Injection of formaldehyde
ppb

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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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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.

[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.
Phenylhydrazine—sodium nitroprusside—sodium hydroxide.	Meth: Chem. Ztg., 30: 666, 1906. Utz, F.: Chem. Zentr., 1: 602, 1906. Rimini, E.: Chem. Zentr., 1: 1152, 1898.
Apomorphine—sulfuric acid	Same as above and— Aweng, E.: Apoth. Ztg., 17: 159, 1912.
Pepton—ferric chloride	Rimini, E. and T. Jona: Chem. Zentr., 1: 1147, 1912. Bono, A.: Chem. Ztg., 36: 1171, 1912.
Reduced fuchsine—sulfuric acid	Wolff, H.: Chem. Ztg., 43: 555, 1919. Salkowski, E.: Z. Untersuch. Nahrungs. u. Genussmittel, 36: 262, 1918.
β-naphthol—hydrochloric acid	Denigès, G.: Compt. rend. acad. sci., 90: 529, 832, 1910; Bull. soc. chim., ser. 4, 7: 951, 1910.
Hexamethylene—mercuric chloride	Mullikan, S. P.: A method for the identification of pure organic compounds. New York and London, 1: 24, 1911. 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-dihydroresorcinol), 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.[3] 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-

[3] 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 $\frac{\text{oil}}{\text{water}}$ 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.

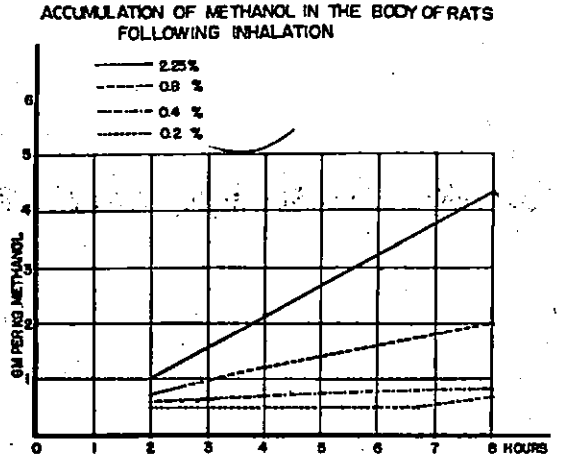

FIGURE 1.—This figure illustrates the accumulation of methyl alcohol in the body of rats following inhalation of various concentrations of methanol in air. (Redrawn from Loewy and von der Heide, 1914.)

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 content. 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	0.80
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 3 dogs*	*Average of 3 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	[1] 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	89.6
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 formaldehyde 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

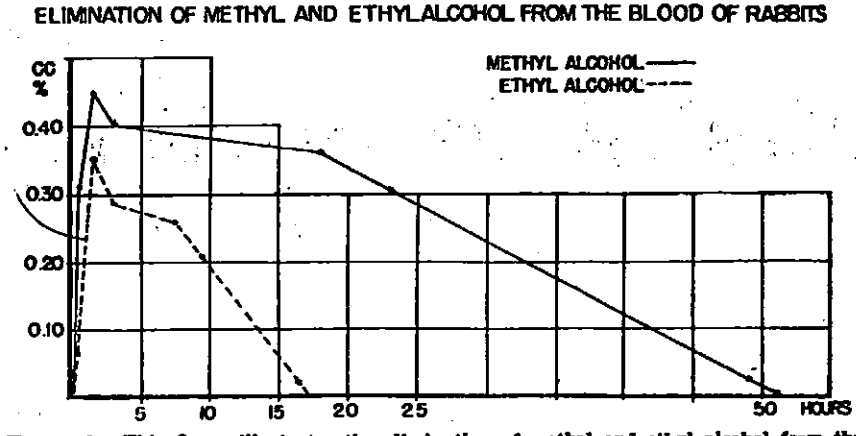

FIGURE 2.—This figure illustrates the elimination of methyl and ethyl alcohol from the blood of rabbits following ingestion of 5 cc. per kg. body weight of these alcohols in 10 percent solution. (Redrawn from Nicloux and Placet, 1912.)

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		
28.5	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 $\frac{1}{60}$ 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), Willems (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 Benedict, 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), Burhans (1930) and others. In very severe cases these symptoms may be associated with opisthotonus (Król, 1913). Later ataxia and peripheral 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 characteristic phenomena in methyl alcohol poisoning, as reported by MacFarlan (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 (deSchweinitz, 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), Jelliffe (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:

(Skull and crossbones)
POISON
CONTAINS OVER _____ PERCENT METHANOL
CAN NOT BE MADE NONPOISONOUS

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

(Skull and crossbones)
POISON
CONTAINS OVER _____ PERCENT METHANOL
CAN NOT BE MADE NONPOISONOUS
AVOID PROLONGED BREATHING OF VAPOR

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 progagation 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]

[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, paraldehyde, acridine, naphthalene and naphthalene derivatives, dimethyl, ethyl-methyl, and ethyl-phenyl esters of phthalic acid, oxalic acid ethyl ester, nitric acid ethyl ester, dimethyl