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* Amnesia 441

* Acidosis cannot be accounted for by formic acid 433
Lactic acid 433

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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ated spirit, acetone alcohol) is an important and useful solvent. In past years, its extensive use in industry resulted in many instances of poisoning via the respiratory tract or skin (1-12) and many investigations of the hazards of its use in industry have been carried out (13-27). With proper precautions, it is now used safely in the manufacture of many articles including synthetic textiles, linoleum, shoes, dyes, explosives, anti-freeze compounds, varnishes and shellacs, rubber goods, felt hats, etc. (28).

It is cheaper than ethyl alcohol and easily available; despite wide advertisement of its toxicity, it is still frequently substituted for ethyl alcohol as a beverage with resultant poisoning, permanent visual impairment and death. Wholesale poisonings are commoner in circumstances of economic hardship or military mobilization and have constituted a problem in the armed forces of the United States (29-35).

With the exception of occasional reports such as those of MacFarlan in 1855 (36) and Poincaré in 1878 (37), there is little mention of wood alcohol in the medical literature until after 1890. This can be attributed to the development at about this time of methods for producing large quantities of pure methanol at low cost. The classic method, which relied upon wood distillation and fractionation, resulted in limited amounts of a foul-smelling, distasteful material which tempted no one as a beverage. For reasons which will be discussed at length in a later section, the toxicity of methanol was not appreciated for a number of years and remained a subject of considerable debate in medical circles well into this century. Methanol was freely substituted for the more expensive ethyl alcohol in cheap cosmetics and liquors. Ziegler (4) reported that as late as 1910, many wines, brandies and whiskeys sold on New York's East Side contained methyl alcohol in proportions ranging from 24 to 43 per cent. Occasional instances of poisoning after ingestion of methanol were attributed to contaminants such as acetaldehyde, allyl alcohol, acetone, or fusel oils. So little was the toxicity of wood alcohol considered that Ehrlich (38) once used it as a solvent for salvarsan. The results of many early animal experiments were inconsistent or, at least, subject to more than one interpretation and, despite pleas of a few (1, 4, 39-44), it was not until Reif demonstrated in 1923 (45) that a group of dock-workers in Hamburg had been poisoned by chemically pure methanol that the toxicity of wood alcohol was generally accepted as a fact. Nevertheless, doubts as to its poisonous properties were still voiced as late as 1936 (46). In a comprehensive monograph, Røe (46) has outlined the history of methyl alcohol poisoning with detailed descriptions of the bitter arguments over the toxic properties of this material.

CLINICAL MATERIAL AND BACKGROUND

This study is based on observation of 323 patients who had ingested bootleg whiskey containing methyl alcohol in Atlanta during a five-day period in October, 1951. There were 308 colored and 15 white patients; 210 were males and 113 females with an age distribution of 10 to 78 years. Forty-one deaths occurred; 22 victims were dead when brought to the hospital or succumbed within 30 minutes

after arriving. The other 19 fatalities were in patients treated for a period of longer than 30 minutes in the Emergency Clinic or hospital wards. Although only 31 patients were officially admitted to the hospital, many more were treated in the Receiving Ward for periods up to 24 hours or longer.

Approximately 90 gallons of illicit whiskey had been distributed widely throughout the city of Atlanta 24 hours before the first patients were seen. Later analysis of confiscated samples revealed 35 to 40 per cent methanol (by weight) and less than four per cent ethanol. As word of the poisonings spread by rumor, newspaper, and radio, a minor panic developed and numerous asymptomatic individuals presented themselves to be checked for evidences of poisoning; in many instances, these persons had drunk no alcoholic beverage at all and were simply frightened. It was estimated that no less than 100 such patients were seen in addition to the 323 who had actually ingested the poisonous mixture.

There was available no rapid test for blood methanol. However, because acidosis is a common sequel of the ingestion of wood alcohol, a routine was hastily set up whereby a plasma bicarbonate determination was performed initially on each suspected victim. Many tests were done by the Van Slyke technique (47) but a majority were performed by the rapid method of Scribner (48). Periodic checks of the results obtained by Scribner's bedside technique against the Van Slyke CO₂ capacity readings showed no variation greater than 2.0 mEq. Of the 323 patients who had actually ingested the contaminated "moonshine," 115 were acidotic (carbon dioxide combining power less than 20 mEq.) when seen initially.

Because of the confusion attendant upon the care of large numbers of acutely ill patients, it was not possible to obtain a complete medical history and all routine laboratory tests or to record a complete physical examination on every patient. However, in nearly every instance the amount of methanol ingested, the length of time between ingestion and onset of symptoms, a brief list of symptoms and a description of the patient's respirations (i.e., Kussmaul in type, etc.) and the findings on careful ophthalmoscopic examination were recorded. Special laboratory determinations, including methanol levels, were performed on smaller groups of patients, usually those with signs of severe intoxication, and in the case of all inpatients, complete clinical records were kept.

Autopsies were performed on 10 of the 41 patients who died in this outbreak. In addition, tissues from seven fatal cases of methanol poisoning autopsied in December, 1946, were available for review and comparison.

CHEMISTRY AND PHARMACOLOGY

Pure methanol is colorless, possessing an odor distinctly different from that of ethyl alcohol. It boils at about 65° C. and has a specific gravity of 0.81. It is easily absorbed through the skin, respiratory tract or gastrointestinal tract and human poisoning is possible by any of these routes. According to several authorities (12, 23, 28), 200 parts of methanol per million parts of air is the maximum limit of safety in industry.

Dosage. The extreme variation in the individual response to a given amount of methyl alcohol has long been a source of confusion and was undoubtedly one of

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.

6 ml
methanol



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

in the body for as long as a week (11, 54-56). Its distribution in the body generally corresponds to that of water (being practically immiscible with fat) (21) and higher levels are attained in the humors of the eye, the cerebrospinal fluid, and gastric secretions than in the blood. It is apparently re-excreted into the stomach for many days after ingestion (57). Many have explained the selectivity of methanol's effect on the eye by the high content of water in the aqueous and vitreous humors and experiments in rabbits and dogs have demonstrated a higher concentration of methyl alcohol in the eye than in any other organ (12). Leaf and Zatman (23) mention experiments *in vitro* with surviving ox retina in which high concentrations of methanol failed to exert any effect on metabolism; formate inhibited respiration weakly while formaldehyde inhibited both aerobic and anaerobic glycolysis strongly. This is in contrast to Goldschmidt's report that methyl alcohol reduced retinal cell respiration (14). Pronnie, Kritzler and Calhoun (32) found methyl alcohol levels of 20 to 270 mgm. per 100 ml. in the cerebrospinal fluids of human cases but did not state the blood levels at the time these determinations were done. We were able to make a limited number of observations of methanol levels in various body fluids, finding that cerebrospinal fluid and gastric juice consistently contained higher concentrations of this substance than blood and that detectable amounts remained after the blood became negative. Table I summarizes the results of serial determinations for methyl alcohol in blood, spinal fluid and gastric juice.

Methyl alcohol is apparently oxidized in the body at less than one-fifth the rate of ethyl (12, 58-63), hence its long persistence. A small proportion (3-5 per cent) is excreted unchanged in the urine (8, 23, 61) but a much larger amount is lost in expired air. Few satisfactory data are available from human studies. In rats, Haggard and Greenberg (64), using a technique of tracheal cannulation, demonstrated that 70 per cent of an administered dose was excreted by this route. Earlier studies (65, 66) using a chamber method had shown 30 to 50 per cent excretion through the lungs. Leaf and Zatman (23) found that only about 2 per cent of a small dose (2.5 to 7.0 ml.) of methanol given to human volunteers was eliminated via the respiratory and urinary routes. These workers pointed out, however, that while such tiny amounts may be disposed of by enzymatic action alone, larger quantities probably result in increased proportions being excreted by lungs and kidneys.

The oxidation of methanol proceeds to formic acid, probably via formaldehyde. Pohl showed in 1893 that excretion of formic acid in the urine was increased after ingestion of wood alcohol (67) and the presence of formic acid in both urine and blood of humans and animals with wood alcohol poisoning has been repeatedly demonstrated (46, 61, 66, 68, 69). The evidence that formaldehyde is important in methanol poisoning is mostly circumstantial; it has not been regularly demonstrable *in vivo*, possibly due to its affinity for protein or to its rapid oxidation to formic acid. However, the oxidation of methyl alcohol to formaldehyde proceeds rapidly *in vitro* and Keeser and Vincke (70) have shown clearly that liver tissue is capable of producing formaldehyde from methanol. Furthermore, Keeser (71) has reported the finding of formaldehyde in the cere-

brospinal fluid and the vitreous humor. Pohl (67) first demonstrated that the urine of methyl alcohol workers contained formic acid in quantities sufficient to reduce Fehling's solution, a point of considerable significance in avoiding diagnostic confusion with diabetes mellitus. Bartlett (61) has studied the metabolism in rats of methanol labeled with C^{14} . He found that, independent of concentration, the rate of destruction of this substance was 25 mgm. per kilo of rat per hour as contrasted to a rate of 175 mgm. per kilo per hour for ethanol. Nearly

TABLE I
Methanol concentrations in body fluids. Blood specimens collected simultaneously with cerebrospinal fluid or gastric juice

PATIENT	DAYS AFTER INGESTION	METHANOL (MGM./100 ML)		
		Blood	Spinal Fluid	Gastric Juice
J. B.	3	92	114	—
W. R. M.	3	224	272	—
	4	124	176	—
	5	41	53	—
	6	30	60	—
	7	6	27	—
R. F.	3	30	100	—
	4	17	80	—
	5	0	26	—
	6	0	14	—
W. M.	3	4	17	—
	4	0	9	—
	5	0	0	—
	6	0	0	—
R. J.	3	51	84	—
	4	0	14	—
	5	0	0	—
	6	0	0	—
N. D.	6	22	—	100
	10	7	—	84
	14	0	—	0

90 per cent of the administered dose of C^{14} was recoverable within 48 hours, 65 per cent as carbon dioxide in expired air, 14 per cent as methanol in expired air, 3 per cent as methanol and 3 per cent as formic acid in urine, and 4 per cent fixed in the tissues.

There is, then, abundant indication that the body slowly oxidizes methyl alcohol to formic acid and indirect evidence to suggest that formaldehyde may also be produced. Formic acid and formaldehyde were found by Mayer (72) to be respectively six times and 33 times as toxic as methanol. The latent period be-

tween ingestion of methyl alcohol and the development of symptoms of intoxication could thus be explained by the slow accumulation of toxic end-products of its metabolism.

Relation to ethyl alcohol. The relationship of ethyl alcohol to the metabolism of methanol in the body is of importance because of the light which it sheds on possible mechanisms of the toxicity of wood alcohol as well as from the practical viewpoint of therapy. Wood and Buller (1) recommended ethyl alcohol as a stimulant in the treatment of methyl alcohol poisoning, but others, especially Foerster (73), were greatly opposed to its clinical use on the grounds that methyl alcohol did not appear to exert any toxic action unless ethanol had also been consumed. In 1914, Asser (66) reported the interesting observation that the excretion of formates in the urine of experimental animals given wood alcohol diminished strikingly if other alcohols, including ethanol, were administered concomitantly. This finding was curiously neglected for many years and was not confirmed until 1947 (69). With the extensive clinical studies of Røe, interest in ethanol was again revived. This investigator, in 1943, published an account of 16 cases of methyl alcohol poisoning, pointing out that the symptoms appeared to be milder in patients who had consumed ethyl alcohol along with methyl (74). In 1946, Røe reported an extension of this study to include 82 cases (46). By careful analysis of data obtained from patients, their relatives, and police reports, he concluded that the evidence was clearly in support of his hypothesis that ethyl alcohol exerted a favorable effect upon the course of methyl alcohol poisoning. On the basis of the then available data, he suggested that the adsorption of methyl alcohol to some respiratory enzyme or enzymes produced hypoxia and signs of intoxication. Since the work of Andersen (75) had indicated that surface activity of a substance is an important factor in determining the amount which can be adsorbed, and Livingstone, Morgan and Neidle (76) showed that ethanol's surface activity was double that of methanol, Røe concluded that ethyl alcohol prevented the adsorption of methyl to the respiratory enzyme and consequently its conversion to formic acid.

Since Røe called attention to the possible effect of ethyl alcohol in depressing the oxidation of methanol to formic acid, a number of experimental studies have appeared which support this hypothesis. Keilin and Hartree (58) showed that alcohols are oxidized by catalase in the presence of small concentrations of hydrogen peroxide; under these conditions catalase forms a compound which reacts rapidly with both ethanol and methanol. In studies of the inhibitory effect of anions upon catalase activity, Agner and Theorell (77) showed that what had previously been considered to be an effect of pH upon enzyme activity was actually an anion displacement of a labile hydroxyl group loosely associated with hemin iron which is necessary for catalase activity. Formic acid was found to be 800 times stronger in its catalase-inhibitory action than acetic acid. In later studies, Agner and Belfrage (78) showed that if ethanol and methanol are injected simultaneously into rabbits, the concentration of methanol in the blood remains almost unchanged until the ethanol has been oxidized. Zatman (59) studied the effect of ethanol on the metabolism of its methyl homologue, demon-

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^{14} 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_2 combining power of four patients, all moribund, was zero by the Van Slyke (CO_2 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,

especially lactic acid, have been demonstrated in large quantities in the blood and urine of patients with methanol poisoning. Harrop and Benedict (42) found elevation of lactic acid in the urine of their patient and Røe (46) reported elevation of blood lactate in two cases. Van Slyke (68) noted increase in urinary excretion of lactic as well as formic acid in a patient with methyl alcohol intoxication but he showed that most of the urinary acid was in the form of unidentified organic acids which were not formic, lactic or acetic. Keeney and Mellinkoff (35) have recently suggested that ketosis may play a significant role in the acidosis of methanol poisoning, basing their statement upon the finding of acetonuria in a number of patients who had drunk Korean wine containing 16 per cent methanol. Isolated reports of mild acetonuria such as that of Rabinowitch (56) can be found but it has apparently been an inconstant feature in reported cases. Røe

TABLE II

Plasma carbon dioxide combining power, blood ketone bodies and urine acetone in thirteen patients with methyl alcohol poisoning. All determinations were performed on specimens collected before institution of therapy. The normal value for blood ketone is less than 3 mgm./100 ml.

PATIENT	PLASMA CO ₂ COMBINING POWER (mEq./100 mL.)	BLOOD KETONE BODIES (mgm./100 mL.)	ACETONURIA
1	1.0	8	Not tested
2	3.0	26	+
3	4.5	14	Not tested
4	6.0	17	0
5	7.5	16	++
6	7.5	14	0
7	8.0	5	Not tested
8	9.0	8	++
9	10.0	4	Not tested
10	13.0	5	0
11	16.0	10	Not tested
12	16.0	5	0
13	16.0	5	Not tested

(46) noted acetonuria in only four of 23 cases and in several studies such as that of Voegtlin and Watts (29) who observed six cases with five fatalities, acetonuria was specifically stated to be absent. In our series, complete urinalysis was performed initially in 43 patients. Acetonuria varying from a trace to 2+ was present in ten instances. Albuminuria was commoner than acetonuria, appearing 21 times in the 43 specimens tested. The results of analyses of blood ketone bodies which were performed in 13 patients before institution of therapy are listed in Table II. Although slight to moderate elevations were found, they were never of an order of magnitude to explain the profound reduction of plasma bicarbonate in these patients. The inconstancy of acetonuria in other reported cases of methyl alcohol poisoning and in our own cases is in contrast to Keeney and Mellinkoff's series (35) in which acetone was constantly present in the urine of

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

latter 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,

were seen with the same signs; all died within a few minutes. Mild rigidity of the muscles of the neck and back occurred in several patients who survived. It is of interest that in the outbreak described by Kaplan and Levreault (30) among naval personnel, the first patient seen presented exactly the picture described above.

Mode of death. The prime cause of death in the acutely fatal cases observed by us was a peculiar cessation of respiration. The pattern of events was remarkably uniform in each instance where patients died while severely acidotic. Coma deepened and respirations gradually became shallower and less frequent. As has been noted above, circulatory function was well maintained, with full, strong pulses and normal blood pressure despite clammy extremities. In several patients, when respirations began to fail, sinus bradycardia (rate 30-38) developed with widening of the pulse pressure. This slowing of the pulse is a sign of poor prognosis; no patient who developed bradycardia survived. Gradually, tonic contractions of the limbs appeared, the patient suddenly went into opisthotonos and, at the end of a tremendous single gasp, the chest locked in a position of full inspiration and respirations ceased. It was not unusual for the heart to continue beating for several minutes after this event. Reiner (34a) noted the maintenance of circulatory function in a fatal case for several minutes after respirations ceased. Direct laryngoscopic examination revealed no evidence of laryngospasm in our patients. Manual artificial respiration was impossible because of the complete immobility of the chest wall. Tracheotomy was ineffectual and two patients were placed in respirators without effect. In two instances, endotracheal tubes were inserted and oxygen administered but both patients died within a few minutes. The tonic muscle contractions were unaffected by intravenous sodium amytal.

Seven patients admitted in coma and treated intensively with alkali and supportive measures with full restoration of serum bicarbonate failed to recover consciousness. Despite the presence of normal serum electrolytes, adequate urinary output, and the use of all supportive measures, all died within three to seven days with signs of massive cerebral damage. Three developed hyperpyrexia before death. All of these patients had plasma carbon dioxide combining powers of less than 10 mEq. on admission.

Lastly, emphasis must be given to the necessity for prompt treatment of acidosis no matter how well a patient may appear clinically. Six acidotic patients who complained of no unusual discomfort, were rational and conversing, and in three instances, ambulatory, suddenly became comatose with or without a convulsion, rapidly developed respiratory slowing and died within a period of minutes despite vigorous measures. Røe (46) has emphasized this type of sudden "decompensation" and we agree that acidosis due to methyl alcohol is a true medical emergency.

TREATMENT

Alkalinization. Although there is still controversy over the exact role of acidosis *per se* in the production of the symptoms of methanol intoxication, a review of the literature leaves little doubt that the degree of acidosis correlates well

with prognosis. This has been emphasized by Røe (46, 74, 84, 85) in extensive studies and is borne out in a study of our own figures, given in Table III, which includes data only on patients treated for at least 30 minutes before death.

It was generally recognized after the work of Harrop and Benedict (42) that wood alcohol produced acidosis in human beings but the importance of alkalization was not appreciated until 1946 when the reports of Chew (33) and of Røe (46) made it clearly evident that mortality could be influenced greatly by prompt and generous use of parenteral sodium bicarbonate or sodium lactate. Not only did these observers report better survival rates in patients so treated, but both described the dramatic relief of symptoms of poisoning by alkali.

Our experience with the use of alkali confirms entirely that of these investigators. With the exception of two or three patients who were given sodium lactate early in the outbreak, all patients who were acidotic were treated with *intravenous* five per cent sodium bicarbonate in five per cent glucose. Because of the already mentioned frequency of mild nausea, it was not feasible to attempt the administration of sodium bicarbonate by mouth to large numbers of patients and the surer intravenous route was used almost exclusively in initial treatment,

TABLE III

Mortality among treated patients. These figures do not include patients who died at home or who were moribund on admission

	NO. OF PATIENTS	PER CENT DEATHS
All patients.....	323	6.2
Acidotic ($\text{CO}_2 < 20$ mEq.).....	115	19.0
Severely acidotic ($\text{CO}_2 < 10$ mEq.).....	30	50.0

even in ambulatory cases. In reviewing the accounts of outbreaks described in recent years, one is struck by the number of times that sodium bicarbonate has been used orally or by gavage in severe acidosis because *none for intravenous use was available*. The method employed in preparing the solutions used in this outbreak deserves emphasis because of its demonstrated safety and simplicity. It consisted simply of weighing out 50 grams of baking soda from a newly opened commercial package for kitchen use and dumping it into a liter of five per cent glucose of the type ordinarily used for infusions. This method of preparation of sodium bicarbonate solutions for intravenous administration has been used sporadically for several years at Grady Memorial Hospital without untoward reactions. During the five days of this outbreak of methanol poisoning, approximately 1200 liters of five per cent sodium bicarbonate prepared in this way were infused intravenously with only one mild pyrogenic reaction.

In general, the results of alkali treatment were dramatic. With restoration of plasma bicarbonate levels to normal, there was rapid return of consciousness or lethargy and confusion disappeared. Pain in the extremities and abdomen was relieved as were blurred vision and headache. The relief of initial symptoms of visual disturbance was sometimes striking; some patients with visual impair-

ment such that they could only distinguish light could read the newspaper a few hours later. In several instances, improvement in vision was not maintained; the delayed onset of eye manifestations after initial amelioration has been noted previously (46, 86).

Seven severely acidotic patients died (see above) despite relief of acidosis but in every other instance in which plasma carbon dioxide combining power returned to normal, the patient survived. This fact, coupled with the instances of sudden decompensation and death in patients who appeared relatively well leads us to believe that *massive alkalinization is the mainstay of treatment in methanol poisoning and that its prompt institution is of utmost importance.* All other therapeutic measures now available must be considered secondary to the main objective of prompt restoration of plasma bicarbonate.

As might be expected, the almost indiscriminate use of sodium bicarbonate in large numbers of patients resulted in many instances of overtreatment alkalosis.

TABLE IV

Sodium bicarbonate treatment and response in one patient. All sodium bicarbonate given intravenously as 5 per cent or 3 per cent solution. Patient had onset of symptoms 20 hrs. after drinking approximately 125 ml. of 40 per cent methanol.

TIME AFTER ADMISSION	TOTAL NaHCO ₃ (CUMULATIVE) (GM.)	CO ₂ COMB. POWER (mEq./100 ML.)	REMARKS
0	None	8.2	—
1½ hr.	40	15.0	—
4 hr.	90	20.0	Vision improved; pain gone
7 hr.	115	25.0	—
9 hr.	140	35.0	—
11½ hr.	140	39.0	No complaints
17½ hr.	140	21.0	Headache; nausea
22 hr.	190	38.0	Tetany; Ca gluconate i.v.
60 hr.	190	23.0	No complaints
4 days	190	25.2	Asymptomatic

The highest plasma carbon dioxide combining power recorded was 52 mEq. Despite the frequent occurrence of alkalosis, frank tetany was observed only one time as a complication in a woman whose plasma bicarbonate was 38 mEq. The course of bicarbonate therapy in this patient is outlined in Table IV and serves to illustrate the large amounts of soda which were used. The highest total dose of sodium bicarbonate given to a patient was 420 grams over a period of 28 hours, but at least 50 patients received more than 100 grams intravenously within 12 to 36 hours.

Certain complications of alkali infusion deserve attention. Intense thirst and transient numbness and tingling of the fingers and lips were the only subjective complaints noted with any frequency. It is of interest that both of these have been described as occasional manifestations of methanol poisoning. The numbness and tingling suggest, of course, latent tetany but the Chvostek and Trousseau signs were uniformly absent in these patients. The single instance of tetany

has been mentioned. This patient's symptoms subsided promptly with injection of calcium gluconate. Lastly, the rapid infusion of five per cent sodium bicarbonate was followed by lowering of serum potassium in several patients. Although no clinical manifestations of hypokalemia were seen, electrocardiographic tracings revealed typical changes on a number of occasions. The lowest value for serum potassium recorded was 2.5 mEq. Some of these patients were given potassium chloride by mouth; in others, the serum potassium rose to normal within 48 hours without supplement. This drop in serum potassium was not unexpected in view of the reported effects of alkalinization in animal experiments (87, 88). It is of interest to speculate upon the possibility that hypokalemia may have had a protective action in preventing the development of tetany in light of the studies of Engel *et al.* (89) upon the reciprocal action of calcium and potassium in hypocalcemic tetany. Occasional instances of transient hypernatremia followed sodium bicarbonate infusion. The highest serum sodium recorded was 161 mEq.

Ethyl alcohol. The relationship between the metabolism of ethyl and methyl alcohol has been discussed. Despite the sound experimental basis for its therapeutic use, clinical confirmation of ethanol's efficacy is not yet established. Chew (33) administered whiskey to 26 patients in his series and all recovered but all were also treated with large doses of alkali. Due to the circumstances of the outbreak observed by Chew, an exact record of the ethanol consumed by each patient at the time of ingestion of methanol was available. There was no correlation of ethanol consumption and time of onset of symptoms, their severity, or the ultimate results. In the series reported by Keeney and Mellinkoff (35) blood ethanol levels in the fatal cases were usually much higher than blood methanol. Agner, Höök and von Porat (60) have reported the treatment of two human cases of methyl alcohol poisoning with ethanol (plus alkali) but the results are difficult to assess, especially in view of the fact that one of the patients failed to recover. These investigators were able to demonstrate in both patients that the blood methanol concentration remained relatively constant under ethyl alcohol's influence. Branch and Tønning (90) administered ethanol to one patient with inconclusive results (alkali was also given). Dérobert and Hadenque (91) thought they could see a favorable effect of ethyl alcohol in methyl alcohol poisoning. The only patient given ethyl alcohol in our series was the woman whose course is depicted in Table IV; she was given 50 ml. of absolute ethanol intravenously every four hours for eight injections. No conclusions can be drawn, of course, but it is worth noting that on this regimen her plasma bicarbonate fell from 39.0 mEq. at 11½ hours to 21.0 mEq. at 17½ hours and further alkalinization was necessary. Inspection of Table V, which depicts the findings in 25 patients in this study, shows that in the 18 instances where blood methanol and ethanol levels were determined, the amount of ethanol exceeded methanol in five cases.

While it would seem that further trials of ethyl alcohol as an adjunct in methanol poisoning might be advisable, under no circumstances do the available data justify its substitution for alkalinization. The relatively innocuous sequelae of overdosage with bicarbonate in our experience leads us to disagree with Røe (46) who advocates the use of ethyl alcohol in suspected methyl alcohol poison-

ing until arrangements can be made for determination of plasma bicarbonate preliminary to use of alkali.

Spinal drainage; gastric lavage. Lumbar puncture is often mentioned in the treatment or prevention of amblyopia resulting from methanol. Pincus (92) treated three patients in 1920 with inconclusive results. Others (93-95) have reported a few cases but there is actually no theoretical or clinical basis for believing the procedure to be beneficial. Six of our patients underwent daily lumbar puncture for several days (Table I) and several others had a single spinal fluid examination. In no instance was significant elevation of pressure recorded. The clinical course and residual eye damage in these patients were so varied that no statement is possible other than to say that there was no evidence of any modification of the acute intoxication by this procedure. This conclusion is in disagreement with that of Reiner, who found frequent elevation of spinal fluid pressure in victims of methanol poisoning and concluded that reduction of pressure by spinal drainage is an emergency procedure (34a).

Bongers (57) pointed out that methanol is re-excreted into the stomach and suggested gastric lavage as a means of removing methanol from the body. Røe (46) was apparently unaware of Bongers' findings and unequivocally condemns lavage as a useless and possibly harmful procedure. We undertook the treatment of two patients by constant gastric aspiration which, for technical reasons, was unsatisfactory, but it was demonstrated that specimens of gastric juice contain appreciably more methanol than simultaneously collected blood (Table I). Keeney and Mellinkoff (35) point out that there is a strong possibility of perforation of an acute gastric ulcer by a Levine tube and recommend that intubation be attempted with great caution.

BAL; ACTH. Although we recognize that there is no theoretical basis for the use of BAL in methyl alcohol intoxication, approximately 25 patients received a single intramuscular dose of 300 mgm. of this drug during the early hours of the outbreak and several were continued on six-hourly injections for 48 hours. There was no detectable difference in the clinical response of these patients. The reason for giving BAL was simply that although it was recognized that wood alcohol was the ingredient of the "moonshine" responsible for the patients' symptoms, we had no assurance that other toxic materials were not present in the mixture and only after analysis had shown no heavy metals was the routine precautionary use of this drug discontinued.

Five patients were given ACTH in a dose of 15 units subcutaneously every six hours for five days. Each patient was paired carefully with an untreated control whose age, clinical course and ophthalmoscopic findings were similar. We were primarily interested in determining the possible effects of this drug upon retinal lesions and it can be stated that there was no obvious difference in the rate of subsidence of hyperemia or edema in the two groups. Administration of the hormone was not begun until acidosis had been controlled and neither group had further systemic manifestations. These patients did not return regularly for examinations after discharge and nothing definite is known about residual visual abnormalities.

Other measures. Although most reports in the past have suggested that the

TABLE V
Clinical course of methyl alcohol

CASE NO.	AGE, SEX	MeOH DRUNK (G.)	LATENT PERIOD	VISION*	OTHER SYM- TOMS†	T. P., R., BP	SENSORIUM‡	PUPILS§	OPHTHALMO- SCOPIC¶	pH OF URINE	ALBUMINU- RIA	GLYCOSURIA	ACETONURIA	Hgb. WBC
1	19 M	250	36 h	C	Di, H, N, P, V	98.0 68,22 100/70	D	D	H	5.0	0	++	++	13.8 12,100
2	47 M	250	18 h	N	H	99.0 80,20 138/80	R	D	H	5.5	+	++++	++	12.8 6,500
3	27 M	125	8¼ h	F	Dy, W	97.0 120,40 (Kusa) 120/80	D	N	N	5.0	0	++++	0	14.1 7,500
4	35 M	500	40 min	B	H, N, P, V, W	97.4 84,24 128/80	A	N	E, H	5.0	0	0	0	12.7 8,100
5	26 M	?	48 h	C	H, N, P, V	98.4 72,16 135/80	D	D	H	5.0	0	0	0	17.0 6,500
6	58 M	250	48 h	Sk	Di, Dy, H, W	99.0 70,20 123/82	A	N	E, H	5.5	0	0	0	12.3 4,800
7	49 M	100	12 h	B	Dy, N, P, V	98.0 72,30 80/60	S	D	E, H	5.5	Trace	0	Trace	11.0 5,750
8	23 M	250	72 h	C	Di, H, N, P, V, W	99.0 72,20 134/80	N	D	E, H	5.0	Trace	++++	0	15.0 10,500
9	40 M	250	12 h	C	H	98.8 76,22 100/114	D	D	E, H	5.5	0	0	0	13.8 9,100
10	26 M	250	18 h	F	Di, N, P, V	99.8 84,24 120/68	N	D	E, H	5.0	0	0	0	15.5 10,550
11	43 M	?	48 h	C	H, P	98.6 120,18 156/88	S	D	E, H	5.5	Trace	0	0	10.2 12,600
12	29 F	150	18 h	Sn	Di, H, N, V	99.6 00,34 (Kusa) 134/75	N	N	E, H	4.5	0	+++	0	12.9 6,560
13	47 F	100	24 h	C	Di, Dy, H, N, P, V	93.6 83,28 (Kusa) 180/100	N	D	H	5.5	0	0	0	13.3 9,000
14	46 F	250	18 h	Sk	Dy, P	98.0 120,32 (Kusa) 185/120	S	D	H	5.0	0	+++++	0	14.0 6,750

V.
poisoning in 25 patients

INITIAL CO ₂ CP (mEq)	K (mEq)	Na (mEq)	Cl (mEq)	UREA (MGM/100 ML)	AMYLASE (UNITS)	MeOH (MGM/100 ML)	EtOH (MGM/100 ML)	NaHCO ₃ GIVEN IV (GM)	CO ₂ CP AFTER Rx	EKG BEFORE Rx	EKG AFTER Rx	TIME OF RELEASE	CO ₂ CP AT RELEASE	RESULTS AND REMARKS
5.1	4.1	144	94	11	312	22	50	180	33.0	—	Low K	—	—	Recovered
12.0	4.7	139	93	11	332	—	—	180	37.0	Ant. is-chemia	Low K	—	—	Recovered
4.8	—	—	—	6	166	390	90	150	37.5	—	—	8 h	15.9	Developed visual disturbance and eye-ground changes in 24 h. Recovered
13.1	—	—	—	7	361	—	—	220	35.0	—	—	—	—	Recovered
13.7	—	—	—	9	193	250	Trace	80	29.0	—	Low K	12 h	12.0	Died of respiratory failure during treatment of relapse *
12.3	—	—	—	6	216	—	—	240	30.8	Normal	Low K	—	—	Recovered
10.0	—	—	—	6	—	120	30	20	—	—	—	—	—	Died after 30 min. of treatment *
12.1	—	—	—	7	343	—	—	120	31.0	Ant. is-chemia	—	—	—	Recovered
15.0	—	—	—	5	402	100	00	80	23.8	—	—	—	—	Recovered. Diminished vision at time of discharge
12.1	—	—	—	9	508	—	—	50	22.0	—	—	12 h	16.0	Recovered. Diminished vision at time of discharge
8.0	—	—	—	13	76	160	Trace	240	51.2	—	—	—	—	Recovered
14.0	3.9	145	96	9	—	270	0	80	39.0	Normal	Normal (K = 3.5 mEq)	—	—	Recovered
13.5	—	—	—	16	—	—	—	120	40.0	—	—	—	—	Recovered
7.7	—	—	—	6	—	70	20	160	32.0	—	Low K	—	—	Recovered. Residual blurring of vision

TABLE V. — *Conti*

CASE NO.	AGE, SEX	MCHOH DRUNK (ml)	LATENT PERIOD	VISION*	OTHER SYMPTOMS†	T, P, R, BP	SENSORIUM‡	PUPILS‡	OPHTHALMO-SCOPY‡	pH OF URINE	ALBUMINURIA	GLYCOSURIA	ACETONURIA	Hgb, WBC	CP (mEq)
15	47 M	250	36 h	Sk	H, N, P, V	98.8 52, 24 0/0 170/100	S	D	H	5.5	++	++	++	15.8 9,350	1.0
16	53 F	125	48 h	C	P	97.6 86, 28 (Kuss) 150/90	S	D	H	5.0	0	0	0	14.6 4,350	1.0
17	26 F	15	12 h	Sn	Di, H, P	98.4 108, 30 115/70	S	N	E, H	5.5	+	++	0	12.0 11,900	1.0
18	34 F	50	24 h	B	None	99.0 100, 40 120/80	M	D	E, H	5.5	0	0	0	13.7 10,100	1.0
19	41 M	50	18 h	B	None	98.0 88, 24 (Kuss) 122/88	C	D	H	5.5	+	++	++	13.8 5,000	1.5
20	55 M	125	48 h	N	P	99.0 70, 20 140/90	S	D	N	5.5	0	++	0	11.3 9,000	1.5
21	48 M	500	24 h	B	P	98.2 76, 22 (Kuss) 168/98	S	D	H	5.5	+	++	++	13.5 5,550	1.0
22	63 F	50	24 h	B	Di, H, P	99.0 90, 28 (Kuss) 108/68	C	D	H	5.0	0	+++++	0	13.1 9,850	1.0
23	35 F	250	24 h	C	Di, N, P, V	98.2 84, 20 128/92	N	D	H	5.5	++	0	+	15.3 14,500	1.0
24	20 F	100	24 h	F	N, P, V, W	99.2 70, 40 120/80	D	D	E, H	5.0	Trace	0	0	14.1 6,450	1.0
25	34 M	100	18 h	C	N, P, V, W	99.0 104, 26 130/70	S	D	H	5.0	++++	0	0	13.8 9,250	1.0

* B = blind; C = cloudy; F = "flashes"; N = normal; Sk = "skin over eyes"; Sn = "snowstorm".
 † Di = dizziness; Dy = dyspnea; H = headache; N = nausea; P = abdominal pain; V = vomiting; W = weakness.
 ‡ A = anxious; C = comatose; D = drowsy; M = maniacal; N = normal; R = restless; S = stuporous.
 § D = dilated; N = normal.
 ¶ E = retinal edema; H = hyperemia of discs; N = normal.
 † Patient receiving intravenous glucose.

Continued

CO ₂ sp (mEq)	K (mEq)	Na (mEq)	Cl (mEq)	UREA (mgm/100 ml)	AMYLASE (UNITS)	MeOH (mgm/100 ml)	EtOH (mgm/100 ml)	NaHCO ₃ GIVEN IV (GM)	CO ₂ sp AFTER Rx	EKG BEFORE Rx	EKG AFTER Rx	TIME OF RELEASE	CO ₂ sp AT RELEASE	RESULTS AND REMARKS
0	4.5	143	95	14	511	140	110	120	32.0	—	Normal	—	—	Recovered. Residual blurring of vision
0	—	—	—	11	—	—	—	240	27.0	—	—	—	—	Recovered
0	4.2	141.5	—	9	—	0	340	220	46.0	—	Low K (K = 2.5 mEq)	—	—	Remained comatose. Died on third day
0	—	—	—	5	—	52	80	150	36.0	—	—	—	—	Recovered. Vision limited to finger-counting at time of discharge
5	4.2	142	101	10	—	400	0	180	27.0	—	Low K (K = 2.65 mEq)	24 h	11.0	Died during treatment of relapse. CO ₂ sp 17.7 mEq at death
5	—	—	—	9	362	Trace	13	120	27.0	Normal	Low K	16 h	23.0	Remained comatose. Died on second day with convulsions and temp. of 103°
0	—	—	109	13	—	130	0	140	33.5	—	Low K	24 h	20.0	Remained comatose. Died on fourth day
0	4.75	139	86	12	344	240	70	160	22.7	General isochemia	Low K (K = 2.75 mEq)	—	—	Remained comatose. Died on third day. Temp. 107° at death
0	4.2	142	92	10	262	0	0	300	27.0	—	—	—	—	Recovered
0	4.8	140	102	9	—	80	120	275	39.0	—	—	—	—	Recovered
0	—	—	95	12	—	150	Trace	120	18.0	—	—	—	—	Recovered

eyes should be shielded from light in methyl alcohol poisoning, this was not practiced in our patients. Schanz (96) first suggested that light might be injurious but substantiating data are scanty. Schwarzkopf (97) found no evidence of any injury from light in his experiments in animals but Goldschmidt (14) reported a deleterious effect. Occasional clinical observations such as that of Schieck (93) who described a patient in whom amblyopia developed after exposure to sunlight suggest that the best practice might be to protect the eyes from bright light until the symptoms of acute poisoning have subsided.

Intravenous sodium amytal was satisfactory for the control of convulsions. During the early hours of the outbreak, several patients were given morphine or demerol for severe extremity or abdominal pain; the prompt relief of pain by sodium bicarbonate infusion, however, led to the abandonment of the use of narcotics. As others have stated, the use of morphine should probably be avoided because of its possible respiratory depressant effect and because it may intensify pancreatitis (see below).

Several stimulants including coramine, caffeine, adrenalin and benzedrine were used in moribund or comatose patients. Any effect they may have had was a transient one.

Lastly, the use of glucose in methyl alcohol poisoning deserves a short comment. On the basis of the possible role of ketosis in the acidosis which develops, Keeney and Mellinkoff (35) suggest that glucose may be a useful adjunct to alkalization. The question of ketosis has been discussed in detail already. During the early stages of the outbreak observed by us, in addition to sodium bicarbonate in five per cent glucose, all stuporous or comatose patients were given 50 ml. of 50 per cent glucose intravenously. This procedure was carried out with a definite purpose and was abandoned as soon as blood sugar determinations had shown that hypoglycemia was not present in these patients. Because the exact composition of the mixture ingested by these first victims was not known, the possibility of so-called "smoke poisoning" with resultant hypoglycemia led to the use of glucose (98). Sporadic instances of profound hypoglycemia due to consumption of various alcohol substitutes of unknown composition are not uncommon in the population served by Grady Memorial Hospital.

Relapses. Presumably because of methanol's long persistence in the body, correction of acidosis by alkali may be transient, the patient again becoming acidotic as toxic metabolites reaccumulate. Many of our patients were treated in the Emergency Clinic for a period of several hours and then discharged with instructions to take soda by mouth every four hours for the next two days and to return if symptoms again appeared. As a result of this procedure, there were six instances of relapse in outpatients. Two of these patients were admitted to another hospital when symptoms recurred, were treated with sodium bicarbonate, and recovered. Two were moribund when brought back to Grady Memorial Hospital, one 12 and other 24 hours after discharge. The fifth was admitted with mild acidosis and malaise and eventually recovered. This patient had not taken soda at home. The last patient returned 48 hours after discharge. He was

ambulatory and did not appear particularly ill but collapsed suddenly and died within a few minutes after telling the story that during the 24 hours after discharge he had drunk another half-pint of the whiskey which had poisoned him originally! We do not know whether to classify his case as a relapse or a second attack. In addition, return of acidosis, requiring further alkali treatment occurred in a number of inpatients, some of whom were alkalotic after initial therapy (Table V).

Because of this possibility of recurrence, careful observation over a period of a few days is indicated in all patients with methyl alcohol poisoning.

LABORATORY FINDINGS

Urinalysis was performed on 43 patients when seen initially. As has been mentioned, albuminuria was seen in 21 cases and acetonuria in 10. Fifteen specimens gave a positive test for sugar but nine of these were collected after glucose injection and cannot be considered to represent an effect of methyl alcohol. It should be recalled that formates will reduce copper sulfate, a fact discovered by Pohl (67) in 1893. Urinary pH in acidotic patients was invariably 4.5 to 5.5, rising with treatment. Initial specific gravities were 1.011 to 1.019 and microscopic examination of the sediment showed nothing specific.

Hemoglobin, hematocrit, total and differential leukocyte counts are generally within normal limits (99, 100) and were in our patients. Initial serum potassium, sodium and urea nitrogen levels showed no striking changes. Serum chloride was slightly depressed on several occasions. The alteration in serum potassium and sodium following sodium bicarbonate infusions has been referred to previously. Few blood sugars were done; almost all were within normal limits although in one instance, the value before treatment was 185 mgm. Hyperglycemia has been mentioned in previous descriptions of methanol poisoning (46, 56).

Perhaps the most striking abnormality in laboratory findings, other than lowered plasma bicarbonate, was elevation of serum amylase to levels of over 300 units in 14 of 21 patients tested. This elevation was found to persist for as long as a week when serial determinations were performed in a smaller group of patients, gradually returning to normal in each patient but one whose amylase remained elevated (in the absence of symptoms) until the 42nd day, when he was last seen. None of the patients tested had received any narcotic which might influence serum amylase levels (101, 102). This effect of methyl alcohol upon serum amylase is of great interest in view of the regularity with which pancreatic necrosis was found at autopsy in fatal cases observed in this outbreak (103, 104).

Electrocardiographic tracings were obtained initially in seven patients. Three of these were normal, three showed "anterior ischemia" and one "diffuse ischemia." As mentioned previously, typical changes of hypokalemia with prolongation of Q-T interval and broadened, flat T-waves were recorded in several patients after correction of acidosis with sodium bicarbonate. Røe (46) recorded ECG changes in 13 of 31 patients and Weisberger and McLaughlin (34) found alterations in the tracings of seven of eight patients with methyl alcohol poison-

ing. In neither series were the reported changes, which consisted for the most part of decreased amplitude of T-waves in Leads I and II, striking or in any way pathognomonic. The report of a case of methyl alcohol poisoning by Merritt and Brown (54) in 1941 is of particular interest because electrocardiograms on admission were within normal limits but 24 hours after treatment with intravenous sodium bicarbonate, when additional electrocardiograms were made, abnormalities were noted. The abnormal tracing is illustrated in Merritt and Brown's report and is typical of hypokalemia, with prolongation of the Q-T interval and flattened, broad T-waves. The development of electrical abnormalities 24 hours after acidosis had been corrected did not prevent these authors from attributing the observed changes to the acidosis, especially since the work of Bellet and Dyer in 1937 (105) showed that electrocardiographic changes in patients with diabetic acidosis were more marked 24 hours after treatment than during actual acidosis. The changes noted by Bellet and Dyer were long Q-T interval, lowered T-waves and depression of S-T segments. In light of the known likelihood of the development of hypokalemia in patients treated vigorously for diabetic acidosis (106, 107), there can be little question that the changes observed by Bellet and Dyer and also those in Merritt and Brown's case were due to lowered serum potassium rather than any late effect of acidosis *per se*.

PATHOLOGY

Autopsy findings in fatal cases of methyl alcohol poisoning have been described frequently (30, 32, 33, 35, 90, 108-111). There is nothing pathognomonic about the lesions which have been reported and a review of 17 autopsies (10 in the 1951 outbreak and 7 patients who died in 1946) in our own series is in general agreement with published descriptions. There are variable cerebral edema with meningeal and subarachnoid petechiae, congestion of lungs, epicardial hemorrhages, occasional mild fatty infiltration of the liver, gastritis, and general congestion of the abdominal viscera. Histologic examination of the eyes from fatal cases (86, 110, 112-114) shows degeneration of ganglion cells with sparing of the optic nerve and tract. In animal experiments, degenerative changes in peripheral nerves have been mentioned but this has apparently escaped attention in human cases (115).

The occurrence of pancreatic necrosis in 13 of the 17 cases examined at necropsy in our series is of interest in view of the above-mentioned observations on serum amylase levels. We have been able to find only two other descriptions of pancreatic involvement. Burhans (111) found acute hemorrhagic pancreatitis in all of 11 cases and Keeney and Mellinkoff (35) noted small hemorrhages in the pancreas of one of six fatal cases. Histologic study of our cases indicates that most of the damage in the pancreas is secondary to vascular injury and hemorrhage (104). Røe (46) mentions the frequent occurrence of intestinal contractions, particularly in the large gut, at autopsy (108, 109) and Burhans also noted this (111). Although Røe was inclined to attribute the severe abdominal pain of methanol intoxication to these contractions, it seems more likely to us that both pain and abdominal muscle spasm may be secondary to pancreatitis.

Lastly, in his description of fatal cases, Burhans (111) states that patients died at the end of inspiration and that the lungs were full of air. We have no record of any such findings in our necropsy material, but this agrees entirely with our own clinical observations on the characteristic apnea with "freezing" of the chest in a position of deep inspiration which was seen terminally in patients dying from methanol poisoning.

SUMMARY OF CLINICAL COURSE OF POISONING

Table V presents the symptoms, signs, laboratory findings and results of therapy in 25 patients admitted to the hospital for treatment of severe methyl alcohol poisoning in this outbreak.

DISCUSSION WITH SPECIAL REFERENCE TO THE MECHANISM OF POISONING BY METHANOL

The admittedly incomplete data available from the present study and from the investigations of others furnish no more than hints of the true mechanism of methyl alcohol poisoning. However, some speculation seems justified.

Any hypothesis concerning methyl alcohol must explain certain observed phenomena. The absence of great dyspnea in many patients with profound reduction in plasma CO_2 combining power has been mentioned. Furthermore, the presence in terminally ill patients of zero plasma bicarbonate emphasizes the severity of the metabolic derangement which can occur. Examination of Table V reveals that in every instance where adequate chemical determinations are available, the difference between serum sodium and the sum of the CO_2 combining power and serum Cl shows an accumulation of undetermined acids (Cases 1, 2, 12, 15, 19, 22, 23 and 24 giving values of 42, 34, 35, 37, 33, 45, 42 and 32 mEq. of acids respectively). It should be recalled that Van Slyke (68), Harrop (42), and Røe (46) found marked accumulation of lactate in patients who had ingested wood alcohol and that in our patients (Table II), blood ketone levels were entirely inadequate to account for this tremendous increase in undetermined acids. Lastly, depression of CO_2 combining power alone cannot be interpreted as indicating a true acidosis; in respiratory alkalosis, plasma bicarbonate may be reduced despite elevation of blood pH. It should be remembered, however, that urinary pH in most of the severely poisoned patients was 4.5 to 5.0. We were unable to obtain reliable determinations of blood pH in our own patients and have found no reports of such determinations in the literature.

One possibility which suggests itself is that methanol or its derivatives depresses the endogenous production of CO_2 through interference with oxidative enzyme systems, particularly those controlling aerobic glycolysis. Experimental evidence bearing on this point is scanty but highly suggestive. Leaf and Zatman (23) report inhibition of both aerobic and anaerobic glycolysis in surviving ox retina by formate. Bernheim (116) found marked reduction of succinic acid dehydrogenase activity in both kidney and liver in the presence of formaldehyde, a substance which Keeser (71) has successfully demonstrated in patients with methyl alcohol poisoning. Although other enzymes of the Krebs cycle have not

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been studied, it seems probable that formaldehyde or formate might also exert an untoward effect upon several besides succinate oxidase, thus bringing the cycle of aerobic glycolysis and consequently CO₂ production to a standstill. The accumulation of lactic acid in methyl alcohol poisoning would seem to indicate that anaerobic carbohydrate breakdown continues, despite Leaf and Zatman's results with ox retina. In a simple experiment utilizing heparinized human blood shaken at room temperature, we have found only slight interference by a concentration of 6.2 millimoles of formaldehyde with anaerobic glycolysis in erythrocytes. This is the concentration of formaldehyde used by Bernheim in experiments with succinic acid dehydrogenase (116).

Serial determinations of blood pH, and the measurement of respiratory CO₂ output, data now totally lacking, are clinical observations which would be extremely helpful in substantiating this hypothesis of depression of CO₂ production.

On the basis of the now available data, it is suggested that due to interference with controlling enzyme systems including succinic acid dehydrogenase, aerobic glycolysis and hence CO₂ production is depressed or indeed, in severe cases, ceases altogether. This could account for *zero* plasma bicarbonate and the failure of respirations to reflect the results of plasma CO₂ capacity determinations. The accumulation of products of incomplete oxidation as well as lactate could account for the high levels of undetermined acids. Furthermore, the peculiar respiratory cessation which characterized death in acutely poisoned cases might well be the result of simple CO₂ deficiency and consequent lack of stimulation of the respiratory centers. Lastly, in terms of therapy, if methanol poisoning is actually a CO₂ deficit, the use of sodium bicarbonate may represent specific replacement rather than non-specific alkalization and therefore might be indicated rather than other alkaline materials such as sodium lactate. A review of reported cases treated with lactate as well as our own offers no evidence for a difference in effect, however.

In conclusion, it is the opinion of the present authors that serial determinations of blood pH, respiratory CO₂ output, and identification of the accumulated acids are the most important unknowns which should be answered when opportunity again makes available patients with methyl alcohol poisoning. Also to be emphasized is the need for further study of the effect of methanol and its derivatives upon enzyme systems controlling carbohydrate metabolism and CO₂ production.

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