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Methanol poisoning

J. A. Kruse

Division of Critical Care Medicine, Wayne State University School of Medicine, Medical Intensive Care Unit, Detroit Receiving Hospital, Detroit, Michigan, USA

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Abstract. Methanol ingestion is an uncommon form of poisoning that can cause severe metabolic disturbances, blindness, permanent neurologic dysfunction and death. While methanol itself may be harmless, it is converted in vivo to the highly toxic formic acid. The diagnosis is sometimes elusive and requires a high index of suspicion. Because antidotal treatment is available it is important to recognize methanol poisoning promptly. The presence of metabolic acidosis associated with an increased anion gap and increased osmol gap are important laboratory findings. Specific therapeutic measures include correction of the metabolic acidosis with sodium bicarbonate and administration of enteral or parenteral ethanol to competitively inhibit the metabolic breakdown of methanol to formic acid. Hemodialysis accelerates the elimination of both methanol and formic acid and also assists in correction of the metabolic acidosis. Experimental data suggests that administration of folic acid may be of benefit by hastening the metabolism of formic acid to carbon dioxide. Prompt institution of specific therapy can probably decrease the morbidity and mortality associated with this form of poisoning.

Key words: Acidosis – Alcohol, methyl – Formic acids – Osmolar concentration – Poisoning – Poisons

Methanol is a clear, colorless, volatile liquid with a weak odor slightly sweeter than ethanol. It is used in the industrial production of many synthetic organic compounds and is a constituent of a large number of commercially available solvents. Methanol-containing products that may be found in the home include automotive windshield washer fluids and de-icers, "canned heat" (Sterno®) used to warm foods, paints, shellacs, varnishes, wood stains, paint thinners and removers, dry gas, gasohol, and various other solvents and cleaners. It is also added to ethanol specifically to render it unsuitable for consumption. Such products are called *denatured* alcohol.

Toxicology

The lethal dose for humans is not known for certain, but evidence suggests that it can vary over a wide range. The minimum lethal dose is often cited as about 100 ml, but Bennett and associates [1] reported a fatal poisoning following ingestion of only 15 ml of 40% methanol and Ziegler [2] reported a fatal case involving one ounce. On the other hand, ingestions of more than 500 ml have reportedly occurred without causing death or blindness [3]. Ocular morbidity caused by methanol poisoning is well known. Cases of blindness have been reported following consumption of as little as 4 ml [4].

Poisoning with methanol may be the result of either accidental or intentional ingestion. Desperate alcoholics have intentionally substituted methanol-containing substances for ethanol, even knowing that it may have harmful effects. In addition to sporadic cases several large epidemics have been reported [5–8]. One of the largest of these occurred over a five day period in Atlanta following the city-wide distribution of approximately 90 gallons of illicit whiskey [1]. Assays on confiscated samples revealed that the mixture contained 35%–40% methanol. A total of 323 cases, including 41 deaths, were identified in that outbreak.

Metabolism

Methanol itself is essentially nontoxic [4, 9]; it may cause inebriation but does not appear to have cytotoxic properties [10, 11]. It is metabolized by dehydrogenation to formaldehyde and then to formic acid (Fig. 1). These two metabolites are highly reactive, readily bind to tissue proteins, and are known to interfere with oxidative metabolism through inhibition of the cytochrome oxidase system [12, 13]. While most of the toxicity was previously attributed to formaldehyde, it appears that formic acid is more likely responsible for these effects. The ocular manifestations of methanol intoxication can be reproduced in animal models by administering formate alone [14]. Serum

formate concentrations have been shown to correlate better with clinical findings compared to methanol levels [15].

The severe acidosis frequently observed in human cases of methanol poisoning can not be induced in rodents. Methanol can, however, induce severe metabolic acidosis, coma, and death in pigtail and rhesus monkeys [16–19]. Both primates and rodents metabolize methanol to formic acid; however, rodents are capable of rapidly converting formate into carbon dioxide. Formate therefore does not accumulate in rodents and they are spared both the acidosis and other toxic manifestations observed in primates. The metabolism of formate is an enzyme-mediated process that requires the presence of folate as a cofactor (Fig. 1). Although methanol does not cause acidosis in normal rats, it can induce formic acidosis in folate-deficient rats [11, 20]. While primates are capable of this same folate-dependent metabolism of formic acid, the rate of this pathway is much slower compared to that in rodents.

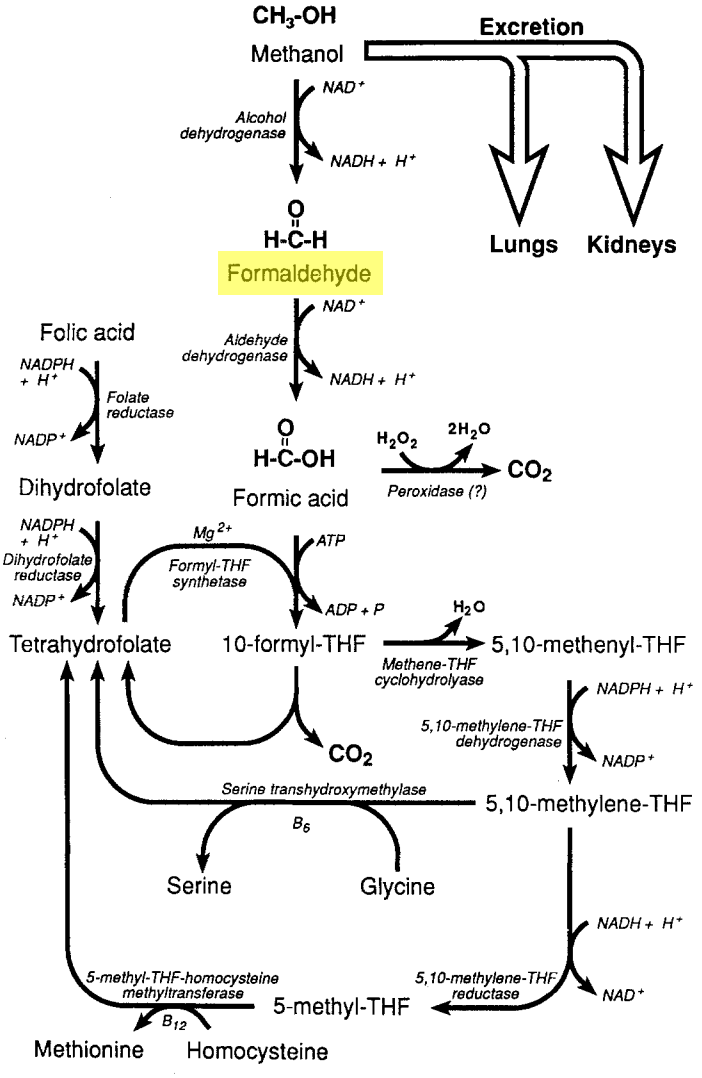

Fig. 1. Metabolic pathways involved in methanol metabolism and relationship with folate metabolism. *THF* = tetrahydrofolate

Clinical manifestations

Following ingestion, there is typically a lag period of about 12–24 h before toxic manifestations occur [3, 9–11, 15–19]. This interval can be quite variable, however, and ranges from less than one hour to over 72 h [1]. Lack of symptoms should therefore not be interpreted as indicating insignificant intoxication, particularly if the patient presents promptly following ingestion. The lag period is due to the slow conversion of methanol to formaldehyde.

Visual disturbances are common and range from dimming or blurring of vision, scintillations, photophobia, visual field defects, or "seeing a snowstorm", to a total loss of light perception [1, 7, 8, 21]. In one large epidemic all patients with at least mild acidosis and over half of those patients without acidosis had some type of visual symptoms [1]. On fundoscopic examination an enlarged blind spot, hyperemia of the optic disc or frank papilledema may be observed [1, 7, 21]. Abnormal pupillary light reflexes have been described and range from a diminished reaction to fixed and dilated pupils [1]. Interference with neural axoplasmatic transport by formaldehyde and/or formate probably accounts for the ocular manifestations [11, 12].

Nausea, vomiting, and abdominal discomfort are common but are not universally seen. Epigastric pain may be severe and accompanied by abdominal rigidity. Like ethanol, methanol is a direct gastric irritant and can cause hemorrhagic gastritis. Pancreatitis has also been implicated as a cause of the abdominal pain, since high levels of serum amylase activity have been detected in many cases and pancreatitis has been confirmed in autopsy studies [1, 5]. In cases with significant acidosis, Kussmaul respirations may be observed. Headache, dizziness, malaise, agitation, generalized weakness, paresthesias and sensorial depression may also occur [1, 10]. Severe degrees of poisoning are associated with cerebral edema, coma, and /or seizures. The characteristic finding of bilateral cerebral infarction selectively involving the putamen and adjacent areas may be demonstrated by computed tomography or at postmortem examination [10].

Laboratory findings

The severity of the metabolic acidosis is variable and may not correlate well with the amount of methanol ingested, but it can be extremely severe [1, 8, 11, 12]. The decrease in plasma bicarbonate closely parallels the increase in plasma formate concentration in both animal models as well as in human methanol poisoning, indicating that most or all of the acidosis is accounted for by formic acid production [11, 15, 18]. A concomitant element of lactic acidosis is present in some cases. This may be due to the increased redox state of body tissues (i.e., increased ratio of NADH to NAD^+) secondary to the oxidation of methanol and formaldehyde (Fig. 1). The increased redox state forces conversion of pyruvate to lactate. In addition, formic acid can interfere with intracellular respiration

[13], thereby promoting anaerobic metabolism and lactate formation. However, in many cases frank circulatory shock and/or seizures are likely the predominant causes of increased lactate production [16].

In their simplest form, serum electrolyte profiles performed by clinical chemistry laboratories include sodium, chloride, and carbon dioxide content determinations. The unmeasured serum anion concentration, or anion gap, can be defined as:

$$\text{Anion gap} = [\text{sodium}] - [\text{chloride}] - [CO_2 \text{ content}]$$

with the traditional normal range varying from 8 to 16 mmol/l. Metabolic acidoses associated with an increased anion gap include lactic acidosis, ketoacidosis, the acidosis associated with renal failure, and several types of poisoning including salicylate, methanol, ethylene glycol, toluene and paraldehyde. In the case of methanol intoxication, the increase in the unmeasured anion fraction, as well as the acidosis, is predominantly due to accumulation of formate and, less consistently and to a smaller degree, to lactate [11, 12, 15, 18]. Due to its simplicity and availability, the anion gap is an important diagnostic indicator of possible methanol intoxication.

Another important laboratory indicator of methanol poisoning is derived from comparison of measured and estimated serum osmolality. Serum osmolality may be estimated by [22]:

$$\text{Estimated osmolality} = 2 \times \text{sodium} + \text{BUN}/2.8 + \text{glucose}/18$$

The osmol gap is the difference between measured and calculated osmolality:

$$\text{Osmol gap} = \text{measured osmolality} - \text{estimated osmolality}$$

The normal osmol gap is approximately 10 mosm/kg water. This difference accounts for other normally occurring osmotically active constituents of serum. Any exogenous solute present in serum will raise the osmol gap. The osmotic effect of an ingested toxin is related to its molecular weight and the molar concentration of the toxin in serum. Since most drugs and toxins are either of high molecular weight or exert their toxicity at relatively low molar concentrations, they do not measurably affect the osmol gap. Methanol, on the other hand, has a low molecular weight and clinical intoxication is frequently associated with relatively high molar concentrations of the alcohol, such that the osmol gap may be appreciably increased. However, the most commonly encountered cause of an increased osmol gap is ethanol intoxication [23]. Thus, serum ethanol concentration should be routinely assessed when evaluating the osmol gap. If ethanol is present in the blood, the gap may be significantly increased and it is then necessary to determine the quantitative contribution of ethanol to the osmol gap. This can be accomplished by including a term for ethanol in the formula for calculating osmolality:

$$\text{Estimated osmolality} = 2 \times \text{sodium} + \text{BUN}/2.8 + \text{glucose}/18 + \text{ethanol}/4.6$$

Using this formula to estimate serum osmolality, the clinician can determine whether a patient's serum ethanol level fully accounts for the osmol gap, or whether there is an otherwise unexplained increase in the gap due to methanol or some other substance. A few other ingested toxins, such as ethylene glycol and isopropanol, can similarly lead to significant increases in the osmol gap.

Diagnosis

In cases where the patient supplies an accurate history of the ingestion, the diagnosis is usually straightforward. However, in situations where the patient is unable or unwilling to supply such information, the diagnosis may prove elusive. Knowledge of the characteristic clinical and laboratory findings (Table 1) and a high index of suspician are crucial in these cases.

Symptoms and physical signs are for the most part non-specific. Although methanol has a characteristic odor, it is not strong and may or may not be noted on the patient's breath. The odor of formalin has reportedly been detectable on the breath or urine of methanol-poisoned patients [24]. Abdominal pain is not infrequent but is also non-specific. Ocular findings are the most specific physical findings and are therefore most important diagnostically. Even more helpful are laboratory tests indicating the presence of metabolic acidosis associated with a high anion gap and high osmol gap. In the appropriate setting, these laboratory findings by themselves are of sufficient specificity to justify a presumptive diagnosis and institution of treatment.

Methanol is frequently included as part of major toxicology screening batteries employed by clinical chemistry laboratories, often utilizing gas-liquid chromatography. However, it would be imprudent to await quantitative toxicologic assay results before making a presumptive diagnosis and initiating therapy, since it is likely that instituting specific treatment early in the course will lessen the morbidity and mortality [10]. An exception to this recommendation would be the situation where the clinician is certain that the institution's toxicology laboratory can routinely return such results within a matter of minutes. In cases where this is not possible, the clinician must make a presumptive diagnosis based on the presenting history, physical findings, and routine laboratory tests.

Table 1. Characteristic clinical and laboratory findings in methanol intoxication

- Physical findings
  - Kussmaul respirations
  - Faint odor of methanol on breath
  - Visual disturbances
  - Nausea, vomiting, abdominal pain
  - Altered sensorium
- Laboratory findings
  - Elevated anion gap
  - Metabolic acidosis
  - Elevated osmol gap
  - Positive serum methanol assay

The constellation of ocular signs or symptoms, metabolic acidosis, and elevated anion and osmol gaps is indicative of methanol poisoning until proven otherwise.

Treatment

As with the initial management of all poisoned patients, general measures should be carried out to assure a patent airway, adequate ventilation, and adequate systemic perfusion. Gastric lavage is conventionally advocated to remove any residual poison, but is useful only soon after ingestion since methanol is rapidly absorbed from the gastrointestinal tract [8, 16]. The use of syrup of ipecac to induce emesis is contraindicated if the patient has an abnormal level of consciousness, since vomiting may result in aspiration of gastric contents. Its use may be hazardous as well in patients that present early with a near-normal sensorium but who may subsequently progress to obtundation after ipecac is administered. Activated charcoal has also been recommended by some, although others have pointed out that its efficacy has not been substantiated [25]. Studies in normal volunteers indicate that enteral absorption of ethanol does not appear to be influenced by activated charcoal [26, 27], suggesting that methanol absorption might be similarly unaffected.

Intravenously administered sodium bicarbonate should be given to methanol-poisoned patients with significant metabolic acidosis [5, 28, 29]. Reports suggest that such therapy can potentially ameliorate ocular manifestations, improve the sensorium, and perhaps reduce mortality.

The mainstay of treatment for methanol intoxication is administration of ethanol [30, 31]. The enzymes responsible for converting methanol to formaldehyde and formic acid are also involved in the metabolism of ethanol to acetaldehyde and acetate. The two alcohols therefore act as competitive substrates. However, the rate of metabolism of methanol by these enzymes is only a fraction of that of ethanol [25, 32–34]. Thus, conversion of methanol into its toxic byproducts is slowed in the presence of ethanol. Typical criteria for initiating ethanol treatment include all patients with peak serum methanol concentrations greater than 20 mg/dl and all patients with acidosis ascribed to methanol intoxication, regardless of whether or not symptoms are present [25]. Because methanol assay results may not be immediately available, it is important to initiate ethanol therapy in patients with a clear history of methanol ingestion and in patients strongly suspected of methanol poisoning.

The clinical goal of ethanol therapy is to achieve a therapeutic serum ethanol level of between 100 and approximately 150 mg/dl [16, 25, 31, 35, 36]. This concentration is necessary to saturate alcohol dehydrogenase [36, 37]. Some reviewers have recommended up to 200 mg/dl as the upper therapeutic limit [4, 24, 35, 36]. To rapidly accomplish this goal it is necessary to administer a loading dose. Recommendations for calculating loading doses are shown in Table 2 [25, 31, 35, 36]. The patient's serum ethanol level should be assessed prior to administering the loading dose. For patients with baseline ethanol levels in excess of 100 mg/dl the loading dose will be unnecessary, while those with lesser degrees of preexisting ethanol intoxication will require appropriate modification of their loading dose. When using the oral route, ethanol should be diluted to a final concentration of less than 40% and preferably less than 20% ethanol, since patients unaccustomed to drinking hard liquor frequently will not tolerate stronger solutions and vomiting is common. Relatively large fluid volumes are required for intravenous loading; eg, over a liter of 5% ethanol in water is necessary to load a 70 kg individual. The advantages and disadvantages of enteral versus parenteral ethanol dosing are summarized in Table 3. Following the loading dose, a maintenance regimen of ethanol can be accomplished using a 10% sterile solution of ethanol in water given by continuous intravenous infusion, or using hourly doses of commercial liquor given orally or by nasogastric tube (see Table 2) [31, 35, 36]. A higher maintenance infusion rate is required in chronic drinkers due to their higher rate of ethanol metabolism [31, 35–37]. It should be stressed that serial serum ethanol levels are necessary to insure that the target therapeutic level of 100 to 150 mg/dl is reached and maintained. This is often difficult to achieve, even when hourly levels are obtained, and it is particularly difficult in chronic alcoholics and during the initiation of hemodialysis [15, 25, 38, 39].

Forced diuresis has little effect on methanol elimination [3, 25, 31, 40]. Dialysis, on the other hand, effectively removes methanol and formate from the circulation [11, 30, 41–43]. In one report the half-life of methanol was reduced from 8 h to 2.5 h following institution of dialysis [31]. Hemodialysis is preferred to peritoneal dialysis because it offers more rapid clearance [8, 30, 44]. Hemoperfusion should not be used since hemoperfusion columns may quickly become saturated with methanol

Table 2. Standard therapeutic ethanol dosing to achieve serum ethanol concentration of 100 mg/dl. Assumes typical volume of distribution and elimination kinetics; actual dosing should be titrated using frequent serum ethanol assays. (Based on data of H.G. McCoy [31])

	Nondrinker	Chronic drinker
Loading dose		
Amount of absolute ethanol[a]	600 mg/kg	600 mg/kg
Volume of 43% oral solution[b]	1.8 ml/kg	1.8 ml/kg
Volume of 90% oral solution[c]	0.86 ml/kg	0.86 ml/kg
Volume of 10% parenteral solution[d]	7.6 ml/kg	7.6 ml/kg
Maintenance dose (not on dialysis)		
Amount of absolute ethanol[a]	66 mg/kg/h	154 mg/kg/h
Volume of 43% oral solution[b]	0.20 ml/kg/h	0.46 ml/kg/h
Volume of 90% oral solution[c]	0.10 ml/kg/h	0.21 ml/kg/h
Volume of 10% parenteral solution[d]	0.83 ml/kg/h	1.96 ml/kg/h
Maintenance dose during dialysis		
Amount of absolute ethanol[a]	169 mg/kg/h	257 mg/kg/h
Volume of 43% oral solution[b]	0.50 ml/kg/h	0.77 ml/kg/h
Volume of 90% oral solution[c]	0.24 ml/kg/h	0.37 ml/kg/h
Volume of 10% parenteral solution[d]	2.13 ml/kg/h	3.26 ml/kg/h

[a] Specific gravity = 0.79
[b] Ethanol content = 34 g/dl (equivalent to 86 proof undiluted liquor)
[c] Ethanol content = 7.1 g/dl
[d] Ethanol content = 7.9 g/dl

Table 3. Advantages and disadvantages of enteral versus parenteral ethanol

	Ethanol treatment	
	Enteral administration	Parenteral administration
Advantages	Simplified preparation and administration of loading dose by mouth or by nasogastric tube Can use relatively concentrated ethanol solutions, thus minimizing the risk of fluid overload	No risk of gastric irritation or aspiration Simple titration of maintenance infusions by adjusting infusion rate Can be used in patients who are vomiting or have gastric bleeding
Disadvantages	Risk of gastritis and emesis; risk of aspiration, especially since sensorium is likely to be depressed Hourly maintenance doses require increased nursing time, possibly increasing risk of missed doses	Central venous catheter required due to hyperosmolality of solution (10% ethanol in 5% dextrose is approximately 2000 mosm/kg water Potential for fluid overload in susceptible patients, especially when using 5% ethanol solutions

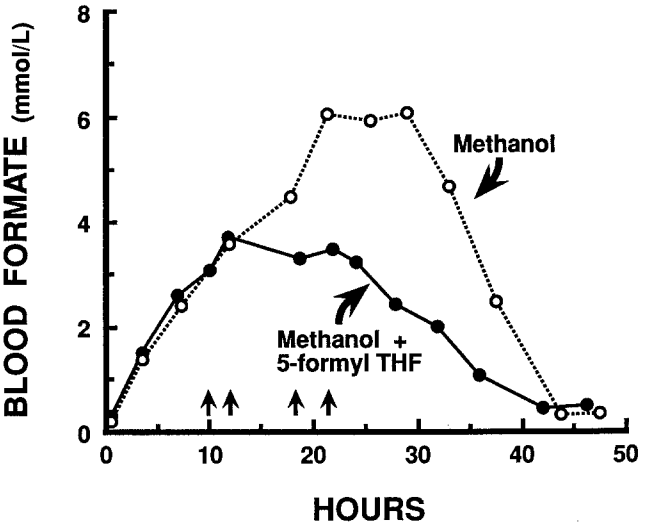

Fig. 2. Blood formate concentrations in two monkeys poisoned with methanol at time zero. One monkey was subsequently treated with 5-formyl-tetrahydrofolate (*5-formyl-THF*; doses indicated by vertical arrows) demonstrating favorable effect on blood formate concentration compared to control animal. (Redrawn from Noker PE et al [17], with permission)

and rendered ineffective [4, 45]. In addition, hemoperfusion can not facilitate correction of the metabolic acidosis or fluid and electrolyte disturbances that are frequently present. Criteria for employing dialysis have varied [15, 16, 46]. In general, dialysis should be employed in all cases developing ocular manifestations and in all cases with renal impairment, regardless of symptoms. A peak methanol level of greater than 50 mg/dl has frequently been cited as an indication for dialysis [4, 15, 25, 30, 31, 42, 43, 47, 48]. However, lower levels may be misleading if the intoxication has advanced to the point where most of the methanol has been metabolized but toxic metabolites are still present. The presence of metabolic acidosis and a high anion gap in the face of a low methanol levels suggests this situation [10]. Since dialysis removes ethanol as well as methanol, patients undergoing dialysis will also require higher maintenance doses (Table 2) [30, 31, 35, 36, 42, 43].

The previously described relationship between formic acid metabolism and folic acid-dependent enzyme systems suggests that folic acid may play a role as a therapeutic adjunct in methanol poisoning. In primate models folate-deficiency increases the sensitivity to methanol poisoning [49] and folate administration increases the rate of formate metabolism during methanol intoxication [17, 19]. Folate has also been shown to reverse methanol toxicity even when the vitamin is administered 10 h after methanol dosing (Fig. 2) [17]. While its therapeutic efficacy in humans has not been examined, the animal data is convincing and administration of the vitamin is probably innocuous. Folic or folinic acid should therefore be administered to all patients with known or suspected methanol intoxication. Extrapolating from experimental data, large and repeated doses are probably necessary. Intravenous doses of 50 to 100 mg of folate every 4 h have been recommended [4, 15, 16, 25].

Pyrazole has long been known to be a potent competitive inhibitor of alcohol dehydrogenase [50, 51]. Its use as a potential therapeutic agent for treatment of methanol poisoning has been tempered by its toxic effects on the liver and other tissues. 4-Methyl pyrazole, on the other hand, is an even more specific inhibitor of alcohol dehydrogenase and appears to be much less toxic [38, 50–54]. The compound has been shown to dramatically inhibit production of formic acid from methanol in experimental models. Monkeys given usually lethal doses of methanol survived when rescued with 4-methyl pyrazole, even when the drug was administered after the methanol [52]. The drug is not currently available for clinical use in the U.S., but has been used investigationally.

Prognosis

Information from one large epidemic demonstrated that the severity of the acidosis correlates with outcome. In this group there was a 19% mortality rate among the 115 patients that had serum carbon dioxide contents below 20 mmol/l, compared to a 50% mortality rate for patients with carbon dioxide contents less than 10 mmol/l [1]. In a review of 725 cases by McNally, there were 335 survivors, of which 90 suffered total blindness and 85 had some degree of visual disturbance during the acute intoxication [35]. However, recovery from visual impairment is common among survivors. In the epidemic reported by Chew and associates, there were 26 survivors, all of whom were acidotic to some degree and 15 of whom had visual impairment during the acute phase, but only two suffered permanent visual loss [29]. Other persistent neurologic deficits include tremor, spasticity, and a syndrome similar

to Parkinsonism [56–58]. Prior or concomitant ethanol ingestion may mitigate the degree of toxicity for a given dose of methanol. Underlying folate deficiency may also be important. These factors, in addition to the ingested dose of methanol, may partially explain the wide variation that has been reported for the minimum toxic dose in humans.

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J. A. Kruse, MD
Detroit Receiving Hospital
Room 55-10
4201 St. Antoine Boulevard
Detroit, Michigan 48201
USA