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The Treatment of Methanol Poisoning with Ethanol

With Report of Two Cases*

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TISSUES seem to be able to oxidize alcohols in two different ways, by alcohol dehydrogenase and by catalase. The oxidation of methanol by alcohol dehydrogenase is, according to Zatman (1), inhibited by ethanol and no detectable oxidation of methanol is demonstrable when the alcohols are present in equimolar concentration. The inhibition was found to be competitive. The same investigator also noted that man excretes greater amounts of unchanged methanol if ethanol is given at the same time. Keilin and Hartree (2) showed that alcohols are oxidized by catalase in the presence of small concentrations of hydrogen peroxide. Under these conditions catalase forms a hydrogen peroxide compound which reacts rapidly with both ethanol and methanol (3). A number of investigations have demonstrated various intermediary products resulting from the oxidation of methanol in the intact organism. Keeser (4) demonstrated formaldehyde in the cerebrospinal fluid and in the vitreous humor of the eye; and Keeser and Vincke (5) found that liver tissue oxidizes methanol to formaldehyde. It has been shown by Asser (6) and by others that after the consumption of methanol relatively large amounts of formate are excreted in the urine. The excretion of formate in the urine of experimental animals diminishes if the animals receive concomitantly other alcohols in addition to methanol. The amount of formic acid that can be formed from methanol in cases of methanol poisoning is too small to cause acidosis, according to the calculations of Egg (7).

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Agner and Theorell (8) showed that catalase forms an enzymatically inactive, spectroscopically defined compound with formate. A calculation based on data given by these authors shows that an amount of formate corresponding to 0.1 per cent of methanol will cause a considerable inhibition of catalase activity. In view of this, it is possible that the acidosis as well as other symptoms of methanol poisoning may be caused indirectly by the inhibitory effect of formate on catalase or on some other as yet uninvestigated tissue enzyme.

The alleviation of all but slight symptoms of methanol poisoning in humans as a result of simultaneous consumption of ethanol has been reported by Røe (9). If symptoms appeared, the onset was usually greatly prolonged. From these clinical observations he concluded that ethanol, as long as it is present in tissues in sufficient concentration, may inhibit the destruction of methanol. He also suggested the administration of ethanol therapeutically in cases of methanol poisoning. In his treatment, however, Røe directed his therapy mainly toward compensation of the acidosis by the administration of sodium bicarbonate. In three cases brandy was given therapeutically, although only in doses of up to 100 ml. and at a fairly late stage of the poisoning. Røe was not able to prevent a fatal outcome with this treatment. Söderström (10) treated a patient with still smaller amounts of ethyl alcohol, also without success. An experimental observation related to the role of ethanol in preventing methanol poisoning is seen in the work of Agner and Belfrage (11). They found that if ethanol and methanol are injected simultaneously into rabbits, the concentration of methanol in the blood remains unchanged until the ethanol has been oxidized.

Because of these experimental and clinical observations, two patients with methanol poisoning were treated with ethanol at the Serafimerlasarettet. The records are summarized below. A preliminary report of this work has been given by Agner, Höök and von Porat (12).

Case 1. E. M., a 41-year-old male chronic alcoholic, had been employed for 6 months at a chemical factory where, in addition to other duties, he was engaged in preparing methyl iodide, using methanol as a raw material. On September 12, 1947, he invited several fellow-workers to drink a glass of "brandy" with him. Two of them accepted the invitation, and both at lunch and at dinner partook of the drink offered them. On the afternoon of September 12 E. M. was intoxicated. He went to bed immediately, slept for a few hours, but was severely indisposed during the night and vomited copiously several times. On the morning of September 13 E. M. complained to his wife that he could

scarcely see anything, and was immediately taken to the hospital. He was able to walk from the ambulance but within half an hour he lost consciousness and sank into a profound coma with respiration of pronounced Kussmaul type. He perspired freely, was cold peripherally and was without reflexes. The fundus oculi were normal, the pulse rate 130 per minute and blood pressure 175/140. Tests were undertaken at once to determine blood sugar, alkali reserve, nonprotein nitrogen and the possible presence of methanol. The analyses showed the following values: blood sugar, 90 mg. per cent; alkali reserve, 5.4 vol. per cent or 2.5 milliequiv. per liter; nonprotein nitrogen, 44 mg. per cent; and methanol, determined by the method of Agner and Beifrage (11), 0.235 per cent. These findings indicated that the symptoms of intoxication manifested by the patient were caused by methanol poisoning.

Large amounts of bicarbonate, initially 1.3-per-cent and later 5-per-cent solutions, were administered intravenously in an effort to counteract the acidosis. Between 9:30 and 10:30 A.M. the level of methanol in the blood fell 0.056 per cent, and in attempting to diminish this rapid oxidation of methanol 70 ml. of ethanol in 1 liter of 1.3-per-cent bicarbonate were administered intravenously. Later, two further amounts of ethanol in bicarbonate were administered, each of 20 ml. In the course of the afternoon the patient received two transfusions of 400 ml. of blood, and as a prophylactic measure against pneumonia he was treated with penicillin, 320,000 I.U. The details of the treatment and the results of analyses are shown in Figure 1.

The patient improved somewhat during the day but his condition grew worse the following night and he died 23 hours after admission.

Autopsy. The following pathological findings were noted:*

BRAIN: The outer parts of the lentiform nucleus showed foci of disruptive hemorrhage on both sides: within, they were swollen and light in color. Bilaterally the lateral aspects of the nuclei were separated from the white matter (capsul externa) and the cavities thus formed were filled with dark red liquid blood. LUNGS: The lungs showed bilateral spreading bronchopneumonia.

Discussion: The extremely low alkali reserve of this patient was compensated by the administration of large amounts of bicarbonate, and 4 hours after his admission the value was 48 vol. per cent or 22 milliequiv. per liter. The rapid oxidation of methanol was checked by the administration of ethanol, the concentration of methanol remaining constant up to the last hours of life. The immediate causes of death were pneumonia and hemorrhages in and about the lentiform nuclei bilaterally.

Case 2. The two men who had drunk the beverage offered them by E. M. were requested on the morning of September 13 to present themselves at the hospital for examination. As no symptoms of methanol poisoning were apparent, they were allowed to go home pending the results of the analyses of the blood

*Courtesy of Dr. H. Sjövall.

for methanol. One of them showed a methanol level of only 0.04 per cent, while the other, Y. C. (Case 2), had 0.236 per cent.

Later during the same day (September 12) when Y. C. had consumed the methanol he had drunk between 100 and 150 ml. of brandy, and immediately after leaving the hospital on the morning of September 13 he consumed between 200 and 300 ml. of brandy. Y. C. was returned to the hospital on the afternoon

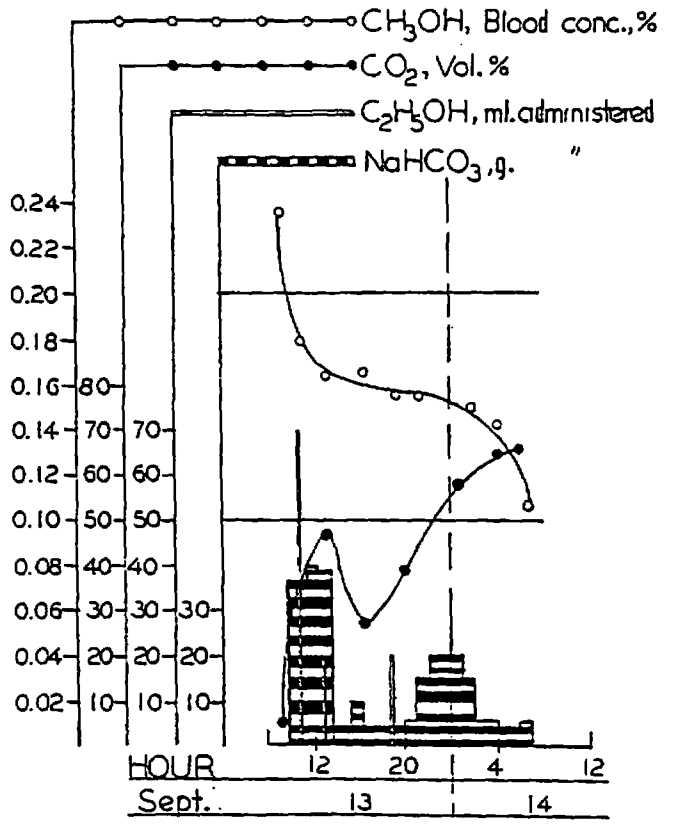

FIGURE 1.—Course and Treatment, Case 1.

of September 13. Analysis at this time showed about the same concentration of methanol in the blood as had been noted previously, namely 0.235 per cent. When admitted, Y. C. was somewhat under the influence of ethyl alcohol, but showed no subjective or objective symptoms of methanol poisoning. The alkali reserve showed a low value, 39 vol. per cent or 13.6 milliequiv. per liter. The patient was treated with bicarbonate *per os*. The laboratory findings, and the treatment of this patient, are shown in Figure 2.

The general state of the patient was carefully controlled and the concentration of methanol and the alkali reserve were followed by repeated analyses.

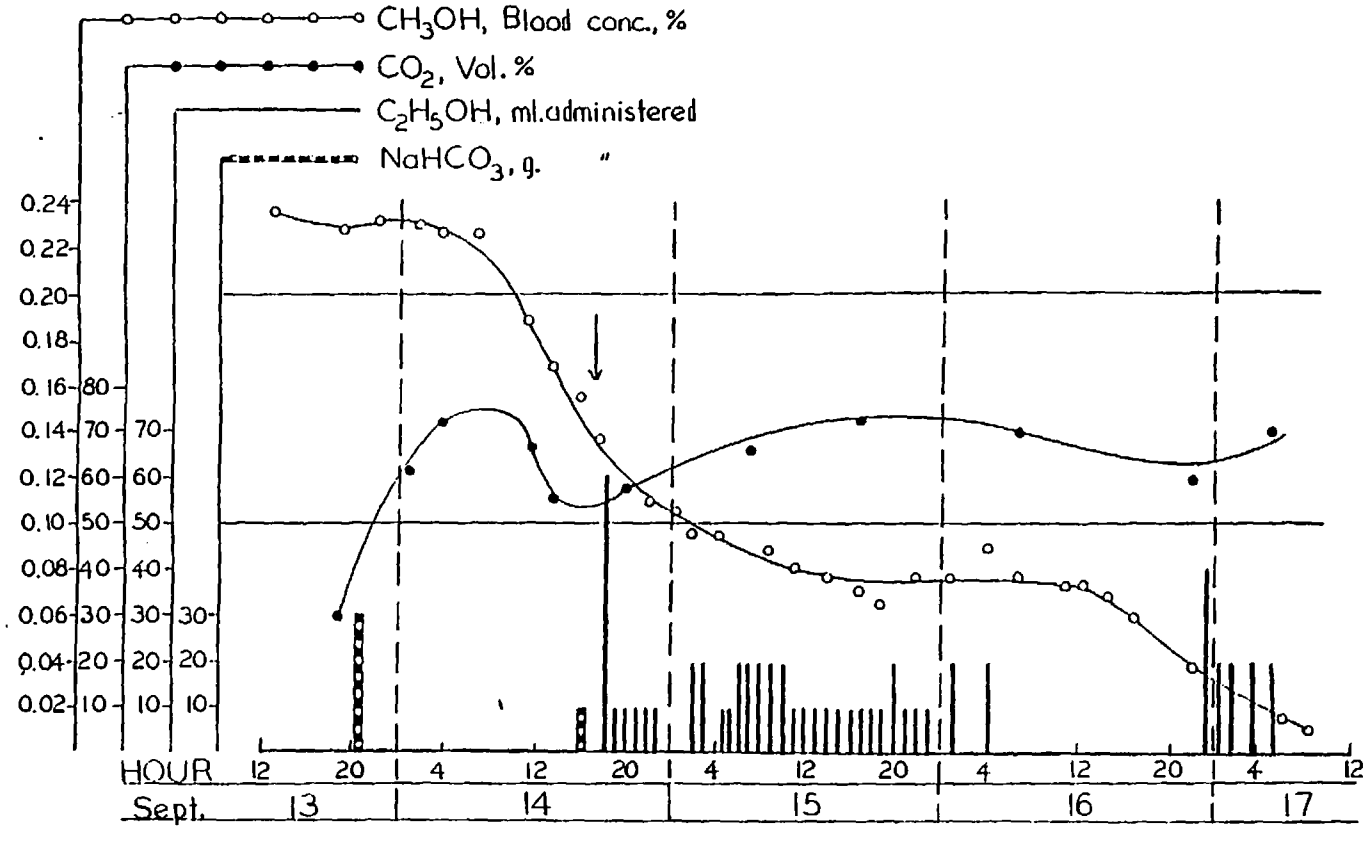

FIGURE 2.—Course and Treatment, Case 2. Arrow indicates symptoms of intoxication.

During the night the concentration of methanol in the blood remained constant (for about the period calculated to be necessary for the oxidation of the ethanol consumed) and it was not until the following morning that the oxidation of methanol began. At 5 P.M. on September 14 the patient, who had hitherto been clear-headed and lucid, began to manifest motor unrest. He became apathetic, with fixed eyes and slow speech. He stated that his vision had become blurred and that he had a twilight sensation in his eyes. The alkali reserve was 55 vol. per cent. Ethanol *per os* was prescribed; an initial dose of 60 ml. of ethanol diluted in fruit juice was given, followed by 10 to 20 ml. every hour. In this way we attempted to maintain an ethanol level of 0.1 per cent in the blood. The administration of ethanol was continued for 34 hours. Within 2 hours of the beginning of treatment with ethanol, the patient became clear-headed; his motor unrest, apathy and ocular symptoms disappeared. After 34 hours the ethanol medication was discontinued. The oxidation of methanol, as indicated by a decreased level in the blood, began once more 19 hours later. Although no symptoms of methanol poisoning whatever appeared, small amounts of ethanol, totaling 120 ml., were administered during this phase. Previously, a total of 450 ml. of ethanol had been administered. Daily examination of visual acuity and of the visual fields showed no abnormalities. On September 18 a liver function test with galactose gave normal results. The patient was discharged, completely free of all symptoms, on September 19. Examination of the patient's visual fields on January 9, 1948, showed no abnormalities.

Discussion: Two days after drinking methanol the patient showed incipient signs of methanol poisoning. The alkali reserve at this time was normal (55 vol. per cent) and the symptoms could not be explained by acidosis. The symptoms appeared about 10 hours after the oxidation of the methanol had commenced and when the level of methanol in the blood had fallen about 0.08 per cent. The administration of ethanol was successful in checking the oxidation of methanol. The ethanol was administered in such amounts that a blood concentration of about 0.1 per cent was maintained. During this period all symptoms of methanol poisoning disappeared. When ethanol medication was discontinued the oxidation of methanol was renewed.

Conclusions and Summary

According to some recent investigations, the symptoms of intoxication in methanol poisoning appear to be caused by the acidosis which usually results within 20 to 30 hours after the consumption of methanol. In one of the cases (Case 2) reported here, however, we observed incipient symptoms of methanol poisoning at a time when the alkali reserve was somewhat depressed but not at an acidotic level. We believe that the acidosis as well as the visual and other symptoms

appears concomitantly as a result of the influence of toxic products arising from the oxidation of methanol. A slower rate of methanol oxidation will result in a lower concentration of these toxic products and the symptoms of poisoning will be less pronounced. The administration of ethanol to persons rapidly oxidizing methanol causes retardation or cessation of this oxidation. Manifest symptoms of methanol poisoning disappear when ethanol is administered in amounts sufficient to maintain a blood concentration of about 0.1 per cent. After the administration of ethanol the level of methanol in the blood remains relatively constant. Thus the amount of methanol eliminated by excretion and by expiration appears to be comparatively small.

On the basis of our experience the following therapeutic principles are suggested.

1. If symptoms of methanol poisoning have appeared, ethanol should be administered in addition to the usual treatment for acidosis. An ethanol concentration in the blood of about 0.1 per cent should be maintained. The ethanol can be given by mouth or, if a more rapid effect is desired, intravenously as a dilute solution in bicarbonate or in saline. This administration should be continued until the symptoms of poisoning have disappeared and analyses show that the oxidation of methanol has been checked. The administration of ethanol may then be interrupted and the methanol oxidation allowed to proceed until a reduction of the methanol concentration in the blood of 0.05 per cent has been attained. Thereafter ethanol may be administered intermittently until all of the methanol has been oxidized.

2. If no symptoms of methanol poisoning have appeared, the rate of oxidation of methanol must be controlled by repeated analyses. During the period of time when methanol is oxidized rapidly, there is a risk of the accumulation of toxic products. If the oxidation rate is rapid, ethanol should be administered in order to retard it. Thus the therapy to be prescribed depends on the rate of oxidation of methanol and on the value of the alkali reserve. This emphasizes the usefulness of effective laboratory service in the treatment of patients suffering from methanol poisoning.

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