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# ACUTE METHYL ALCOHOL POISONING: A REVIEW BASED ON EXPERIENCES IN AN OUTBREAK OF 323 CASES

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## INTRODUCTION

It is the purpose of this report to describe experiences in a major outbreak of wood alcohol poisoning due to adulterated contraband whiskey and to review in detail the clinical problem of acute methanol intoxication.

Methyl alcohol (methanol, wood alcohol, Columbian spirit, Eagle spirit, Manhattan spirit, Pyroxylic spirit, colonial spirit, Hastings spirit, Lion d'Or, methyl-

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the major reasons that the general recognition of the toxicity of wood alcohol was so long delayed. During Christmas week in 1911 an outbreak of 163 cases of poisoning with 72 deaths which occurred in Berlin (44, 49) provoked considerable discussion in a meeting of the Medical Society of Berlin. In the course of this, Aronson (50) described the ingestion of four liters of 40 per cent methanol by six Russian workers who had survived without ocular sequelae or other symptoms than mild gastrointestinal irritation. Wood and Buller (1) pointed out that blindness had followed the ingestion of as little as two teaspoons of methyl alcohol and Duke-Elder (51) mentions blindness after a total dose of only four ml. Uthoff (52) stated that only 50 of 200 persons who drank the same amount of wood alcohol became ill and only 12 died. Goldflam (53) called attention to the extreme variation in dosage producing toxic symptoms and Zeigler (4) observed fatalities after as little as one ounce. Pronnie *et al.* (32) commented on the great variation in response after drinking wood alcohol, estimating that for each patient they saw in an outbreak at an Army installation, four others had drunk the same material and remained without significant symptoms. The smallest amount which produced a fatal result in the outbreak observed by the present authors was three teaspoons (about 15 ml.) of 40 per cent methyl alcohol. The highest dose recorded in a survivor was one pint (500 ml.) of the same mixture.

Although instances of remarkable resistance or susceptibility to many other toxic materials are well known, the striking range of methanol's effects is one of the unusual features of this type of poisoning and is not yet fully explained.

*Latent period.* A second peculiarity of methyl alcohol poisoning is the presence of a latent period of about 24 hours between ingestion and the development of toxic symptoms. Although many cases have been reported with a delay of less than 12 hours before development of symptoms, the usual time which elapses is 24 to 48 hours and even longer latent periods are not uncommon. In Chew's group of 26 cases, the time between ingestion and onset of symptoms was 1 to 40 hours (33). It is understandable that this latency, in combination with the aforementioned variability in response to wood alcohol caused some of the confusion in early arguments about methanol's toxicity. Among the patients in the outbreak which forms the basis of this report, the usual story was that symptoms began approximately 24 hours after ingestion. The longest lag observed was slightly more than 72 hours. Several patients noted visual disturbances in less than 6 hours and in one instance, sudden amblyopia developed in a patient 40 minutes after he had downed one-half pint of adulterated moonshine. This patient was severely acidotic within two hours after drinking wood alcohol. In our series, as in Røe's (46), the severity of poisoning generally bore little relation to the length of the lag-period, although in occasional instances, patients with rapid development of symptoms were among those most ill.

The presence of a characteristic latent period offers support for the hypothesis that most of the manifestations of methanol poisoning are effects of the breakdown products of its oxidation in the body, i.e., formic acid and, presumably, formaldehyde.

*Distribution, metabolism, and excretion.* After ingestion, methanol may persist

strating that alcohol dehydrogenase was able to oxidize methanol at only one-ninth of the rate for ethanol and that ethanol in equimolar concentration completely inhibited the oxidation of methanol. Inhibition was also demonstrable with molar ratios of ethyl alcohol as high as 1:16. Concluding that the *in vivo* operation of such a mechanism would result in diminished oxidation of ingested methanol and therefore increased excretion, Leaf and Zatman (23) demonstrated an increase in urinary methanol in five volunteers given methanol and ethanol. Using C<sup>14</sup> labeled methanol in rats, Bartlett (62) showed that ethyl alcohol produced a striking depression of the oxidation of methanol in the intact animal as well as the isolated liver slice. As will be discussed under Treatment, the clinical usefulness of ethyl alcohol in the therapy of methanol poisoning is still unsettled although the experiments described above certainly furnish a background for clinical trials. It is still possible to find the statement that ethyl alcohol increases susceptibility to methanol in current writings (28). Recent experiments by Kendal and Ramanathan (63) indicate that the enzymatic breakdown of methanol by the liver, presumably a function of alcohol dehydrogenase, may be a much more complex process than other studies have shown, involving not only oxidation to formaldehyde and formic acid, but also "dismutation" of formaldehyde to a volatile ester, probably methyl formate.

*Acidosis.* By far the most striking metabolic disturbance in human cases of methyl alcohol poisoning is severe acidosis. Although the demonstration of increased urinary ammonia in human beings by Schmiedeberg (79) and in dogs by Króhl (80) had led to speculation on the possibility that methanol produced acidosis, Harrop and Benedict (42) are credited with the first demonstration of acidosis in a patient with wood alcohol poisoning. This was subsequently confirmed by Rabinowitch (56) and by Van Slyke (68) and has been found on innumerable occasions since. It is noteworthy that animal experiments have failed to demonstrate striking changes in acid-base balance in dogs, rabbits, and rats although there can be no doubt of the prominence of acidosis in man. There is much variation in the susceptibility of various laboratory animals to methyl alcohol, and as is always the case, the results of animal work must be interpreted with great caution when applied to man. The lack of parallelism in animal and human poisoning was probably a major factor in the failure of clinicians to appreciate the importance of acidosis until the reports of Chew *et al.* (33) and Røe (46) less than ten years ago.

The acidosis produced by methanol may be extremely severe. Of 115 patients with lowered plasma bicarbonate observed in the Atlanta outbreak, there were 30 with levels below 10 mEq. and the plasma CO<sub>2</sub> combining power of four patients, all moribund, was zero by the Van Slyke (CO<sub>2</sub> capacity) method.

The mechanism of the acidosis is not entirely clear. Early workers generally assumed that formic acid was responsible but Egg, in 1927 (81), pointed out that the amount of formic acid that can be formed from methanol in cases of poisoning is far too small to account for the lowered plasma bicarbonate. Similar calculations have been made by Røe (46) and without question, the liberation of formic acid can account for only a fraction of the acidosis. Other organic acids,

eight acidotic patients. One explanation which suggests itself is the possibility that the rice wine drunk by all of these patients may also have contained isopropyl alcohol as an adulterant. The ingestion of isopropyl alcohol is frequently followed by marked acetonuria although acidosis is not usual with this substance (82, 83).

The best explanation of the acidosis of wood alcohol poisoning would appear to be that due to inhibition of oxidative enzyme systems by methanol or formate, there is accumulation of acids including lactic acid and others unidentified. The question of the importance of acidosis *per se* in the production of the clinical symptoms of poisoning will be considered under Treatment.

#### SYMPTOMS

Some idea of the confusion which may arise in the clinical recognition of this type of poisoning is evident from the list of diseases which have been first suspected in patients seen sporadically or in various outbreaks. These include: cholera, botulism, diabetic acidosis, "hangover" after ethanol, pancreatitis, ureteral calculus, perforated peptic ulcer, intestinal obstruction, meningitis, bronchopneumonia, congestive heart failure, brain tumor and various types of cerebrovascular accidents including subarachnoid hemorrhage.

Some of the manifestations of methanol intoxication are sufficiently characteristic to suggest the proper diagnosis but many are non-specific. In the present discussion an attempt is made to stress certain features of the symptomatology because of their diagnostic import or because they may serve to confuse or mislead the inexperienced observer.

*Visual disturbances.* Most writers have stressed damage to the eye in wood alcohol poisoning; the occurrence of blindness after drinking "bad liquor" is a phenomenon which is widely appreciated by the lay public. In discussing the eye manifestations of methanol intoxication, it is necessary to distinguish carefully between the incidence of subjective visual disturbances as a *presenting complaint* in acute poisoning and *residual damage* after subsidence of acute systemic symptoms. For instance, McNally's summary (6) of 725 cases with 390 deaths, 90 survivors with total blindness and 85 with visual impairment fails entirely to emphasize the enormous frequency of complaints referable to the eyes early in the course of the poisoning. Of 53 severely acidotic patients seen by Røe (46), 45 complained of cloudy or diminished vision and of the remaining 13, nine were comatose and died without a complete interview. The outbreak among Navy personnel reported by Chew and his co-workers (33) resulted in five deaths. Among the 26 survivors, all of whom were acidotic when seen initially, visual disturbance was a symptom in 15. After recovery, permanent impairment in the form of contracted fields or scotomata remained in only two patients.

In the outbreak of poisoning observed by the authors, visual disturbance was a universal complaint. All of the 115 patients who were frankly acidotic when first admitted suffered some degree of visual impairment and at least half of the patients whose plasma bicarbonate was within normal limits when initially examined had noted transient difficulty in seeing (records were incomplete in the

Blatter group). These ranged from six instances of total loss of light perception (the four patients who survived had some return of vision) to mild photophobia. By far the most frequent complaint was blurred or indistinct vision, in many instances of a bizarre type. Patients described a "skim over the eyes," "brightness," "dancing spots," "a snowstorm," "flashes," or "seeing the wind." The correlation of ophthalmoscopic findings with the patients' subjective complaints or indeed, with the results of objective tests of vision, was extremely poor.

The development of dim vision in any patient after a drinking bout should immediately arouse the suspicion of wood alcohol ingestion.

*Central nervous system manifestations.* Methyl alcohol exerts a profound effect upon the central nervous system, producing symptoms ranging from those of an ethanol "hangover" to convulsions or profound coma.

*Headache* was a complaint in 62 per cent of our patients and dizziness occurred in 30 per cent of those interviewed in detail. The story of *weakness* or "just feeling bad all over" was heard repeatedly. Many moribund or severely acidotic patients were stuporous or comatose and terminal *convulsions* were common. However, a number of patients who were completely unresponsive on admission or who had repeated convulsions responded promptly to treatment and recovered completely. Coma and convulsions are not necessarily indicative of a hopeless prognosis.

Although Røe (46) mentions a few instances of neurologic disturbance, including one patient with monoplegia suspected of brain tumor, reports of focal weakness are rare. We observed no instance of *paralysis* although *paresthesias and tingling* of the extremities were occasionally mentioned by patients during the first few days of recovery and after alkali infusions.

Many patients remarked on their inability to recall clearly the events leading up to admission. This complaint was not limited to patients admitted in a stuporous state; several patients who were *ambulatory and apparently rational* when first seen later denied vigorously any recollection of coming to the hospital, etc. The occurrence of *amnesia* has been noted by previous authors in methyl alcohol poisoning (46) but cannot be regarded as in any way specific as it is not uncommon in diabetic acidosis, etc. Two patients, both severely acidotic, were admitted in a *maniacal state* which was controlled with difficulty and subsided promptly with response to alkali treatment. Both patients professed *complete amnesia for their actions*.

*Gastrointestinal symptoms.* The occurrence of *nausea and vomiting* is frequently mentioned as a symptom of wood alcohol poisoning. Røe (46) comments that vomiting often becomes persistent and violent. Fifteen of Chew's 26 patients were nauseated (33). Nausea and vomiting occurred in 52 per cent of our patients in whom symptoms were recorded. However, in only one instance was there persistent vomiting. Rather, we were impressed by the fact that although mild nausea and anorexia had been present, actual emesis usually had occurred only once or twice in most patients. Although our records indicate *diarrhea* in the form of at least one loose stool in 10 per cent of cases, this symptom is difficult to evaluate in view of the liberal administration of sodium bicarbonate by

the oral route to many outpatients. Certainly diarrhea was not a prominent feature of the clinical picture in any instance. On the other hand, in patients admitted to the hospital and observed for several days, *constipation* and *obstipation* were common and often difficult to relieve.

*Pain.* Headache has been discussed. Although Chew (33) mentions abdominal cramps in only seven of 26 cases, most authors have emphasized the frequent occurrence of severe abdominal pain. Keeney and Mellinkoff (35) speak of "violent epigastric pain" in some of their patients. Røe (46) gives the following description: "The abdominal pain in particular seems to be very violent. It is usually localized to the epigastrium and is, apparently, of a colicky character, making the patients very restless. During the most violent attacks of pain they may throw themselves out of bed, and others hold their hands on their stomachs, shrieking loudly." This graphic portrayal coincides with our experience. Among hospitalized patients, 67 per cent complained of excruciating upper abdominal pain. It is undoubtedly this striking symptom which has accounted for the numerous instances of confusion of methyl alcohol poisoning with acute surgical diseases recorded in the literature. Certain findings in regard to the mechanism of production of these abdominal complaints will be discussed below. In addition to abdominal pain, pain in the muscles of the back and extremities produced marked discomfort in several patients. In one woman with obvious acidosis due to methanol ingestion, flank pain was so severe that concomitant renal colic was strongly suspected at first.

*Dyspnea.* The presence of dyspnea or breathlessness has been emphasized by various observers, probably because of the well-known association of Kussmaul respiration and acidosis. Although one-fourth of the acidotic patients observed by us admitted on direct questioning that they had noticed respiratory distress sometime during the course of their illness, there was not a single instance of dyspnea as a major complaint. We were impressed by the fact that dyspnea is a poor indication of severity of acidosis in patients with methyl alcohol poisoning and, as noted below, true Kussmaul respirations were unusual even in patients with marked reduction of serum bicarbonate. The significance of this finding in the possible mechanism of acidosis is considered below.

#### PHYSICAL FINDINGS

*General.* Even ambulatory patients appeared apprehensive and uncomfortable. The skin was cool, with profuse perspiration. In a number of stuporous patients, moist, clammy extremities suggested profound shock but, in general, cardiovascular function was well-maintained. Ruddy cyanosis of a peculiar type, what Røe (46) calls a "combination of cyanosis and rubeosis," has been greatly emphasized as a typical finding in patients poisoned by wood alcohol. Although we devoted special attention to this finding in our patients, it was not at all prominent. Most of the patients we observed were colored which may well account for some difficulty in detecting discoloration, but among the white patients, the skin was characterized by pallor rather than cyanosis. Cyanosis appeared as respirations ceased in fatal cases but this is not surprising. There was no notable change in

body temperature with the sole exception of one patient who had a chill following an infusion. In this case there was a transient febrile reaction which subsided within a few hours. In a few patients who remained comatose and died after several days, there was terminal hyperpyrexia.

Another notable finding was the infrequency of deep, sighing respirations of the Kussmaul type in patients with severe acidosis. Only about 25 per cent of patients whose plasma bicarbonate was less than 10 mEq. had characteristic acidotic breathing. As the outbreak progressed, it became increasingly obvious that one could not predict what the carbon dioxide combining power would be by the patient's respirations unless obvious overbreathing was present. The poor correlation of dyspnea as a symptom and the serum bicarbonate has been mentioned; this may have been due to the fact that many patients were lethargic and perhaps not alert enough to interpret their increased respiratory rates as dyspnea.

*Eyes.* Dilated, non-reactive pupils, not necessarily associated with any objective visual impairment, are present in most patients with acute methanol poisoning. Mydriasis, with absent or sluggish reaction to light and accommodation was routinely present in most of our patients. The combination of apprehension and mydriasis often resulted in a characteristic staring, anxious facies. In a few patients, the mydriasis was found to be unaffected by eserine, but the administration of sodium amytal to patients with convulsions uniformly resulted in the development of miosis. There was no tenderness on pressure over the eyeballs and no complaint of pain on motion of the eyes. Slight lateral nystagmus was noted on rare occasions but was in no way characteristic. Røe (46) described nystagmus in three of 82 cases. Photophobia was not prominent.

Ophthalmoscopic examination revealed changes typical of wood alcohol poisoning in most patients with acidosis when seen initially and in many patients with normal serum bicarbonate as well. The severity of eye-ground changes was found to correlate better with acidosis than any other clinical finding and by the last days of the outbreak, we had come to rely heavily upon ophthalmoscopic findings. However, a small number of fatal cases had normal eyegrounds and, in several other patients with visual impairment, no changes in the fundus could be seen.

The changes observed were *hyperemia of the optic disc* and *retinal edema*. Hyperemia of the disc was often striking and was the earliest change noted. In our experience, marked reddening of the nerve-head is difficult to appreciate at a single examination although the examination of a normal fundus for comparative purposes quickly makes unusual hyperemia evident. This injection of the disc usually subsided after about three days. Retinal edema developed more slowly and persisted for as long as two weeks. In no instance was true papilledema observed; the swelling was peripapillary (with resultant blurring of the margins of the nerve-head) and spread radially as grayish streaks throughout the retina. Occasionally, edema extended to the macular area, resulting in a volcano-like cone with the attachment of the macula forming a central depression. No consistent or characteristic changes in vessel caliber were noted. It is

beyond the scope of this review to describe in detail the serial changes in ophthalmoscopic findings and objective tests of vision after subsidence of the acute systemic manifestations of poisoning. A long-term follow-up study of the ocular findings in this group of patients is underway.

*Cardiovascular.* The pulse rate was within normal limits in most patients. There were seven instances of tachycardia (over 120 per minute). Excluding patients known to have pre-existing hypertension, blood-pressure levels were within normal limits in all patients until terminally. Despite the clinical picture of shock with cool skin and marked diaphoresis in many severely ill patients, in only one instance was blood-pressure unobtainable on initial examination, and, after one infusion of sodium bicarbonate the pressure in this patient rose to 170/100 (he had a record of previous hypertension). Not only was hypotension rare in patients who subsequently recovered, but the circulation in terminally ill patients was well-maintained until several minutes after respirations ceased. This peculiar maintenance of blood pressure in patients who appear to be in collapse corresponds with Merritt and Brown's (54) description of a patient with acidosis due to methyl alcohol: "On arrival the patient was still in a state resembling shock. . . He was cyanotic and his extremities were cold. . . The systolic blood pressure was 160 mm. of mercury and the diastolic 100 mm."

Bradycardia developed terminally in several fatal cases. This will be discussed under Mode of Death.

*Abdominal examination.* Severe abdominal pain was often accompanied by striking rigidity of the abdominal muscles and exquisite tenderness; this was noted by Røe (46) and is, of course, a source of confusion, especially in sporadic instances of methanol poisoning. Rebound tenderness was not recorded in any instance.

*Neurologic signs.* Changes in the sensorium were frequent in the acidotic patients and have been noted repeatedly by other observers. Confusion, amnesia, lethargy, stupor and deep coma as well as two instances of acute maniacal reactions were seen. We were able to detect nothing characteristic in the pattern of reactions which might be helpful in suggesting the diagnosis of methanol poisoning in a sporadic case. As mentioned under Symptoms, we observed no instance of focal weakness. The first patient brought to the hospital at the beginning of the outbreak presented a combination of signs which we came to call "*pseudomeningitis*." This patient was a 19 year old colored male who was deeply comatose when first seen. The only history available was obtained from an ambulance driver who stated that the patient had complained of severe headache, vomited one time, and quickly lapsed into unconsciousness. Rapid physical examination revealed a pulse rate of 32, respirations of eight per minute, slightly elevated blood pressure, dilated, non-reactive pupils, and generalized hyperactivity of tendon reflexes. The patient was completely unresponsive to painful stimuli and the neck was rigid. A tentative diagnosis of spontaneous subarachnoid hemorrhage was made and lumbar puncture was done revealing clear spinal fluid under normal pressure. The patient died within 15 minutes after arriving in the Emergency Clinic. During the period of the outbreak, five other patients, all comatose,

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**INTRODUCTION**

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the major reasons that the general recognition of the toxicity of wood alcohol was so long delayed. During Christmas week in 1911 an outbreak of 163 cases of poisoning with 72 deaths which occurred in Berlin (44, 49) provoked considerable discussion in a meeting of the Medical Society of Berlin. In the course of this, Aronson (50) described the ingestion of four liters of 40 per cent methanol by six Russian workers who had survived without ocular sequelae or other symptoms than mild gastrointestinal irritation. Wood and Buller (1) pointed out that blindness had followed the ingestion of as little as two teaspoons of methyl alcohol and Duke-Elder (51) mentions blindness after a total dose of only four ml. Uhthoff (52) stated that only 50 of 200 persons who drank the same amount of wood alcohol became ill and only 12 died. Goldflam (53) called attention to the extreme variation in dosage producing toxic symptoms and Zeigler (4) observed fatalities after as little as one ounce. Pronnie *et al.* (32) commented on the great variation in response after drinking wood alcohol, estimating that for each patient they saw in an outbreak at an Army installation, four others had drunk the same material and remained without significant symptoms. The smallest amount which produced a fatal result in the outbreak observed by the present authors was three teaspoons (about 15 ml.) of 40 per cent methyl alcohol. The highest dose recorded in a survivor was one pint (500 ml.) of the same mixture.

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*Distribution, metabolism, and excretion.* After ingestion, methanol may persist

6 ml  
methanol

# ALCOHOLS TOXICOLOGY

by

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**1983**

6.7 ml  
The quantity of food stuff in the gastro-intestinal tract and the nutritional status of the victim are important (18), however, the intake of food is less liable to interfere with methanol concentration in the blood than in the case with ethanol. Death has resulted after ingesting as little as 15 milliliters of a 40 percent methanol solution in one individual while another person survived after drinking over 33 times that amount. (19) Drinking of ethanol prior to or with methanol will usually lessen the poisonous effect. No record exists as to whether this occurred with the above mentioned individual who survived the large consumption but one would strongly expect that this might be the case. A chemical epidemiologic study of a methanol poisoning outbreak in Kentucky involving 18 people of whom 8 died indicated a correlation between severity of the poisoning and the level of ethanol in the body. Of the 26 people screened in the emergency room of the University of Kentucky Medical Center for suspected methanol poisoning, those that also had ethanol in their blood showed less acidosis than the group that had only methanol. Ethanol competes very effectively (metabolized in a competitive preferential ratio of approximately 9:1 to methanol) for the enzyme responsible for the conversion of methanol to formaldehyde and formic acid. (20, 21)

Many years ago, Roe (22) attributed the toxicity of methanol to the metabolites that were produced by its metabolism. Since that time no definitive proof has been brought forth. Formaldehyde has not been found in humans or other primates during methanol poisoning but some researchers feel that is because of its high reactivity. They think that it still may be responsible for some of the toxicity that methanol exhibits. Formate is known to accumulate during methanol poisoning and correlates well with the beginning of metabolic acidosis and the usual ocular toxicity. (23, 24)

#### D. Inhalation By Humans

Inhalation of the vapor of methanol causes irritation to the mucous membrane. It also may cause headache, vertigo, tinnitus (sounds in the ear), nausea, gastric disturbances, convulsive twitchings, oppression in the chest, visual disturbances, and even loss of vision. In severe cases of exposure, tracheitis, bronchitis and blepharospasm (uncontrollable winking) may take place. (18) Because of methanol's high volatility, the vapors can easily become highly concentrated in a confined space. When at high concentrations, the vapor causes violent inflammation of conjunctiva and epithelial defects on the cornea of the eye. (25)

The permissible exposure limit is 200 ppm (260 mg/m<sup>3</sup>) and the IDLH (Immediately Dangerous to Life or Health) level is set at 25,000 ppm. It is impossible for a human to remain in an atmosphere containing 65 mg per liter of methanol for any prolonged time. (25)

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