THE TOXICITY OF METHYL ALCOHOL.

By Reid Hunt, M. D.,

Associate Professor of Pharmacology, The Johns Hopkins University.

The number of cases of poisoning by methyl (or wood) alcohol has greatly increased in the last few years; this is due very largely to the fact that wood alcohol is now frequently used as a constituent of certain preparations where ethyl (or grain) alcohol was formerly employed. Not only have preparations intended for use in the arts (as varnishes, etc.) or for external use (as bay rum) been made with methyl alcohol as an ingredient, but even medicinal or flavoring agents (essence of Jamaica ginger, peppermint, etc.) intended for internal use have been found to contain it. The use of methyl alcohol in the latter class of preparations has attracted the attention of the medical profession to this substance, as many deaths have resulted from the use of these preparations: and the leading ophthalmologists of this country and of Europe are agreed in ascribing many cases of total or partial blindness to the wood alcohol contained in them.

While much has been written concerning the action of

methyl alcohol upon the eye and considerable experimental work has been done upon this subject (notably by Friedenwald and Birch-Hirschfeld), very little has been published recently concerning the general physiological action of methyl alcohol and the points in which this differs from the action of the much better known grain alcohol. Although it has been known to pharmacologists for many years that the action of methyl alcohol is, in some respects, so markedly different from that of ethyl alcohol that the substitution of the former for the latter in any preparation intended for internal use (especially if the preparation were to be taken for some time) would inevitably be accompanied by the greatest danger,[1] there seems to be much ignorance of this fact even among physicians; this probably results from the fact that little or nothing is said about methyl alcohol in some of the leading English text-books on toxicology (which, as a rule, discuss only those poisons which have already been of medico-legal interest). The subject is discussed, however, in all of the leading German text-books on toxicology. Under the circumstances a brief resumé of our knowledge of the general physiological action of methyl alcohol may be of interest; a number of experiments of my own upon animals will also be described.

There are two forms of methyl alcohol poisoning, acute and chronic. While the chronic, or still more, the subacute form is the one of greater interest (since it differs markedly from poisoning by grain alcohol), a few words may be said about the acute form.

Acute Poisoning with Methyl Alcohol.

The symptoms of acute poisoning of animals with methyl alcohol are, in general, similar to those observed in cases of poisoning by ethyl and other alcohols of this series. These symptoms are too familiar to require description here. The action of methyl alcohol differs from that of ethyl alcohol chiefly in the fact that the symptoms are produced more slowly and the duration of the intoxication is more prolonged. Thus the state of coma does not appear, as was shown by Joffroy and Serveaux, for some little time even when methyl alcohol is injected directly into the vein of an animal, whereas after the injection of ethyl alcohol it appears with great rapidity. The coma caused by methyl alcohol continues for a very much longer time than does that caused by ethyl alcohol; thus it is not uncommon for the coma in the former case to continue for two, three or even four days, whereas that caused by ethyl alcohol may not continue for more than six hours and, in the numerous experiments of Joffroy and Serveaux, was never observed to continue for twenty-four hours.

Similar differences between the action of methyl and ethyl alcohols are well known in the case of man, but there is a tendency to explain the long continued narcosis caused by the former to the presence of various impurities; no support for this view has been offered and numerous experiments on animals with pure methyl alcohol have shown that the long continued after-effect is due to a property inherent in the methyl alcohol itself.

Among the various symptoms caused by methyl alcohol in animals, Joffroy and Serveaux (Arch. de Méd. expér., viii, p. 490) called attention to the marked fall of body temperature and to the partial loss, on the part of the animal, of the power to regulate its temperature according to that of the surrounding air. There are marked changes in the alimentary tract; thus hemorrhages, leading to bloody diarrhoea or to the vomiting of bloody matter, are of frequent occurrence. There are convulsions or convulsive movements of a rhythmic or choreiform character, often continuing for a day or two and followed, finally, by a loss of sensation and of reflex movement; the corneal reflex, however, may persist for a long time. Joffroy and Serveaux also call attention to the marked convulsive movements of the eyes; these often constitute nystagmus of a pronounced type. This nystagmus usually occurs spontaneously, but when it is absent it can be caused very easily by simply moving the head of the animal; there are first convulsive movements of the eyes followed by a nystagmus, at first rapid, then slow. There is usually dilatation of the pupil.

Perhaps the point of greatest interest in connection with the subject of acute poisoning by methyl alcohol is the question of the relative toxicity of methyl and ethyl alcohols, i. e., the relative quantities which, when administered in a single dose to an animal, will cause death in a short time. All who have investigated this subject experimentally are agreed that there is but little difference between the toxicity of the two alcohols in cases of acute intoxication. Some of the earlier writers ascribed slightly greater toxicity to methyl alcohol; thus Dujardin-Beaumetz and Audigé (Comptes rend., 83, p. 80, 1876) placed the lethal dose of methyl alcohol, injected subcutaneously into dogs, at 7 gr. per kilogramme body weight, the lethal dose of ethyl alcohol being, according to these authors, 7.75 gr. per kilogramme. Later writers ascribe a slightly greater toxicity to ethyl than to methyl alcohol. Thus Joffroy and Serveaux in their classical studies on the toxicity of methyl alcohol found the "true toxic equivalent" of methyl alcohol (i. e., the quantity per kilogramme body-weight which, when injected into a vein or into the muscular tissue, would almost always lead to death within a short time—a day or two) to be, for the dog, about 9 ccm. (7.2G.); for the rabbit the dose was about 10 ccm. (7.96G.). The figures were the same whether the "pure methyl alcohol" of commerce or whether chemically pure methyl alcohol was employed. These authors (Arch. de Méd. expér., ix, p. 707) found the true toxic equivalent of ethyl alcohol to be, for the dog, 8.65 ccm. (6.92G), for the rabbit, 8.15 ccm. (6.52G.). The toxicity of the "pure ethyl alcohol" of commerce was slightly greater, being 6.36 G. for the dog and 6.20G. for the rabbit.

[1] This has been the teaching of Professor Abel, for example, ever since the opening of the Johns Hopkins Medical School in 1893.

Baer (Archiv f. Anat. u. Physiol., 1898, p. 289) experimenting on rabbits and introducing the diluted alcohols into the stomach, placed the toxic dose of methyl alcohol at from 7.2 to 9G. per kilogramme body-weight, that of ethyl alcohol at 6.25 to 7.44G.

The slight discrepancies between the results of the authors quoted above can be easily explained by the differences in the methods of experimenting; some authors administered the alcohol intravenously or injected it directly into the muscles, others gave it by the stomach. In some experiments dogs, in others rabbits were used. Indeed it is remarkable that the results have been so uniform when these facts are considered. The above results also show that the various specimens of wood alcohol used in the experiments must have been comparatively pure or that the impurities commonly present in wood alcohol have but little toxic action, for it is highly improbable that the same impurities should occur, and occur in the same quantity, in specimens of wood alcohol obtained at such different places and at such intervals of time.

My own experiments on the subject of acute poisoning were limited to a few observations on the fatal period after the administration, in one or two doses, of equal quantities of methyl and ethyl alcohols. The description of the symptoms will be omitted as there was nothing especially noteworthy.

The preparation of methyl alcohol used in most of the experiments was Kahlbaum's purest methyl alcohol; it was perfectly colorless, entirely free from acetone and other substances giving an iodoform reaction. The specific gravity and boiling point corresponded to methyl alcohol of about 99.6 per cent. The ethyl alcohol used, as a rule, was Squibb's absolute alcohol. The alcohols were diluted with water and introduced into the stomach by means of a soft rubber catheter.

In the first two experiments the dose was 10G. per kilogramme animal.

I. Experiment with methyl alcohol, May 15th. Male rabbit, weighing 2.28K. At 4.55 p. m. a mixture of 22.8G. of methyl alcohol and 68.4G. warm distilled water administered. The animal was soon deeply intoxicated and died on the following afternoon at about 5 o'clock, that is 24 hours after the alcohol was given.

II. Experiment with ethyl alcohol, May 15th. Female rabbit, weighing 2.17K.

5-10 p. m., 21.7G. of ethyl alcohol diluted with 65G. of warm distilled water administered. The animal had convulsions of a mild type in 15 minutes and died at 11 p. m., that is 6 hours after the poison was given.

In the two following experiments both the methyl and ethyl alcohols were diluted to 89 per cent (by weight) and 16G. per kilogramme body-weight of the diluted alcohol was mixed with water and given to the rabbits in two doses; these corresponded to about 14.2 G. of the pure alcohols.

III. Experiment with methyl alcohol, May 16th. Male rabbit, weighing 1.75K.

10 a. m., 14G. of 89% methyl alcohol diluted with 42G. of distilled water given by the stomach.

May 17th, 1.50 p. m. The above dose was repeated.

May 18th. The animal was living but seemed to be at point of death.

May 19th, 7 a. m. The animal has apparently been dead for many hours.

The animal died in from 56 to 69 hours after the first dose.

IV. Experiment with ethyl alcohol, May 16th. Male rabbit, weighing 1.84K. 9.40 a. m., 14.7G.[1] of 89% (92.4% by volume) ethyl alcohol diluted with 45G. of distilled water administered.

May 17th, 1.45 p. m. The above dose was repeated.

May 18th. The animal died about 11 a. m., i. e., about 49 hours after the administration of the first dose.

In the following two experiments the pure alcohols were given in two doses of 6.5G. each, per kilogramme body-weight.

V. Experiment with methyl alcohol, May 16th. Female rabbit, weighing 1.8K.

4.10 p. m., 11.7G. pure methyl alcohol diluted with 35G. distilled water administered.

May 17th, 2 p. m. The above dose was repeated. Convulsive movements of the legs and marked nystagmus were noticed soon afterwards.

May 18th. The animal was alive at 6 p. m.

May 19th. The animal has apparently been dead for many hours.

The rabbit died between 74 and 84 hours after the administration of the first dose.

VI. Experiment with ethyl alcohol, May 16th. Male rabbit, weighing 1.45K.

4 p. m., 9.4G. ethyl alcohol diluted with 28G. distilled water administered.

May 17th, 2.5 p. m. The above dose was repeated.

May 18th. The animal lived throughout the day.

May 19th, 7 a. m. The rabbit was found dead. The animal died between 50 and 60 hours after the administration of the first dose.

The above experiments show that with equal doses of ethyl and methyl alcohols death is caused in a shorter time by the former than by the latter; this agrees with the generally accepted view that in acute poisoning ethyl alcohol is slightly more toxic to dogs and rabbits than is methyl alcohol.

In the following two experiments the methyl alcohol used was a commercial preparation known as Columbian Spirits; it was not the purest preparation known by this name, but was of a light yellow color and gave a fairly well marked iodoform reaction (acetone?). The specific gravity was 0.802 (at 15.5° C.), which would correspond to about 98 per cent pure methyl alcohol, provided that only methyl alcohol and water were present.

VII. Experiment with Columbian Spirits, June 23d. Rabbit weighing 1.2K.

2 p. m., 12G. Columbian Spirits diluted with 36G. water administered.

[1] This dose, which corresponds to 7.1G of absolute ethyl alcohol per kilogramme body-weight is just about the minimal lethal dose, i. e. most rabbits would probably have died from it.

June 24th. The animal is in the deepest coma and seems barely alive.

June 25th. Animal conscious and able to crawl about a little; living at midnight.

June 26th, 6 a. m. Dead. Died between 58 and 64 hours after the alcohol was given.

In this experiment the animal lived much longer than did the one which received an equal dose of pure methyl alcohol (see Experiment I); whether this was due to the fact that the Columbian Spirits contained a slightly smaller percentage of methyl alcohol or to greater resistance on the part of this animal or to the fact that this experiment was performed in warmer weather than was the one with pure methyl alcohol it is impossible to state.

In the second experiment the Columbian Spirits was given in two doses of 8G. per kilogramme body-weight.

VIII. Experiment with Columbian Spirits, May 16th. Male rabbit, weighing 1.81K.

9.45 a. m., 14.5G. Columbian Spirits diluted with 45 G. distilled water administered.

May 17th. The above dose was repeated. The animal was living at 6 p. m.

May 18th, 7 a. m. The rabbit was found dead, having died between 32 and 44 hours after the administration of the first dose.

The results of the above experiments are shown in the table above:

The above experiments show that death is caused more rapidly by one or two large doses of ethyl than by corresponding doses of pure methyl alcohol and so may be looked upon as offering some confirmation of the view that in acute intoxication the former is slightly more toxic for the lower animals than is the latter.

The question which of these alcohols is the more poisonous to man in acute cases, i. e., which would cause death in the smaller quantity, is a very difficult one to answer. Even the minimal fatal dose of ordinary alcohol for man is not known with anything like the accuracy with which it is known for the lower animals; still less is known in regard to methyl alcohol. The question is further complicated by the fact that a fairly large percentage of the human race (at least of that part of it living in America and Europe) have acquired a certain degree of tolerance of ethyl but not of methyl alcohol; this is almost always true of those who die from methyl alcohol poisoning.

There are also other considerations which make the pharmacologist hesitate in concluding from these experiments on the lower animals that ethyl alcohol is more toxic to man than is methyl alcohol. The organs most powerfully affected by methyl alcohol are the most highly differentiated nervous structures as is shown by the deep and prolonged coma and in man and the monkey by blindness (due to degenerative changes in the nerve elements of the retina and of the optic nerve). Even in the rabbit the coma is much more prolonged after methyl than after ethyl alcohol. Now it is a well recognized fact in pharmacology that poisons which affect the highly differentiated nerve structures very powerfully are proportionately more dangerous the

Date.	Alcohol.	Animal.	Weight of animal.	Quantity of alcohol given.	Dose per kilogramme.	Number of doses.	Result.	Remarks.
I. May 15th.	Kahlbaum's purest, acetone free methyl alcohol.	Rabbit.	2.28K.	22.8G. alcohol, 68.4G. water.	10G.	1	Death in 24 hours.	
II. May 15th.	Absolute ethyl alcohol.	Rabbit.	2.17K.	21.7G. alcohol, 65G. water.	10G.	1	Death in 6 hours.	
III. May 16th.	Kahlbaum's purest methyl alcohol diluted to 89% (by weight).	Rabbit.	1.75K.	28G. alcohol, 84G. water.	16G.	2	Death 56 to 69 hrs. after first dose.	Interval between doses 27 hours 50 minutes.
IV. May 16th.	Pure ethyl alcohol, 89% by weight; 92.4% by vol.	Rabbit.	1.84K.	29.4G. alcohol, 90G. water.	16G.	2	Death 49 hours after first dose.	Interval betweendoses 28 hours.
V. May 16th.	Kahlbaum's purest methyl alcohol.	Rabbit.	1.80K.	23.4G. alcohol, 70G. water.	6.5G.	2	Death 74 to 84 hrs. after first dose.	Interval between doses 21 hours 50 minutes.
VI. May 16th.	Absolute ethyl alcohol.	Rabbit.	1.45K.	18.8G. alcohol, 56G. water.	6.5G.	2	Death 50 to 60 hrs. after first dose.	Interval between doses 22 hours 5 minutes.
VII. June 23d.	Columbian Spirits.	Rabbit.	1. 2K.	12G. Col. Spirits, 36G. water.	10G.	1	Died in 58 to 64 hours.	
VIII. May 16th.	Columbian Spirits.	Rabbit.	1.81K.	29G. Col. Spirits.	16G.	2	Died 32 to 44 hours after first dose.	Interval between doses 28 hours 25 minutes.

more highly developed the nervous system of the animal; hence it would be expected that man would be relatively more suspectible to such a poison as methyl alcohol than would the dog or rabbit.

Under these circumstances it would not be safe to conclude that because ethyl alcohol is slightly more toxic, in acute poisoning, to the lower animals than is methyl alcohol, the same would be true in the case of man. As a matter of fact, a number of cases are reported in which men died from methyl alcohol when equal quantities of ethyl alcohol could almost certainly have been taken with impunity. Physicians who have had extensive hospital experience state that very few of those who are brought to the hospital intoxicated with wood alcohol recover. One explanation often offered for this apparently greater toxicity of methyl alcohol is that the commercial preparations of wood alcohol contain impurities which greatly increase the toxicity; there is little evidence, however, that this is true of any of the preparations of wood alcohol accessible to the public.

In the above discussion the toxicity of the two alcohols has been considered only so far as life is concerned. It is certain that some organs are much more susceptible to the injurious action of one alcohol than to that of the other. That this is the case with the eye, for example, is clearly shown by the cases of wood alcohol blindness in man. As Birch-Hirschfeld expresses it, these cases show that methyl alcohol is capable of injuring the eye to a far greater extent, and also in smaller doses, than is ethyl alcohol; thus cases are reported in which blindness occurred in the most acute form of methyl alcohol intoxication and also after very small doses, a result which probably never occurs with ethyl alcohol.

CHRONIC POISONING WITH WOOD ALCOHOL.

The fact that the effects of a single dose of methyl alcohol are long continued suggests that it would be an especially dangerous substance to give at short intervals for any length of time, for it may readily be supposed that under these circumstances the effect of the first dose would not have disappeared when the second was given, and so on. In this way a form of cumulative action would result depending, probably, on the retention within the body of methyl alcohol or of some of its decomposition products. As a matter of fact, all who have investigated this subject have found such a result to be produced, so that methyl alcohol which when taken in a single dose is, as a rule, no more dangerous (at least to the lower animals) than an equal amount of ethyl alcohol, becomes, when its use is continued for even a short time an extremely dangerous poison.

Pohl, in his well known work on the oxidation of alcohol in the animal body (Archiv f. Exper. Path. u Pharm., 31. p. 281; 1893), stated that chronic poisoning by methyl alcohol is markedly different from that caused by ethyl and other alcohols of this series.

While ethyl and isobutyl alcohols and even amyl alcohol (fusel oil) could be given to animals (dogs and rabbits) in doses sufficient to cause intoxication for months (and even for almost a year) without causing marked anatomical or functional disturbances, methyl alcohol given in small doses every other day was tolerated for but a few weeks; the animals remained comatose for days, did not eat and died, although the administration of the alcohol was discontinued. Extensive fatty degeneration of the liver was always found; thus in one experiment the ether extract (consisting largely of fat) of the dried liver of a dog poisoned by methyl alcohol was 37.7 per cent, while that of the liver of the control (normal) animal was but 16.6 per cent.

Joffroy and Serveaux, the most experienced investigators on the subject of the toxicity of the various alcohols, also lay great emphasis upon the extraordinary toxicity of methyl alcohol in chronic poisoning; they found that it was not only much more poisonous than ethyl alcohol, when given for some time, but that animals could tolerate comparatively large doses of furfurol for longer periods than they could methyl alcohol. These authors conclude that it is not possible to foretell the toxicity of an alcohol in chronic poisoning from experiments on acute poisoning.

The great toxicity of methyl alcohol in chronic or subacute poisoning is well illustrated by some recent experiments of Birch-Hirschfeld (v. Graefe's Arch. f. Ophthal., liv, p. 68). This writer, who was investigating the effects of methyl alcohol upon the retina and optic nerve, speaks of the difficulty he experienced in keeping the animals alive for even short periods when small doses of methyl alcohol were administered at short intervals. The experiments of Birch-Hirschfeld upon monkeys are of especial interest since these animals react towards narcotic poisons in much the same way as does man; and also because the effect of the poison upon the eye can be studied to far better advantage upon monkeys than upon dogs and rabbits. Birch-Hirschfeld describes experiments upon three monkeys; pure methyl alcohol, diluted with several times its volume of water, was given in doses of from three to six or seven c. cm. every one or two days. When it became evident that the animals were at the point of death they were killed in order that the eyes and optic nerves could be obtained in good condition for microscopical study. The first monkey received 28 c. cm. of methyl alcohol in this way and was in a dying condition on the eighth day; the second animal was moribund on the fifteenth day after having received 79 c. cm. of the alcohol, while the third animal was in a dying condition on the eleventh day after having been given 56 c. cm. of the alcohol. Two of the monkeys had marked degenerative changes in the retina and one was totally blind. Similar histological changes were found in the retinas of three dogs poisoned by methyl alcohol, although it had not been possible to detect disturbances of vision during life.

It is very interesting to compare the above results of

Birch-Hirschfeld with those obtained by de Schweinitz (Toxic Amblyopias, p. 51; 1896) in an experiment with grain alcohol. De Schweinitz gave a small monkey (weight eight pounds) an average daily dose of 3.75 c. cm. of 95 per cent grain alcohol for over six months; at times as much as 7.5 c. cm. of alcohol was given every day for several days in succession. The animal was repeatedly very drunk but showed no symptoms of permanent injury and no indications whatever of disturbances of vision could be made out. The animal was finally killed and the eyes and optic nerves were examined microscopically; no degenerative or inflammatory changes were found.

Holden (Arch. of Ophthal., 28, p. 129) reports an interesting experiment in which a form of chronic or subacute poisoning resulted from two large doses of methyl alcohol. A dog weighing ten kilogrammes was given 50 c. cm. of wood alcohol diluted with an equal quantity of water; this dose was repeated five days later. The dog died eleven days after the second dose; the ganglion cells of the retina showed degeneration changes.

The Writer's Experiments on Subacute Poisoning.—I have performed a number of experiments upon dogs and rabbits in connection with the question of subacute poisoning by methyl alcohol. Special attention was given to the subacute form of poisoning (i. e., that form in which comparatively large, but not immediately fatal, doses were given at short intervals), as this is the form of poisoning seen most often in man; in a number of the cases of methyl alcohol poisoning in man in which death or blindness has resulted, there has been a history of a "spree" continuing for several days. My attention was directed largely to a comparison of the general physiological effects produced by equal doses of methyl and of grain alcohols. But little attention was given to the influence of the alcohols upon vision, for, as is well known, it is very difficult to determine with much accuracy the effects of drugs upon the sight of dogs and rabbits. In most of the experiments upon dogs, however, a purulent or fibrino-purulent conjunctivitis was noticed and in at least one case the animal seemed to be blind.

Most of the experiments were performed in groups of two; to one animal methyl, to the other ethyl, alcohol in equal quantity (per kilogramme body-weight of the animal) were given at the same intervals and in the same way. Several different specimens of methyl alcohol were used; these will be described in the proper place.

In the following two experiments the alcohols were given in doses of first six, then of three grammes per kilogramme body-weight; in each case the alcohol was diluted with four times its weight of warm distilled water and introduced into the stomach by means of a tube. The methyl alcohol was a commercial preparation obtained from Eimer and Amend; it was labeled "Methylic Alcohol, Pure," but it yielded a small quantity of iodoform on treatment with iodine and potassium hydroxide; the specific gravity was 0.802 (15.5° C.), which would correspond to about 98 per cent absolute methyl alcohol, assuming almost nothing but alcohol and water to be present.

IX. Experiment with methyl alcohol, May 21st. Dog, weighing 7.84K.

4.45 p. m., 47G. methyl alcohol diluted with 188G. of water administered.

May 22d, 10 a. m. Animal lying down, unable to get up; conscious. 2.10 p. m., 23.5G. alcohol and 94G. water given. There is a watery discharge from the eyes.

May 23d. The animal is in a deep stupor from which he can, however, be aroused. Is unable to stand. There is a muco-purulent discharge from the eyes.

May 24th. Fibrino-purulent conjunctivitis; cornea hazy. Animal seems unable to see; reacts well to slight noises but shows no reaction when hand is passed before eye.

May 25th. Animal just able to stand; eats a little. Cornea bluish; almost certain that animal does not see.

11.50 a. m., 23.5G. alcohol and 94G. water given. The dog was soon in a deep stupor.

May 26th. Unable to stand; eats nothing; very stupid. Purulent conjunctivitis in one eye; the other eye is not so bad as yesterday.

4.15 p. m., 23.5G. alcohol and 94G. water given.

May 27th. Condition about the same as yesterday but the stupor is greater.

May 28th, 3.35 p. m., 23.5G. alcohol and 94G. water given. At 9.30 p. m. the dog was alive.

May 29th. Found dead at 7. a. m.; has apparently not been dead long. The stomach contained much blood-stained mucus; small ecchymoses were found in the mucous membrane. The urine was strongly reducing towards silver nitrate.

X. Experiment with absolute ethyl alcohol, May 21st. Bitch, weighing 5.02K.

5 p. m., 30.1G. of alcohol diluted with 120G. water administered.

May 22d, 10 a. m. Is able to stand but is somewhat intoxicated.

1.55 p. m., 15.1G. alcohol and 60G. water given.

May 23d. Is able to stand and drinks a little water but refuses food.

May 24th. Lies down most of the time; does not eat. There is no discharge from the eye and the animal undoubtedly sees well.

May 25th. Is standing and seems very bright; eats greedily.

11.40 a. m., 15.1G. alcohol and 60G. water given; animal soon deeply intoxicated.

May 26th. Dog bright; eats a little. 4.10 p. m., 15.1G. alcohol and 60G. water given.

May 28th, 3.30 p. m., 15.1G. alcohol and 60G. water given.

The animal was kept until June 3d, during which time no bad effects whatever were noticed; she ate well and increased in weight to 5.64K.

The following experiments were made in the same way as the above except that the intervals between the doses were somewhat different and different preparations of the alcohols were used. The methyl alcohol was the specimen of Columbian Spirits described above in the description of the experiment on the rabbit (VII); the ethyl alcohol was a 93 per cent solution made by adding distilled water to some commercial absolute alcohol. The effects of these two preparations were compared because Columbian Spirits seems to be used sometimes in place of ordinary grain

alcohol, which usually contains about 93 per cent of absolute ethyl alcohol.

XI. Experiment with Columbian Spirits, May 15th. Bitch, weighing 6K.

5.50 p. m., 36G. Columbian Spirits diluted with 108G. distilled water administered.

May 16th. Animal unable to stand; has diarrhœa with slightly bloody discharges.

4.35 p. m., 18G. Columbian Spirits and 54 G. water given.

May 17th. Lies perfectly still with slow labored respiration; unable to hold head up when aroused.

4 p. m., 18G. Columbian Spirits and 54G. waetr. In a short time animal was in deepest coma; corneal reflex absent.

May 18th, 11 a. m. Completely paralyzed; slight corneal reflex. Has vomited much watery matter and passed soft bad-smelling feces containing blood.

May 19th. Slow, deep respiration; no corneal or other reflexes. Has passed much thin feces containing decomposing blood and with a very disagreeable odor. Was living at 6 p. m.

May 20th. Has evidently been dead many hours.

During the first two days of the experiment there was much lachrymation; before death there was a slightly purulent discharge from the eyes.

XII. Experiment with 93% ethyl alcohol, May 15th. Dog, weighing 10.5K.

6.5 p. m., 63G. of 93% ethyl alcohol diluted with 189G. of water administered.

May 16th. Animal is standing but is intoxicated.

4.40 p. m., 31.5G. alcohol and 94G. water given.

May 17th. Dog standing and is bright and lively; very playful and eats greedily.

3.55 p. m., 31.5G. alcohol and 94G. water given.

May 18th, 11 a. m. Very bright and lively.

May 19th. Seems entirely normal.

The animal was kept 10 days longer; nothing abnormal could be detected and he gained slightly in weight.

In the following experiments the effects of the purest methyl alcohol obtainable (Kahlbaum's "acetone free" methyl alcohol) were compared with those caused by pure absolute ethyl alcohol; the alcohols were given in doses 5G. per kilogramme animal.

XIII. Experiment with pure methyl alcohol, June 5th. Bitch, weighing 6.84K.

2.30 p. m., 34.2G. methyl alcohol diluted with 130G. of water administered.

June 6th. Animal unable to stand but is conscious; does not eat. There are irregular twitchings of the legs. There is a little pus in one eye.

3.20 p. m., 34.2G. of alcohol and 130G. of water given.

June 7th. Lies in a deep stupor; corneal reflex present but very sluggish. Both eyes contain a gelatinous secretion.

2.35 p. m., 34.2G. alcohol and 130G. water given; much of it was vomited soon afterwards.

June 9th. Is conscious but unable to stand; head sways back and forth rhythmically. Both eyes have an extremely viscid purulent discharge which contains a large number of bacteria of various kinds.

2.35 p. m., 34.2G. alcohol and 130G. water given.

June 10th, 8 a. m. Lying in deepest coma; not the slightest reflex of any kind. Much brown, very bad-smelling matter has escaped from the anus. Animal died at 1.35 p. m.

The rugae of the stomach were bright red and bleeding slightly. The intestines, especially in the lower part, were greatly inflamed and showed a number of minute bleeding points; there were a few ulcers in the rectum. The intestinal contents were of a dirty brown color due to the altered blood and had a very foul odor.

XIV. Experiment with absolute ethyl alcohol, June 5th. Bitch, weighing 7.57 K.

3.15 p. m., 37.9G. ethyl alcohol diluted with 148G. water given.

June 6th. Stands and is very lively; tries to fight with another dog.

3.25 p. m., 37.9G. alcohol and 148G. water given.

June 7th. A little unsteady on its feet but eats and drinks well.

2.45 p. m., 37.9G. alcohol and 148G. water given.

June 9th. Seems entirely normal; bright and active.

2.40 p. m., 37.9G. alcohol and 148G. water given.

June 10th. Slightly intoxicated but eats greedily.

The animal was kept for 14 days and showed no symptoms whatever; her weight increased to 8.5K..

In the following experiment the purest commercial preparation of Columbian Spirits obtainable was given in the same doses (5G. per kilogramme body-weight) as the alcohols in the above experiments. This preparation of Columbian Spirits was perfectly colorless, gave a very slight iodoform reaction; the specific gravity was 0.8 (15.5° C.), which corresponds to a preparation containing slightly more than 98 per cent absolute methyl alcohol and a little less than 2 per cent of water.

XV. Experiment with Columbian Spirits, June 6th. Dog, weighing 6.97K.

3.50 p. m., 34.9G,. Columbian Spirits diluted with 132G. water administered.

June 7th. Eats and drinks, but trembles continuously; vomited soon after eating.

2.50 p. m., 34.9G. Columbian Spirits and 132G. water given.

June 9th. Lies in deepest coma; corneal and other reflexes entirely absent; respiration very slow. Occasionally has convulsive movements.

2.30 p. m., 34.9G. Columbian Spirits and 132G. water.

June 10th, 7 a. m. The animal has evidently been dead for many hours. Stomach contained a small amount of altered blood with an extremely foul odor.

In the following experiment the ordinary grain alcohol of commerce (often called "Western alcohol") was used. It contained 92.5 per cent (by volume) of absolute ethyl alcohol. It was given in doses of 6G. per kilogramme body-weight; this corresponds to about 5.3G. absolute ethyl alcohol. Hence the results of this experiment may be compared with those of Experiments XIII and XIV, in which 5G. of absolute methyl or ethyl alcohol were given; the administration of the alcohol was continued longer in this experiment, however.

XVI. Experiment with 92.5% commercial ethyl alcohol, June 19th. Dog, weighing 13.6 K.

2.55 p. m., 81.6G. of alcohol diluted with 245G. water administered. Was soon deeply intoxicated.

June 20th, 7 a. m. Still somewhat intoxicated; eats a little and drinks; vomited later.

1.25 p. m., 81.6G. alcohol and 245 G. water given.

June 21st. Lies down most of the time but is able to stand; eats and drinks a little.

1.10 p. m., 81.6G. alcohol and 245G. water given.

June 22d, 10 a. m. Seems about normal; eats greedily.

June 23d. Seems normal; eats a great deal.
1 p. m., 81.6G. alcohol and 245G. water given.
June 24th. In good condition.
1.45 p. m., 81.6G. alcohol and 245G. water given.
June 25th. Seems to be entirely normal; very hungry.
The animal was kept under observation for 16 days during which time it seemed entirely normal; its weight increased 2.3K.

The results of the above experiment are shown in the following table:

In all of these experiments the dog which received the methyl alcohol died, while those which received equal or larger doses of ethyl alcohol in exactly the same way recovered. The differences between the action of the two alcohols could probably have been brought out still more strikingly if more attention had been given to the dosage.

Date.	Alcohol.	Animal.	Weight of animal.	Quantity of alcohol given.	Dose per K. body weight.	Number of doses.	Result.	Remarks.
IX. May 21st.	"Methylic Alcohol, pure." E. and A.	Dog.	7.84K.	141G. alcohol, 564G. water.	6G. once. 3G. 4 times.	5	Died on 9th day.	Doses given on 1st, 2d, 5th, 6th and 8th days. Distinct changes in the eyes.
X. May 21st.	Absolute ethyl alcohol.	Bitch.	5.02K.	90.5G. alcohol, 360G. water.	6G. once. 3G. 4 times.	5	Survived.	Doses given as in above experiment During the next week the animal's weight increased to 5.64 K.
XI. May 15th.	Columbian Spirits.	Bitch.	6K.	72G. Col. Spts., 216G. water.	6G. once. 3G. twice.	3	Died on 5th day.	Doses given at intervals of about 24 hours on 3 successive days. Conjunctivitis.
XII. May 15th.	Pure ethyl alcohol, 93%.	Dog.	10.5K.	126G. alcohol, 377G. water.	6G. once. 3G. twice.	3	Survived.	Doses given at intervals of about 24 hours on 3 successive days.
XIII. June 5th.	Kahlbaum's purest acetone free methyl alcohol.	Bitch.	6.84K.	136G. alcohol, 520G. water.	5G.	4	Died on 6th day.	Doses given on 1st, 2d, 3d and 5th days. Purulent conjunctivitis.
XIV. June 5th.	Absolute ethyl alcohol.	Bitch.	7.57K.	151.6G. + 592G. water.	5G.	4	Survived.	Doses given on 1st, 2d, 3d and 5th days.
XV. June 6th.	Highest grade Columbian Spirits.	Dog.	6.97K.	104.7G. + 396G. water.	5G.	3	Died on 5th day.	Doses given on 1st, 2d and 4th days.
XVI. June 19th.	Commercial ethyl alcohol, 92.5%.	Dog.	13.6K.	408G. + 1225G. water.	6G.	5	Survived.	Doses given on 1st, 2d, 3d, 5th and 6th days. During the 16 days following the dog's weight increased to 15.9K.

Experiments on Rabbits.—Results in entire accordance with the above were obtained in a series of experiments upon rabbits. These animals are not, however, well adapted for studies on the comparative toxicity of methyl and ethyl alcohols in subacute poisoning, for the doses necessary to cause death within a short time (a few days) vary within narrow limits. The difficulty may be expressed in the following manner: There is a certain optimum dose for subacute poisoning, i. e., a dose with which the difference between the action of the two alcohols is best seen. When the dose of the alcohols is slightly greater than this optimum death is produced almost as rapidly by one alcohol as by the other; when the doses are below this optimum the action is very prolonged and the poisoning takes on a more chronic character. With the optimum doses, however (and in my experiments this was found to be about 5G. per kilogramme body-weight), the differences between the effects of the two alcohols are just as marked with rabbits as with dogs. I mention these facts for it is possible that experimenters who work only upon rabbits may overlook the difference between the action of the two alcohols unless special attention is given to the dosage.

In the first three experiments rather large doses of the alcohols were given (6G. per kilogramme body-weight). The Columbian Spirits used in the first two experiments was the inferior grade of this preparation already described.

XVII. Experiment with Columbian Spirits, May 15th. Male rabbit, weighing 2.19K.

5.25 p. m., 13G. Columbian Spirits diluted with 52G. water administered.

May 16th. Sits in one place and does not try to escape when handled; eats a little.

4.15 p. m., 13G. Columbian Spirits and 52G. water given.

May 17th. Animal comatose; corneal reflex present but very sluggish.

Unnecessary to hold animal when stomach tube was passd.

4.10 p. m., 13G. Columbian Spirits and 52G. water given.

May 18th, 10.45 a. m. The animal has evidently been dead for many hours. The urine reduces silver nitrate very strongly and decolorizes potassium permanganate; does not undergo fermentation with yeast.

XVIII. Experiment with Columbian Spirits, May 19th. Female rabbit, weighing 1.44K.

3 p. m., 8.65G. Columbian Spirits diluted with 34.6G. water administered. An hour afterwards the animal was deeply intoxicated; was unable to hold head up. There was marked nystagmus.

May 20th. Seems to have recovered almost completely.

4.25 p. m., 8.65G. Columbian Spirits and 34.6G. water.

May 21st. Semi-comatose all day; has eaten nothing.
4.5 p. m., 8.65G. Columbian Spirits and 34.6G. water given.
May 22d. Reflexes entirely absent; seemed barely alive at 6 p. m.
May 23d, 7 a. m. Found dead.

XIX. Experiment with absolute ethyl alcohol, May 19th. Female rabbit, weighing 1.45K.
3.10 p. m., 8.7G. alcohol diluted with 35G. water administered.
May 20th. Seems to be entirely normal.
4.30 p. m., 8.7G. alcohol and 35G. water given.
May 21st. Active; eats well.
4.10 p. m., 8.7G. alcohol and 35G. water given.
May 22d. Very active; difficult to catch.
May 23d. Condition same as that of yesterday; animal eats well.
2.30 p. m., 8.7G. alcohol and 46G. water given.
May 24th, 9.30 a. m. Very lively. Has aborted two very imperfect embryos.
1.45 p. m., 8.7G. alcohol and 46G. water given.
May 25th. Seems normal. 11.30, 8.7G. alcohol and 46G. water given.
May 26th, 7 a. m. Found dead.

In this experiment the administration of the ethyl alcohol was continued until it caused death—a result which did not occur until just twice the amount (in proportion to the body-weight) which was fatal in the case of Columbian Spirits had been given.

In the following experiment ethyl alcohol of the strength of 93 per cent was given in doses of 6G. per kilogramme.

XX. Experiment with 93% ethyl alcohol, May 15th. Male rabbit, weighing 2.17K.
5.35 p. m., 13G. alcohol diluted with 52G. water administered.
May 16th. Seems entirely normal; difficult to catch; eats well.
4.25 p. m., 13G. alcohol and 52G. water given.
May 17th. Seems entirely normal; very lively and difficult to catch.
4.5 p. m., 13G. alcohol and 52G. water given.
May 18th. Very lively. Weighs 2.05K.
The animal was kept for 16 days, during which time it exhibited no symptoms whatever.

In the following experiment ordinary commercial ethyl alcohol (containing about 92.6 per cent of absolute ethyl alcohol) was used; it was given in doses of 6G. each on four days.

XXI. Experiment with commercial ethyl alcohol (92.6%), June 19th. Female rabbit, weighing 1.96K.
2.10 p. m., 11.8G. alcohol diluted with 35G. water administered.
June 20th. Animal lively; eats a little.
2.10 p. m., 11.8G. alcohol and 35G. water given.
June 21st. Seems to be in good condition; eats a little.
2.25 p. m., 11.8G. alcohol and 35G. water given.
June 23d, 3 p. m., 11.8G. alcohol and 35G. water given.
June 25th. Seems to be normal.
The animal was kept for 16 days during which time it remained in good condition, its weight remained about the same.

The doses in the above two experiments (6G. of the 93 per cent (by volume) alcohol) corresponded to about 5.4G. pure absolute alcohol, hence the results may be compared with those of the following experiment in which doses of 5.5G. of Kahlbaum's purest methyl alcohol were given.

XXII. Experiment with Kahlbaum's purest methyl alcohol, May 19th. Female rabbit, weighing 2.55K.
2.30 p. m., 14G. alcohol diluted with 56G. water administered.
May 20th. Eating well.
4.17 p. m., 14G. alcohol and 56G. water given.
May 21st. Looks sick but has been eating.
3.55 p. m., 14G. alcohol and 56G. water given.
May 22d, 7 a. m. Found dead.

On comparing this experiment with the two described above (Experiments XVII and XVIII) it is seen that the purest methyl alcohol obtainable is about as toxic as the commercial preparation of Columbian Spirits; in fact, death was caused more rapidly by a slightly smaller dose of the former.

The difference between the effects of ethyl and methyl alcohols is well brought out in the following four experiments: the doses used in these experiments (4 to 5 grammes per kilogramme) seem to be those best adapted for causing subacute poisoning in rabbits. The methyl alcohol used in the first experiment was "Kahlbaum's Methyl Alcohol;" it was not the purest specimen prepared by Kahlbaum and gave a slight iodoform reaction; the specific gravity, however, was 0.796 (15.5° C.), which corresponds to a strength of 99.5 per cent. The methyl alcohol used in the third experiment was Kahlbaum's purest methyl alcohol.

XXIII. Experiment with Kahlbaum's methyl alcohol, June 3d. Female rabbit, weighing 1.98K.
3.15 p. m., 7.9G. (i. e. 4G. per kilo) diluted with 30.3G. water administered.
June 4th. Seems entirely normal.
12.25 p. m., 7.9G. alcohol and 30.3G. water given.
June 5th. Very lively; eats well.
2.25 p. m., 7.9G. alcohol and 30.3G. water given.
June 6th, 3.10 p. m., 9.9G. alcohol (i. e. 5G. per kilo) and 37G. water given.
June 7th. Lies down most of the time but eats.
2.30 p. m., 9.9G. alcohol and 37G. water given.
June 9th. Weak and sluggish; does not eat well.
2.40 p. m., 9.9G. alcohol and 37G. water given.
June 10th. Unable to stand; does not eat.
2 p. m., 9.9G. alcohol and 37G. water given.
June 11th. Died about 8 a. m.

XXIV. Experiment with absolute ethyl alcohol, June 3d. Female rabbit, weighing 1.95K.
3.10 p. m. 7.8G. alcohol (i. e. 4G. per kilo) diluted with 30.3G. water administered.
June 4th. Seems entirely normal.
12.20 p. m., 7.8G. alcohol and 30.3G. water given.
June 5th. Very lively; eats well.
2.50 p. m., 7.8G. alcohol and 30.3G. water given.
June 6th. Same condition as yesterday.
3.5 p. m., 9.75G. alcohol (i. e. 5G. per kilo) and 37G. water given.
June 7th. Lying down most of the time but eats well.
2.25 p. m., 9.75G. alcohol and 37G. water given.
June 9th. Seems entirely normal; is quite lively. Eats well.
2.20 p. m., 9.75G. alcohol and 37G. water given.
June 10th, 1.55 p. m., 9.75G. alcohol and 37G. water given.
June 11th. The animal seems to be entirely normal; is quite lively and eats well. Nothing unusual was noticed about it but on the morning of June 14th it was found dead. On autopsy

a smooth typical gastric ulcer was found and bloody peritonitis.

XXV. Experiment with Kahlbaum's purest methyl alcohol, May 19th. Female rabbit, weighing 2.49K.

2.10 p. m., 11.2G. alcohol (i. e. 4.5G. per kilo) diluted with 44.8G. water administered.

May 20th, 7 a. m. Seemed entirely normal. At about 11.30 a. m. aborted 6 embryos; a little hæmorrhage.

4.10 p. m., 11.2G. alcohol and 44.8G. water given.

May 21st. Looks sick but has been eating a little.

3.45 p. m., 11.2G. alcohol and 44.8G. water given.

May 22d. Seems completely paralyzed; unable to hold head up.

May 23d. Seems somewhat better but is unable to crawl or to sit.

2.57 p. m., 5.6G. alcohol (i. e. 2.25G. per kilo) and 22.5G. water given.

May 24th. Almost completely paralyzed; slight reflexes.

2.5 p. m., 5.6G. alcohol and 22.5G. water given.

May 25th. Seemed barely alive at noon.

May 26th, 7 a. m. Found dead.

XXVI. Experiment with absolute ethyl alcohol, May 19th. Female rabbit, weighing 2.4K.

2.20 p. m., 10.8G. alcohol (i. e. 4.5G. per kilo) diluted with 43G. water administered.

May 20th. 10.8G. alcohol and 43G. water given.

May 21st. Movements somewhat uncoordinated in the morning but animal eats well.

3.50 p. m., 10.8G. alcohol and 43G. water given.

May 22d. Very lively; apparently unaffected.

May 23d. Seems to be entirely normal.

3 p. m., 5.4G. alcohol (i. e. 2.25G. per kilo) and 21.5G. water given.

May 24th. Animal lively; eats well.

2 p. m., 5.4G. alcohol and 21.5G. water.

May 25th. Seemed entirely normal at noon.

May 26th. Animal seems entirely normal; eats well.

The animal was kept for 13 days longer during which no symptoms whatever could be observed.

The following two experiments in which small doses of methyl alcohol were given for several days may be quoted although the results can scarcely be included under the subject of subacute poisoning.

XXVII. Experiment with Columbian Spirits, May 23d. Male rabbit, weighing 1.96K. This rabbit was given 4.9G. Columbian Spirits (i. e. 2.5G. per Kilogramme) diluted with 24.8G. water daily for 8 days. The animal was slightly intoxicated a number of times but seemed to remain in fair condition although its weight decreased by 300G. 8 days after the administration of the last dose the animal was found dead.

XXVIII. Experiment with pure methyl alcohol, May 23d. Female rabbit, weighing 1.52K. This rabbit received 4.6G. methyl alcohol (i. e. 3G. per kilogramme) diluted with 22.4G. water daily for 8 days. The animal was slightly intoxicated a number of times but showed no marked symptoms; its weight decreased to 1370G. The animal was kept for 20 days without any symptoms being noticed.

The results of the above experiments are shown in the table on opposite page:

The results of these experiments upon rabbits agree entirely with those obtained in the experiments upon dogs and show how toxic methyl alcohol is when its administration, in suitable doses, is continued for even a few days. The great difference between the toxicity of methyl and ethyl alcohols might be overlooked entirely in experiments in which only the effects of single large doses were studied.

Fate of Methyl Alcohol in the Body.—The explanation of the difference between the toxicity of methyl and ethyl alcohols in subacute and chronic poisoning is to be found in the work of Pohl and others upon the fate of methyl alcohol in the body. The interesting and highly important discovery has been made that methyl alcohol differs markedly from ethyl alcohol (and apparently from the other alcohols of this series) in that it is but partially oxidized in the body and that its administration leads to the formation within the body of a markedly poisonous acid (formic acid). It has been shown by numerous investigators that ethyl alcohol is largely oxidized in the body to water and carbon dioxide, i. e., to harmless products, and Pohl found that not even a trace of an acid formed by its oxidation could be detected in the urine. On the other hand, when methyl alcohol is given to an animal, or to man, a considerable quantity of formic acid can always be found in the urine. The formic acid is excreted very slowly; thus in one of Pohl's experiments 60 ccm. of methyl alcohol were given to a dog by the stomach and the maximum amount of formic acid did not appear in the urine until the fourth day and there was an abnormal amount present three days later. In another experiment the methyl alcohol was injected into a vein and the maximum amount of formates in the urine were not found until the fourth day and two days later they were still present to the extent of 0.42G. Even when small quantities of methyl alcohol are administered (quantities too small even to cause narcosis), formic acid is still found in the urine; this shows how difficult it is for the body to completely oxidize methyl alcohol.

Pohl found a close parallelism between the intensity of the intoxication and the excretion of formic acid; just as the former gradually increased and then decreased so did the amount of formic acid found in the urine.

In my own experiments I frequently tested the urine of animals poisoned by methyl alcohol for formic acid. I found that the urine of such animals decolorized potassium permanganate and was strongly reducing towards silver nitrate, but that it did not undergo fermentation with yeast.

In this formation of formic acid from methyl alcohol we have an interesting illustration of the fact that at times the body converts one poison into another of greater power; this fact is evident when the toxicity of sodium formate is compared with that of methyl alcohol. Mayer (Archiv f. experm. Path. u. Pharm., 21, p. 122) found that 2.5G. of sodium formate injected into the vein of a rabbit weighing 2 kilogrammes caused death in one hour and ten minutes, i. e., 1.25G. per kilogramme is fatal to rabbits. Now, as was pointed out above, Joffroy and Serveaux found that it required about 7.96G. of methyl alcohol per kilogramme

body-weight to cause death; in other words, formic acid is about six times as poisonous as methyl alcohol.

The extent to which the methyl alcohol is converted into formic acid is not known; Pohl obtained 4.58G. of formates from the urine after the intravenous injection of 20 c.cm. of methyl alcohol and the experiment was discontinued when the excretion of formates was still very large (0.42G. on the last day). Pohl thought it probable that all the oxidation products are eliminated.[1] The slow excretion of the formic acid has already been noted; Pohl showed that this was apparently not due to a retention of the acid in the body, for the intravenous injection of a large quantity of sodium chloride (by which great diuresis and so a thorough "washing out" of the tissues was brought about) had but little effect upon the course of the formic acid excretion. Pohl also failed to find any excess of formic acid in

Date.	Alcohol used.	Animal used.	Weight of animal.	Amount of alcohol given.	Dose per kilogramme.	Number of doses.	Result.	Remarks.
XVII. May 15.	Columbian Spirits.	Rabbit.	2.19K.	39 G. + 156G. water.	6G.	3	Died on 3d day.	Doses given at intervals of about 24 hours on 3 days in succession.
XVIII. May 19.	Columbian Spirits.	Rabbit.	1.44K.	25.95G. + 103.8G. water.	6G.	3	Died on 4th day.	Doses given at intervals of about 24 hours on 3 days in succession.
XIX. May 19.	Absolute ethyl alcohol.	Rabbit.	1.45K.	52.2G. + 210G. water.	6G.	6	Died on 7th day.	Doses given on 1st, 2nd, 3d, 5th, 6th and 7th days.
XX. May 15.	Ethyl alcohol, 93%.	Rabbit.	2.17K.	39G. + 156G. water.	6G.	3	Survived.	Doses given at intervals of about 24 hours on 3 successive days.
XXI. June 19.	Commercial ethyl alcohol, 92.6%.	Rabbit.	1.96K.	47.2G. + 140G. water.	6G.	4	Survived.	Doses given on 1st, 2nd, 3d and 5th days.
XXII. May 19.	Kahlbaum's purest, acetone free methyl alcohol.	Rabbit.	2.55K.	42G. + 168G. water.	5.5G.	3	Died on 3d day.	Doses given at intervals of about 24 hours on 3 successive days.
XXIII. June 3.	Kahlbaum's methyl alcohol.	Rabbit.	1.98K.	63.3G. + 202G. water.	4G., then 5G.	7	Died on 9th day.	Doses given on 1st, 2nd, 3d, 4th, 5th, 7th and 8th days.
XXIV. June 3.	Absolute ethyl alcohol.	Rabbit.	1.95K.	62.4G. + 202G. water.	4G., then 5G.	7	Died from peritonitis caused by gastric ulcer.	Doses given on 1st, 2nd, 3d, 4th, 5th, 7th and 8th days.
XXV. May 19.	Kahlbaum's purest, acetone free methyl alcohol.	Rabbit.	2.49K.	44.8G. + 179.4G. water.	4.5G., then 2.25G.	5	Died on 8th day.	Doses given on 1st, 2nd, 3d, 5th and 6th days.
XXVI. May 19.	Absolute ethyl alcohol.	Rabbit.	2.40K.	43.2G. + 172G. water.	4.5G,. then 2.25G.	5	Survived.	Doses given on 1st, 2d, 3d, 5th and 6th days.
XXVII. May 23.	Columbian Spirits.	Rabbit.	1.96K.	39.2G. + 198.4G.	2.5G.	8	Died on 17th day.	Doses given daily the first 8 days.
XXVIII. May 23.	Kahlbaum's purest, acetone free methyl alcohol.	Rabbit.	1.52K.	36.8G. + 179.2G. water.	3G.	8	Survived.	Doses given daily for the first 8 days.

methyl alcohol administered is converted into formic acid and that part of the latter is then oxidized to carbon dioxide. Bongers (Archiv f. exper. Path. u. Pharm., 35, p. 429), on the other hand, asserts that after the administration of methyl alcohol considerable quantities of it are excreted in the urine; if this is the case we have further evidence of the difficulty with which the body oxidizes methyl alcohol. After even large doses of ethyl alcohol only mere traces of it can be found in the urine.

The long continued effects of methyl alcohol in acute poisoning and the ease with which a condition of chronic poisoning is produced by small, repeated doses doubtlessly depends upon the slowness with which the poison and its the various organs. These observations of Pohl made it probable that either methyl alcohol itself or some derivative of it is retained in the body and is then slowly converted into formic acid. The later observations of Bongers have shown that methyl alcohol itself is retained in the body for some time. This author made the interesting observation that when methyl alcohol was given by the rectum some of it (as well as some formic acid) was excreted into the stomach and that this excretion did not reach its maxi-

[1] This is probably the cause of the blindness which so frequently follows methyl alcohol poisoning in man; highly differentiated nerve structures (such as those of the retina) are especially likely to suffer when exposed to the action of a poison for some time.

mum for 27 to 78 hours. These experiments of Bongers are of interest in another connection. The methyl alcohol excreted into the stomach is presumably reabsorbed, either from the stomach or from the intestine, and some of it again excreted into the stomach, so that there is a "circulation" of methyl alcohol just as there is of the bile salts and of morphine; the result is that the irritant action of the methyl alcohol upon the digestive tract is exerted time after time. Now one of the most marked symptoms of methyl alcohol poisoning is great irritation of the alimentary tract; it is probable that this is due in part to the above mentioned peculiarity of the excretion of the drug.[3]

From chemical grounds it seems very probable that formaldehyde is formed as an intermediate product in the conversion, within the body, of methyl alcohol into formic acid. It is true that Pohl failed to find support for the view that any "considerable quantities" of formaldehyde are formed, but it may be that formaldehyde is formed and that it is then quickly converted into formic acid; Pohl himself showed that formaldehyde when administered to an animal is converted into formic acid. If it is supposed that some formaldehyde is formed then we would have another factor in explaining the toxicity of methyl alcohol, for Aronsohn (Berl. klin. Woch., 1892, p. 751) found that 0.24G. of formaldehyde per kilogramme body-weight is fatal to rabbits; in other words, part of the methyl alcohol would be converted into a substance about thirty-three times more poisonous.

Before leaving the subject of the formation of formic acid from methyl alcohol an interesting observation of Pohl's may be mentioned. Pohl showed that the administration of sodium bisulphite simultaneously with the methyl alcohol caused a great increase in the excretion of formic acid in the urine; it would be an interesting problem to determine whether this salt would be of any therapeutic value in cases of poisoning by methyl alcohol.

Finally attention should be called to the fact that Pohl found that methyl alcohol underwent the same change in the human body as in that of the lower animals; its administration to man led to the appearance of formic acid, which was slowly excreted in the urine.

A few words may be said in conclusion upon the subject of the toxicity of the by-products or impurities of methyl alcohol. There is a tendency, especially prevalent among chemists, it would seem, to attribute the poisonous properties of many substances to the presence of "impurities." Thus it is not so very long since it was taught that the accidents attributed to chloroform were due largely to the impurities present; now it is known that these play but a small part in such accidents. There is still a widespread belief that the impurities (fusel oil, furfurol, etc.) found in most alcoholic drinks are very important factors in the toxic action of such drinks. Some of these impurities are very much more poisonous than equal quantities of ethyl alcohol, but it has been shown time and time again that they are present in even the worst grades of liquors to such a small per cent that a person would have to consume an amount of the liquor containing many times the fatal dose of ethyl alcohol in order to get a fatal dose of these impurities. The latter undoubtedly somewhat increase the toxicity of the liquor, i. e., a slightly smaller quantity of a liquor containing them would prove fatal than would an equal quantity of pure ethyl alcohol diluted to the same extent, and they may further cause some especially severe symptoms (severe headaches, etc.), but the fact remains (undisputed by competent investigators) that in such liquors the toxic principle par excellence is ethyl alcohol.

It was only to be expected that views similar to the above would be expressed regarding the toxicity of methyl alcohol; in fact, the statement is made in a leading English work on organic analysis that methyl alcohol when free of impurities is not deleterious! Most of the experiments quoted above were made with pure methyl alcohol or with preparations of methyl alcohol so nearly pure that it may be safely assumed that the traces of impurities had no essential influence upon the course of the intoxication. It is undeniable that in some of the crude commercial preparations of "wood alcohol" certain impurities are present in large amount and that the toxicity of such preparations is increased by their presence. It would lead us too far to consider this subject here in detail, but it may be said that the toxicity of these impurities has been tested and that it is doubtful whether in the most impure preparations the impurities are present in sufficient quantity to cause death; in other words, while the toxicity of the preparation may be considerably increased by them, methyl alcohol is still the chief toxic agent. The experiments of Dujardin-Beaumetz and Audigé are of interest in this connection; these authors working as long ago as 1876 found the fatal dose of ordinary commercial wood alcohol to be, for the dog, 5.75G. per kilogramme, while that of pure methyl alcohol was placed by these authors at 7G. per kilogramme.

In this connection the conclusion of Kuhnt (Zeitsch. f. Augenheilkunde, 1, p. 42) relative to two cases of wood alcohol poisoning, in one of which blindness, in the other, death had occurred, may be quoted; this author was considering the question whether the symptoms could have been due to the impurities in the wood alcohol; he says that assuming the wood alcohol in question to have been of the most impure variety (one containing even 20 per cent of acetone), it was certain that the symptoms could not have been caused by any of the impurities or by all combined and that they were due to the methyl alcohol and to the methyl alcohol alone.

These experiments on the physiological action of methyl

[3] It would be very interesting to determine whether any formic acid or methyl alcohol is excreted in the tears; the irritation of the conjunctiva noted in my experiments upon dogs suggest such a possibility. Holden also speaks of signs of irritation of the eye in a dog after the administration of methyl alcohol.

alcohol and its fate in the body show conclusively that, however pure the preparation may be, it is totally unfit for use as a substitute for grain alcohol in any preparation which is to be taken internally and especially in preparations which are to be taken for any length of time; this was the conclusion drawn by pharmacologists years ago from Pohl's work and the sad results which have recently followed the consumption of preparations containing methyl alcohol show the danger of departing from the recognized methods of pharmacy in the manufacture of compounds without full knowledge of the physiological action of the ingredients.