Ethanol-cure
Methanol-Excretion
Acidosis
Symptoms
Lactic Acid
Catalase

The Roles of Alkaline Salts and Ethyl Alcohol in the Treatment of Methanol Poisoning

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THE present communication has been prompted primarily by certain articles by Agner, Höök and von Porat (1, 2) and Agner and Belfrage (3). These articles have given an inaccurate account of my investigations in 1943 (4) and 1946 (5); in my opinion, their description of the work of Söderström (6) is also unsatisfactory. The discussion of these articles and of the investigations in recent years of certain other observers will be facilitated by a brief recapitulation of the most important results of my own investigations:

1. The outcome of methanol poisoning hinges most decisively on the degree of acidosis. Severe manifestations, including amblyopia and amaurosis, are not seen until the poisoning has provoked severe acidosis. In conformity with this observation, treatment of the acidosis with sodium bicarbonate has been found to be highly effective when adequate doses are given and at a sufficiently early stage of the poisoning. It is most important to bear in mind that the risk of recurrence of the acidosis is very great because of the slow elimination of methanol from the organism.

2. By preventing the development of acidosis, ethyl alcohol acts as a very effective antidote to methanol. This observation has led me to recommend *supplementary* treatment with alcohol after the acidosis has been treated with bicarbonate.

3. I have advanced the following hypothesis in explanation of this effect of ethyl alcohol: As the surface activity of ethyl alcohol is greater than that of methanol, the latter becomes displaced from the respiration ferments when the former is present in the tissues. Ethyl alcohol must consequently be assumed to inhibit the oxidation of methanol, and the production of formic acid will diminish or cease altogether.

4. It may be assumed that formic acid inhibits cell respiration by binding the ferment iron in the cells. Lactacidemia occurs and it is mainly this condition which is responsible for the marked diminution of the bicarbonate content of the blood.

5. Blindness always develops some time before the patient dies of methanol poisoning. In explanation of this fact I have referred to Otto War-

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burg's observation that the oxygen requirement of the retina in relation to its iron content is greater than that of any other tissue. Inactivation of the ferment iron must therefore induce a greater degree of hypoxia in the retina than in other organs.

Asser (7) was not the first, as Agner and Belfrage (3) believe, to observe the antitoxic action of ethyl alcohol in cases of methanol poisoning. As a matter of fact, Asser did not investigate methanol poisoning in human beings. He held that ethyl alcohol probably raises the toxicity of methanol, witness the following quotation:

"Man könnte sich wohl das Bild konstruieren, dass bei gleichzeitiger Anwesenheit von Methylalkohol und Aethylalkohol der letztere Alkohol seiner fast totalen Oxydationsfähigkeit entsprechend besonders leicht verbrannt, der Methylalkohol in seiner Verbrennung zurückgedrängt wird; dann müsste er eben noch länger als sonst unverändert im Körper kreisen und könnte hierdurch besonders schädlich wirken. . . ."

Agner, Höök and von Porat (1, 2) investigated the concentration of methanol in the blood before and after the administration of ethyl alcohol. They found that this concentration diminished very little while there was ethyl alcohol in the blood, and from this they concluded that ethyl alcohol checks the oxidation of methanol. The question may be raised, however, whether it is justified to study the oxidation of methanol only by following its concentration in the blood. It is an established fact that a very considerable quantity of methanol—in animal experiments up to about 70 per cent—is eliminated by diffusion through the lungs and kidneys [e. g., Haggard and Greenberg (8)]. It seems remarkable that Agner, Höök and von Porat (1, 2) found practically no fall in the concentration of methanol in the course of 24 hours in a patient given ethyl alcohol. There is no conceivable rationale for the prevention of the diffusion of methanol through ethyl alcohol. Zatman (9), indeed, found that ethyl alcohol *increases* the excretion of methanol through the kidneys. It is also quite surprising that Agner, Höök and von Porat found that the concentration of methanol in one of their patients fell 0.056 per cent in the course of an hour, i.e., more than three times as rapidly as ethyl alcohol is eliminated from the blood. In another case, with about the same concentration of methanol in the blood, there was a fall of 0.08 per cent of the concentration in the course of 10 hours. Both these patients were examined while there was no ethyl alcohol in the blood.

Referring to my investigations in 1946, these authors write: "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. Röe was not able to prevent a fatal outcome with this treatment."[1] This refers, I presume, to Case No. 71 in my work (5) of 1946 (p. 231). This patient was not given a small quantity of alcohol by the doctor on duty until his alkali reserve had fallen to 13 vol. per cent and he had collapsed with intermittent respiration. He had been admitted to the hospital the day before in a very drunken state but showing no signs of methanol poisoning. His alkali reserve was not determined and he was not given adequate bicarbonate treatment until his condition was hopeless.

Exception may also be taken to the way the authors (2) have quoted Söderström (6): "Söderström treated a patient with still smaller amounts of ethyl alcohol, also without success." Söderström himself stated: "In our first case we also tried brandy, but this case was undoubtedly too advanced to justify anticipation of any effect. On account of its simplicity, this method is well worth bearing in mind in acute cases."[2] Elsewhere in the same article Söderström draws attention to the facts that this patient was so restless that it was impossible to give him an injection of bicarbonate and that he died about 2 hours after his admission to the hospital.

It is thus apparent that in their discussion of these two cases, Agner, Höök and von Porat did not mention two important circumstances: (*a*) that the treatment given was not that which I have recommended, and (*b*) that the patients were already in a hopeless state when they received treatment. These references to treatment with ethyl alcohol may thus give the impression that it is of doubtful value. In this treatment, as in treatment with bicarbonate, the time at which it is given as well as the dosage is, of course, important.

In my publication (4) of 1943 I presented an account of the principles governing treatment with ethyl alcohol. There I expressly pointed out that treatment with ethyl alcohol is a supplementary measure which, carried out correctly, will prevent the recurrence of acidosis. If the alkali reserve is low, bicarbonate must be given in the first instance. I also pointed out that treatment with ethyl alcohol should be considered particularly when a lengthy transportation of the patient renders prompt and adequate treatment with bicarbonate difficult or impossible. I have several times observed patients who,

[1] Reference 2, p. 516; see also reference 1, p. 995.
[2] Söderström (6), p. 967. Translated from the Swedish text.

clinically symptom-free at the beginning of transportation, were blind or dead before they reached the hospital. The vision or lives of these patients would have been saved had they been given ethyl alcohol.

It is possible that Agner, Höök and von Porat overlooked the fact that the evidence for the efficacy of the treatment with ethyl alcohol is not based on the course of the poisoning in the three cases in which the doctor in charge administered small quantities of brandy but on the observation that patients who had drunk ethyl alcohol as well as methanol always suffered less from the poisoning than those who had drunk methanol only. As a rule, patients who drank ethyl alcohol daily after they were poisoned by methanol showed no signs of the poisoning and several of them were therefore not hospitalized.

On the basis of the course of the poisoning in one of their two cases, Agner, Höök and von Porat maintain that characteristic manifestations of poisoning such as amblyopia may develop at a time when the alkali reserve is high and the patient has not suffered from severe acidosis. They describe these manifestations in the following way: "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."[2] The patient was given 60 ml. of ethyl alcohol diluted by fruit juice and water, followed by 10 to 20 ml. every hour for 34 hours; all his symptoms disappeared within 2 hours.

The symptoms described are not manifestations of methanol poisoning but must be attributed to the fact that the patient was in the "hang-over" stage of drunkenness. The fact that the patient complained of blurred vision is by no means proof positive of amblyopia. I have often noticed that alcoholics after a spree of several days, afraid that they may have drunk methanol, complain of blurred vision although diminution of vision is not demonstrable. With regard to the other symptoms, it should be especially noted that motor restlessness does not develop in methanol poisoning before dyspnea has become serious, severe pain has set in, or psychic disturbances have occurred—i.e., not before severe acidosis has developed.

It seems unfortunate that formulations based on insufficient anal-

[2] Reference 2, p. 520; see also reference 1, p. 998.

ysis should cast doubt on the decisive significance of acidosis in methanol poisoning. This attitude, adopted by several investigators on the basis of findings in experiments with animals, has cost the life or vision of many human beings. For an unexplained reason even very large doses of methanol do not cause an appreciable reduction of the alkali reserve in the animals usually employed in research, and they do not therefore present the same morbid picture that human beings do (10). Undoubtedly it is chiefly on account of the experimental findings that most textbooks and handbooks propagate the teaching that acidosis plays no very important part in this matter.

In 1946 Zatman (9) published a study of great interest. With my first study of 1943 as his starting point, he investigated the effect of ethyl alcohol on the oxidation of methanol. He found that the oxidation of methanol with alcohol dehydrogenase was considerably inhibited by ethyl alcohol. No oxidation took place when ethyl alcohol and methanol were present in equimolar quantities. A definite inhibition of methanol oxidation is demonstrable even when the molar relationship of ethyl alcohol to methanol is only 1:16.

Zatman's investigations of the excretion of methanol in the urine of the three persons on whom he experimented are also very important. He found that the concentration of methanol in the urine *rose* after the administration of ethyl alcohol. I presume that this phenomenon also can be explained as a surface action of ethyl alcohol. Some of the methanol taken becomes adsorbed to the surfaces and to the firmer constituents of the cells. When ethyl alcohol is given, methanol is displaced from these surfaces and the concentration in the fluid of the organism becomes higher than it was before. As the excretion of methanol through the kidneys takes place by diffusion, the concentration in the urine will rise in conformity with the concentration in the blood plasma. The excretion through the lungs is also by a process of diffusion and we must therefore assume that the elimination of methanol in the expired air will also increase when ethyl alcohol is given.

In connection with my hypothesis of 1943 (4) that formic acid may conceivably paralyze the ferment iron, it is interesting to note that in 1946 Agner and Theorell (11) showed that formate, in a concentration corresponding to 0.1 per cent methanol, has a considerable inhibitory effect on the activity of catalase.

Söderström (6) believes that the lactacidemia of persons poisoned

by methanol may be due to their violent struggles for life. But I doubt the validity of this explanation, for an increased quantity of lactic acid has also been found in patients with a moderate degree of acidosis, and at this stage patients do not suffer from motor restlessness. Thus Branch and Tonning (12) found lactic acid values of about 70 mg. per 100 cc. in two patients with alkali reserves of about 40 vol. per cent. These findings support the hypothesis that it is hypoxia which is the central factor in the pathogenesis of methanol poisoning.

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A Critique of Physiopathological Theories of the Etiology of Alcoholism

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Recent studies on alcoholism have branched off in two different directions: the psychiatric and the pathophysiological. While it is a most desirable development for a problem to be approached along various lines—in fact, along all the lines possible—it is of equal importance to maintain communication between them, just as a two-pronged attack on a strategic objective in war might fail if one army group did not know or did not understand the tactics of the other. For that purpose, in military as well as in medical and psychiatric strategy, the groups concerned should speak the same language. An attempt is made, along these lines, to establish the common ground of understanding between medicine and psychiatry, as far as alcoholism is concerned.

Smith[1] emphatically states his conviction that alcoholism is a metabolic disease. No one familiar with the signs and symptoms of acute intoxication and chronic alcoholism can challenge this statement. Recent contributions, such as those cited by Smith himself, have shed light on this subject. It is probably true that the syndrome of delirium tremens is an adaptation syndrome in the sense of Selye,[2] in which adrenal hypofunction due to the repeated toxic stimuli associated with alcoholism plays an important part. The parallel between delirium tremens and Addisonian crisis is most interesting.

If the clinical problem of alcoholism is approached in this way, however, it is hardly justified to state, as Smith does, that "alcoholism manifests itself primarily as a behavior problem." Neurologists would certainly meet this statement with raised eyebrows. If the slurred speech, motor restlessness, tremor, hyperidrosis, staggering, and—eventually—coma of the alcoholic are to be defined as behavior problems, so are the signs of multiple sclerosis, brain tumor, poly-

[1] Smith, J. J. A medical approach to problem drinking. Preliminary report. Quart. J. Stud. Alc. 10: 251–7, 1949.

[2] Selye, H. The general adaptation syndrome and diseases of adaptation. J. clin. Endocr. 6: 117–230, 1946.