamyl	.039			52½		.230
Teritary butyl	.637			62¾		Miscible
Tertiary amyl	.184			57¼		1.420

[1] Concentrations causing cardiac arrest.
[2] Concentrations causing 50 percent reduction of heart beat.
[3] Concentrations causing reduction of response of frog's ventricle to ½ normal

the depressant action on the heart of aliphatic alcohols increases with their molecular weight up to dodecyl alcohol; that the iso compounds are less effective than the normal alcohols; and that the tertiary alcohols are less effective than the former. Similar results were reported by Wolff (1922) who stated that with methyl alcohol the isolated frog heart developed diastolic tendencies in contrast to systolic tendencies observed with the higher homologues. He noted, with ethyl and isopropyl alcohol, some indication of a stimulant action. Similary, Takahashi (1933) noted, with low concentrations of methyl, ethyl, n-propyl, n-butyl, n-amyl, n-hexyl, and n-octyl alcohol, mostly depression of the ventricular action and only a questionable stimulation of the auricle. He believed that intermediate and high doses cause damage of the myogenic and neurogenic apparatus, characterized by a decrease of the amplitude of the contraction, bradycardia, extrasystoles, and slowing of the auricular ventricular conduction of stimuli, and, finally, cardiac arrest. As indicated in table 30 and as found by Clark (1930) there is a close parallelism between the effect of the lower alcohols on the heart, their faculty to lower the surface tension of water, and the fact that both increase with the molecular weight. As pointed out by Clark (1930), this uniform increase is the more remarkable because the lower alcohols form true solutions whereas those higher than butyl alcohol form colloidal suspensions. He assumed that the depressant effect of alcohols depends on a surface action which occurs rapidly and that the drug also enters the cells but that, thereafter, it ceases to produce pharmacological effects. Continued exposure of the cell to the same concentration of alcohol will, therefore, increase its concentration within the cell without increasing the pharmacological action. Since recovery by lavage removes only the alcohol adsorbed to the surface of the cell, which is replaced by alcohol coming from the interior of the cell, recovery takes more time after continued exposure than after short exposure to the same concentration. Table 31 gives the amounts of alcohol

Table 31.—*The concentration of alcohols calculated to occur within the cells of the cardiac muscle*

[Clark, 1930]

Alcohol	Millimolar concentration applied to the outside	Millimolar concentration calculated to occur in the cells	Ratio between the concentrations inside and outside of the cells	Alcohol	Millimolar concentration applied to the outside	Millimolar concentration calculated to occur in the cells	Ratio between the concentrations inside and outside of the cells
Methyl	1600	2000	1.3	Octyl	.22	6.0	27.0
Butyl	52	68	1.3	Decyl	.03	1.5	50.0
Amyl	20	50	2.5	Dodecyl	.006	1.0	170.0
Heptyl	0.7	2.5	3.0				

taken up by the cells of the frog's ventricle when sufficiently strong concentrations are applied to reduce the response to one-half its normal

value. It shows that in the case of the less potent alcohols (methyl to amyl alcohol) the amount of alcohol present in the cells when the depression is of equal intensity varies from 2,000 to 50 millimolar concentrations, whereas with the more potent alcohols (heptyl to dodecyl alcohol) the concentration calculated to occur within the cell when an equal degree of depression is produced varies only from 6 to 1.0 millimolar. This observation appears to support the hypo-

FIGURE 14.—This figure illustrates the effect of aliphatic alcohols on the tortoise heart.

Methyl alcohol	I	Tertiary amyl alcohol	VI
Ethyl alcohol	II	Isobutyl alcohol	VII
Isopropyl alcohol	III	Normal butyl alcohol	VIII
Normal propyl alcohol	IV	Isoamyl alcohol	IX
Tertiary butyl alcohol	V		

(Redrawn from Vernon, 1911.)

thesis that the depressant action of these alcohols depends largely on the amount adsorbed on the surface of the cell. With the higher alcohols the quantity fixed in this way is of the order necessary to cover the cell surfaces with a monomolecular film, which supports Warburg's hypothesis that narcotics form a monomolecular layer over the cell surfaces. Similar studies with regard to the effect of alcohols on the turtle heart were reported by di Cristina and Pentimalli (1910) who found that the effects of ethyl, butyl, and amyl alcohol increase with their molecular weight and that they reduce the dynamic force of the heart muscle and interfere with the intrinsic regulatory mechanism. Vernon (1911) compared the toxic action of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl,

tertiary butyl, isoamyl, and tertiary amyl alcohol on the tortoise heart. As illustrated in figure 14, the toxicity of these alcohols increases with the molecular weight, the iso compounds being less toxic than the normal alcohols, the secondary alcohols less effective than the iso alcohols, and the tertiary alcohols less potent than the secondary alcohols. The parallelism between these findings and the hemolytic effect of these alcohols confirms the supposition presented above that in the isolated heart of cold-blooded animals the toxic action of alcohols is closely affiliated with a surface tension phenomenon. Spealman (1940) believed that only those substances which are osmotically active cause slowing of the heart beat.

With regard to the *effect of aliphatic alcohols on the mammalian heart*, Hemmeter (1889a, b) studied this in the heart-lung preparation of dogs, using the reduction of the output within a period of 30 seconds as criterion and perfusion this with 0.2 percent solutions in blood. He found that with perfusion of methyl alcohol the output was reduced by 19.46 cc.; with ethyl alcohol, by 17.45 cc.; with propyl alcohol, by 79.705 cc.; with butyl alcohol, by 161.121 cc.; and with amyl alcohol, by 322.32 cc. It will be noted that in the mammalian heart also the depressant action of the alcohols increases with the molecular weight but that methyl alcohol is apparently more potent than ethyl alcohol. This discrepancy, with similar observations made in the frog heart, is presumably due to the fact that the greater toxicity of methyl alcohol is caused by its metabolites—formaldehyde and formic acid—which may be formed under these conditions, and which, as was shown, are more toxic than methyl alcohol itself. Kuno (1913) determined the concentrations of various aliphatic alcohols which were just sufficient to depress the function of the mammalian heart and those which were sufficient to cause cardiac arrest within a few seconds, as illustrated in table 32, which confirms the findings of Hemmeter (1889a, b).

Table 32.—*The effect of aliphatic alcohols on the mammalian heart*

[Kuno, 1913]

Alcohol	Minimal effective concentration in mole/liter	Minimal paralyzant concentration in mole/liter	Alcohol	Minimal effective concentration in mole/liter	Minimal paralyzant concentration in mole/liter
Methyl	0.025 to 0.2	0.5	Normal butyl	.0025 to .002	0.66
Ethyl	.17	.5	Amyl	.00066 to .0005	.066
Normal propyl	.005	.1			

Genuit (1940) studied the *effect of aliphatic alcohols on the blood vessels* by determining, in the perfused rabbit's ear, the dose of alcohol required to antagonize the vasoconstrictor effect of a standard dose of

epinephrine. He found that the following molar concentrations produce this effect:

Methyl alcohol_____ 2.19 to 2.8 (7 to 9 percent).
Ethyl alcohol_____ 0.436 to 0.65 (2 to 3 percent).
Normal propyl alcohol_____ 0.33 to 0.5 (2 to 3 percent).
Normal amyl alcohol_____ 0.0017 to 0.0023 (0.15 to 0.3 percent).
Fusel oil_____ 0.2 to 0.3 percent.

It appears, therefore, that the vasodilator effect of alcohols increases from the methyl to the amyl compound. A similar relation was observed with regard to the depressant effect of these alcohols on the body temperature.

With regard to the *effect of aliphatic alcohols on the blood*, Vandevelde (1903 and 1905), Fühner and Neubauer (1907), and Fühner (1923) studied their hemolytic action on *red blood cells*. As pointed out by Fühner (1923) the hemolytic action varies to a certain extent with the treatment of the blood cells—whether and how long they have been washed, centrifuged, or kept before use; the temperature at which the experiments were performed; and other factors—so that experiments carried out at different times with different blood samples do not give identical results. This may explain minor discrepancies in the data found by these investigators as illustrated in table 33 which gives

Table 33.—*The hemolytic action of aliphatic alcohols on red blood cells*

Alcohol	Hemolytic concentration				Solubility in water mole/liter [5]	Molecular concentration reducing surface tension of water to 63 dynes/cc.[6]
	Volume percent [1]	Mole/liter [2]	Volume percent [3]	Mole/liter [4]		
Methyl_____	36. 0	7. 34	26. 00	6. 5	Miscible	1. 5
Ethyl_____	24. 7	3. 24	17. 00	2. 92(2. 3)	Miscible	. 5(3. 0)
Normal propyl_____	11. 0	1. 08	7. 00	. 93(3. 14)	Miscible	. 14(3. 6)
Normal butyl_____		. 318	3. 00	. 32(2. 9).	0. 92	. 043(3. 2)
Amyl_____	12. 52	. 091(3. 4)				. 018(2. 4)
Heptyl_____	[7]. 84	. 012(7. 6)			. 008	. 0024(7. 5)
Octyl_____	[7]. 89	. 004(3. 0)				. 0006(3. 0)
Isopropyl_____	16. 0		12. 00	1. 56	Miscible	
Isobutyl_____	[7] 28. 79		4. 25	. 46	1. 35	
Isoamyl_____			1. 50	. 14	. 31	
Tertiary amyl_____			5. 2	. 48	1. 42	

[1] Vandevelde, 1903.
[2] Fühner and Neubauer, 1907.
[3] Fühner, 1923.
[4] Fühner, 1923.
[5] Fühner, 1923.
[6] Clark, 1930.
[7] Vandevelde, 1905.

a summary of their results. As will be seen from this table, the hemolytic action increases with the molecular weight from methyl to octyl alcohol, the iso compounds are less effective than the normal alcohols, and the tertiary alcohols are less effective than the iso alcohols. Fühner (1923) pointed out that with the higher members of this series (normal and isobutyl alcohol, iso and tertiary amyl alcohol) there is

a certain relation between their hemolytic action and their solubility in water, in that the ratio of their solubility in water, in mole per liter, over their hemolytic concentration, expressed in the same way, is approximately constant, being 2.9. But such a relation cannot be established for the lower homologues (methyl, ethyl, and propyl alcohol) which are miscible in water. The last column in table 33 gives the molar concentrations necessary to reduce the surface tension of water to 63 dynes per cc., as determined by Clark (1930) for the normal alcohols. Comparison of the increase of the hemolytic action, as produced by adjoining homologues, and their effect on the surface tension of water (both figures being given in parentheses) shows that there is a very close relation between the two functions. This appears also to be the intrinsic phenomenon in the depressant effect of aliphatic alcohols on the *leucocytic* movements which, as shown by Baglioni (1927), increases, with the molecular weight, from methyl over ethyl to propyl alcohol.

The *effect of aliphatic alcohols on the striated muscle* was studied by Blumenthal (1896) and Kemp (1908) both of whom found that the depressant effect on the muscular contractibility increases with the molecular weight. According to the latter, the iso, secondary, and tertiary butyl alcohols are decreasingly less effective than the normal butyl alcohol. Schwenker (1914) showed that, in addition to this depressant effect on the excitability of the muscle, the aliphatic alcohols cause a contracture of the muscle, and that their effectiveness in this respect increases rapidly with their effect on the surface activity. The contracture may continue after the excitability of the muscle has been completely abolished, therefore it must be caused by a different mechanism. Laporta (1929) found, by perfusing the gastrocnemius of the frog in vivo with solutions of aliphatic alcohols in Ringer's solution, that the time between the beginning of the exposure and the contraction decreased with increasing concentrations of the alcohols. With the use of equimolecular concentrations he found that a similar decrease occurred with the increasing molecular weight of the alcohols. He noted, however, that the form and the general behavior of the contracture varied with different alcohols, in that with all concentrations of methyl alcohol used the main contraction was interspersed with rapid, almost rhythmical, jerks which were less distinct with ethyl and propyl alcohol and absent with isoamyl alcohol. With lower concentrations the contracture is reversible, whereas with higher concentrations it is permanent.

With regard to the *effect of aliphatic alcohols on structures with smooth muscles*, Kuno (1914) found that this increases, with the molecular weight, from methyl to amyl alcohol.

Several studies deal with the *effect of aliphatic alcohols on the oxygen metabolism of cells*. Warburg (1910 and 1921) studied the effect

of several alcohols on the respiration of nuceleated red blood cells by determining the concentration causing 50 percent inhibition of the respiration. As illustrated in table 34, the depressant effect in-

Table 34—*Effect of alcohols on the oxygen metabolism of cells*

[Warburg, 1910 and 1921]

Alcohol	Concentration causing 50 percent inhibition of respiration in mole/liter	Surface tension $\frac{\sigma W - \sigma L}{\sigma W} \cdot 100$ of these solutions	Solubility in oil over that in water (according to Overton, 1901, and Meyer and Gottlieb-Billroth, 1920)
Methyl	5.0	31	More soluble in water than in oil.
Ethyl	1.6	28	0.03
Propyl	.8	35	0.13 .
Butyl	.15	28	{Sol. water 10 percent. {Sol. oil ~. .
Amyl	.045	28	{Sol. water 2 percent. {Sol. oil ~.
Isopropyl	.8		
Isobutyl	1.5		{Sol. water 2 percent. {Sol. oil ~.
Dimethyl-ethyl-methyl	.19		{Sol. water 8 percent. {Sol. oil ~.

creases with the molecular weight, but the data are evidently not sufficiently quantitative to demonstrate the difference between normal and isomeric alcohols. As pointed out by Warburg (1910) there is a certain parallelism between their effectiveness and their solubility in oil and in water, respectively, but the available information with regard to their partition coefficient oil/water is far too vague to establish a definite relation. On the other hand, as shown in column 3 of table 34, the alcoholic solutions causing approximately a 50 percent inhibition of the respiration reduce the surface tension of water to approximately the same extent. Subsequent investigators, Vernon (1912a) and Battelli and Stern (1913), confirmed these findings. The former pointed out the parallelism between the effect of these alcohols on the respiration and the hemolytic action of these alcohols, and the latter directed attention to the parallelism with regard to the precipitant action for proteins. A similar relation between the increase of the molecular weight of alcohols and their effect on the oxygen metabolism of organs was demonstrated by Iziri (1939) by means of the Warburg technique.

With regard to the *effect of aliphatic alcohols on the activity of enzymes*, Warburg and Wiesel (1912) showed that, in sufficient concentrations, alcohols prevent fermentation by yeast, and that this effect increases with the molecular weight of the alcohols from methyl to amyl alcohol. Linossier (1899) found that these alcohols inhibit the digestive action of pepsin, trypsin, and sucrase and that this effect increases with their molecular weight. Similar findings for other ferments were reported by Meyerhof (1914), Bournot (1914) and Plattner and Galehr (1928). Chapman (1914) found that the action

of invertin is readily inhibited by ethyl and propyl alcohol, that it is less readily inhibited by isobutyl and amyl alcohol, and that it is not inhibited by heptyl and octyl alcohol. He found propyl alcohol to be the most toxic, causing complete inhibition in concentrations of 2 moles per liter. The action of pepsin is said to be more readily affected by aliphatic alcohols, definite inhibition being produced by ethyl, propyl, and isobutyl alcohol, less inhibition being produced by amyl alcohol, and no inhibition at all being produced by heptyl and octyl alcohol. The action of trypsin and catalase was inhibited in a way similar to that of other enzymes. The action of lipase is stimulated by alcohol in concentrations up to 5 moles per liter, whereas higher concentrations cause inhibition, this effect becoming evident with propyl alcohol in concentrations of 3 moles per liter. Chapman (1914) was unable to establish a relation between the effects of the different alcohols on the enzymatic action and their effects on the surface tension, but found that concentrations of alcohols which caused marked inhibition also precipitated egg albumen to the same extent.

With regard to the *precipitant action of aliphatic alcohols on proteins*, Spiro (1904) found that they lower the coagulation temperature, that this effect increases with the molecular weight, and that the iso compounds are less effective than the normal alcohols. Similar results were reported by Kamm (1921) and by Simon (1908). The latter distinguished between a salt action and a direct precipitant action. In his opinion the precipitant action is due partly to a disturbance of the physical-chemical equilibrium between salt and proteins which becomes manifest with very small concentrations of the alcohols. It is also partly caused by a change of the protein hydrosol to a hydrogel which occurs with higher concentrations, but this precipitation is reversible. In high concentrations the alcohols precipitate the proteins by changing their chemical structure and such precipitates are no longer reversible.

With regard to the *toxicity of aliphatic alcohols*, Dujardin-Beaumetz and Audigé (1875) and Féré (1894a) found that this increases with the molecular weight. This was confirmed by Joffroy and Serveaux (1895a, b), Picaud (1897), Cololian (1901), Fühner (1905), Macht (1920), Lehman and Newman (1937b) and others. As pointed out before, the systemic toxicity is the product of several factors, such as the rate of absorption, which may vary considerably with different forms of administration, the rate of the oxidation of the different alcohols in the metabolism, and their fate in the metabolism, which may result in the formation of more toxic substances. The only route of administration which allows a fair comparison with regard to the absolute toxicity of these alcohols in vivo is the intravenous injection, and, for this reason, only the results of Joffroy and Serveaux (1895a, b), Macht (1920), and Lehman and Newman (1937b) are summarized

in table 35. This table shows that the systemic toxicity increases with the molecular weight and that the iso compounds are less toxic than the normal alcohols.

Table 35.—*Toxicity of aliphatic alcohols with intravenous administration to cats and rabbits*

[Joffroy and Serveaux, 1895 (1) ; Macht, 1920 (2) ; and Lehman and Newman 1937b (3)]

Alcohol	Minimal fatal dose			Alcohol	Minimal fatal dose		
	(1) for rabbits gm./kg.	(2) for cats gm./kg.	(3) for rabbits gm./kg.		(1) for rabbits gm./kg.	(2) for cats gm./kg.	(3) for rabbits gm./kg.
Methyl	15.25	4.67	15.9	Normal butyl		0.24	
Ethyl	11.7	3.94	9.4	Isobutyl	1.5	.72	2.64
Normal propyl	3.4	1.61	4.04	Normal amyl		.122	
Isopropyl		1.97		Isoamyl	.63	.211	1.57

Toxicity studies with other biological test objects were carried out by Kissa (1914) on colpidia, and he found that the different alcohols have only additive effects. Bills (1923) found, in paramacia, no uniform relation between equinarcotic and equitoxic concentrations, and Irwin (1922) studied the anesthetic action in allolobophora worms and found the same relation between homologous and isomeric alcohols as had been found by others. This was also established by Loeb (1909–10) in a study with copepodes, by Kisch (1912) with yeast cells, by Bokorny (1913) with seeds, by Vandevelde (1900) with regard to the plasmolysis of onion skin, and, to a certain extent, by Eisenmenger (1930) in a study of the root growth of soy beans.

The question as to what extent the physiological effects of alcohols are controlled by their partition coefficient in oil over water, and to what degree they are controlled by changes of the surface tension, has aroused much comment. Meyer (1899) and Overton (1901) were inclined to affiliate the narcotic action of alcohols with their lipoid solubility, and pointed out the parellelism between their narcotic action and their partition coefficient, as illustrated in table 36. Warburg (1910) and Vernon (1912a) believed, from their studies on the effect of alcohols on the cellular respiration and on the oxidase of tissues, respectively, that their lipoid solubility is more important than their solubility in water, and Meyer and Gottlieb-Billroth (1920) believed that narcosis was bound to a certain concentration (0.06 mole/liter) in the lipoids of the brain.

Traube (1904) pointed out the parallelism existing between the capillary activity of alcohols and their narcotic action on tadpoles, and Kisch (1912) claimed that concentrations of alcohols sufficient to inhibit the germination of yeast cells had about the same surface tension. It has been pointed out that Clark (1930) found a certain parallelism between the effect of alcohols on the isolated frog heart

Table 36.—*Narcotic action of alcohols on tadpoles in relation to their partition coefficient oil/water*

Alcohol	Parts by weight of water per 1 part by weight of alcohol to cause complete narcosis in tadpoles	Gm. mole/liter	Partition coefficient oil/water; respectively, the approximate solubility of alcohols in both solvents
Methyl	50 to 60	0. 52 to 0. 62	Solubility in water ~. Solubility in oil only—in more than 50 parts.
Ethyl	70 to 80	. 27 to . 31	Partition coefficient about 1/30.
Normal propyl	150	. 11	Partition coefficient about 1/8.
Isopropyl	130	. 13	
Normal butyl	350	. 038	Solubility in water—12 parts. Solubility in oil~.
Isobutyl (ferment)	300	. 045	Partition coefficient about 6. Soluble in 10 parts of water.
Tertiary butyl (trimethyl carbinol).	100	. 13	Solubility in water and oil ~. Partition coefficient considerably less in favor of oil than with preceding.
Isoamyl (ferment)	500	. 023	Soluble in 2 parts of water. Solubility in oil ~.
Amylene hydrate (dimethyl ethyl carbinol).	200	. 037	Soluble in 8 parts of water. Solubility in oil ~.
Caprylic	20, 000	. 0004	Soluble in about 2,000 parts of water. Solubility in oil ~.
Cetyl	(1)		Slightly soluble in water. Difficult to dissolve in cold oil.

1 No narcosis in saturated solution.

and their ability to lower the surface tension. A similar parallelism was found by Cole and Allison (1930b) between the irritant action of alcohols and their effect on the surface tension, but these authors cautioned against attempts to base such findings exclusively on Traube's rule. They preferred to apply Langmuir's principle of independent surface action, according to which the distribution and orientation of polar organic molecules are determined by the number and character of more active and less active portions of the molecule. They believed that the stimulant effect of alcohols is produced by the nonpolar groups (CH_2 groups) and that each additional CH_2 group exerts an exponently increasing effect on the shift of the molecular equilibrium at the receptive surface. Nothmann-Zuckerkandl (1912) determined the effect of alcohols on protoplasmic movements but found no strict parallelism between this effect and the surface tension. Stiles and Stirk (1931 a, b and 1932) studied the effect of alcohols on two types of potato tuber by determining the exosmosis of electrolytes, as indicated by conductivity measurements of the surrounding fluid at certain intervals. They came to the conclusion that changes of the surface tension may be a factor in determining the toxicity of alcohols, but since they increase at different rates other factors may also be involved. They found that changes of the toxicity produced by substitution of one hydrogen atom by a methyl group depend apparently upon the position of the substitute relative to the hydroxylic group, and the toxicity increases with the distance of the methyl group from the hydroxylic group and diminishes when both are brought closer together.

It appears, therefore, that in many instances the physiologic action of alcohols is closely affiliated with their lipoid solubility; in other instances there seems to exist a striking parallelism with their ability to lower the surface tension. In this connection, an observation of Fühner (1912a) may be mentioned. He noted that, with certain plants and lower animals, the effectiveness of normal alcohols increased, like their capillary activity, in the ratio $1:3:3^2$, etc. whereas, with regard to the narcotic action in higher animals, the increase was of the order of $1:4:4^2$, etc. He suggested that the nerve structures of higher animals might be richer in lipoid substances and that for this reason, in such species the solubility of alcohols in oil, as expressed by their partition coefficient, may play the more important role. But there are also conditions in which the dehydrating action of alcohols, and other factors, seem to play a role, and it is probable that the various toxicological reactions may be affected by one or the other mechanism to a different extent.

B. THE BIVALENT OR DIHYDRIC ALCOHOLS

The dihydric alcohols or glycols of the type HO–R–ROH are, as a rule, less volatile than the monohydric alcohols. They find less extensive use in the lacquer industry, but some of them are used in the explosives industry and as solvents for cosmetics and pharmaceutical products. On the other hand, the ethers and esters of some of these materials are used quite extensively as solvents, and since these may be decomposed in the organism with the formation of bivalent alcohols, a knowledge of the toxicity of the latter is important for the appraisal of the potential hazards of the former.

a. Ethylene glycol

The lowest member of this series is *ethylene glycol*, glycol, ethandiol-1,2, HO–CH$_2$–CH$_2$–OH, of the molecular weight 62.07. It is a colorless liquid of the specific gravity 1.113 at $\frac{19°}{4°}$ C. which solidifies at $-15.6°$ C. and boils at 197.4° C. and which is miscible with water and alcohol but is less soluble in ether. Lawrie (1928) gave an extensive review of its physicochemical properties, and Schierholtz and Staples (1935) determined its refractive index as 1.43192 at 20° C. and as 1.43072 at 25° C. and its density as 1.1140 at 20° C. Lehmann and Flury (1938) gave its flash point as 117° C.

Uses.—Ethylene glycol is used as a solvent for dyes and gelatinized cellulose and also as solvent for many heavy metal salts, barbital, alkaloids, iodine, and others (Browning, 1937). It is used in the cosmetic and perfume industry, as antifreeze in radiators, and in the explosives industry.

Chemical characteristics.—Ethylene glycol yields oxalic acid upon oxidation with nitric acid, and with acid potassium permanganate it yields glycol aldehyde, HOCH$_2$CHO, and glyoxalic acid, HOOC-COOH.

Following oxidation of 1 gm. ethylene glycol with 10 cc. of fresh 3 percent bromine water for 20 minutes on a boiling water bath and removal of the excess of bromine, the oxidation product (G) gives the following reactions which are also characteristic for glycerol (Rosenthaler, 1923):

> 1. 0.2 cc. G mixed with 0.1 cc. 5 percent alcoholic codeine solution, 0.2 cc. water and 2 cc. concentrated H$_2$SO$_4$ and heated for 2 minutes yields a greenish blue color.

2. 0.4 cc. G mixed with 0.1 cc. of a 2 percent alcoholic solution of β-naphthol and 2 cc. H₂SO₄ and heated for 2 minutes yields a fluorescent color.

3. 0.4 cc. G mixed with 0.1 cc. of a 5 percent alcoholic solution of resorcinol and 2 cc. H₂SO₄ and kept for 2 minutes at room temperature yields a blood red color which turns red-yellow to yellow after dilution with acetic or sulfuric acid.

Antiseptic properties.—Ethylene glycol has moderate antiseptic properties, but when used as fine mist, as "aerosol", it is about as effective as propylene glycol, as was shown by Robertson, Bigg, Miller, and Baker (1941).

The absorption, fate, and elimination of ethylene glycol.—It appears questionable whether the *absorption of ethylene glycol* through the skin may cause toxic effects as indicated by the negative findings reported in mice by Sander (1933) and as assumed by Hunt (1932). The absorption of ethylene glycol through the lungs is evidently of no practical importance, as indicated by the reports of Flury and Wirth (1934) and Wiley, Hueper and von Oettingen (1936). It is, however, readily absorbed from the gastro-intestinal tract.

With regard to *its fate in the organism and its elimination*, Pohl (1896) found, in experiments in dogs with Thiry-Vella fistula, that an appreciable fraction of ethylene glycol is oxidized to oxalic acid. This was confirmed in rabbits by Dakin (1907), in dogs by Bachem (1917), and by others. With regard to the extent of this oxidation and excretion of oxalic acid, the results of different investigators are not in agreement, as illustrated in table 37. Whereas the majority of investigators, Pohl (1896), Dakin (1907) and Bachem (1917), found

Table 37.—*Excretion of oxalic acid following administration of ethylene glycol*

Species	Route of administration	Dose of ethylene glycol Total gm.	Gm./ kg.	Corresponding to gm. oxalic acid	Total oxalic acid excreted in gm.	Period of time in days	Percent conversion of ethylene glycol to oxalic acid	Author
Dog	Orally	4.45	1.0	6.45	0.1349	3	2.1	Pohl (1896).
Do	do	5.56	1.4	8.06	.1825	3	2.3	Pohl (1896).
Do	do	20	2.6	29	.1572	2	.54	Bachem (1917).
Do	do	20	2.6	29	.625	2	2.2	Bachem (1917).
Rabbit	do	5	2.2	7.25	.0282	2	.4	Mayer (1903).
Do	Subcutaneously	2.5	1.1	3.625	.054	3	1.5	Dakin (1907).
Do	do	2.5	1.1	3.625	.069	3	1.9	Dakin (1907).
Man	Orally	20		29	.1674	2	.54	Bachem (1917).
Do	do	20		29	.1184	2	.41	Bachem (1917).

REPEATED ADMINISTRATION

Species	Route of administration	Dose total	Gm./kg.	Corr.	Total oxalic	Period	Percent	Author
Dog	Subcutaneously	(1)		6.7	0.216	7	0.43	Wiley, Hueper, Bergen, and Blood (1938).
Do	do	(1)		6.7	.247	7	.49	
Rabbit	do	(2)		22.62	.053	7	.26	
Do	do	(2)		22.65	.041	7	.20	

1 5 cc. daily for 7 days, corresponding to 35 cc. or 38.95 gm.
2 2 cc. daily for 7 days, corresponding to 14 cc. or 15.6 gm.

that approximately 2 percent of the ethylene glycol administered is excreted as oxalic acid, others, Mayer (1903), and Wiley, Hueper, Bergen and Blood (1938), found considerably lower values of 0.2 to 0.49 percent. With regard to the formation of other metabolites of ethylene glycols, Mayer (1903) was unable to detect glycol aldehyde or glyoxalic acid in rabbits' urine but he was able to isolate glycolic acid $(HOCH_2COOH)$ in quantities corresponding to one-fourth of the amount of ethylene glycol given and was inclined to consider this as an intermediate in the formation of oxalic acid. According to Bernheim and Handler (1941), ethylene glycol is oxidized by liver preparations containing active alcohol oxidase. As found by Höckendorf (1909–10) and confirmed by Page (1927), it is not converted to sugar in the organism, and Newman, van Winkle, Kennedy and Morton (1940) found that it is not utilized by the perfused cat's liver. Miura (1911) stated that the administration of ethylene glycol does not cause the appearance of reducing substances or glucuronic acid in the urine. Lepkovsky, Ouer and Evans (1935) showed that, in contrast to the ethyl alcohol esters of fatty acids, the corresponding ethylene glycol esters are poorly utilized as food by rats.

The effect of ethylene glycol on the nervous system is not very marked. According to Macht and Ting (1922), the depressant effect of doses of 120 mg. per 100 gm. body weight on the activity of rats in a maze corresponds to that of 80 mg. per 100 gm. of ethyl alcohol, and similar observations were reported by van Winkle and Kennedy (1940). Von Oettingen and Jirouch (1931) found that ethylene glycol causes only a moderate depression of the central nervous system. This was confirmed by Hunt (1932) and Hofbauer (1933). Latven and Molitor (1939) determined the minimal hypnotic dose for mice, with subcutaneous injection, as 1.0 cc. per kg.; with oral administration as 1.0 cc. per kg.; and, by intravenous route, as 2.0 cc. per kg., this dose causing immediate effect. Von Oettingen and Jirouch (1931) noted, in frogs, following the subcutaneous injection of ethylene glycol, convulsions which they believed to be due to a peripheral rather than a central effect. This was confirmed by Busquet (1938). Hofbauer (1933) observed, in rats, on the first and second days following the subcutaneous administration of 2 gm. per kg. of ethylene glycol, clonic convulsions and opisthotonus; Hanzlik, Seidenfeld and Johnson (1931) saw, in rabbits, twitchings, tremors and convulsions; and Hanzlik, Newman, van Winkle, Lehman and Kennedy (1939) reported that, in dogs, the intravenous administration of 20 cc. per kg. of ethylene glycol caused convulsions without demonstrable anesthesia. As shown by Page (1927), the intravenous administration of ethylene glycol causes, in dogs, a primary increase and subsequent slowing of the respiration. This was confirmed by Hanzlik, Seidenfeld and Johnson (1931). With respect to the effect of inhalation of

vapors of ethylene glycol on the central nervous system, Flury and Wirth (1934) and Wiley, Hueper and von Oettingen (1936) found that even air saturated with vapors of ethylene glycol had no distinct depressant effect on mice.

With regard to the *irritant action of ethylene glycol*, Bachem (1917) stated that its subcutaneous injection caused local irritation and slight inflammation. This was confirmed by Hanzlik, Seidenfeld, and Johnson (1931) who showed, in addition, that the local application of the undiluted glycol to the conjunctiva of rabbits caused chemosis and that it also exerted a moderately irritant action on the frog's skin (Türck's experiment) and on the sciatic nerve of the frog. Similar results were reported by Ajazzi-Mancini (1935) and by Page and Coryllos (1926), but it should be pointed out, as all investigators agree, that only concentrated ethylene glycol, not the diluted solutions, has this irritant effect. Von Oettingen and Jirouch (1931) showed that ethylene glycol causes no depression of the peripheral nerve fiber as might be expected from its low partition coefficient oil/water which is 0.5.

With regard to the *effect of ethylene glycol on the circulation*, von Oettingen and Jirouch (1931) found that even 1 and 2 percent solutions caused only a slight depression of the isolated frog's heart. Huddleston (1939) studied the electrocardiographic changes in young dogs, following the oral administration of a 4 percent solution of ethylene glycol, and found, among other changes, that these cause bradycardia, exaggerated sinus arrhythmia, sinus-auricular block, slight displacement of the S–T segment, and, sometimes, diphasic T waves. Adult dogs treated in the same way showed sinus arrhythmia, less marked bradycardia and, less frequently, A–V block, which appears to be exceptional in ethylene glycol poisoning. The effect of ethylene glycol on the blood pressure appears to be not very marked. Bachem (1917) found that the intravenous injection of 1 cc. caused only a moderate fall of the blood pressure in rabbits, and Page (1927) noted that this was followed by a marked increase of the amplitude of the heart beat, occasionally associated with a slight slowing of the pulse rate.

Bachem (1917) and von Oettingen and Jirouch (1931) found that, in vitro, ethylene glycol causes hemolysis, and the former believed that this may also result from intravenous injections. Di Prisco and Swarc (1940) showed that in rabbits the repeated intravenous and subcutaneous administration of alcohol causes a reduction of the number of red and white blood cells and of the hemoglobin and the appearance of immature red blood cells which was not seen with oral administration or inhalation. In view of the fate of ethylene glycol in the organism, resulting in the formation of oxalic acid, it was

thought that the latter might affect the calcium level in the blood. Hofbauer (1933) found, however, that only fatal doses caused a marked reduction of the blood calcium whereas smaller doses, causing no distinct toxic effect, did not affect the calcium level noticeably; and similar negative results were reported by Dille (1934).

With regard to the *effect of ethylene glycol on muscular structures*, von Oettingen and Jirouch (1931) found that pure ethylene glycol causes a hyaline shrinkage of the muscle fibers and that diluted solutions cause some depression of the isolated muscle. Busquet (1938) showed that ethylene glycol does not antagonize the action of curare but that it does antagonize the action of strychnine iodomethylate and decrease the chronaxy of the nerve. Hanzlik, Seidenfeld and Johnson (1931) found that concentrations of ethylene glycol of 1:500 and less had no effect on smooth muscle organs, and that only concentrations of 1:250 to 1:100 caused a moderate reversible depression. This agrees with the findings of von Oettingen and Jirouch (1931).

With regard to the *effect of ethylene glycol on metabolism*, Cerabona (1939) showed that about two-thirds of the rabbits chronically poisoned with ethylene glycol showed an increase of the chloride level of the blood which he attributed to renal injury. Mauro (1939a, b, c) found that in chronic poisoning with ethylene glycol the creatinine level in the blood of rabbits is increased, especially when the urinary excretion is impaired, and there may be a considerable degree of glucemia, indicating injury of liver and kidney. He found also an increase of the cholesterol, neutral fats, soaps, and phosphatides in the blood of such animals, indicating a disturbance of the fat metabolism.

The *toxicity of ethylene glycol* has aroused much comment. Earlier investigators believed that it has comparatively little toxicity. Bachem (1917) and others suggested its use as a substitute for glycerol in pharmaceutical products, and Haag and Bond (1927) advocated its use as a solvent for chloretone in anesthesia of dogs. Hunt (1932) pointed out that with oral, intraperitoneal, and intravenous administration it is distinctly toxic for mice, rats, guinea pigs, rabbits, cats, and dogs. Table 38 gives a résumé of the minimal fatal doses, as determined by various investigators for different species of animals and with various routes of administration. It shows that the results of various investigators may show considerable variation which may be partly explained by the limited number of animals and possibly also by differences in the grade of the ethylene glycol used, the technical and less pure products being more toxic. The symptoms observed in acute ethylene glycol poisoning are characterized by weakness, lack of coordination, tremors, twitchings and convulsions, progressive prostration, coma, and death which may occur after 18 to 28 hours or after several days, depending upon the dose given.

Table 38.—*The minimal fatal doses of ethylene glycol for various species with different forms of administration*

ORAL ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	Pure 9.0 technical 5. 5.	Scholz (Lehmann and Flury, 1938).
Do	7.5 (M. F. D. 50)	Latven and Molitor (1939).
Do	13.1 (M. F. D. 50)	Laug, Calvery, Morris, and Woodward (1939).
Rat	5.5 (M. F. D. 50)	Do.
Do	7.7 (M. F. D. 50)	Smyth, Jr., Seaton, and Fischer (1941).
Guinea pig	7.4 (M. F. D. 50)	Laug, Calvery, Morris, and Woodward (1939).
Do	6.0 (M. F. D. 50)	Smyth, Jr., Seaton, and Fischer (1941).
Rabbit	8.1	Hildebrandt (Lehmann and Flury, 1938).

SUBCUTANEOUS INJECTION

Species	Dose cc./kg.	Author
Mouse	Approx. 2.5	von Oettingen and Jirouch (1931).
Do	4.5 (M. F. D. 50)	Latven and Molitor (1939).
Do	Pure 6.5 technical 4.5	Scholz (Lehmann and Flury, 1938).

INTRAMUSCULAR INJECTION

Species	Dose cc./kg.	Author
Rat	3.9	Hanzlik, Seidenfeld and Johnson (1931).
Do	3.5	Ajazzi-Mancini (1939).
Rabbit	5.9	Hanzlik, Seidenfeld and Johnson (1931).
Do	3.7	Ajazzi-Mancini (1939).

INTRAPERITONEAL INJECTION

Species	Dose cc./kg.	Author
Rat	3.5	Page (1927).
Rabbit	9	Do.

INTRAVENOUS INJECTION

Species	Dose cc./kg.	Author
Mouse	3 (M. F. D. 50)	Latven and Molitor (1939).
Rat	2.5	Hanzlik, Seidenfeld, and Johnson (1931).
Do	5.5	Ajazzi-Mancini (1939).
Rabbit	3.9 to 4.9	Hanzlik, Seidenfeld, and Johnson (1931).
Do	5.7	Ajazzi-Mancini (1939).

In contrast to the comparatively low acute toxicity, the toxic effects of repeated administration of comparatively small doses are much more marked. Hanzlik, Seidenfeld, and Johnson (1931) fed rats drinking water containing various concentrations of ethylene glycol with the following results: With 10 percent ethylene glycol the majority of the rats had died by the end of the third day; with 5 percent, after 5 days; with 3 percent, after 6 days; with 2 percent, after 14 days; and, with 0.5 to 1.0 percent, the animals survived but suffered from stunted growth. Similarly, Holck (1937) found that substitution of 2.92 percent ethylene glycol for the drinking water killed rats in an average of 4 days. Morris, Nelson, and Calvery (1942) found that the continued administration of 1 and 2 percent ethylene glycol to rats, over a period of 2 years, showed no significant changes of growth rate and food consumption as compared with the control animals. At the end of the experiment, in 4/10 of the animals receiving 1 percent ethylene glycol and in 2/10 of the animals receiving 2 percent ethylene glycol, laminated mul-

berry bladder stones of 0.8 to 1.7 cm. diameter were found, the bladder showing marked chronic cystitis. The stones consisted essentially of calcium oxalate. Otherwise, the animals showed signs of marked damage of the kidneys and moderate chronic injury of the liver.

Toxic effects from continued exposure to vapors of ethylene glycol have not been observed (Flury and Wirth, 1934). Wiley, Hueper, and von Oettingen (1936) showed that even continued exposure for 5 days a week over 16 weeks had no deleterious effects aside from a moderate irritation.

The toxicity of ethylene glycol for humans is illustrated by five cases of acute poisoning resulting from the ingestion of ethylene glycol, three of which ended fatally, as reported in "Queries and Minor Notes" in the Journal of the American Medical Association (1940 and 1942) and by Brekke (1930) and Hansen (1930). After several hours (over night) all the victims were in stupor and coma. One patient of Brekke (1930) and one of Hansen (1930) developed a bilateral abducens paresis and paralysis of the soft palate, and in both the pupils were dilated and nonreactive. The other patients showed negative patellar reflexes and a positive Babinski. The patients were nauseated and they vomited, the vomitus containing blood. The pulse was accelerated, small and soft. The respiration was slow and stertorous in two patients and rapid in two others who died. The urine became scanty and contained albumen and blood but no sugar, and the nonprotein nitrogen in the blood rose to 3.0 and 3.3 per thousand. The patients of Brekke (1930) and Hansen (1930) recovered following decapsulation of the kidney, but the two other patients mentioned died from convulsions and respiratory paralysis.

It was estimated that these patients had ingested approximately 100 cc. of ethylene glycol. Smaller single doses have been tolerated without apparent harm, as reported by Bachem (1917) who ingested 20 gm. diluted with water; and Page (1927) ingested 15 cc. diluted with water without ill effects.

With regard to industrial poisoning from ethylene glycol no definite information is available. According to a report by Hackett (1935), one case of such poisoning received compensation in the State of New York, but neither the type of the injury nor details of the exposure are available.

Pathological changes in ethylene glycol poisoning are mainly characterized by injury of the kidneys. Lepkovsky, Ouer, and Evans (1935) noted, following oral administration of ethylene glycol esters, enlargement of the kidneys, dilatation of the collecting and convoluted tubules, flattening of the epithelium of the collecting tubules, and, in places, complete degeneration. Hanzlik, Newman, van Winkle, Leh-

man, and Kennedy (1939) reported, after oral administration to dogs, marked necrosis and complete destruction of the convoluted tubules and swelling of the glomeruli, and Laug, Calvery, Morris, and Woodward (1939) saw, in mice, hydropic degeneration of the cells lining the cortical convoluted tubules. Wiley, Hueper, Bergen, and Blood (1938) noted, in dogs and rabbits, mild degrees of nephrosis and scattered calcium casts in the pyramidal tubules of dogs. With regard to other organ changes, Laug, Calvery, Morris, and Woodward (1939) found, in mice, following oral administration, congestion and hemorrhages in the lungs and hemorrhagic areas in the stomach. Following fatal doses of ethylene glycol, Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939) found marked degeneration of the liver and fatty infiltration of the liver cells with nuclear changes. These data indicate that injury of the kidneys is the most outstanding phenomenon in ethylene glycol poisoning and that mainly the tubular apparatus and, to a much lesser extent, the glomeruli are involved in the effect. This appears to be supported by an observation of Cortese (1941) who found that, following subcutaneous injection of small amounts of ethylene glycol for periods up to 28 days, the tubular apparatus was damaged whereas the glomeruli were not affected, as indicated by the outcome of the Rehberg test which is indicative of the filtering power of the glomerular apparatus. With regard to the cause of the renal injury, many investigators associated this with the formation of oxalic acid and calcium oxalate deposits in the kidney. However, it appears, as pointed out by Hunt (1932) and Wiley, Hueper, Bergen, and Blood (1938), that aside from this effect ethylene glycol must exert some other toxic action on the kidney.

Prophylaxis and treatment of ethylene glycol poisoning.—As pointed out by Flury and Wirth (1934) and Wiley, Hueper, and von Oettingen (1936), poisonings from the inhalation of vapors of ethylene glycol appear to be remote on account of its low volatility, and absorption through the skin is, at best, too slow to permit the absorption of injurious quantities. This appears to be supported by a report by the Factory Inspection Department of the Home Office, quoted by Browning (1937), on the examination of workers in a plant in which ethylene glycol was handled in an electrolytic process. This examination revealed very little with regard to definite symptoms. One worker engaged in the operation for 2 years complained of "phlegm" and another one who had been employed for 9 months complained of loss of appetite and "dopiness". Two of four workers examined showed considerable albuminuria and increased urobilin, and one of these showed "more red blood corpuscles than would be expected in a normal specimen"; a third showed a trace of albumen but neither red blood cells nor casts; and the fourth was normal. (The patient with considerable albuminuria had recently had influenza.) In case ethyl-

ene glycol has been taken by mouth the stomach should be emptied by gastric lavage and the diuresis should be increased by administration of copious amounts of fluid. As indicated by the reports of Brekke (1930) and Hansen (1930), decapsulation of one kidney may improve the renal function and thus prevent fatal outcome.

b. Propylene Glycol

Physico-chemical properties.—Propylene glycol, propandiol-1,2, $CH_3CHOHCH_2OH$, has the molecular weight 76.09. It is a colorless fluid of the specific gravity 1.040 at 19.4° C., which boils at 188° to 189° C. and which is miscible with alcohol and water and soluble in ether to the extent of 8 percent. Its flash point is 107.2° C. Its physico-chemical properties have been discussed by Lawrie (1928), and Schierholtz and Staples (1935) determined its refractive index as 1.43162 at 25° C. and its density at 1.0354 at 23° C.

Uses.—Propylene glycol is used in cosmetic and pharmaceutical preparations and in coloring extracts (Newman and Lehman, 1937a; Brown, 1935; and Rae, 1935a, b). According to Robertson, Bigg, Miller, and Baker (1941) it may be used in the form of an aerosol for the disinfection of air. These authors found that a suspension of 1 gm. propylene glycol per 2,000 liters (161 p. p. m.) of air sterilized an atmosphere containing 200,000 *Staphylococci albus* per liter. In the opinion of Robertson, Loosli, Puck, Bigg, and Miller (1941), the disinfecting action of propylene glycol is mainly due to the rapid evaporation of its minute droplets. They found that mice exposed to concentrations of 1 gm. propylene glycol in 2,000 and 3,000 liters (161 and 106.3 p. p. m) of air and, in addition, for 15 to 60 minutes, to influenza virus (0.2 to 1.0 cc. of a 10^{-2} dilution of the virus in the form of a mist) remain well, whereas controls exposed to the same concentration of the virus died within 4 to 10 days. Robertson, Bigg, Puck, and Miller (1942) showed that gram-positive bacteria killed by exposure to propylene glycol retained their gram-positiveness as well as their morphological integrity and that they retained their antigenic properties. It appears that propylene glycol inhibits but does not destroy the autolytic enzyme system of the cell (pneumococcus).

The determination of propylene glycol in air.—Puck (1942) determined the concentration of propylene glycol in air by bubbling 2 liters of air at the rate of 0.25 liters per minute through 10 cc. of water with the aid of a sintered glass filter. This solution is quantitatively transferred to an Erlenmeyer flask, mixed with 1 cc. m/10 solution of sodium periodate, and kept in an ice box for 15 minutes. After this time 5 cc. of 7 percent solution of sodium bicarbonate are added, followed by 2.5 cc. n/10 sodium arsenite and 2 cc. of a freshly prepared, 20 percent solution of potassium iodide, and allowed to stand for 15

minutes. Then 1 cc. of a 1 percent starch solution is added and the solution is titrated with 0.01 normal iodine solution, 1 cc. of which corresponds to 0.38 mg. of propylene glycol.

For the *determination of propylene glycol in blood and urine*, Newman and Lehman (1937a) treated protein-free blood filtrate with a solution of potassium bichromate in strong sulfuric acid and estimated the amount of reduced chromate colorimetrically. The difference between this value and that obtained in the same way from blank blood allows the calculation of the amount of propylene glycol present in the original sample. A simple procedure may also be applied to urine.

The absorption, fate, and excretion of propylene glycol.—No information is available as to whether or not, or to what extent propylene glycol is absorbed through the intact skin and the respiratory tract, but it appears reasonable to assume that these routes of entry are of no practical importance. As shown by Lehman and Newman (1937a) and van Winkle (1941b), in rabbits, cats, and rats, propylene glycol is rapidly absorbed from the intestinal tract, especially from the jejunum and, to lesser extents, from the duodenum, colon, and stomach, in the order given. They also showed that diluted solutions are more readily absorbed than concentrated ones and that high concentrations of propylene glycol in the blood reduce the rapidity of the absorption.

With regard to the fate of propylene glycol in the organism, Pohl (1896) found, in dogs with Thiry-Vella fistula, that propylene glycol is, apparently, completely oxidized, and Lehman and Newman (1937a) stated that after its absorption it is rapidly distributed through all tissues and readily oxidized. In the opinion of Neubauer (1901) and Miura (1911) propylene glycol is partly excreted in conjugation with glucuronic acid. Newman and Lehman (1937a) found that the concentration of propylene glycol in the blood is proportional to the concentration in the body, in contrast to ethyl alcohol which disappears at a constant rate, perhaps on account of a more rapid elimination through the kidneys. In dogs which ingested propylene glycol in 5 percent solution as drinking water over a period of 5 to 9 months, corresponding to an average daily intake of 5.1 cc. per kg., van Winkle and Newman (1941) determined the average propylene glycol level in the blood as 325 mg. percent which evidently caused no toxic effects.

According to Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939), in dogs the excretion of propylene glycol is completed within 24 hours following the oral administration of 8 cc. per kg. Newman and Lehman (1937a) were able to recover from the urine about one-half the amount of propylene glycol given orally or intravenously, and van Winkle (1941b) recovered from the urine one-third of the amount

given in the form of a 5 percent solution as drinking water to rats and found that the concentration in the urine did not exceed 10 percent.

The *effect of propylene glycol on the central nervous system* is not very marked. Van Winkle and Kennedy (1940) found that its depressant effect on the central nervous system is less marked than that of ethylene glycol when substituted for carbohydrate to the extent of 25 percent (representing 12 percent of the total diet). Hanzlik, Newman, van Winkle, and Kennedy (1939) determined, in dogs, the average anesthetic dose with intravenous injection as 21.2 cc. per kg., and Latven and Molitor (1939) determined the minimal hypnotic dose for mice as 10 cc. per kg. with subcutaneous, 8.0 cc. per kg. with oral, and 2.0 cc. per kg. with intravenous administration. According to Newman and Lehman (1937a) the concentration of propylene glycol in the blood required to produce the same degree of narcosis produced by ethyl alcohol is 1,100 mg. percent as compared with 350 mg. percent of the latter. As shown by Ajazzi-Mancini (1939) the slow intravenous injection of 20 cc. per kg. causes, in rabbits, a primary increase and then a decrease, and, finally, paralysis of the respiration.

Propylene glycol has *irritant properties*. Seidenfeld and Hanzlik (1932) stated that, when applied to the tongue, propylene glycol causes a burning sensation, and, when given subcutaneously, it is more irritant than ethylene glycol. When tested on the rabbit's eye, the undiluted glycol causes chemosis, but in 50 percent solution it causes only lacrimation. Braun and Cartland (1936) and Latven and Molitor (1939) found that it caused distinct irritation with subcutaneous injection, but, according to the former investigators, the irritant effect is only transient.

With regard to the *effect of propylene glycol on the circulation*, Spealman (1940) found that 0.1 molar solutions had no apparent effect on the isolated frog heart and 0.2 molar solutions caused no changes in the weight of the ventricle, indicating that propylene glycol is only slightly active osmotically. Ajazzi-Mancini (1939) found that the slow intravenous injection of 20 cc. per kg. of propylene glycol causes, in rabbits, a fall of the blood pressure.

Weatherby and Haag (1938) found that solutions of propylene glycol of more than 0.14 molar (32.8 percent) strength cause hemolysis in vitro, and they assumed that this was due to a dilution of the isotonic saline which thus was rendered hypotonic. Similarly, van Winkle (1941b) found that concentrations of 38 percent of propylene glycol in normal saline cause partial, and in 45 percent solution complete hemolysis of red blood cells. He also found that the administration of propylene glycol does not increase the calcium level in the blood, whereas according to the findings of Hofbauer (1933) in cats, doses of 3 to 6 gm. per kg. usually increase the concentration of calcium in the blood.

With regard to the *effect of propylene glycol on the metabolism*, Salter, Robb and Scharles (1935) found that, in contrast to ethylene glycol, feeding of propylene glycol increases the liver glycogen of guinea pigs. This was confirmed by Hanzlik, Lehman, van Winkle, and Kennedy (1939) who showed that, within certain limits, it may be substituted for carbohydrates with optimal results in the diet of rats. Van Winkle and Newman (1941) doubted, however, whether propylene glycol should really be considered as a readily available source of energy and suggested the possibility that it may increase the glycogen content of the liver by depressing its metabolism since it was shown by Newman, van Winkle, Kennedy and Morton (1940) that propylene glycol depresses the oxygen consumption and carbon dioxide production of the perfused cat's liver. In contrast to these findings with an isolated organ, Hanzlik, Lehman, van Winkle, and Kennedy (1939) found that propylene glycol has no demonstrable effect on the basal metabolic rate in man or on the respiratory quotient of rats. More recently, van Winkle (1942) showed that, in rats, propylene glycol in doses of 5 and 10 cc. per kg. decreases the oxygen consumption (average cc. of oxygen consumed per 100 cm.^{2} of body surface per minute at 22° C.) to an average of 1.142 cc. from the control average 1.363.

The *toxicity of propylene glycol* is lower than that of ethylene glycol and its acute toxicity is less than one-half that of ethyl alcohol (Lehman and Newman, 1937a). The minimal fatal doses for different animals with different routes of administration, as found by different investigators, are summarized in table 39. After oral administration of large doses the animals rapidly become incoordinated, their motor and sensory functions become more and more depressed, they become comatose, and die after several hours or even days have elapsed. With intravenous administration of fatal doses animals may show first a stimulation and later a depression of the respiration, followed by motor and sensory depression, coma, and death. Weatherby and Haag (1938) and Kesten, Mulinos, and Pomerantz (1939) also noted hematuria and hemoglobin casts in the renal cortex following the intravenous injection of fatal doses, but according to Lehman and Newman (1937a) this is not observed after oral administration. Gross (Lehmann and Flury, 1938) noted a temporary albuminuria and red blood cells in the urine of rabbits which had received 7.0 gm. per kg. by stomach tube in the form of a 50-percent solution, and a dog fed 4 gm. per kg. of the same concentration developed diarrhea.

With regard to the chronic toxicity of propylene glycol, this is much less than that of ethylene glycol. Hunt (1932) noted no toxic effects in animals which received 5 percent propylene glycol as drinking water over a long period of time; and Seidenfeld and Hanzlik (1932) showed that rats which were fed 1, 2, 5, and 10 percent propylene glycol as

Table 39.—*The minimal fatal doses of propylene glycol for different species of animals by various routes of administration*

ORAL ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	22 (M. F. D. 50)	Latven and Molitor (1939).
Do	23.9 (M. F. D. 50)	Laug, Calvery, Morris, and Woodward (1939).
Rat	32.2 (M. F. D. 50)	Weatherby and Haag (1938).
Do	21 (M. F. D. 50)	Laug, Calvery, Morris, and Woodward (1939).
Do	25.3 (M. F. D. 50)	Smyth, Jr., Seaton, and Fischer (1941).
Guinea pig	18.9 (M. F. D. 50)	Laug, Calvery, Morris, and Woodward (1939).
Do	17.8 (M. F. D. 50)	Smyth, Jr., Seaton, and Fischer (1941).
Rabbit	19.2	Braun and Cartland (1936).

SUBCUTANEOUS ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	18.5 (M. F. D. 50)	Latven and Molitor (1939).
Rat	22.2	Braun and Cartland (1936).
Do	21.6 (M. F. D. 50)	Weatherby and Haag (1938).

INTRAMUSCULAR ADMINISTRATION

Species	Dose cc./kg.	Author
Rat	14.1	Seidenfeld and Hanzlik (1932).
Do	15.1	Braun and Cartland (1936).
Do	13.4	Weatherby and Haag (1938).
Do	13.9	Ajazzi-Mancini (1939).
Rabbit	7.1	Seidenfeld and Hanzlik (1932).
Do	7.85	Ajazzi-Mancini (1939).

INTRAVENOUS ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	4.8	Gross (Lehmann and Flury, 1938).
Do	8	Latven and Molitor (1939).
Rat	16.1	Seidenfeld and Hanzlik (1932).
Do	6.5	Weatherby and Haag (1938).
Do	11.6	Ajazzi-Mancini (1939).
Rabbit	4.1	Seidenfeld and Hanzlik (1932).
Do	6.2	Weatherby and Haag (1938).
Do	4.5	Ajazzi-Mancini (1939).
Dog	25	Hanzlik, Newman, van Winkle, Jr., Lehman, and Kennedy (1939).

drinking water for one-eighth of their life span showed no demonstrable toxic effects. Braun and Cartland (1936) noted no cumulative effect with daily administration of 8 cc. per kg; and Holck (1937) found that of rats which were fed 3.58 percent propylene glycol as drinking water, 1 died after 10 weeks, 1 was sick, and others started to lose weight. Ajazzi-Mancini (1939) found no evidence of any toxic effects in rats after average daily doses of 11.87 gm. per kg. over a period of 42 days; and Weatherby and Haag (1938) found that concentrations up to 3 percent of propylene glycol as drinking water had no effect on the growth of rats over a period of 100 days whereas 10 percent caused a temporary slowing of the growth rate. Van Winkle and Newman (1941) found that daily feeding of 5-percent propylene glycol as drinking water for 5 to 9 months, corresponding to a daily intake of 5.1 cc. per kg., caused neither toxic effects nor pathological and functional changes of liver and kidneys although the average concentration of propylene glycol in the blood ran as high as 325 mg. per 100 cc. Higher hypertonic concentrations of 10 percent in drinking water caused the animals to become thirsty and ingest

much greater doses of propylene glycol, so that the average concentration of propylene glycol rose to 800 mg. per 100 cc. The increased intake of 10 percent glycol resulted in the production of coma, and the dogs died of marked central depression or of a subsequent pneumonia. If, however, 600 cc. of a 10-percent solution were fed in the morning and pure water in the evening, so that the average daily intake was 4.5 cc. per kg., the animals remained in good health and showed no functional changes of liver or kidneys. Gross (Lehmann and Flury, 1938) found that in rabbits 12 daily doses of 2.0 and 4.0 gm. per kg. over a period of 14 days caused no noticeable toxic effects, but, on autopsy, liver, kidneys, and spleen showed moderate edema and hyperemia. Morris, Nelson and Calvery (1942) showed that continued feeding of propylene glycol in concentrations of 2.45 and 4.9 per cent with the food, over a period of up to 2 years, caused no changes in the rate of growth and food consumption. The animals developed no bladder stones, as seen with ethylene glycol, and showed no signs of chronic injury of the kidneys and only slight chronic liver damage. It appears, therefore, as stated by Ajazzi-Mancini (1939), van Winkle and Newman (1941) and others, that there is good reason to believe that the ingestion of moderate doses of propylene glycol involves no individual or public health hazards. Robertson, Bigg, Puck, Miller, and Baker (1942) kept a colony of rats in an atmosphere containing a high concentration of propylene glycol in a mist form for a period of 7 months. At the end of this period they showed no evidence of any deleterious effects on growth rate, fecundity or general condition. The histological examination of liver, lungs, and kidneys revealed no abnormal changes.

With regard to *pathological changes in propylene glycol poisoning*, information is very scanty. Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939) found no evidence of liver and kidney injury following continued feeding. With the oral administration of single fatal doses, Laug, Calvery, Morris, and Woodward (1939) noted no definite gross pathology except for hemorrhagic areas in the small intestine, and, histologically, they found only a little damage to the kidney, characterized by nuclear pyknosis, vacuolar degeneration and protein debris, and loose casts in the cortical tubules. The liver showed slight congestion and hyperemia but no fatty changes.

There are no reports on injurious effects from industrial or other use of propylene glycol, and it appears, as pointed out above, that its industrial use does not involve any special hazards.

c. Trimethylene Glycol

Physico-chemical properties.—Trimethylene glycol, propandiol-1,3, $HOCH_2-CH_2-CH_2OH$, is the isomer of propylene glycol, propandiol-

1,2. It has the molecular weight 76.09 and represents a colorless oily fluid of the specific gravity 1.060 at $\frac{20°}{4°}$ C. which rapidly turns yellow-brown on standing (van Winkle, 1941a), which boils at 214° C., and which is miscible with alcohol and water. It is a byproduct in the saponification of fats and, presumably, is formed by fermentation of glycerol (Lawrie, 1928). Schierholtz and Staples (1935) determined its refractive index as 1.43847 at 25° C. and 1.43940 at 21° C. and its density as 1.0538 at 20° C.

According to Robertson, Bigg, Miller, and Baker (1941), its antiseptic efficiency as aerosol is of the same order as that of propylene glycol. But, according to van Winkle (1941a), it is about twice as toxic as propandiol-1,2, causing, in toxic doses, depression of the central nervous system which, in his opinion, is due in part to a different fate in the organism because propandiol-1,2 is said to be oxidized to lactic acid and hence either burned or converted to glycogen, and propandiol-1,3 is oxidized to malonic acid which forms insoluble calcium salts and, therefore, may act in a way similar to oxalic acid. The minimal fatal dose was found to be: For rabbits, with intravenous injection, 4.5 cc. per kg. of body weight (given as 50 percent solution); for rats, with intramuscular injection, 6 to 7 cc. per kg.; and, for rats, with oral administration, about 16 cc. per kg. Cats appear to be more sensitive, and 3 cc. per kg. by mouth may be fatal in this species. Continued feeding of trimethylene glycol in concentrations up to 5 to 12 percent with the food was found to have a definite inhibiting effect on the weight, and, in contrast to propylene glycol, it is said to have no glycogenic action .

d. Butylene Glycol

The higher homologue of propylene glycol is *butylene glycol*, butandiol-1,3. $CH_3CHOHCH_2CH_2OH$, of the molecular weight 90.12. It is an oily liquid of the specific gravity 1.026 at $\frac{20°}{4°}$ C., which boils at 203 to 204° C., and which is very soluble in water and alcohol but insoluble in ether.

According to Gross (Lehmann and Flury, 1938) it is used as a lubricant for special purposes, and it is an intermediate in the manufacture of artificial rubber by the butadiene-Buna process. Also, it has been suggested that it be substituted for glycerol in the cosmetic, tobacco, paper, and textile industries.

As stated by the same author, it does not cause irritation of the skin, even after contact for 72 hours. He refers further to unpublished data of Hildebrandt who found that, in rabbits, single doses of 7 gm. per kg., given orally, cause light narcosis and no albuminuria, and that, in dogs, single doses of 2.4 gm. per kg. have no toxic effect and 0.2 gm. per kg., given daily for 2 weeks, caused only moderate

albuminuria. Gross, himself, found that feeding of 10 and 12 gm. per kg., diluted with 10 percent water, was tolerated by rabbits, which showed temporary dyspnea, staggering, and slight narcosis but no albuminuria and recovered rapidly; whereas doses of 15 gm. per kg. were fatal, causing diarrhea, narcosis, and death. Smyth, Seaton, and Fischer (1941) determined the minimal fatal dose with oral administration for rats as 18.61 gm. per kg. and for guinea pigs as 11.46 gm. per kg.
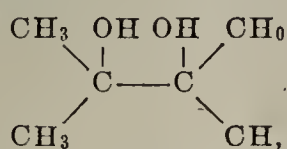
In a rabbit killed by the oral administration of butylene glycol, Gross (Lehmann and Flury, 1938) noted irritation of the gastro-intestinal tract, broadening of the intermediate layer of the kidney, and spotty reddening of the marrow, the urine, however, being free of albumen.

There are no reports on toxic effects of butylene glycol on the human organism, and it appears to offer very little potential danger.

One of the isomers of butandiol-1,3 is *pseudo-butylene glycol*, butandiol-2,3 $H_3C-CHO-CHOH-CH_3$, which has the molecular weight 90.12. It is a liquid of the specific gravity 1.048 at 0° C., which boils at 183 to 184° C. and which is miscible with water and ether.

According to Neuberg and Gottschalk (1925), it is excreted in rabbits largely as conjugated glucuronic acid, and from the fact that no acetoin could be isolated from the urine of the animals these investigators concluded that it is not oxidized to any considerable extent in the organism. Rabbits can tolerate doses of 5 cc. per kg., given in 2 fractions diluted with 40 cc. of water, without any toxic effects. The minimal fatal dose and toxic doses have apparently not been established.

The tertiary glycol, *pinacol*, 2,3-d i m e t h y l-butandiol-2,3,

$$\begin{array}{c} CH_3 \;\; OH \;\; OH \;\; CH_0 \\ \diagdown \; | \quad\;\; | \; \diagup \\ C \!\!-\!\! C \\ \diagup \quad\quad\; \diagdown \\ CH_3 \quad\quad\quad CH, \end{array}$$

has the molecular weight 118.17 and forms colorless needles of the specific gravity 0.967 which melt at 41 to 43° C. and boil at 171 to 172° C. at 739 mm. Hg. It is soluble in cold water, alcohol, and ether.

Thierfelder and von Mering (1885) found that a single dose of 3 gm. had no effect on a large rabbit, whereas 10 gm. caused sleep of 5 to 6 hours duration, and they found that the urine contained conjugated glucuronic acid.

There are a number of *bivalent alcohols which represent ethers formed by the condensation of 2 or more molecules of bivalent alcohols*, such as diethylene glycol, dipropylene glycol, triethylene glycol, etc.

e. Diethylene Glycol

The lowest member of this series is *diethylene glycol*, glycol ether, $HOCH_2-CH_2-O-CH_2CH_2OH$, of the molecular weight 106.2. It is a

colorless liquid of the specific gravity 1.132 at 0° C., which boils at 250° C., and which is soluble in water, alcohol, and ether. According to Gross (Lehmann and Flury, 1938) its flash point is 124° C.

Diethylene glycol is used in the manufacture of lacquers, as solvent for nitrocellulose and dyes (Browning, 1937), and as hygroscopic agent for tobacco (Mulinos and Osborne, 1934–35). It is also used as lubricant for special purposes (Gross—Lehmann and Flury, 1938) and for the sterilization of surgical instruments (Gurchot and Mellars, 1940).

The absorption, fate, and excretion of diethylene glycol.—No information is available with regard to the *absorption* of diethylene glycol through the skin or the respiratory tract. However, the latter route of entry appears to be insignificant in view of the high boiling point of this material. As shown by Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939), it is quite readily absorbed from the gastrointestinal tract. Very little is known regarding its fate in the metabolism, but it is evidently not oxidized to oxalic acid, presumably on account of the stability of the ether linkage (Wiley, Hueper, Bergen, and Blood, 1938). Morris, Nelson, and Calvery (1942) found laminated mulberry stones in the bladders of 3 out of 20 rats kept for 2 years on a diet containing 1.71 and 3.42 percent diethylene glycol, and they considered this a possible indication that, in the rat, the ether linkage of diethylene glycol may be broken up and result in the excretion of oxalic acid. According to Haag and Ambrose (1937), it is mostly excreted unchanged in the urine, the excretion being completed in 36 hours (Hanzlik, Newman, van Winkle, Lehman, and Kennedy, 1939).

With regard to the *effect of diethylene glycol on the nervous system*, Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939) found that, in dogs, the intravenous injection of 20 cc. per kg. causes no anesthesia, but convulsions, and, in contrast to propylene glycol, it produces, in equal or smaller doses, a temporary depression of the voluntary running movements of rats (van Winkle and Kennedy, 1940). It has been claimed that the use of diethylene glycol as hygroscopic agent for tobacco results in less irritant smoke than that obtained with the use of glycerol (Mulinos and Osborne, 1934–35 and 1935; Wallace, Reinhard, and Osborne, 1936; and Flinn, 1935 and 1937). This was not confirmed by Sharlit (1935) or by Haag (1937), and Holck and Carlson (1937) found no difference in the irritant action of smoke produced by tobaccos containing glycerol and diethylene glycol as hygroscopic agents.

With regard to the *effect of diethylene glycol on other physiological functions*, von Oettingen and Jirouch (1931) found that concentrations of 1 percent in Ringer's solution caused a reversible depression and a 2 percent solution caused arrest of the isolated frog's heart in

2 minutes, and, therefore, in this respect it is more toxic than ethylene glycol. In rabbits the intravenous injection of ethylene glycol causes a fall of the blood pressure, and in concentrations of 1:300 it produces a moderate depression of the isolated rabbit's intestine. Like ethylene glycol, pure diethylene glycol causes hyaline shrinkage of the isolated muscle fibers and causes hemolysis in vitro. As shown by Newman, van Winkle, Kennedy, and Morton (1940), it is not utilized by the perfused cat's liver but reduces the oxygen consumption and carbon dioxide formation and increases the lactic acid level in the perfusate.

The *toxicity of diethylene glycol for animals* is illustrated in table 40, which shows that the acute toxicity of diethylene glycol is not very

Table 40.—*The minimal fatal doses of diethylene glycol for different species with different forms of administration*

ORAL ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	23.7 (M. F. D. 50)	Laug, Calvery, Morris, and Woodward (1939).
Rat	Approx. 11.1	Poe and Witt (1937).
Do	15	Haag and Ambrose (1937).
Do	15	Geiling, Coon, and Schoeffel (1937).
Do	14.8	Laug, Calvery, Morris, and Woodward (1939).
Do	18.4	Smyth, Jr., Seaton, and Fischer (1941).
Guinea pig	11.7	Do.
Do	7.8	Laug, Calvery, Morris and Woodward (1939).

INTRAMUSCULAR ADMINISTRATION

Rat	7	Haag and Ambrose (1937).
Rabbit	4	Do.

SUBCUTANEOUS ADMINISTRATION

Mouse	Approx. 5	von Oettingen and Jirouch (1931).
Rat	5	Haag and Ambrose (1937).

INTRAPERITONEAL ADMINISTRATION

Rat	Approx. 11.1	Poe and Witt (1937).

INTRAVENOUS ADMINISTRATION

Rabbit	2	Haag and Ambrose (1937).

considerable. The oral administration of fairly large doses of diethylene glycol may cause thirst, vomiting, and diarrhea. The animals may show a bloated appearance; their fur becomes rough; their movements become incoordinated and staggering; and they show progressive depression, finally fall of the body temperature and coma, and, sometimes, convulsions before death. As pointed out by Geiling, Coon, and Schoeffel (1937), there is a marked difference between the acute toxicity of single doses of diethylene glycol and the effect of repeated administration of much smaller doses which may prove fatal or at least injurious. Haag and Ambrose (1937) showed that inges-

tion of 3 and 10 percent diethylene glycol as drinking water is rapidly fatal to rats. Similarly, Kesten, Mulinos, and Pomerantz (1939) found that ingestion of 3 percent solutions killed 50 percent of the rats within 2 months and that ingestion of 5 percent solutions killed one-fourth of the rats within 1 week. This is in agreement with the findings of Holck (1937) who found that 5 percent solutions, as drinking water, killed rats in 8 days; that 4 percent solutions resulted in the death of some animals and the stunted growth of others; and that even 0.25 percent solutions gave some indication of impaired growth. However, Haag and Ambrose (1937) found no evidence of a toxic action with concentrations of 0.1 to 0.03 percent, and Kesten, Mulinos, and Pomerantz (1939) noted no toxic effects or renal damage in animals fed 0.5 to 1.0 percent solutions over a period of 1 to 5 months. When mixed with solid food to the extent of 20 percent, diethylene glycol was fatal to all rats within 2 weeks, and 5 and 10 percent was fatal to some animals (Holck, 1937). Morris, Nelson, and Calvery (1942) fed rats a diet containing 1.71 and 3.42 percent diethylene glycol for a period of 2 years. These animals did not show any significant changes of the growth rate and the food consumption as compared with control animals. Three out of 20 animals showed laminated mulberry stones in the bladder. These consisted partly of calcium oxalate and partly of calcium phosphate. These animals showed a lesser degree of chronic cystitis than was observed with animals which were fed ethylene glycol, and they showed slight chronic damage of the kidneys and the liver.

The *toxicity of diethylene glycol for humans* is illustrated by a series of fatalities (60 up to 1937) which occurred in the United States from the ingestion of an "elixir" of sulfanilamide which contained 72 percent diethylene glycol. According to Ruprecht and Nelson (1937) and Geiling and Cannon (1938), the clinical picture of these poisonings may be described as follows: Upon the ingestion of the "elixir" the victims experienced heartburn, nausea, abdominal cramps, dizziness, and malaise; and they suffered from vomiting, diarrhea, and pain in the kidney region and the abdomen. In the course of from 2 to 5 days they developed oliguria and anuria; they became drowsy and showed puffiness of the face and sometimes slight jaundice; and died from 2 to 7 days after the onset of oliguria, in uremic coma. In addition, they showed pallor of the face without cyanosis, slow and deep respiration; they suffered from varying degrees of pulmonary edema, subnormal temperatures and slow pulse; and there was usually a moderate leucocytosis. The urine contained a large amount of albumen, casts and, occasionally, leucocytes; the nonprotein nitrogen in the blood rose to 200 mg. and the creatinine to 12 mg. per 100 cc.

Pathological changes in animal organs caused by diethylene glycol refer mainly to the kidneys. Geiling and Cannon (1938) observed a

picture characteristic for chemical nephrosis, with cellular edema of most epithelial cells of the convoluted tubules, resulting in tubular obstruction by compression and by intraluminal formation of casts. Similarly, Kesten, Mulinos, and Pomerantz (1939), Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939) and Laug, Calvery, Morris, and Woodward (1939) noted extensive injury of the convoluted tubules, leading to obstruction and uremia, whereas the effect on the glomerula apparatus was much less severe. With regard to the latter, Laug, Calvery, Morris, and Woodward (1939) noted a distention of Bowman's capsule by protein precipitates which was also reported by Wiley, Hueper, Bergen, and Blood (1938) who, in addition, reported on swelling of the glomeruli, with occasional lack of nuclei in the capillary tufts. With regard to other organ changes following oral administration the gastro-intestinal tract may show signs of irritation, characterized by hemorrhages, as seen by Holck (1937) and by Laug, Calvery, Morris, and Woodward (1939). The liver may be soft and fragile and may show widespread, diffuse, hydropic changes, degeneration of the central portions of the lobules—as seen by Laug, Calvery, Morris, and Woodward (1939), or fatty infiltration with nuclear changes—as reported by Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939). According to the former authors the lungs may show more or less marked edema and hemorrhages and the spleen may show extensive phagocytosis of blood pigments. As pointed out by Geiling and Cannon (1938), it appears open to discussion whether the intracellular changes in the convoluted tubules of the kidneys are due to hypoxemia with subsequent cellular edema, necrosis, and desquamation, or to the hygroscopic properties of diethylene glycol.

With regard to *pathological changes observed in human cases of diethylene glycol poisoning*, Hagebusch (1937) noted, in 4 autopsies, pulmonary edema, marked nephrosis with hemorrhages in the cortex of the kidneys, and hemorrhages in the pericardium, the mucosa of the stomach and duodenum and the serous surface of the lungs. According to Lynch (1938) the most characteristic changes concern the kidneys and are characterized by necrosis of the secretory tubules. In addition, there may be central necrosis of the liver. According to Cannon (1937) and Geiling and Cannon (1938) the general picture of the injured kidney is that of severe chemical nephrosis, characterized by intracellular edema of most epithelial cells of the convoluted tubules, leading to internal disorientation of these cells. In some of the cases the kidneys showed cortical necroses and recent hemorrhages and were flabby and swollen. Microscopically there was severe vacuolization of the epithelium of the convoluted tubules whereas the glomeruli were affected very little. The liver showed hydropic degeneration of the liver cells which was most marked in

the center of the lobules, and there were some fatty changes, especially around the border of the hydropic areas, with little sign of necrosis. The lungs of these patients showed marked congestion, edema, and broncho-pneumonia, and, in severe cases, there were also ascites, hydrothorax, and hydropericardium. In some instances, they noted also recent hemorrhages in the gastro-intestinal tract and in the lungs, presumably caused by increased capillary permeability due to acidosis and uremia.

There are no reports on industrial diethylene glycol poisonings, and it appears that the danger of such injuries is quite remote.

f. Dipropylene Glycol

The higher homologue of diethylene glycol is dipropylene glycol, $HOCH_2-CH_2-CH_2-O-CH_2-CH_2-CH_2OH$, which has the molecular weight 137.17 and the specific gravity 1.0252 at $\frac{20°}{20°}$ C., which boils at 231.8° C., and which is soluble in water and alcohol. Its flash point is 137.78° C.

Its use as partial solvent for low and high viscosity cellulose acetate and as solvent for rosins has been suggested.

According to Hanzlik, Newman, van Winkle, Lehman, and Kennedy (1939), it is absorbed rapidly from the gastro-intestinal tract and excreted within 24 hours. The minimal fatal dose for dogs, with intravenous injection, is 11.5 cc. per kg; doses of 5.9 cc. per kg. causing anesthesia. In dogs, oral administration of 4 doses of 5 cc. per kg., 6 of 1.5 cc. per kg., and 6 of 2 cc. per kg. gave no evidence of toxic effects. Four animals surviving the repeated administration of dipropylene glycol showed very little evidence of liver damage, and one showed moderate degenerative changes of the convoluted tubules. Kesten, Mulinos, and Pomerantz (1939) noted, after oral and intravenous administration to rats, injuries similar to those seen after the administration of diethylene glycol, namely, hydropic degeneration of the tubular epithelium of the kidneys; but these were less frequent than observed with diethylene glycol and resulted only from higher doses. Van Winkle and Kennedy (1940) found that, in contrast to propylene glycol, dipropylene glycol depresses, in equal or smaller doses, the voluntary running movements of rats; and, in contrast to their behavior after the administration of diethylene glycol, they did not recover from this depression. As found by Newman, van Winkle, Kennedy, and Morton (1940), dipropylene glycol is not utilized by the perfused cat's liver, but it decreases the consumption of oxygen and the formation of carbon dioxide and increases the lactic acid level in the blood, being, however, less toxic than ethylene and diethylene glycol.

g. Triethylene Glycol

The condensation of 3 molecules of ethylene glycol yields *triethylene glycol*, $HO-CH_2-CH_2-O-CH_2-CH_2-OCH_2CH_2OH$, which has the molecular weight 150.17, and which is a colorless liquid with a specific gravity of 1.138 and a boiling point of 290° C. It is miscible with water and alcohol, and its flash point is 165.56° C.

Robertson, Puck, Lemon, and Loosli (1943) studied the germicidal action of triethylene glycol when used as aerosol. They found that concentrations of 1 gm. in 100 million cc. of air (1.6 p. p. m.) and of 1 gm. in 200 million cc. of air (0.8 p. p. m.) almost immediately cause disappearance of streptococci and pneumococci from the air, and within 10 minutes the test plates were essentially sterile. Dilutions of triethylene glycol as high as 1 gm. in 600 million cc. of air (0.3 p. p. m.) were found to exert a definite killing effect on pneumococci and a group of C streptococci. Concentrations of 1 gm. per 200 million cc. of air (0.8 p. p. m.) were found to protect mice completely against an airborn amount of influenza virus which a short time before had caused the death of all exposed (control) animals.

It is proposed that triethlyene glycol be used as a solvent for nitrocellulose and various gums and rosins. According to Latven and Molitor (1939), the minimal fatal doses (M. F. D. 50) for mice are: With subcutaneous injection, 8.75 cc. per kg.; with oral administration, 18.5 cc. per kg.; and, with intravenous injection, 6.5 cc. per kg. Smyth, Seaton, and Fischer (1941) determined the minimal fatal doses with oral administration as 22.06 gm. per kg. for rats and as 14.66 gm. per kg. for guinea pigs. Lauter and Vrla (1940) determined the minimal fatal doses for rats as 8.4 cc. per kg. with intramuscular injection and 11 to 15 cc. per kg. with oral administration, and they stated that doses of 10 cc. per kg. cause definite toxic symptoms. They found that continued ingestion of 5 percent solutions as drinking water was fatal to adult rats, whereas young animals thrive well on 3 percent solutions—in contrast to diethylene glycol which, in concentrations of 0.25 percent, caused definite impairment. As stated by Latven and Molitor (1939), the oral administration of 8 cc. per kg., the subcutaneous injection of 9 cc. per kg., and the intravenous injection of 3 cc. per kg. cause sleep in mice. According to the same authors, the irritant action of triethylene glycol is not very marked.

There are no reports on human poisonings resulting from triethylene glycol.

h. Polyethylene Glycol

Smyth, Carpenter, Shaffer, Seaton, and Fischer (1942) studied the toxicity of polyethylene glycols of the molecular weights, 1,250 and

3,600 which are known commercially as "Carbowax" compound 1,500 and 4,000. They found only that very large doses of the order of 50 gm. per kg. orally caused injury to the kidneys and, to a lesser extent, to the liver. Both compounds could be fed in comparatively large doses given in the drinking water in concentrations of 1 to 16 percent over a period of 90 days without causing definite toxic effects, and it was found that with local application both polyglycols were less irritant to the skin than petrolatum.

i. Relation Between Chemical Constitution and Physico-chemical Properties of Glycols

With regard to the *relation between the chemical constitution and the physico-chemical properties and the toxic action,* table 41 gives a synopsis of the few comparable data in the entire series. Comparison of the toxicity of ethylene glycol with that of propandiol-1,3 shows that the former is about twice as toxic as the latter. Unfortunately, no information is available with regard to the toxicity of butandiol-1,4, so it is impossible to state whether the separation of the two alcoholic groups by additional methylene radicals decreases the toxicity further, or whether it is due solely to the formation of oxalic acid, whereas, under similar conditions, propandiol-1,3 might form malonic acid and butandiol-1,4 might form succinic acid, both of which are less toxic. As in the case of monovalent alcohols, glycols with a secondary alcohol group appear to be less toxic than the corresponding primary alcohols. Propandiol-1,2 is much less toxic than propandiol-1,3, and butandiol-1,3 is of comparatively low toxicity, although, as pointed out above, no information is available with regard to toxicity of butandiol-1,4.

With regard to the toxicity of the polyalkyl glycols—diethylene glycol, dipropylene glycol, triethylene glycol, tetraethylene glycol, hexaethylene glycol, and nonaethylene glycol—the acute toxicity appears to decrease with the molecular weight. The available data indicate that the lowest member of this series, diethylene glycol, is by far the most toxic with continued administration.

With regard to the relation between the chemical constitution and the toxicological action of bivalent and monovalent alcohols, comparatively few data are available which lend themselves for such comparison. Table 42 gives a few data for ethyl, propyl, isopropyl, and secondary butyl alcohol, and for ethylene glycol, propandiol-1,3, propandiol-1,2 and butandiol-1,3 which may give some indication regarding such relationship. It should be pointed out that the fatal dose for monovalent alcohols, as listed in column 5, refers to rabbits as determined by Munch and Schwartze (1925), and those for the glycols to rats as determined by Smyth, Seaton, and Fischer (1941) because no serial determinations of the toxicity of alcohols with oral

Table 41.—The toxicity and hypnotic action of glycols with regard to their physico-chemical properties

Name	Formula	Molecular weight	Specific gravity	Boiling point °C.	Minimal fatal dose cc/kg.—orally			Minimal hypnotic dose cc./kg. orally[4]	Nephrotoxic action
					Mouse[1]	Rat[2]	Guinea pig[3]		
Ethylene glycol	$HOCH_2—CH_2OH$	62.07	$1.113\ \frac{19°C}{4°}$	197.4	7.5	7.7	6.0	1.0	+++
Propylene glycol (propandiol-1, 2).	$CH_3—CHOH—CH_2OH$	76.09	$1.040\ \frac{19.4°C}{}$	188 to 189	22.0	25.3	17.8	8.0	±
Propandiol-1, 3	$HOCH_2—CH_2—CH_2OH$	76.09	$1.060\ \frac{20°C}{4°}$	214	-------	ca 16[5]	-------	-------	++
Butylene glycol (butandiol-1, 3)	$CH_3CHOHCH_2CH_2OH$	90.1	$1.02\ \frac{20°C}{4°}$	185, to 195	-------	18.2	11.2	-------	±
Diethylene glycol	$HOCH_2CH_2—O—CH_2CH_2OH$	106.2	$1.132\ \frac{0°C}{}$	250	[6]23.7	18.4	11.7	-------	+++
Dipropylene glycol	$HO—CH_2CH_2—CH_2OCH_2—CH_2CH_2OH$	137.17	1.0252	231.8	-------	-------	-------	-------	±
Triethylene glycol	$HOCH_2CH_2—O—CH_2CH_2—O—CH_2CH_2OH$	150.17	1.138	290	18.5	19.5	13.0	8.0	+
Tetraethylene glycol	$HOCH_2CH_2—O—CH_2CH_2—O—CH_2CH_2—O—CH_2CH_2OH$	194.23	$1.1247\ \frac{20°C}{20°}$	327.3	-------	29.2	-------	-------	-------
Hexaethylene glycol						*gm./kg.* 31.64	*gm./kg.* 19.58		
Nonaethylene glycol						37.41			

[1] Latven and Molitor (1939).
[2] Smyth, Jr., Seaton and Fischer (1941).
[3] Smyth, Jr., Seaton and Fischer (1941).
[4] Latven and Molitor (1939).
[5] According to van Winkle (1941a) who considers it twice as toxic as propandiol-1, 2.
[6] According to Laug, Calvery, Morris, and Woodward (1939).

Table 42.—*Comparison of the toxicity of certain monovalent and bivalent alcohols with regard to their chemical constitution*

Name	Formula	Boiling point °C.	Solubility in			Fatal dose orally cc./kg.
			Water	Alcohol	Ether	
Ethyl alcohol_____	CH_3CH_2OH	78.4	~	~	~	12.5 (rabbit).
Ethylene glycol_____	$HOCH_2CH_2OH$	197.4	~	~	1:100	7.7 (rat).
Propyl alcohol_____	$CH_3CH_2CH_2OH$	97.8	~	~	~	3.5 (rabbit).
Propandiol-1,3_____	$HOCH_2—CH_2—CH_2OH$	214	~	~	8:100	16 (rat).[1]
Isopropyl alcohol_____	$\begin{array}{c} CH_3 \\ \mid \\ CH_3—CHOH \end{array}$	82.5	~	~	~	10.0 (rabbit).
Propandiol-1,2_____	$\begin{array}{c} CH_3 \\ \mid \\ HOCH_2—CH—OH \end{array}$	188 to 189	~	~	8:100	25.3 (rat).
Secondary butyl alcohol_	$\begin{array}{c} CH_3 \\ \mid \\ CH_3—CH_2—CH_2OH \end{array}$	99.5	12.5	~	~	6.00 (rabbit).
Butandiol-1,3_____	$\begin{array}{c} CH_3 \\ \mid \\ HOCH_2—CH_2—CHOH \end{array}$	185 to 195	~	~	(2)	18.2 (rat).

[1] Quoted from van Winkle (1941a).
[2] Slightly soluble.

NOTE.—Toxicity data for rabbits are quoted from Munch and Schwartze (1925); data for rats are quoted from Smyth, Seaton, and Fischer (1941).

administration are available for rats. Comparison of the acute toxicity of the monovalent alcohols and the corresponding glycols, with the exception of ethyl alcohol and ethylene glycol, shows that the monovalent alcohols are generally more toxic than the corresponding glycols and that this is evidently, at least in part, paralleled by their solubility in ether and presumably also in oils and fats. The exceptional position of ethyl alcohol and ethylene glycol may possibly be explained by the different rates of absorption, the former being absorbed more readily than the latter. With regard to the chronic toxicity of these compounds, ethylene glycol appears to be definitely more toxic than ethyl alcohol, presumably because it is oxidized to oxalic acid which forms insoluble calcium salts, whereas the monovalent alcohol is completely oxidized in the organism.

C. TRIVALENT ALCOHOLS

Glycerol

The main representative of trihydric alcohols is glycerol or glycerin.

Chemical characteristics.—Glycerol, HO CH$_2$CH OH CH$_2$OH, has the molecular weight 92.09. It is a colorless liquid with a sweetish taste. It has the specific gravity 1.260 at $\frac{20°}{4°}$ C. Its melting point is 17.9° C. but it solidifies at a much lower temperature, and it boils at 290° C. It is miscible with water and alcohol but is insoluble in ether, fats, and oils. Glycerol is very hygroscopic and can be volatilized with steam.

Identification.—1. Interaction with hydroiodic acid yields allyl iodide (C$_3$H$_5$I) which boils at 101° to 102° C., and, further, isopropyl iodide (C$_3$H$_7$I) which boils at 59.5° C. (Rosenthaler, 1923).

2. When shaken with six times its volume of benzoyl chloride and an excess of sodium hydroxide it forms tribenzoyl glycerol which represents long needles melting at 76° C. (Rosenthaler, 1923).

3. Short heating with 5.1 parts of α-naphthylisocyanate and recrystallization from pyridine yields glycerol-α-naphthyl urethane, (C$_{10}$H$_7$NOCO)$_3$OC$_3$H$_5$, which represents needles melting at 279° to 280° C. (Rosenthaler, 1923).

4. It may be identified by dehydration or oxidation to acroleine, or by oxidation to dioxyacetone by heating it with bromine water. The latter method gives the same reactions mentioned for the oxidation product of ethylene glycol (Rosenthaler, 1923).

Uses.—Glycerol is used extensively as a vehicle in the pharmaceutical and cosmetic industries, as lubricant for specific purposes, as plasticizer, and as starting material in the manufacture of nitroglycerol and nitroglycerol explosives.

Determination.—According to Fleury and Fatôme (1935), glycerol may be determined by oxidation with an excess of standardized periodic acid and titrimetrical determination of the remaining periodic acid. In case sugars are present, these first have to be removed by precipitation with barium hydroxide and alcohol and filtration; the excess barium is precipitated with sulfuric acid or carbon dioxide and the alcohol by careful evaporation.

Nicloux (1903b, d) worked out a method for the *determination of glycerol in blood* which can also be applied to urine. The proteins are precipitated by boiling with 1 percent acetic acid, filtered, and

from the filtrate glycerol is removed by vacuum distillation with steam. After the distillate is concentrated by careful evaporation, glycerol is determined by oxidation with chromic acid. If a concentration of 1.9 percent potassium bichromate is used for this purpose, the number of cubic centimeters used for the oxidation corresponds approximately to those of glycerol present.

Antiseptic properties.—Glycerol has moderate antiseptic properties. According to Winslow and Holland (1919), a concentration of 9 percent has no appreciable effect on the vitality of *B. coli*, but concentrations of 28 to 100 percent are increasingly effective.

Absorption, fate, and excretion.—As demonstrated by animal experiments with mice and rabbits, glycerol evidently is not absorbed through the intact skin in sufficient quantities to cause toxic effects (Sander, 1933 and Deichmann, 1941). According to Johnson, Carlson, and Johnson (1933), it is not absorbed readily from the stomach, but 50 percent of the glycerol introduced into the intestine of anesthetized dogs was absorbed during the first 2 to 3 hours. Similarly, Höber and Höber (1937) found that 73 percent is absorbed from isolated loops of rat's intestine. As indicated by the reports of Mueller (1894) and Pfannenstiel (1894), sufficient quantities of glycerol may be absorbed from the pregnant uterus to cause severe toxic effects. There is no information available as to what extent glycerol may be absorbed through the lungs, but, in view of its high boiling point (290° C.), this possibility appears to be quite remote.

With regard to the *fate of glycerol in the metabolism*, Berthelot (1857) suggested that certain tissues may metabolize glycerol to glucose. Cremer (1902) and Luthje (1904) (both quoted from Voegtlin, Thompson, and Dunn, 1925) found that the feeding of glycerol to rabbits increases the blood sugar level. Höckendorf (1909–10) noted that, in phlorhizinized dogs, glycerol increases the sugar excretion, indicating that it may be metabolized into sugar; and Chambers and Deuel (1925), reported that in such animals 55.9 to 98.4 percent of the glycerol given could be accounted for in the urine as extraglucose. Similarly, Ferber and Rabinowitsch (1929) found that, in diabetic patients, the administration of glycerol caused, in 67.5 percent of the cases, an increase of 20 mg. or more in the blood sugar level. Voegtlin, Thompson, and Dunn (1925) showed, in rabbits, that the oral and intraperitoneal administration of glycerol (4 gm. orally) causes a progressive rise of the blood sugar, the maximum of 100 percent being reached in 1 hour, followed by a rapid decline, indicating that glycerol may be converted into sugar. Johnson, Carlson, and Johnson (1933) found, in feeding experiments with rats, indications that, within limits, glycerol may replace carbohydrates in the diet. Whereas Noble and MacLeod (1923) claimed that, in rabbits, insulin convulsions were not relieved by the subcutaneous injection of glycerol although

there was a very moderate increase of the blood sugar level (from 0.054 to 0.064 percent) shortly after the injection. Voegtlin, Dunn, and Thompson (1925) found that the administration of adequate doses of glycerol may relieve the symptoms of hypoglycemia in rats treated with minimal fatal doses of insulin. It appears, therefore, that glycerol may be partly converted into glucose in the organism. Luchsinger (1874) demonstrated that the administration of glycerol increases the glycogen content of liver and muscle which he interpreted as assimilation of glycerol to glycogen. Catron and Lewis (1929) showed that the feeding of 2 cc. of 50 percent glycerol to starved rats increased the glycogen content of the liver in the course of 1 to 6 hours, progressively, to an average of 142.55 mg. per 100 gm. body weight (3.24 percent) as compared with 0.09 percent in the controls. Similar results with rabbits and rats were reported by Lederer (1936) who also showed that in vitro liver tissue may form glycogen from glycerol. He found that in a dog the intravenous injection of 1 gm. of glycerol per kg. caused an increase of the glycogen content of the liver and a rise of the blood sugar level. He noted that four-fifths of the glycerol injected disappeared from the blood after 5 minutes and the rest disappeared within 90 minutes. Nicloux (1903a, b, c, d, e) studied the rate of disappearance of glycerol from blood following its intravenous injection in rabbits and dogs, as illustrated in table 43, which shows that the glycerol level is reduced very rapidly at first, then gradually, until after $3\frac{1}{2}$ hours, glycerol has disappeared almost entirely from the circulating blood. According to the same author (1903c) the "normal" glycerol level in the blood of dogs is, on an average, 0.0033 gm. per 100 cc. with 0.0019 and 0.0049 gm. per 100 cc. as extremes; and this is said to be essentially the same whether the animals are starved or fed a diet rich in fat. Trabucchi (1932) claimed that the rate of disappearance of glycerol from the blood is increased after the administration of insulin.

With regard to the *excretion of glycerol*, the results of different investigators do not agree, and this may be attributed, in part, to the analytical methods used for its determination. Ustimovitsch (1876) noted in the urine of dogs, after oral administration of glycerol, a reducing substance other than sugar, and he assumed that this was a metabolite of glycerol. Plósz (1877) claimed that he had isolated glycerol aldehyde under similar conditions but the validity of this statement appears to be questionable. Miura (1911) was unable to detect glycerol in the urine of dogs and rabbits after oral and subcutaneous administration; nor did he find evidence that it is excreted in conjugation with glucuronic acid. Catillon (1877) was able to recover from human urine 3 to 3.5 gm. after the ingestion of 30 gm. of glycerol, and he pointed out that with very large doses the excretion is not proportionate to the dose but relatively smaller. Leo (1902)

showed that the excretion of glycerol with the urine depends, in part, upon the dose administered, in that he found no glycerol in human urine after the administration of 8.93 gm., only traces after 20.08 gm. and quantities (0.5 to 1.0 gm.) after the ingestion of 26.76 gm. Similarly, Munk (1879) found only traces of glycerol in the urine of dogs after the oral administration of 25 to 30 gm. of glycerol, and Lederer (1936) detected only small amounts in the urine of man and rabbits. Tschirwinsky (1879), on the other hand, recovered from 38 to 60 percent of the glycerol administered from the urine of dogs which had been fed doses up to 200 gm. mixed with the food; and according to Arnschink (1886) 25 percent is excreted by dogs after oral administration. Nicloux (1903b, c) found that, following the intravenous injection of 2 cc. per kg. in 20 percent solution into a 14 kg. dog, 0.112 gm. was excreted after the first 15 minutes, 3.067 gm. during the next 75 minutes, 1.409 gm. during the subsequent 67 minutes, and 0.158 during the last 3 hours of the experiment. It appears, therefore, that the concentration of glycerol in urine depends to a large extent upon the time of its collection after the administration, and this may offer an explanation for the contradictory findings reported by different students of the subject. In the experience of Nicloux (1903b, c) 17 percent of 28 gm. of glycerol given intravenously was recovered from the urine after 5 hours and 37 minutes, and in another experiment 27.7 percent of 19.5 gm. was recovered after 7 hours and 45 minutes; and Schübel (1935–36) was able to recover a total of 40 to 50 percent of the amount of glycerol given intravenously to cats.

The effect of glycerol on various physiological functions.—With regard to the *effect of glycerol on the nervous system*, Macht and Ting (1922) found that glycerol has only moderate narcotic properties, in that doses of 160 mg. per 100 gm. body weight produce the same degree of depression in rats in a maze as is produced by 80 mg. per 100 gm. of ethyl alcohol and by 120 mg. per 100 gm. of ethylene glycol. This was confirmed by Latven and Molitor (1939) who determined the minimal hypnotic dose in mice as 10 cc. per kg. with oral, 8 cc. per kg. with subcutaneous, and 3 cc. per kg. with intravenous administration, the corresponding figures for ethyl alcohol being 3 cc., 2 cc. and 0.8 cc. per kg. body weight. Schübel (1936) noted, in frogs, that the depression is preceded by excitation, and he saw, in mice, after fatal doses, dyspnea, circus movements and convulsions which could be elicited by auditory stimuli similar to those observed in strychnine poisoning; and Deichmann (1941) noted inactivity and tremors after oral administration to rabbits. Langendorff (1891), who had noted tetanic and clonic convulsions also, believed these to be partly of central, partly of peripheral neural, and partly of muscular origin.

Langendorff (1891) believed that glycerol caused irritation of the *peripheral nerves* by its dehydrating action, and Santesson (1903)

Table 43.—Rate of disappearance of glycerol from blood of rabbits and dogs

[Nicloux, 1903e]

Amount of glycerol found in blood following intravenous injection

Species	Interval after injection	Glycerol gm. per 100 cc. of blood	Interval after injection	Glycerol gm. per 100 cc. of blood	Interval after injection	Glycerol gm. per 100 cc. of blood	Interval after injection	Glycerol gm. per 100 cc. of blood	Interval after injection	Glycerol gm. per 100 cc. of blood	Interval after injection	Glycerol gm. per 100 cc. of blood
Rabbit 1	2 minutes	0.37	4½ minutes	0.27	30 minutes	0.18						
Rabbit 2	30 seconds	.54	5 minutes	.33	40 minutes	.15						
Dog 1	30 seconds	.54	5 minutes	.37	30 minutes	.15	90 minutes	0.115				
Dog 2	1 minute	.38			30 minutes	.15	120 minutes	0.03	210 minutes	0.008	450 minutes	0.004

showed, in frogs, that glycerol lowers the threshold of the peripheral nerves to electric stimuli.

Several investigators (Catillon, 1877; Plósz, 1877; and Arnschink, 1886) noted an increase of the *body temperature* after administration of large doses of glycerol, and similar observations were made by Mueller (1894) and Pfannenstiel (1894) following the intrauterine injection of glycerol. Johnson, Carlson, and Johnson (1933) noted no increase of the body temperature following the administration of smaller doses, and there is no definite explanation of the observations of the earlier authors.

Glycerol causes definite *irritation* of mucous membranes when in direct contact, presumably on account of its dehydrating action. According to Braun and Cartland (1936) the subcutaneous injection causes severe but transient irritation, and in the experience of Latven and Molitor (1939) the intradermal injection is distinctly irritant and application to the rabbit's eye causes edema and hyperemia. As pointed out by Flinn (1935), the combustion products of glycerol cause distinct irritation of the throat when used as hygroscopic agent in tobacco.

With regard to the *effect of glycerol on the circulation*, Schübel (1936) found that the energy of the isolated frog's *heart* is moderately reduced by concentrations of 1 : 1,000 of glycerol in Ringer's solution, that concentrations of 1 : 50 cause a moderate decrease of systole and diastole, and that concentrations of 1 : 8 cause reversible cardiac arrest. In the experience of Spealman (1940) 1/10 molar solutions (9 : 1,000) do not affect the heart rate, and twice this concentration causes no change in the weight of the frog's ventricle, as observed with some of the monovalent alcohols.

As found by Schübel (1936), concentrations of 1 : 1,000 to 1 : 10 do not affect the diameter of the *blood vessels* of the perfused frog, but according to Maignon and Grandclaude (1930) repeated intravenous injection at the same site may lead to obliteration of the veins.

With regard to the *effect of glycerol on the blood pressure*, Amidon (1881) noted that the intravenous injection of 0.5 to 1.0 cc. per kg. of glycerol causes a fall of the blood pressure accompanied by a diminution of the force of the heart beat, increased frequency of the heart rate, and irregularities of the heart action. These effects are not altered by decerebration, dissection of the vagi and atropinization, and, therefore, must be due to some peripheral mechanism. Similarly, Schübel (1936) noted that, in cats, following the intravenous injection of 0.5 to 1.0 cc. per kg., the blood pressure first was reduced and then rose again, sometimes above the original level. He believed that the primary fall was caused by a temporary impairment of the heart action and the secondary rise by a hydremic plethora. However, such changes should not be expected after the oral admin-

istration of moderate doses, as indicated by the negative findings of Johnson, Carlson and Johnson (1933).

With regard to the *effect of glycerol on the blood*, numerous studies deal with its *hemolytic action*. Simon (1915) showed that in vitro concentrations of 15 to 55 percent cause hemolysis of red blood cells. However, in the opinion of Schübel (1936) this effect is not as marked as is usually assumed. He saw no hemolysis with concentrations up to 40 percent in normal saline, and 50 percent in normal saline caused hemolysis after 16 to 24 hours whereas the same concentration in water caused hemolysis within 1½ hours. He found aqueous solution of 2.55 percent glycerol isotonic with 0.9 percent solutions of sodium chloride, therefore the hemolytic action of glycerol must be due to other than osmotic properties. Parpart and Shull (1935) studied the penetration of glycerol into red blood cells, and Jacobs, Glassman, and Parpart (1935) pointed out that the glycerol hemolysis is greatly affected by small amounts of copper salts and by changes of the pH, both factors affecting considerably the permeability of the cells. The effect of glycerol on leucocytes is much less marked than that of ethyl alcohol. Baglioni (1927) found that concentrations of 0.25 percent and 0.50 percent have no effect on the motility and survival of leucocytes, only 2 percent showing a distinctly injurious effect.

Simon (1920) claimed that, in rabbits, the intravenous injection of 4.5 gm. per kg. caused stimulation of the leucopoietic apparatus, as indicated by the increase in the number of erythrocytes and white blood cells. However, it appears to be questionable whether or not this cellular increase is due to an actual stimulation of the blood-forming organs, and it is more likely that this is the result of the increased viscosity of the blood on account of dehydration, as assumed by Schübel (1936), especially since Piras (1925) found no indications of hyperactivity of the bone marrow of such animals. That such changes are not the result of a permanent damage of the blood-forming organs is also indicated by the findings of Tompkins (1929) who noted, following the intraperitoneal injection of 5 cc. of 10 to 25 percent solutions of glycerol, leucocytosis which increased with the dose, increase of the number of polynuclear neutrophiles, and usually a slight increase of the monocytes. During the first 12 hours after the injection there was, at times, a moderate lymphopenia, but usually the number of lymphocytes remained within normal limits or increased with that of the leucocytes, and within 48 hours after the injection the blood picture had returned to normal. After the repeated administration of 12 doses of 2 to 6 cc. per kg. over a period of 7 weeks, to rabbits, Deichmann (1941) noted a diminution of the red blood cells from 6 to 4 millions, reduction of the hemoglobin, and variations in the number of leucocytes; it should be pointed out that these animals were suffering from hemoglobinuria. Similar changes

were observed after intracardiac injections, whereas the intraperitoneal injection was followed by a temporary leucocytosis. It should be pointed out that after oral administration of glycerol neither blood changes nor hemoglobinuria was observed, and this appears to indicate that the blood changes observed by various investigators were due partly to destruction of the blood cells, partly to local irritation of the tissues at the site of the injection, and partly to thickening of the blood.

Much attention has been paid to the *effect of glycerol on the musculature*. Husemann and Unmethun (1866) (quoted from Santesson, 1903) noted that the injection of glycerol causes, in frogs, spastic and convulsive symptoms which they attributed to the dehydrating effect of this chemical. Amidon (1881) noted that the subcutaneous injection of glycerol into frogs caused, after a primary irritation, clumsiness of the movements due to stiffness of the musculature, followed by fibrillary twitchings of the voluntary muscles and tetanic convulsions elicited by moderate pressure on the muscle; and that, later on, even moderate stimulation of this type may elicit general tetanic convulsions. In contrast to such stimulation, sensory stimuli caused only attempts at ordinary reflex action. He showed, in addition, that neither decapitation, pithing of the spinal cord and dissection of the peripheral nerves, nor curarization prevents the convulsion—which was confirmed by Schübel (1935–36)—but that exclusion of the blood supply by ligation of the vessels would suppress the convulsions in the ligated limb. He concluded that this effect of glycerol is located in the muscle tissue proper. Langendorff (1891) made similar observations but claimed that decerebration attenuated and curare prevented these convulsions which, in his opinion, were partly of central origin, caused by dehydration of the central nervous system. He assumed that the muscular tetanus was the result of "endogeneous" electric currents produced by pressure on the muscle. Santesson (1903) pointed out that the subcutaneous injection of glycerol into frogs caused the animals to make flash-like extensor movements, but, after this, permitted only slow adduction of the limbs. In isolated nerve-muscle preparations of such animals, single electric stimuli of the nerve caused abnormally high and long-lasting contraction of the muscle (tetanus) and the plateau of the contracture curve showed, after some time, a sudden decrease which later flattened out gradually, this effect being attenuated rather than abolished by curarization. He concluded that this hyperexcitability was due to an increased excitability of the nerve endings. He also pointed out that at the height of the tetanic contraction the muscle was refractory to electric stimulation and the glycerol contracture represented a real tetanus, whereas with veratrine, which causes a similar picture, the curve is only a single twitch contracture; and he believed, like Langendorff (1891),

that on account of the increased hyperexcitability, the muscle is stimulated continuously by its own action currents. Verzár and Péter (1925) believed that the prolonged contracture of the glycerolized muscle is due to an increased permeability of the cell membrane; and Dux and Löw (1921) showed that glycerol causes a high degree of dehydration of the muscle which may reduce its weight to one-fifth of its normal value, and that such muscles show a rapid increase and subsequent decrease of their swelling curve, the former being due to the avidity of the tissue for water and to the accumulation of lactic acid.

With regard to the effect of glycerol on smooth muscle structures, Pelzer (1891) (quoted from Mueller, 1894) showed that, in situ, the injection of glycerol stimulated the contraction of the uterus. Reach (1926) found that the local application of glycerol to the upper section of the duodenum caused relaxation of the sphincter muscles of the ductus choledochus. This may favorably affect the discharge of bile, the formation of which, however, is not favorably affected by glycerol, as was demonstrated by Winogradow (1927). Pal and Prasad (1935) showed that 0.4, 0.6, 0.8 and 1.0 percent solutions of glycerol in Ringer's solution cause a temporary increase of the height of the contractions of the isolated rabbit's intestine, the tone showing a primary fall and subsequent improvement, and that contractions of the large intestine were increased proportionately to the concentration of the solution. Schübel (1936) found that concentrations of 1:1,000 increase the peristaltic activity of the isolated ureter, concentrations of 1:100 increase the tone and the number of contractions, and concentrations of 1:20 cause rapid depression of all movements. In his experience, concentrations of 1:1,000 to 1:150 reduce the tone of the isolated uterus and the intestine, and such solutions may antagonize the spasmodic effect of barium chloride (1:200) but not that of physostygmine.

With regard to the *effect of glycerol on the kidney function*, this is characterized by a diuretic action and by hemoglobinuria. Ustimovitsch (1876) found that in dogs the intravenous injection and the oral administration of glycerol had a definite *diuretic effect*. Lewin (1879) made the same observation and attributed it to the hygroscopic properties of glycerol. Cugusi (1922) pointed out that the effect of glycerol on the kidney function varies with the dose, in that he found, in rabbits, that the intravenous injection of small and moderate doses stimulates the renal activity whereas large doses inhibit the renal function. According to Schübel (1935–36) the same dose of glycerol, given intravenously, increases the urinary output to 10 times its normal amount, whereas with oral administration it is increased only by 3 to 5 times. He believed that the diuretic action is responsible for the increased viscosity of the blood of such animals.

In the experience of Johnson, Carlson and Johnson (1933) the oral administration of glycerol always is followed by diuresis, whereas with intravenous injection, causing a fall of the blood pressure, the urinary secretion is reduced. In man, 3 doses of 30 cc. each, taken daily with orange juice after each meal, had no diuretic action.

Rosenfeld (1924) pointed out that the repeated daily oral administration of glycerol increased considerably the *excretion of uric acid* in man, and Grabfield and Swanson (1942) believed that uricosuric action of glycerol is due to a specific effect on the protein metabolism, whereas the diuretic action is presumably a function of its hypertonicity.

Many experimenters have reported *hemoglobinuria* following the administration of glycerol. Amidon (1881), Filehne (1889), Miura (1911), Simon (1920), Deichmann (1941) and others noted it after the subcutaneous administration of glycerol; others, like Amidon (1881), Ustimovitsch (1876) and Deichmann (1941), saw it after intravenous injection, but it seems that hemoglobinuria has not been observed after the oral administration of glycerol. Afanassiew (1883) believed that the hemoglobinuria is not the result of injury to the kidneys but that it is due to the removal of hemoglobin from the blood cells because he noted in such cases of hemoglobinuria shadow cells in the blood and hemoglobin in the serum, so that it appears that the glycerol hemoglobinuria is of the same type as paroxysmal hemoglobinuria in man. As shown by Pfeiffer and Arnove (1937), premedication with ascorbic acid afforded protection against glycerol hemoglobinuria.

With regard to the *effect of glycerol on the metabolism*, Catillon (1877) claimed that glycerol decreased the protein metabolism as indicated by a reduction of the urea level in the blood and the urea excretion with the urine. However, Munk (1879) and Lewin (1879) found no evidence to show that it decreases the *protein metabolism* and that it has no food value in this respect. Tschirwinsky (1879) pointed out that findings indicating an increase of the protein metabolism possibly may be overshadowed by a decrease of the urea excretion, caused by its dehydrating and diuretic action. As pointed out above, Grabfield and Swanson (1942) believed that glycerol somehow affects the purin metabolism, as judged by its uricosuric action and the increased excretion of allantoin in dogs.

It has been pointed out above that glycerol may be substituted, within limits, for *carbohydrates;* and this also was shown by Johnson, Carlson and Johnson (1933).

With regard to the effect of glycerol on the *fat* metabolism, very little information is available. Catillon (1877) believed that glycerol decreases the fat metabolism, and Arnschink (1886) thought that glycerol may save an equivalent caloric amount of fat.

Data regarding the *effect of glycerol on the oxygen metabolism* are contradictory. Leo (1902) refers to Scheretjewski (1869) as having observed an increase of the respiratory metabolism after the administration of glycerol. Similarly, Catillon (1877) found that, following administration of glycerol to dogs, the percent of carbon dioxide in the exhaled air increased from 4.3 to 6.0 and 7.0 percent after doses of 3 to 4 and 6 to 8 gm. per kg., respectively. Chambers and Deuel (1925) found, after feeding glycerol to phlorhizinized dogs, a decrease of the respiratory quotient from 0.703 to 0.678; and Johnson, Carlson and Johnson (1933) noted no consistent effect in man after 3 daily doses of 30 cc. each.

Table 44.—*Fatal doses of glycerol for different species of animals by various routes of administration*

ORAL ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	25 (M. F. D. 50)	Latven and Molitor (1939).
Rat	21.8 (M. F. D. 50)	Smyth, Jr., Seaton and Fischer (1941).
Guinea pig	6.1 (M. F. D. 50)	Do.
Rabbit	21 to 23 (M. F. D. 60)	Deichmann (1941).

SUBCUTANEOUS ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	0.05	Schübel (1936).
Do	10	Latven and Molitor (1939).
Do	ca 10	Leake and Corbitt (1917).
Rat	12.5	Braun and Cartland (1936).
Do	15 to 16	Deichmann (1941).
Dog	8 to 10	Plósz (1877).
Do	6.4 to 8	Dujardin-Beaumetz and Audigé (1876).
Horse	1	Plósz (1877).

INTRAMUSCULAR ADMINISTRATION

Species	Dose cc./kg.	Author
Rat	6.0	Braun and Cartland (1936).

INTRAPERITONEAL ADMINISTRATION

Species	Dose cc./kg.	Author
Rat	5 to 6	Deichmann (1941).

INTRAVENOUS ADMINISTRATION

Species	Dose cc./kg.	Author
Mouse	6.0	Latven and Molitor (1939).

With regard to the *toxicity of glyercol for animals*, table 44 gives the minimal fatal doses for different species by various routes of administration as determined by various authors. The picture of acute poisoning, as described by various investigators quoted in this table, is essentially the same. Following the administration of toxic doses of glycerol, rabbits first show an increase of the respiration; the pulse rate is first increased, later weakened and irregular; the animals first develop weakness of the musculature and, later, tremors, twitchings, convulsions, diuresis, and diarrhea; and they die of respiratory fail-

ure and cardiac arrest. Mice first show gnawing movements of the jaws; they become dyspneic, discharge soft stools, develop trismus, show circus movements, and develop spasticity and strychnine-like convulsions; and with fatal doses death may occur after some time has elapsed. Dogs may show, in addition, vomiting and diarrhea, and colic has been reported in horses.

Johnson, Carlson and Johnson (1933) saw no evidence of any toxic effects in rats from the continued feeding over a period of 40 weeks of a diet in which 41 percent of the starch had been replaced by glycerol. With complete replacement of starch by glycerol they noted a distinct impairment of growth which, however, evidently was caused not by a toxic action of glycerol but by an inadequate intake of food, as proved by the fact that the addition of 50 percent of glycerol to the complete diet not only did not impair the growth but even promoted it on account of the additional calories furnished. Similarly, Holck (1937) saw no unfavorable effects on the growth of young rats fed a diet containing 20 percent of glycerol.

Cases of glycerol poisoning in humans are exceptional. Kobert (1906) reported on one fatal and one nonfatal poisoning in children after the ingestion of large doses of glycerol. Jaroschi (1889) reported on one patient who, after the repeated oral and rectal administration of glycerol over a period of 2 weeks, suffered from debility, vomiting, diarrhea, and muscular cramps which disappeared promptly after discontinuation of glycerol. In view of the irritant action of glycerol on mucous membranes, and because of its dehydrating action, it appears quite possible that the above symptoms may result from such abuse, but in this specific instance it appears possible that the glycerol in question was contaminated with appreciable amounts of arsenic trioxide. Three other cases of glycerol poisoning were reported by Mueller (1894) and Pfannenstiel (1894). In these instances, 100 gm. of glycerol had been injected into the pregnant uterus in order to stimulate uterine contractions. One patient suffered, after 10 minutes, from vomiting and diarrhea and had, repeatedly, paroxysmal attacks of a fever which was of a different type from that produced by infection. The second patient became cyanotic, the pulse was slowed, and there was a short but definite rise of the temperature. All three patients suffered from more or less severe hemoglobinuria.

There are no reports on industrial poisonings from the handling of glycerol, and the possibility of toxic effects from its industrial use appears to be remote.

With regard to *pathological changes in glycerol poisoning*, very little information is available. Plósz (1877) saw, after oral administration of single large doses, hyperemia and inflammation of the mucous membranes of the gastro-intestinal tract, hyperemia and cloudy

swelling of the kidneys, hyperemia of the liver, and hyperemia and edema of the lungs. Piras (1925) noted, after repeated daily subcutaneous administrations of 0.5, 1.0, and 2.0 cc. per kg. for 45 days, hyperemia, hemorrhages and, with the largest dose, fatty degeneration of the liver; hemorrhages and cloudy swelling of the kidneys, and, with the largest dose, destruction of the tubular epithelium; and hyperemia, inflammatory reactions and small hemorrhages of the intestinal mucosa, even with small doses. The spleen was affected less and the lungs showed only moderate hyperemia. Other organs, including adrenals and bone marrow, were essentially normal. Similar but more marked changes were reported by Simon (1915) after the administration of single fatal doses of glycerol. Maignon and Grandclaude (1930) studied the local effects of repeated intravenous injection of glycerol on the vascular walls. They found that in 7 out of 14 experiments the first injection caused no changes of the vascular walls; in 4, the walls were somewhat thickened; and in 3 instances they were markedly sclerotic, with complete, or nearly complete, obliteration of the lumen. These changes became more marked after the second injection. Microscopically, the layers of the vascular walls became separated by sclerotic areas and infiltrated with leucocytes, the endothelium became indistinct and finally fused with a mass in the lumen, thus obstructing completely the lumen of the vessel, this clot finally becoming completely organized.

Comparison of the narcotic actions of glycerol and propylene glycol shows that they are of the same order but that they are considerably inferior to that of the monohydric alcohol, propanol. This is paralleled by the reduced solubility of propylene glycol and glycerol in fats and oils which, as pointed out before, is one of the factors controlling the narcotic action of alcohols. On the other hand, glycerol more nearly approaches the polyvalent alcohols and sugars, in that, within certain limits, it may be utilized by the organism and give rise to the formation of glycogen.

D. THE POLYVALENT ALCOHOLS WITH MORE THAN THREE CARBONS

The polyvalent alcohols with more than three alcoholic groups are of such low toxicity that they are of no toxicological importance. The tetravalent alcohol, *erythritol* or butantetrol, $HOCH_2(CHOH)_2 CH_2OH$, is said to cause diuresis in rats in doses of 18 gm. per kg. when given orally as 50 percent aqueous solution. It is excreted unchanged with the urine to the extent of 20 to 40 percent, and it does not significantly increase the respiratory quotient of rats nor favor the deposition of glycogen in the liver (Beck, Carr, and Krantz, 1938). According to Höber and Höber (1937), it is absorbed from the intestine of the rat to the extent of 41.4 percent, whereas the corresponding figure for glycerol is 73 percent.

The pentavalent alcohol, *adonitol*, $HOCH_2(CHOH)_3CH_2OH$, evidently has not been studied pharmacologically. According to Höber and Höber (1937) its absorption from the gastrointestinal tract is slower than that of erythrol.

The hexavalent alcohol, hexanhexol, exists in the form of several isomeres—*mannitol*, *dulcitol* and *sorbitol*—of the general formula $HOCH_2(CHOH)_4CH_2OH$. None of these has a distinct toxic action. Ellis, Carr, Wiegand and Krantz (1943) found that sorbitol comprising 5 percent of the food intake did not affect deleteriously the rate of growth, liver glycogen storing capacity, or important metabolic viscera of white rats through three generations. Smith, Finkelstein and Smith (1940) noted no toxic manifestations in man after the intravenous injection of 80 gm. sorbitol or mannitol or 50 gm. of dulcitol over a period of 2 hours. Jaffé (1883) believed that mannitol is not oxidized readily in the organism of dogs. Carr, Musser, Schmidt, and Krantz (1933) found that mannitol increases the storage of glycogen in the liver of rats after oral administration, and Carr and Krantz (1938) reported that it may cause moderate hyperglycemia in rabbits. Ellis and Krantz (1941) and Ellis and Carr (1941) found that it increases the glycogen deposit in the liver of monkeys in contrast to sorbitol, with which such effect is absent. Dulcitol, on the other hand, increases, to a moderate extent, the glycogen storage in the liver of monkeys but does not increase the respiratory coefficient of rats. Spealman (1940) showed that $\frac{1}{10}$ molar solutions of mannitol slow the beat of the isolated heart and twice this concentration decreases the ventricular weight, presumably by dehydration.

As shown by Höber and Höber (1937), the rate of absorption of

polyhydric alcohols from the intestinal tract decreases with the increase of their molecular weight. None of them appear to have a specific toxicologic action and some of them may be converted to glycogen in the organism. Any effect on the functions of the organism presumably are affiliated closely with their osmotic action. Smith, Finkelstein, and Smith (1940) found that after intravenous injection in man only 32 percent of 9 gm. sorbitol and 87 percent of 4 gm. dulcitol were excreted with the urine within 10 hours, indicating that the former is more readily metabolized. Grabfield and Swanson (1942) showed that the intravenous injection of 15 cc. of a 50 percent solution of sorbitol caused, in dogs, considerable diuresis and increase of the excretion of uric acid during the first hour to the extent of 3 times the original amount. Since mannitol and dulcitol do not share this uricosuric action, it appears that the optical configuration plays a role in this respect. The uricosuric action appears to be due to a specific effect on the purine metabolism, whereas the diuretic action is presumably the outcome of the hypertonicity of the solution of these alcohols.

It appears, therefore, that alcohols with 4, 5, and 6 hydroxylic groups have none of the properties usually attributed to monovalent alcohols, and that, with increasing number of hydroxylic groups, they assume more and more the character of carbohydrates.

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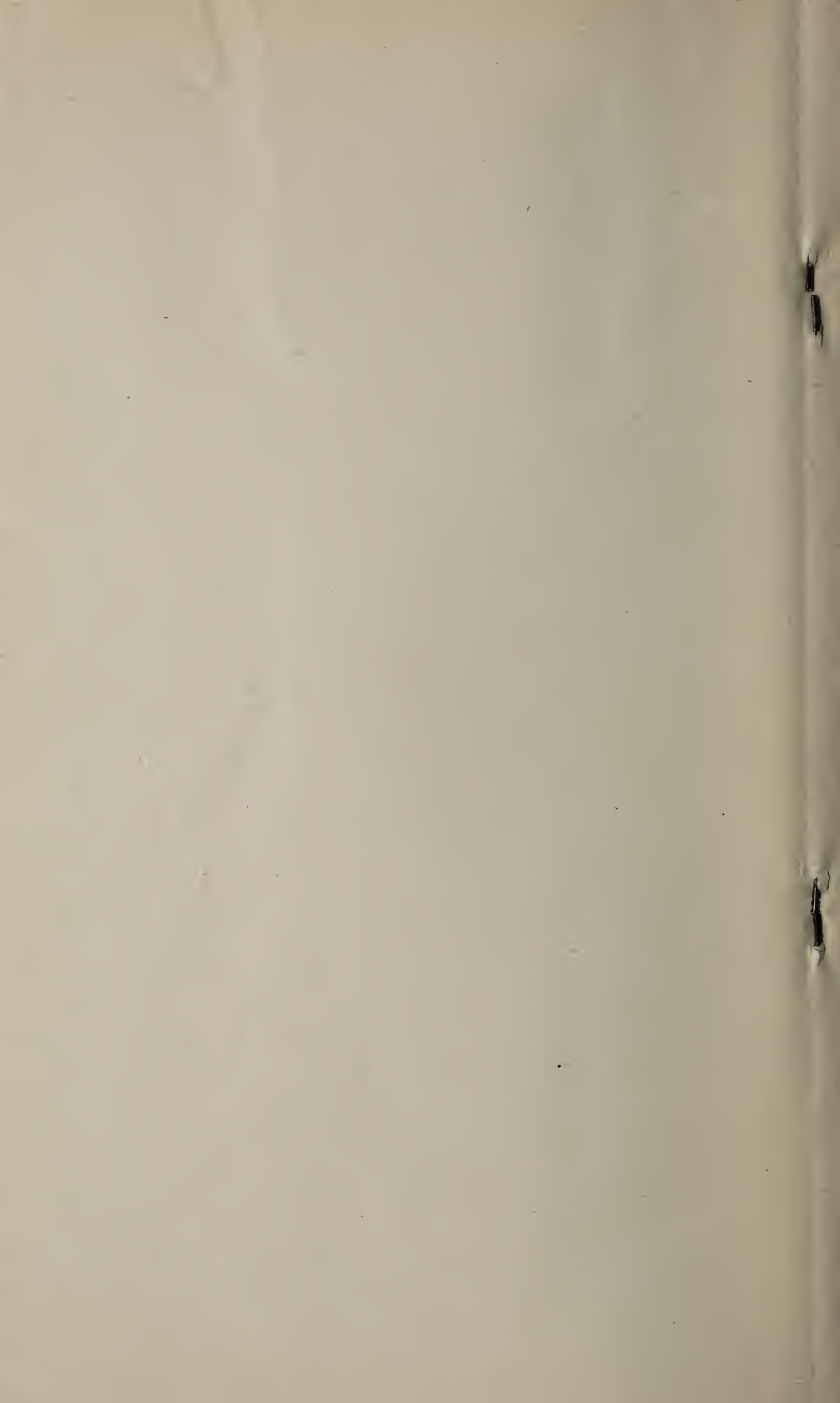Voegtlin, C., J. W. Thompson, and E. R. Dunn: Hyperglycemia produced by glycerol. J. Biol. Chem., 64: 639, 1925.

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