III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Methyl alcohol, CH3OH, also called methanol, is the first member of a homologous series of monohydric aliphatic alcohols. At room temperature, methyl alcohol is a colorless, neutral liquid possessing a mild distinctive odor. [1] Additional chemical and physical properties of methyl alcohol are presented in Table XIII-1. [2,4]

The greater part of methyl alcohol manufactured in the US is produced synthetically. [5] One widely used synthetic process is the "medium pressure process" which involves the reduction of carbon monoxide (containing small amounts of carbon dioxide) with hydrogen. The reduction step is carried out at 250-400 C and at 100-600 atmospheres pressure using a catalyst. [1]

During the years 1968-73, synthetic methyl alcohol production in the US increased at an average annual rate of over 13.2%. In 1973, the production of synthetic methyl alcohol amounted to slightly over seven billion pounds, around one billion gallons. In addition, an estimated 10 million pounds (1.5 million gallons) of "natural" (eg, from wood distillation) methyl alcohol were produced. [5]

Methyl alcohol is used in a variety of industrial processes. The major use is in the production of formaldehyde which amounted to 39% of the methyl alcohol consumed in the US in 1973. [5] Other commercial uses of methyl alcohol are in the production of chemical derivatives, such as dimethyl terephthalate, methyl halides, methyl methacrylate, acetic acid, and methylamines, and because of its solvent properties, methyl alcohol is

also used in paints, varnishes, cements, and other formulations such as inks and dyes. [1,5] Table XIII-2 lists the consumption of methyl alcohol by product and quantity produced in the US for the year 1973. [5]

A number of occupations with potential exposure to methyl alcohol are listed in Table XIII-3. [6]

NIOSH estimates that approximately 175,000 workers in the US are potentially exposed to methyl alcohol.

Historical Reports

Taylor [7] first identified methyl alcohol in 1812 when he isolated it from the pyroligneous acid which resulted from the destructive distillation of wood. Because of its reaction with sulfuric acid, he incorrectly classified it as an ether and named it "pyroligneous aether." Dumas and Peligot [8] isolated methyl alcohol (wood alcohol) in a similar fashion and correctly identified it as an alcohol. In addition, they studied some of the chemical and physical properties of wood alcohol.

In 1855, MacFarlan [9] reported on the industrial utility of "methylated spirit" as a substitute for the higher priced, strictly regulated "spirit of wine" (ethyl alcohol). Methylated spirit was a mixture of "wood naphtha" (methyl alcohol) and "spirit of wine" (ethyl alcohol) usually in a proportion of 1 to 9, respectively. MacFarlan also noted the toxic hazard associated with the industrial use of pure methyl alcohol, "as opposed to methylated spirit," indicating that the former affected the eyes of workers while the vapor of the latter rarely did. This constitutes one of the earliest references to the occupational hazard

of methyl alcohol found in the literature.

Wood in 1906 [10] stated that since the wood alcohol in commercial use prior to 1896 was a vile-smelling, "nauseous-tasting" liquid, there was little possibility of its being voluntarily ingested and he reported that cases of methyl alcohol poisoning by ingestion were rare prior to the turn of the century. Around 1896, commercial preparations in which the wood alcohol was deodorized and purified began to appear on the market. [10] Along with this development and an increase in production and use, there was also a dramatic increase in the number of reported cases of serious systemic poisoning resulting from the ingestion, inhalation, or percutaneous absorption of methyl alcohol. By 1904, Wood and Buller [11] were able to compile a collection of case histories of methyl alcohol poisoning. This collection included 54 previously published cases of blindness or blindness followed by death attributed to the drinking or the inhalation of the vapors of liquids containing methyl alcohol; 90 previously unpublished cases of blindness or blindness followed by death resulting from the drinking of methylated liquids; 9 previously unpublished cases of blindness from methyl alcohol absorbed through the lungs or the skin, or both; and 82 previously unpublished case reports of fatal methyl alcohol poisonings with no associated blindness.

From a report by Baskerville, [12] it is apparent that by 1913 a dramatic increase in the industrial use of methyl alcohol was accompanied by an increased number of poisonings. The production of crude wood alcohol in the US increased from about one million gallons in 1890 to eight and one half million gallons in 1910, and the number of reported methyl alcohol poisoning cases in the US increased from almost none in 1890 to the point

where, in 1913, Baskerville was able to collect several hundred such case reports from various medical periodicals. Baskerville felt that these cases represented a small percentage of the total number because many physicians did not report cases in the scientific press and many others failed to recognize the industrial and occupational diseases of chronic methyl alcohol poisoning. [12] For an extensive summary of numerous poisoning cases from drinking wood alcohol or inhaling its vapor, the reader is referred to the Baskerville review. [12]

One of the earliest case reports of methyl alcohol poisoning in an occupational setting was by De Schweinitz [13] in 1901. He described the case of a 39-year-old man who suddenly became totally blind after a brief illness. The patient had been employed intermittently (3-4 days at a time) for 3 years as a painter and varnisher. The varnish was dissolved in methyl alcohol, and the patient stated that he generally used methyl alcohol to clean the varnish off his hands and arms, and sometimes off his face. He denied drinking the alcohol. During these 3 years, he had several times become dizzy when varnishing the insides of small articles of furniture or closets on hot days. For 2 months prior to the onset of blindness, he had worked every day as a varnisher in a shop. This was the longest period of uninterrupted exposure to the varnish during the 3-year period. He frequently noted attacks of what he called "misty vision," which disappeared 10-15 minutes after he left work. The day prior to his loss of sight, the patient was unable to work because of chills, numbness, and shooting pains in his lower extremities, and he returned home and went to bed. When he awoke the following morning, he was totally blind. Although treated by a physician, the blindness persisted for 2 weeks

whereupon the patient reported to the hospital. Upon admission, his pupils were dilated and almost unresponsive to light. Ophthalmoscopic examination revealed clear media, but pallid discs. The veins were filled with dark blood and reduced in size. Upon treatment with pilocarpine and induction of daily vigorous sweats, the patient recovered some light sensitivity and, by the end of 2 weeks, he could distinguish objects sufficiently to walk unaided. One week later, however, his vision began to fail; when seen again approximately 3 months later, he was totally blind. The author made no attempt to estimate the quantity of methyl alcohol to which the patient had been exposed.

De Schweinitz [13] advanced the opinion that exposure to methyl alcohol (notably by percutaneous absorption and inhalation) may result in slow poisoning as a result of its gradual accumulation in the body. In turn, when a threshold level was reached a sudden and complete blindness would occur similar to that observed in individuals who ingest great quantities of methyl alcohol. This case report indicated that blindness can occur as a result of inhalation or percutaneous absorption of methyl alcohol.

In 1917, the New York State Department of Labor [14] published a special bulletin entitled Dangers in the Manufacture and Industrial Uses of Wood Alcohol. This report enumerated cases of poisoning resulting from occupational exposure to methyl alcohol in various industries. It proposed rules designed to limit future exposures.

Perhaps as a result of increased awareness of the dangers of methyl alcohol coupled with better work practices, relatively few cases of serious poisoning (such as blindness and death) resulting from inhalation or

percutaneous absorption of methyl alcohol in an industrial setting have been found in the literature since 1920. This is in contrast to the many cases of serious poisonings resulting from the ingestion of this substance which have been continued to be reported. Some of the case reports of methyl alcohol intoxication resulting from occupational exposure between 1900 and 1921 are discussed in the Section Effects on Humans because of their current relevance. [15-19] Although these reports may well be historical in nature, the effects of methyl alcohol poisoning observed in these studies are discussed below since they clearly depict the clinical symptoms encountered with occupational exposure to methyl alcohol.

Effects on Humans

In 1958, Scherberger et al [20] described the development of a dynamic apparatus (air blender) for preparing air-vapor mixtures of known concentrations for various compounds. The concentration range of methyl alcohol vapor prepared by this apparatus was 12-1,870 ppm. Using this apparatus, the authors determined the average minimum identifiable odor level for methyl alcohol. Although exact experimental details were not presented, a photograph in the article indicated that the subjects sniffed an airstream within a few centimeters of its emission source. Using 3 subjects, the authors found that the average minimum identifiable odor level for methyl alcohol was 1,500 ppm (approximately 2,000 mg/cu m). The authors suggested these concentrations were only a rough estimate for this method, since the same subjects tested on different days showed a varying capacity for odor detection.

In 1966, May [21] determined the odor thresholds of 37 organic

solvents. Samples were prepared by evaporating a known amount of a given solvent in stoppered glass bottles. The resulting vapor concentrations were verified by gas chromatographic analysis. The subjects inhaled the air mixture directly from the bottles by taking 3 short sniffs followed by a deep respiration. The subjects first breathed samples of decreasing concentrations until no more odor could be perceived. Secondly, they breathed increasing concentrations until the odor was just barely perceptible. They then breathed increasing concentrations until they judged the odor to be distinctly perceptible. The odor thresholds reported represented the average response of 16 people, including the author and his technician, ranging in age from 30 to 63 years and equally divided as to the sexes. The average odor threshold (minimum perceptible odor) for methyl alcohol vapor was reported to be 5,900 ppm (7,800 mg/cu m), whereas the average distinct odor concentration was 8,800 ppm (11,700 mg/cu m). For comparison, the author cited an odor threshold of 2,000 ppm (2,600 mg/cu m) for methyl alcohol from a data sheet provided by the Dragerwerk Company of Lubeck. The source and purity of the methyl alcohol used in these experiments were not stated. The experimental design described does not actually eliminate the problem of olfactory fatigue. The results demonstrated, however, that with the slightest perception of an odor of methyl alcohol, the concentration of the solvent in the air already greatly exceeds the existing federal standard (200 ppm). Based on these data by May, the worker cannot rely on olfactory perception for warning purposes, except at high concentrations.

In 1959, Chao Chen-Tsi [22] reported the effects of inhaled methyl alcohol vapor on humans and animals. Using 13 subjects, the author

determined that the minimum airborne concentration of methyl alcohol that could be determined by odor ranged from 4.3 to 11.0 mg/cu m (3.3-8.5 ppm). The author also studied the effects of methyl alcohol vapor inhalation on the light sensitivity of the eye adapted to darkness in 3 subjects. The most sensitive subjects showed diminution of light sensitivity at a level of 3.3 mg/cu m (2.5 ppm), but at 2.4 mg/cu m (1.8 ppm) no such effect was detectable. On the basis of these results, the author proposed 1.5 mg/cu m (1.1 ppm) of methyl alcohol vapor in air as the maximum permissible concentration for occupational exposures.

In 1967, Ubaydullayev [23] reported on the methyl alcohol odor threshold range, on eye sensitivity to light during dark adaptation, and on alterations in the electrical activity of the cerebral cortex. For 25 subjects ranging in age from 18 to 40 years, the maximum imperceptible airborne methyl alcohol concentration was 3.9 mg/cu m (3.0 ppm) and the minimum perceptible concentration was 4.5 mg/cu m (3.4 ppm).

For eye adaptation to dark, or sensitivity to light, 3 subjects, aged 18-25, were tested. [23] The results showed that at 4.1 mg/cu m (3.1 ppm) of airborne methyl alcohol a sharp change in the subjects' eye sensitivity was observed. One individual showed a change in eye sensitivity at a concentration of 3.5 mg/cu m (2.7 ppm). No response was seen at 3.1 mg/cu m (2.4 ppm).

A group of 6 subjects most sensitive to olfactory stimuli were tested by the author [23] for alterations in activity of the cerebral cortex measured by an electroencephalograph. All 6 showed an alpha-rhythm amplitude change at a concentration of 1.5 mg/cu m (1.0 ppm) and none responded at 1.0 mg/cu m (0.8 ppm).

It is not clear whether any of these effects, reported by Chao Chen-Tsi [22] or by Ubaydullayev, [23] are to be interpreted as psychologic, physiologic, or toxicologic.

Thus, there are 2 sets of studies estimating the odor threshold for methyl alcohol: Scherberger et al [20] giving 1,500 ppm and May [21] giving 5,900 ppm (while citing 2,000 ppm as the figure suggested by the Dragerwerk Company of Lubeck) and, in marked contrast to these, Chao Chen-Tsi [22] giving 3.3-8.5 ppm and Ubaydullayev [23] giving 3.4 ppm as the minimal perceptible concentration of methyl alcohol by odor. It is difficult to reconcile such a wide discrepancy between these 2 sets of studies, even allowing for different experimental techniques. Small traces of impurities can have a very marked effect upon odor, but in the absence of any data in any of these 4 papers on the source or purity of the methyl alcohol used, the issue of impurities is a matter for conjecture.

In 1905, Jelliffe [15] reported 2 cases which he described as multiple neuritis in men engaged in shellacking furniture with shellac dissolved in methyl alcohol. Symptoms reported were paresthesia, numbing, prickling, and shooting pain in the back of the hands and forearms, in addition to edema of the arms. Both men sought medical aid promptly, and the resultant cessation of exposure probably prevented the development of serious sequelae of methyl alcohol intoxication. Jelliffe considered that these 2 cases were due to the inhalation of the vapor of the wood alcohol employed. In contrast, he described the case of a businessman who had been in the habit of drinking quite regularly, in small quantities, for a period of at least 3 months an illicit whiskey which apparently contained 35% Columbian spirits (methyl alcohol). When seen by the author, [15] the

subject was suffering from severe gastric irritability, marked hyperesthesia in both arms and hands, incomplete paralysis of the extensors, and wrist-drop. He also had a mild degree of ptosis of the eyelids and a restricted partial amblyopia. He recovered after 4 months of treatment but still had some residual blurring of vision. The author then lost touch with the patient. In summarizing all 3 cases, Jelliffe commented upon a postulated "greater susceptibility of the ganglion cells of the retina" to poisoning by methyl alcohol.

In 1905, Hawes [16] described a case of occupational poisoning that was attributed to the inhalation of methyl alcohol vapor. Methyl alcohol was used by a painter as a paint remover and for mixing shellac. The work consisted of pouring a quantity of methyl alcohol on furniture, rubbing the furniture with a cloth, and repeating the procedure. The painter worked in rooms no larger than 10 x 12 feet with the doors and windows kept closed. During the first day of work, he began to experience headache, nausea, weakness, and some smarting of the eyes. He completed the second day of work despite the persistence of the aforementioned symptoms as well as slight blurring of vision by the end of the second day. On the third day, as a result of increased severity of the above symptoms, he was unable to work past 8:30 AM. The painter was then hospitalized. Fifteen days after admission, on ophthalmological examination he was found to have no vision whatever. The airborne concentration of methyl alcohol in the rooms was not determined. From the author's description of this man's mode of work, he probably had had considerable skin contact with methyl alcohol, so that inhalation was probably not the sole route of absorption.

In 1912, Tyson [17] described a case of methyl alcohol poisoning in a worker who was involved in varnishing the inside of beer vats. Work was commenced on December 3, 1911, and continued on the following day with no medical complaints. On December 5, the worker experienced headache, vertigo, unsteady gait, nausea, vomiting, and acted as if intoxicated; consequently he did not work on this day. The author did not state if the subject worked on December 6. On December 7, the worker began having visual disturbances. At this time, he consulted a physician who diagnosed methyl alcohol poisoning. On December 12, an ophthalmologist made the following observations: the pupils were practically nonreactive to light, there was retinal edema, and initial vision (eccentric) was right 1/200 and left 2/200. In three weeks, his vision had improved to 20/30 in each eye. Six to 7 months later, with no additional methyl alcohol exposure, visual acuity remained stable, while the pupillary response to light remained sluggish. In addition, the author described a progressive contraction of the visual fields during the entire period of observation. Tyson also indicated that the progressive constriction of visual fields corresponded to degenerated bundles of fibers and groups of ganglion cells becoming confluent as the degenerative process spread. He also concluded that this case was produced solely by inhalation of methyl alcohol vapor. The airborne concentration of methyl alcohol to which the worker was exposed was not determined.

In a review article published in 1912, Wood [18] commented on 4 workers (one of which was the case previously described by Tyson [17]) poisoned while varnishing beer vats. Methyl alcohol was reported as a constituent of the varnish. All 4 workers had been involved in varnishing

the inside of beer vats 12-15 feet high. After the first day, one worker complained of dizziness and, after the second day, displayed an unsteady gait. On the third day, he could not return to work because of sweating, vomiting, a rash on the face and body, and progressive loss of vision. The 3 remaining workers continued to work through the third day, at the end of which they experienced varying degrees of poisoning. Two of these 3 workers died 1 and 3 days later without further occupational exposure. The remaining worker of the last 3 experienced some symptoms ("reeling, headache, etc") and apparently recovered. The airborne concentrations of methyl alcohol to which they were exposed were not reported.

In 1921, Ziegler [19] described 2 cases of methyl alcohol poisoning resulting from inhalation of the vapor. One individual experienced fading of vision and constriction of the visual fields. The author attributed this condition to exposure to methyl alcohol vapor through daily visits to a china cement factory, since analysis of the cement had shown methyl alcohol to be a constituent of the cement. The patient's vision improved after he discontinued his visits to the factory.

The second case described by Ziegler [19] involved a painter who varnished the engine room of a submarine with a methyl alcohol-based varnish. At the end of the first day, the painter experienced dizziness. On the second day, he appeared euphoric and on the third day he was nervous. He also experienced gastric pain, insomnia, and double vision. Temporary blindness occurred after termination of occupational exposure. When first seen by the author, this individual was acidotic, although the basis for the diagnosis was not reported. Three weeks following the exposure, the worker had improved considerably and his eyesight was nearly

normal. In both these cases, Ziegler claimed that the application of "negative galvanism" for prolonged periods contributed significantly to the recovery of vision, suggesting that this treatment stimulated revascularization of the optic disc. Again, no estimate was made of the airborne concentration of methyl alcohol to which the painter was exposed.

The author [19] suggested that methyl alcohol was a protoplasmic poison possessing a selective affinity for the nerve tissue of the eye, and that the proximal agents of toxicity of methyl alcohol could be formaldehyde and formic acid, both "corrosive poisons". He also proposed that the "primary and fundamental lesion" of methyl alcohol poisoning was injury to the pituitary gland. This implication of the pituitary has not, however, found support with later observers.

Thies, [24] in his 1928 report on "Eye Damage in the Chemical Industry," stated that liquid methyl alcohol coming in contact with the eyes caused severe edema of the ocular conjunctiva (chemosis) and lesions of the corneal surface that were rarely complicated and usually healed in a few days with proper treatment.

In 1941, Humperdinck [25] reported a case of methyl alcohol poisoning that occurred in a nitrocellulose plant where a worker had been exposed to damp nitrocellulose that he had unloaded, weighed, and stored. The dampened material contained 35-40% methyl alcohol. The worker had been on this job for 4 years and had not previously reported any symptoms. He became ill following the institution of wartime blackout measures which impaired plant ventilation. The initial diagnosis of pleurisy was changed retrospectively to one of acute hepatitis. He also became blind in the right eye with marked narrowing of the visual field in the left eye. An

examination of the workplace air showed methyl alcohol concentrations ranging from 1,600 to 10,900 mg/cu m (approximately 1,200 to 8,300 ppm). The diagnosis of acute hepatitis in this case appears to have been based purely upon retrospective clinical impressions, unsupported by any clinical or laboratory findings. The author suggested that methyl alcohol poisoning was confined to this one worker among a total of 23 exposed because of individual variations in susceptibility and the possibility of hereditary weakness of this worker's neuro-optical system manifested by his congenital fixation of the pupils and color blindness. The author indicated that, while relatively high airborne methyl alcohol concentrations ranging from 2,000 to 10,000 mg/cu m (1,500-7,600 ppm) may be tolerated for many years without determinable damage, however, this range of concentrations should not be considered harmless because of individual susceptibility, development of tolerance, and the cumulative effect of methyl alcohol. He therefore recommended that airborne methyl alcohol concentrations be maintained below 1,000 mg/cu m (760 ppm).

In 1957, Burk [26] described a case of occupational poisoning which he attributed to the inhalation of methyl alcohol. The worker had been employed for 7 years in a chemical-pharmaceutical factory, having spent the previous 4 years in the methyl alcohol department. In early January of 1955, the worker had complained of visual disorders, and had suffered asthenia and numbness of the hands and arms. On June 20, 1955, the worker cleaned a boiler in which crude nicotinic acid was boiled with methyl alcohol. The author reported that scraping off the residue on the inside of the boiler generated methyl alcohol fumes. During the first 50 minutes of work, the employee used a gas mask fitted in succession with 2 Type A-90

Drager respiratory filters which were impermeable to methyl alcohol. The next filter used was a Drager Type K-90, which was permeable to methyl alcohol. The latter filters were changed 4 times since they became very wet within a period of 20-30 minutes. Occasionally during the first day of scraping the boiler, the worker suffered from vertigo. During break periods in fresh air, he saw colored rings. The first day's operation required about 5 hours. The next morning, the worker became nauseated upon entering the boiler room which had been used the preceding night. Despite the nausea, the worker emptied the boiler, liberating small quantities of methyl alcohol vapor. He then suffered visual disturbances for the rest of the second day, despite the fact that he underwent no further methyl alcohol exposure. On the third day upon entering the boiler room, the worker suffered nausea and visual disorders and was then hospitalized. Ophthalmoscopic examination showed papilledema of both eyes that began to clear after a few days. After 5 weeks, full visual acuity returned. Blood, urine, and cerebrospinal fluid tests, as well as physical examination, disclosed no abnormal findings. Formic acid, found in the urine in the first 11 weeks following the initial examination, was no longer detectable after 11 weeks. The presence of formic acid confirmed the author's belief that the toxicity was due to methyl alcohol exposure. Questioning of the patient revealed that he was in the habit of frequently washing his hands with methyl alcohol. The author [26] therefore concluded that the exposure involved a single acute intoxication by inhalation superimposed upon a chronic condition resulting from percutaneous absorption of methyl alcohol along with inhalation of low concentrations of methyl alcohol over a period of years. In his theoretical discussion of

this case, Burk [26] attributed the toxic effects of methyl alcohol to formaldehyde and formic acid, indicating that both compounds were oxidation products of methyl alcohol. The author stated that the diagnosis of methyl alcohol poisoning is sometimes very difficult, and would be more easily verified by quantitative determinations of formic acid in the urine of persons suspected of being poisoned with methyl alcohol.

The preceding 6 reports [15-17,19,25,26] all describe cases in which the mode of entry of methyl alcohol into the body was believed to be predominantly by inhalation, with the possibility in some cases of additional absorption through the skin. The following report of a collected series of cases involving infants and young children, [27] though clearly unrelated to occupational exposures, is reviewed by way of contrast as it illustrates that percutaneous absorption of methyl alcohol can lead to serious consequences, including death. In 1968, Gimenez et al [27] reported an analysis of 19 cases of children, ranging in age from 1.5 months to 4 years, who were poisoned as a result of having cloths soaked in methyl alcohol applied to their abdomens to relieve gastrointestinal troubles or other unspecified complaints. There were 2 additional cases reviewed in which both methyl and ethyl alcohols had been employed in this way, making a total of 21 cases. Although absorption of methyl alcohol via the respiratory tract was possible in these cases, the fact that the cloths were held in place by rubber baby pants would favor percutaneous absorption of the alcohol as the significant route of exposure. The length of time between application and onset of symptoms of intoxication was 1-13 hours (7 1/4 hours average). The early signs of intoxication were described by the authors as central nervous system depression with 13 children having

exhibited severe respiratory depression and 11 of these having convulsions. Blood pH in the 21 patients ranged from 6.4 to 7.38 (normal: 7.36-7.41 [28]), indicating acidosis in most cases. Twelve of the 21 children died of cardiac or respiratory arrest 2-10 days after hospital admission. The survivors recovered without apparent permanent damage. Papilledema and ocular fundus bleeding were observed in 2 of the infants who subsequently died. Abdominal skin lesions were present in 5 patients, 3 of the erythematous type and 2 of the scaling type. The authors [27] commented that while there was no relationship between methyl alcohol blood levels as tested in 11 children (57-1,130 mg%) and prognosis, there was a relationship between the initial blood pH and the subsequent course of the illness. In general, treatment consisted of administering sodium bicarbonate, glucose, ethyl alcohol, fluids, and electrolytes. Other forms of treatment included peritoneal dialysis, exchange transfusion, mechanical respiration, and the administration of anticonvulsant drugs. It must be pointed out that the absorptive properties of the skin of infants are probably different from those of adults and consequently infant susceptibility to, and manifestations of, methyl alcohol intoxication may not parallel those seen in adults.

The New York State Department of Labor bulletin on the industrial dangers of methyl alcohol [14] also reported several cases of dermatitis. While uncommon, several cases of dermatitis of the hands were reported in hat factories where shellac dissolved in methyl alcohol was used to stiffen hats. In several Panama hat factories where shellac was dissolved in methyl alcohol and where the workers' hands were in direct contact with the solution, only one case of dermatitis was found.

The studies discussed in the remainder of this section are concerned with methyl alcohol absorption, elimination, and metabolism in the human. The effect of ethyl alcohol on the metabolism and elimination of methyl alcohol and the explanation why ethyl alcohol administration is effective in preventing or ameliorating some of the symptoms of acute methyl alcohol intoxication in humans will also be examined.

In 1949, Agner et al [29] reported on the successful treatment of methyl alcohol intoxication in humans with ethyl alcohol. Three workmen ingested unknown quantities of methyl alcohol. Of these 3, only one became intoxicated and about 12 hours later, he vomited and complained of losing his vision. He was admitted to the hospital the following day and lapsed into a coma within 1 hour after admission. In spite of iv administration of bicarbonate and ethyl alcohol, he died 23 hours after admission. Upon admission of this patient to the hospital, his 2 drinking companions were also admitted and examined. Neither showed signs of methyl alcohol poisoning, and they were discharged the same day pending analysis of blood samples for methyl alcohol content. One showed a blood methyl alcohol concentration of 40 mg/100 ml and never displayed signs or complained of symptoms of poisoning. The other, however, had a blood methyl alcohol concentration of 236 mg/100 ml. The authors found that, on the day the latter patient ingested the initial methyl alcohol, he had also consumed an additional 100-150 ml of brandy not known to have been adulterated. Upon leaving the hospital the following morning, he consumed an additional 200-300 ml of brandy (again not known to be adulterated) before being rehospitalized that afternoon. This patient was also treated with bicarbonate for a low alkali reserve. During the next 8 hours, his blood

methyl alcohol concentration decreased only slightly, and he remained clearheaded and lucid. However, when the blood level of methyl alcohol began to decrease, the patient showed signs of motor unrest, as well as unresponsive pupils and slowness of speech. He also complained of blurred vision. An initial oral dose of 60 ml of ethyl alcohol was administered, followed every hour by additional 10-20 ml doses. Blood methyl alcohol concentration was measured every 2-3 hours. During the 10 hours immediately prior to ethyl alcohol administration, the blood concentrations of methyl alcohol decreased from approximately 210 to about 140 mg/100 ml. However, in the 24-hour period following the initiation of ethyl alcohol therapy, the level of methyl alcohol in the blood decreased to about 80 mg/100 ml. The blood methyl alcohol concentration remained nearly constant at this level for approximately 8 hours after the ethyl alcohol therapy was discontinued. The concentration of methyl alcohol in the blood then continued to decline for the next 24 hours, at which point it was no longer detectable. Within 2 hours after the first administration of ethyl alcohol, the patient became clearheaded and the motor unrest and ocular symptoms disappeared. The authors [29] concluded that the visual and other symptoms of methyl alcohol intoxication observed in this patient were caused by toxic products resulting from the oxidation of methyl alcohol rather than by methyl alcohol itself. The administration of ethyl alcohol at a level sufficient to maintain a concentration of 1.0 mg/ml in the blood caused a retardation or cessation of this oxidation, and thus inhibited the toxic action of the methyl alcohol metabolites. The authors also noted that while the patient had a low alkali reserve he was not acidotic, yet showed symptoms of methyl alcohol poisoning. The authors commented that

this observation was contrary to the belief of other investigators that acidosis is the cause of methyl alcohol-poisoning symptoms. Additionally, the authors advocated treating methyl alcohol poisoning with ethanol in addition to treating acidosis.

In 1952, Leaf and Zatman [30] reported on experiments in which 5 male volunteers ingested 2.5-7.0 ml of methyl alcohol diluted to 100 ml with water. These amounts of methyl alcohol corresponded to doses of 29-84 mg/kg. Two blood samples were taken from 3 subjects, 2-5 hours after the ingestion. Urine was collected frequently for 11-16 hours following methyl alcohol administration. Both the blood and urine samples were analyzed for methyl alcohol by a colorimetric method based on the oxidation of methyl alcohol to formaldehyde and formation of a colored complex with a modified Schiff's reagent. The results of this experiment indicated that under these conditions methyl alcohol was rapidly absorbed from the gastrointestinal tract. The maximum methyl alcohol concentration in the urine was achieved approximately one hour after ingestion and then decreased exponentially. The ratio of blood to urine methyl alcohol concentrations remained almost constant for the 3 subjects in which it was determined, and the authors [30] concluded that the change in the concentration of methyl alcohol in the urine was an accurate indicator of the change in methyl alcohol concentration in the body. At the levels used in this experiment, the concentration of methyl alcohol in the urine declined to control values within 13-16 hours after ingestion. Leaf and Zatman [30] also stated that only 0.4-1.2% of the ingested methyl alcohol was eliminated unchanged in the urine and that the elimination of unchanged methyl alcohol in the expired air accounted for a similar fraction of the

dose, although the experimental evidence supporting the latter statement was not given.

In another experiment in the same study, [30] 2 male volunteers ingested 15 ml of ethyl alcohol and 4 ml of methyl alcohol simultaneously. They then ingested 10 ml of ethyl alcohol every hour for the next 7 hours. The same individuals served as their own controls in a previous experiment in which they ingested only 4 ml of methyl alcohol. Urine was collected hourly and analyzed for methyl alcohol. The maximum urinary methyl alcohol concentrations for those individuals who ingested both methyl alcohol and ethyl alcohol were 8.82 and 9.20 mg/100 ml, compared to values of 6.05 and 5.50 mg/100 ml when methyl alcohol alone was ingested. Moreover, the total amount of methyl alcohol excreted unchanged in the urine in the first 7 hours after ingestion was 107.1 mg and 125.5 mg (3.7 and 3.96% of the administered dose respectively) when both methyl alcohol and ethyl alcohol were ingested, whereas only from 18.2 to 30.8 mg (0.57-0.97% of the administered dose) was excreted unchanged in a similar time period after ingestion of 4 ml methyl alcohol alone. The authors [30] concluded that in humans ethyl alcohol interfered with the normal oxidation of methyl alcohol, causing more of it to be excreted unchanged in the urine. Moreover, according to the authors' conclusion, higher concentrations of methyl alcohol in the blood are maintained in the presence of ethyl alcohol at any given time after absorption, as compared to concentrations achieved in the absence of ethyl alcohol.

Leaf and Zatman [30] studied the absorption of methyl alcohol via the respiratory route. Two human male volunteers were exposed on several different occasions to methyl alcohol vapor at concentrations of from 650

to 1,430 mg/cu m (approximately 500-1,100 ppm). These exposures took place in a 22.9-cu m capacity room, where desired concentrations were achieved by evaporating known quantities of methyl alcohol on a hot plate in the draft of a fan. Concentrations were verified by analyzing air samples collected at frequent intervals during and after exposure for methyl alcohol content. Using urinary methyl alcohol concentrations as an index of methyl alcohol absorption, the authors concluded that the rate of absorption was proportional to the concentration of the vapor inhaled. Exposure to methyl alcohol vapor at a concentration of 1,430 mg/cu m (approximately 1,100 ppm) for 2 1/2 hours resulted in a urinary methyl alcohol concentration of 2.56 mg/100 ml. Exposure periods were not sufficiently long to determine whether the rate of excretion would increase to equal the rate of absorption. The authors remarked that an exposure period of 3-4 hours was all that could be reasonably tolerated, but did not specify whether the direct effect of methyl alcohol or personal discomfort due to the design of the experiment was the reason for the time limitation. From their studies, Leaf and Zatman [30] did calculate what they believed to be a safe inhalation dose for methyl alcohol for an 8-hour work period. They calculated the threshold of intoxication for these two workers as 2,800 ppm (3,670 mg/cu m) and 3,000 ppm (3,930 mg/cu m) respectively, and using an arbitrary safety factor, they therefore recommended a standard of 300 ppm (390 mg/cu m).

In 1953, Kendal and Ramanathan [31] studied the excretion of formate (an oxidation product of methyl alcohol) in humans. The same 2 adult males studied 4 years earlier by Leaf and Zatman [30] ingested 4 ml of methyl alcohol (approximately 50 mg/kg body weight) diluted to 100 ml with water.

In one set of experiments, methyl alcohol was ingested by itself, whereas in another, 15 ml of ethyl alcohol was ingested simultaneously with methyl alcohol, and at hourly intervals thereafter, 10 ml of additional ethyl alcohol was consumed for 5 hours. Urine was collected every 1-2 hours for about 12 hours following administration. Samples were analyzed for methyl alcohol by the method used by Leaf and Zatman, [30] and for formate by the method of Bastrup, [32] which is based on the oxidation of formate to carbon dioxide with mercuric chloride. When the volunteers ingested 4 ml of methyl alcohol without ethyl alcohol, they excreted 36 mg of methyl alcohol and 41 mg of formic acid in the first 6 hours following the ingestion. On the other hand, when the volunteers ingested ethyl alcohol with the methyl alcohol, they excreted 69 mg of unchanged methyl alcohol and no measurable formic acid during the same 6-hour period. For the period from 6 to 12 hours after simultaneous methyl alcohol and ethyl alcohol ingestion, the volunteers excreted 12 mg of formic acid as opposed to only 7 mg of formic acid in the experiment without ethyl alcohol. The authors [31] interpreted the results to indicate that ethyl alcohol interfered with the oxidation of methyl alcohol to formic acid, resulting in decreased urinary excretion of formic acid and an increased urinary excretion of unmetabolized methyl alcohol during the initial 6-hour period. During the second 6-hour period after ethyl alcohol administration ceased, however, the formic acid excretion actually increased, presumably as a result of an uninhibited methyl alcohol oxidation process. Another significant conclusion of these authors was that the kidneys must have a considerable power of concentrating formate.

In vitro studies have been carried out on highly purified preparations of alcohol dehydrogenase (ADH) isolated from human livers. [33,34] In the first study, both methyl and ethyl alcohols were found to be substrates for this enzyme system. [33] In the second study, [34] it was demonstrated that the affinity constant of human ADH for methyl alcohol as a substrate was only 1/30 of that for ethyl alcohol. Neither of the studies [33,34] reported any in vitro experimental data on competitive inhibition between ethyl and methyl alcohols for human ADH. However, in the first report, Von Wartburg et al [33] implied that ethyl alcohol would inhibit the oxidation of methyl alcohol by ADH when both substrates were available to the enzyme, and this may explain the efficacy of giving ethyl alcohol in cases of methyl alcohol poisoning. In the second study, Blair and Vallee [34] indicated that ethyl alcohol may act as a competitive inhibitor of methyl alcohol and thereby may protect against methyl alcohol toxicity in vivo. Furthermore, a study by Goodman and Tephly [35] showed that the human hepatic catalase-peroxidase system has relatively little oxidizing activity with respect to methyl alcohol in vitro, but rather oxidation proceeds through an alcohol dehydrogenase system. Thus, these in vitro studies [33-35] provide a reasonable explanation for the mechanism of action of ethyl alcohol in the studies cited previously [29-31] which indicated that ethyl alcohol is capable of blocking the oxidation of methyl alcohol in vivo. For more information concerning the pharmacology of ethyl alcohol (which includes its metabolism by alcohol dehydrogenase and other enzyme systems) the review by Ritchie [36] is recommended.

In 1971, Majchrowicz and Mendelson [37] described a study in which 19 adult male volunteers were confined in a hospital research ward, fed a

standard daily 2,000-calorie diet with multivitamin supplements, and permitted to consume up to 32 ounces/day of either bourbon (50% ethyl alcohol) or 50% USP ethyl alcohol (grain alcohol) on a spontaneous drinking regimen for a period of 10-14 days. The subjects remained confined under observation for 7-10 days after the drinking period. Fingertip blood samples were taken every morning during the drinking and observation periods. These samples were analyzed by gas chromatography for ethyl alcohol, methyl alcohol, acetaldehyde, and acetone. During the predrinking observation period, blood methyl alcohol concentrations were always less than 0.1 mg/100 ml. After one day of drinking bourbon or grain alcohol, blood methyl alcohol concentrations ranged from 0.1 mg/100 ml to 0.2 mg/100 ml, and methyl alcohol concentrations ranging from 1.1 mg/100 ml to 2.7 mg/100 ml were achieved by the last day of the drinking period. In the postdrinking period, blood methyl alcohol concentrations remained relatively constant until blood ethyl alcohol concentrations dropped below 20 mg/100 ml, at which point blood methyl alcohol concentrations began to decline. In general, the blood methyl alcohol concentration increased and decreased in concert with blood ethyl alcohol concentration, although the changes were not simultaneous. The authors also determined the concentration of methyl alcohol in the bourbon (40-55 mg/liter) and in the grain alcohol (approximately 1 mg/liter). Using the known amount of bourbon consumed and assuming an even distribution of methyl alcohol throughout the body water, body weight of 70 kg, and no loss due to metabolism or excretion, the concentration of methyl alcohol was calculated to be 0.06 mg/100 g of body water after one day and 0.84 mg/100 g of body water after 14 days. Only negligible quantities of methyl alcohol would

have been exogenously introduced by the ingestion of grain alcohol. Since the average bourbon drinker excreted more methyl alcohol per 100 ml of urine than would theoretically have been present in the same amount of body water, the authors suggested that most of the methyl alcohol in the bourbon drinker and virtually all of the blood methyl alcohol in the grain alcohol drinker arose from endogenous sources, and in the absence of ethyl alcohol, the rate of metabolism and excretion of endogenously produced methyl alcohol were sufficient to prevent its accumulation in the body. In their discussion, the authors indicated that blood concentrations of ethyl alcohol higher than 20 mg/100 ml seemed to effectively block the oxidation of methyl alcohol in vivo. This in turn resulted in a buildup of endogenously produced methyl alcohol, which was reversed only after blood ethyl alcohol concentrations dropped below 20 mg/100 ml. The authors, taking into consideration their experimental findings and those of other investigators, suggested that ethyl alcohol may inhibit the oxidation of methyl alcohol in vivo by competing (competitive inhibition) for the alcohol dehydrogenase system. It is conceivable, therefore, that chronic alcoholics might exhibit measurable concentrations of methyl alcohol in the blood or urine even though they have not been exposed to methyl alcohol.

In summary, an integration of in vitro [33-35] and in vivo studies [29-31,37] indicates that in humans methyl alcohol is oxidized primarily by alcohol dehydrogenase. The results discussed in the section on Animal Toxicity, however, suggest that in nonprimates methyl alcohol is oxidized primarily by the catalase-peroxidase system.

Epidemiologic Studies

In 1912, Tyson [17] described a factory in New York City in which 25-30 young women worked in a 20 x 50 foot room polishing wooden lead pencils with a varnish solution containing methyl alcohol. During damp or cold weather the windows of this room remained closed in order to maintain the quality of the finished pencils. All of the women in the room experienced headaches and an unspecified number exhibited what the author termed gastric disorders. One woman missed 8 weeks of work because of chronic gastritis. Two cases from the same work area were reviewed by Tyson. The initial symptoms of a 30-year-old woman described in the first case were headache, vertigo, weakness (unspecified), and nausea without vomiting. She also had dizziness and obscuration (sic) of vision while working. The woman stated that the symptoms occurred principally during the day when the windows were closed. After working about 3 hours, she experienced blurring of vision, changes in color perception, and the symptoms mentioned previously. After half an hour in fresh air, the symptoms subsided. The same condition then occurred in the afternoon. Upon examination, her optic discs were hyperemic, the edges were blurred, and the veins were dilated. The other case was similar in that approximately 3 hours after beginning work the woman would on certain days experience frontal headache, dizziness, and nausea. At times, she experienced what she called a mist before her eyes. She was examined initially because of failing vision. The eye examination showed pallor, blurring, and edema of the discs, as well as dilated retinal veins. Upon questioning, both patients stated that they used methyl alcohol on occasion to cleanse their skin. The author suggested that the visual disturbances or loss of function were related to

adverse effects on nerve fibers and ganglion cells of the retina. No measurements of methyl alcohol concentration in the workroom air were reported.

Included in the New York State Department of Labor's special 1917 bulletin on the dangers of the industrial use of methyl alcohol [14] was a study of a shop in New York City where the employees dyed artificial flowers by dipping them in methyl alcohol solutions of aniline dyes. Physical findings were noted in 20 workers including dermatitis, anemia, nearsightedness, and conjunctivitis. Anemia and nearsightedness have not been reported elsewhere as signs of methyl alcohol intoxication. There was no mention in this report of headache, dizziness, nausea, or visual disturbances other than nearsightedness. Although the methods of sampling and analysis were not described, the report stated that analysis of the room air revealed a methyl alcohol concentration of 200 ppm by weight. The failure to describe sampling and analytical methods, the expression of air concentrations as a weight ratio, and the lack of comment on the possibility of skin contact make the relationship between the effects noted and the airborne concentrations reported of doubtful significance.

In 1938, Greenburg et al [38] published the results of a study of a plant in New York in which 19 workers operated steam presses in order to fuse shirt collars made of cellulose acetate and cotton impregnated with a solvent consisting of 3 parts acetone and 1 part methyl alcohol. Two air samples collected at the breathing level in the center of the workroom over a 2 1/2 hour period revealed methyl alcohol concentrations of 22 and 25 ppm and acetone concentrations of 40 and 45 ppm. The authors did not mention how the samples were taken or how they were analyzed. The employees

examined had been engaged in this operation for a period ranging from 9 months to 2 years. Physical examination, including neurological tests, detected no abnormal findings and the ocular fundi appeared normal. No visual disturbances were reported. Blood findings on all 19 were essentially normal and urinary analysis on 17 revealed nothing of significance other than a positive test for acetone. The blood tests performed included hemoglobin concentration, red cell count, reticulocyte count, total and differential white cell counts, platelet count, bleeding and coagulation times, red cell fragility, erythrocyte sedimentation rate, and serum bilirubin. The urine was examined microscopically for casts, and determinations of protein, sugar, and acetone content were made. The authors concluded [38] that these airborne concentrations of methyl alcohol and acetone were apparently not high enough to cause or produce adverse changes. While no effects were seen at 22-25 ppm of methyl alcohol, the presence of acetone in the air and in the urine precludes any definitive conclusion regarding possible adverse effects of methyl alcohol alone at these levels because of the remote possibility that acetone may interfere with the metabolism of methyl alcohol.

In 1955, Kingsley and Hirsch [39] reported that an unspecified number of employees at the Sandia Laboratory, Albuquerque, New Mexico, complained of frequent and recurrent headaches. According to the authors, all of the people affected worked in the immediate vicinity of direct process duplicating devices. These duplicating devices used different brands of duplicating fluids containing 5-98% methyl alcohol. The other ingredients in the duplicating fluids were not identified. The authors stated that those individuals situated closer to the machines experienced more severe

headaches, those who actually operated the equipment suffered the most, and that with the onset of cold weather, when the doors and windows were closed, the severity and frequency of the headaches increased.

Air sampling was performed by what the authors [39] referred to only as standard air sampling techniques. Moreover, the method of analysis for methyl alcohol was not reported. Results revealed that air concentrations of methyl alcohol in the breathing zone of the workers ranged from 15 ppm (20 mg/cu m) to 375 ppm (490 mg/cu m) and varied with the concentrations of the methyl alcohol in the duplicating fluids. Air samples taken 10 feet from the duplicating machines showed concentrations of 100 ppm (130 mg/cu m) which, depending on the extent of ventilation, persisted for up to 4 hours. The authors indicated that the concentrations were generally in excess of 200 ppm but less than 375 ppm. As a result of this study, there was a change in the duplicating fluids used (selecting those with a lesser concentration of methyl alcohol), and the duplicating devices were moved to areas with better ventilation. The authors [39] failed to mention whether these measures had any effect on the headaches of the workers. This study may imply that methyl alcohol vapor in the air in concentrations in the range of 200 to 375 ppm may cause headaches. However, the presence of other volatile substances arising from the other ingredients in the duplicating fluid (the other ingredients of various brands of fluids used ranged from 2 to 95% of the total) could have contributed significantly to the symptoms encountered.

In 1953, Bennett et al [40] reported on a study of 323 individuals who ingested various quantities of bootleg whiskey in Atlanta, Georgia, over a 5-day period in October 1951. An analysis of the contaminated

whiskey showed that it contained 35-40% methyl alcohol by weight and less than 4% ethyl alcohol. The procedure for analysis of the contaminated liquor was not given by the authors.

Of the 323 individuals involved in this incident, [40] 41 died. The smallest amount of ingested alcohol that caused death was 3 teaspoons (approximately 15 ml) of 40% methyl alcohol, while one individual consumed 1 pint (approximately 500 ml) of the same mixture and recovered. Upon admission to a hospital, 115 patients were acidotic with CO2-combining capacities less than 20 meq, as compared to the normal range of 24-30 meq. [40] In most cases, the latent period between ingestion of the alcohol and the onset of toxic symptoms was about 24 hours. The longest observed lag was slightly more than 72 hours, while in one instance visual symptoms developed only 40 minutes after one individual drank about half a pint of whiskey. Several patients had visual disturbances in less than 6 hours. Although the authors indicated that medical records were incomplete, they gave the following description of symptoms:

Visual disturbances - All of the 115 patients who were overtly acidotic on admission had some degree of visual impairment. More than half of the patients whose plasma bicarbonate was within normal limits when first examined had noticed at least transient difficulty in seeing. The most frequent complaint was blurred or indistinct vision.

Central nervous system manifestations - Headache was a complaint in 62% of the patients and dizziness occurred in 30% of those interviewed in detail. Complaints of weakness or general malaise were frequent. Many moribund or severely acidotic patients were stuporous or comatose, and several had repeated, sometimes terminal, convulsions. Many patients had

some degree of amnesia for the events preceding their admission to the hospital. Two patients, both severely acidotic and admitted in a maniacal state, suffered total amnesia for their actions over the period of mania.

Gastrointestinal symptoms - Nausea and vomiting occurred in 52% of those patients whose symptoms were recorded. Persistent vomiting, however, was only noted in one individual. At the time of oral treatment with a sodium bicarbonate solution, diarrhea was recorded in 10% of the cases, but constipation was a common complaint after several days in the hospital.

Pain - Apart from the headache discussed under central nervous system manifestations, 67% of the hospitalized patients complained of excruciating upper abdominal pain.

Dyspnea - Despite the severity of acidosis in many patients, dyspnea was not a major complaint in any case. Twenty-five percent of the acidotic patients had some degree of respiratory distress at some time during their illness. True Kussmaul respirations were unusual even in severely acidotic patients, occurring only in about 25% of the patients whose plasma bicarbonate was less than 10 meq/liter.

In addition to these symptoms, physical findings were described as follows:

General - Skin pallor was observed in the white patients, but no distinct discoloration was observed in the majority of the patients who were black. Body temperature was normal in the vast majority of patients.

Eyes - Dilation of the pupils and sluggish or absent reaction to light and accommodation were present in most of the cases. Photophobia was not prominent and the eyeballs were not tender to pressure. On ophthalmoscopic examination, eyeground changes characterized as hyperemia

of the optic disc and retinal edema were seen in most patients with acidosis. The severity of these eyeground changes was found to correlate better with acidosis than any other clinical finding. True papilledema was not seen.

Cardiovascular symptoms - The pulse rate was increased in only 7 cases. Blood pressure appeared to be unaffected by the poisoning.

Abdominal examination - Abdominal muscles were very rigid and tender.

Neurologic signs - Confusion, amnesia, lethargy, stupor, and deep coma were seen, as well as acute mania in the 2 cases already mentioned. Six patients, all of whom died within minutes of admission, were in deep coma with signs suggestive of meningitis.

Cause of death - The primary cause of death in acute cases was respiratory failure.

The authors indicated that when plasma bicarbonate levels were restored to normal by alkalinization, the patients experienced a rapid relief of most of their symptoms. Moreover, the authors emphasized the importance of prompt massive alkalinization by iv administration in severe cases of poisoning by methyl alcohol since prognosis was associated with the severity of acidosis. Table III-1 illustrates the correlation between severity of acidosis and mortality.

Laboratory findings - Hemoglobin concentrations, hematocrits, and total and differential white cell counts were within normal limits. Urinalysis was performed on 43 patients on admission; there was albuminuria in 21 cases and acetonuria in 10. Urinary pH in acidotic patients was invariably between 4.5 and 5.5, rising with treatment. Apart from the acidosis, the most striking finding was an elevation of serum amylase to

TABLE III-1

MORTALITY IN TREATED PATIENTS*

	No. of patients	% mortality
Total patients	323	6.2
Acidotic: CO2-combining power less than 20 meq	115	19.0
Severely acidotic: CO2-combining power less than 10 meq	30	50.0

*These figures do not include patients who died at home

From Bennett et al [40]

levels of over 300 units in 14 of 21 patients tested. The authors felt that this finding could be associated with the frequency of pancreatic necrosis found at autopsy in this series.

Autopsy findings - The authors concluded from their pathologic findings that there was nothing pathognomonic concerning the lesions encountered as a result of methyl alcohol poisoning. Findings included variable cerebral edema with meningeal and subarachnoid petechiae, congestion of the lungs, epicardial hemorrhages, occasional mild fatty infiltration of the liver, gastritis, and general congestion of the abdominal viscera. In 13 of 17 autopsies reviewed (10 of which were from the 1951 outbreak and 7 from patients who had died from methyl alcohol poisoning in 1946) pancreatic necrosis was observed. This necrosis was described by the authors as being secondary to vascular injury and hemorrhage. Based on the complaint of upper abdominal pain, the occurrence

of elevated serum amylase levels, and the microscopic findings of pancreatic necrosis, the authors concluded that acute hemorrhagic pancreatitis resulted from acute methyl alcohol intoxication. Reports of acute hemorrhagic pancreatitis following methyl alcohol poisoning other than by the oral route have not been found.

Animal Toxicity

In 1942, Sayers et al [41] exposed 4 dogs (3 male and 1 female) to methyl alcohol vapor at concentrations of 450-500 ppm (590-650 mg/cu m) for 8 hours/day, 7 days/week, for 379 days. The dogs were exposed in a continuously ventilated (8 air changes/hour) chamber. High purity industrial methyl alcohol was supplied to gauze ribbons in the chamber at a constant rate using a chemical proportioning pump. Calculated methyl alcohol vapor concentrations were verified by trapping the methyl alcohol contained in a known volume of air in 100 ml of water. The methyl alcohol concentration of the water was then determined using a wet chemical colorimetric method based on the oxidation of methyl alcohol to formaldehyde and the subsequent production of a purple color upon addition of Schiff's reagent. Twenty-eight days into the experiment, the female was mated to 1 of the exposed males and had a litter of 5 pups on the sixty-second day after breeding. One of the pups accidentally died shortly after birth. The 4 surviving pups were exposed in the same manner as the other dogs for the remainder of the experiment.

Laboratory hematologic determinations (RBC count, differential WBC, platelets, hemoglobin content, and coagulation time) were made before (9 samples) and during (28-30 samples) the exposure, and blood chemistry

determinations (nonprotein nitrogen, creatinine, and sugar) were made before (3 samples) and during (9 samples) the exposure period. All results were within control limits. Thirteen ophthalmoscopic examinations on each adult dog (5 preexposure and 8 during exposure) indicated no significant or abnormal eye changes due to exposure. The pups were similarly examined 3 times and showed no evidence of impaired vision. All the adult dogs either maintained their preexposure weights or gained weight. The pups also gained weight normally. Gross and microscopic examinations at autopsy revealed no deviations from usual minor abnormalities except for some (severity not described) inflammation of the meninges of the brain in 5 animals. Microscopic examination of the brain of 3 animals was essentially normal; however, 5 showed changes in the brain, attributed to intercurrent disease based on examination of controls and other unexposed dogs. The concentration of methyl alcohol in the blood at the end of an 8-hour exposure generally ranged between 10 mg and 15 mg/100 ml of blood, but on certain occasions concentrations as high as 52 mg/100 ml were found. This study [41] is one of the few in which animals of any species were exposed to methyl alcohol under conditions which approximate those expected in an industrial exposure. The lack of interpretable findings as well as the relatively small number of animals exposed allow few definite conclusions about chronic methyl alcohol intoxication. Moreover, as will be discussed later, the course of acute methyl alcohol intoxication is different in dogs and humans and thus, the results of experiments on dogs have limited relevance to possible adverse effects on humans.

In 1955, Gilger and Potts [42] published the results of a study of the comparative toxicity of methyl alcohol in rats, rabbits, dogs, and

rhesus monkeys. Administration of methyl alcohol (reagent grade 99.5% pure) was accomplished by gavage in all except 4 rabbit experiments where it was injected iv. Prior to oral administration, the methyl alcohol was dissolved in either water or aqueous sucrose solution in varying proportions depending on the size of the animal and its tendency to vomit the administered solution. After administration, the animals were observed for clinical signs of intoxication, blood samples were taken at variable intervals so that CO2-combining capacities (a measure of acidosis) could be determined, and repeated ophthalmoscopic examinations were performed on the rabbits, dogs, and monkeys.

Among 23 rats receiving 4.75 g of methyl alcohol/kg of body weight, (as a 50% aqueous solution) approximately 70% died. [42] Blood samples were obtained at 4.5, 27, and 47 hours after administration of 4.5 g of methyl alcohol/kg (as a 50% aqueous solution) to 9 male rats. CO2-combining capacities ranged from 47 to 80 volumes % in these samples. The authors stated that no acidosis was seen although they did not report control or normal CO2-combining capacities for rats.

Three rabbits given 2.1 g of methyl alcohol/kg of body weight (as a 30% aqueous solution) died between 24 hours and 3 days after oral administration. [42] One additional rabbit died in less than 24 hours after being given 3.5 g of methyl alcohol/kg orally (as a 50% aqueous solution). The results of ophthalmic investigation revealed no fundus changes. The results of acidosis studies in treated rabbits were ambiguous in that CO2-combining capacities ranged from 19 to 56 volumes % in untreated animals. None of the methyl alcohol-treated rabbits exhibited a CO2-combining capacity below the normal range at any time.

Among 9 dogs administered [42] oral doses of methyl alcohol ranging from 2.5 g/kg to 9.0 g/kg, 7 survived while 1 dog receiving 4.0 g/kg died between 29 and 46 hours after administration and another receiving 9.0 g/kg died 28-42 hours after administration. The highest nonlethal dose was 8.0 g/kg. It is not clear whether these doses are absolute methyl alcohol or a dilute solution. None of the dogs exhibited ophthalmoscopic changes. CO2-combining capacities dropped below the approximate range of normal values (42-54 volumes %) in only 2 of the 9 treated dogs. The surviving dog which was administered the highest dose, 8.0 g/kg, had the largest decrease in CO2-combining capacity. Its CO2-combining capacity returned to normal approximately 55 hours later. In neither case did the CO2-combining capacity decrease to levels similar to those observed in monkeys which were poisoned with methyl alcohol.

Six rhesus monkeys received oral doses of from 1.0 to 8.0 g methyl alcohol/kg. [42] Two monkeys receiving 1.0 and 2.0 g methyl alcohol/kg, respectively, survived while 4 monkeys receiving 3.0, 4.0, 6.0, and 8.0 g/kg, respectively, died. One monkey receiving 8.0 g/kg body weight died between 6 and 23 hours, while the monkey receiving 6.0 g/kg body weight died 29 hours following the administration of methyl alcohol. Two of the fatally poisoned monkeys showed definite eyeground changes while the other 4 monkeys showed no changes on ophthalmoscopic examination. Changes included retinal hemorrhage in one monkey and blurring of the disc, venous engorgement, and possible hyperemia of the disc in the other. Of the 6 monkeys, the one receiving the lowest dose (1.0 g/kg) did not become acidotic and the one receiving the highest dose (8.0 g/kg) died before the CO2-combining capacity was determined. The remaining monkeys all became

severely acidotic with minimum CO2-combining capacities ranging from 9.8 to 15.9 volumes %. Three died while acidotic at doses of 3.0, 4.0, and 6.0 g/kg, respectively. The CO2-combining capacity in the other monkey (2.0 g/kg) had returned to normal 21 days after administration.

Gilger and Potts [42] concluded from their studies that the results of oral administration of methyl alcohol to rats, rabbits, and dogs differed from those reported on humans in 4 important areas, namely, lethal dose, time course of development and signs of intoxication, eye effects, and acidosis. The authors also concluded that following intoxication with methyl alcohol, the responses of primates more closely approximated human responses than did those of nonprimates. An extensive review of the literature dealing with the oral toxicity of methyl alcohol in humans and nonprimates was supportive of their conclusion. The authors concluded that the approximate lethal oral dose of methyl alcohol in humans (0.85-1.4 g/kg) was 1/3 the equivalent dose in monkeys and 1/9 the equivalent dose in rats. Moreover, nonprimates exhibited severe early intoxication with narcosis lasting until death whereas primates showed much less early intoxication followed by a symptomless latent period, then by sickness and death. The only eye changes observed with certainty in nonprimates were early pupillary changes and corneal opacities following exposure keratitis. Some monkeys, however, and many humans developed partial or complete blindness accompanied by eyeground changes such as hyperemia of the optic discs and venous engorgement. Finally, humans and monkeys often developed severe acidosis (CO2-combining capacity less than 20 volumes %) after methyl alcohol ingestion; this condition was rare in nonprimates and occurred only at near lethal or lethal doses.

Also in 1955, Roe [43] reviewed the literature on the toxicity and metabolism of methyl alcohol and correlated this with his clinical experience. Great emphasis was placed on the importance of acidosis in human patients but not in animals. In humans, treatment of methyl alcohol poisoning with sodium bicarbonate to control acidosis and ethyl alcohol to inhibit the rate of methyl alcohol oxidation was very effective, whereas, in animals this was useless or deleterious. Roe [43] recognized that acidosis in humans was important and that there was a fundamental difference in methyl alcohol metabolism by humans and by animals.

In 1962, Cooper and Kini [44] reviewed the biochemistry of methyl alcohol poisoning with emphasis on enzyme systems. This and their own experimental research led to the conclusion that, while in lower animals methyl alcohol was metabolized to formaldehyde by catalase, in monkeys it was alcohol dehydrogenase, and not the catalase system, that was primarily responsible for methyl alcohol oxidation.

The recent review of the literature including their own research by Tephly et al [45] summarizes and expands on the above concepts. They make a distinction, not between animals and humans but between lower animals and primates, since rhesus monkeys share with humans the phenomena of acidosis and ocular toxicity. The reasons for these differences are not clear, but there are established differences in metabolic mechanisms. In rats, methyl alcohol is oxidized primarily by a catalase-peroxidase system, while in monkeys and humans it is oxidized by a liver alcohol dehydrogenase system. It appears that animal species, other than perhaps monkeys, are inadequate models for elucidating the nature of methyl alcohol poisoning in humans. Therefore, the extensive literature relating to the adverse effects of

parenterally administered methyl alcohol in nonprimate animals will not be treated in this document because the results of those studies are likely to bear little relevance to the occupational hazards to human health resulting from exposure to methyl alcohol. However, a few studies on the effects of methyl alcohol in monkeys and the irritant effects of externally applied methyl alcohol on lower animals will be described in this section. In addition, several studies which indicate a different route of methyl alcohol metabolism in primates and nonprimates will be discussed. For more information on the effects of parenterally administered methyl alcohol on nonprimate animals, the reader is referred to the somewhat old, but very thorough, review by von Oettingen. [46]

In 1931, McCord [47] studied the effects of methyl alcohol by skin absorption and inhalation in monkeys, rabbits, and rats. Skin absorption experiments were carried out by clipping the abdominal hair of the animals, then applying several layers of gauze padding to the clipped area which were held in place with bandages covered by rubber dam and secured with a canvas corset. Methyl alcohol was applied to the gauze pads with a hypodermic needle and syringe, thus precluding concurrent inhalation of the methyl alcohol. He described the results of the skin absorption experiments by stating that all animals subjected to the action of any amount of methyl alcohol by skin absorption had died. The lowest lethal dose was 0.5 ml/kg for one monkey. The author reported that rabbits were far less susceptible to methyl alcohol poisoning by this route than monkeys and rats. In a study of the effects of continuous administration of methyl alcohol, a known amount was dropped onto or injected into the gauze pads 4 times/day. All such treated monkeys displayed dilated pupils within 2

hours after one such administration of 1.3 mg/kg of methyl alcohol. The minimum lethal dose was a total of 4 administrations of 0.5 ml/kg methyl alcohol in one day, and the author concluded that sufficient methyl alcohol could be absorbed through the skin to cause death and that the threshold for immediate danger in monkeys was below the minimum lethal dose. By extrapolation, he concluded that 2.5-3.0 ounces (77.5-93 ml) of methyl alcohol applied once to an average-sized man under conditions favoring retention would be conducive to harm and would be undesirable; the assumptions used to arrive at these figures were not stated. The lack of specific information as to the exact skin area covered by the gauze pads as well as a confusing presentation of results (the author did not include detailed protocols in the report) detract from the quantitative value of this paper.

In order to determine the effects of methyl alcohol by inhalation, McCord [47] placed the animals in gassing chambers for from 1 to 18 hours. Air was continuously pumped through the chamber at a known rate. Methyl alcohol vapor was generated by dripping liquid methyl alcohol at a constant rate on a heated glass plate. Concentrations were calculated from the known volume of methyl alcohol evaporated in the chamber and the volume of air moved through the chamber, but air samples were not analyzed to confirm the validity of these calculations. Thus the true airborne concentrations may have been lower than those reported. The results of these studies were not presented in a clearly tabulated form. However, the author noted that the threshold of danger was well below 1,000 ppm, a concentration that led to the death of some of the animals. He reported marked differences in individual and species susceptibility. Thus one monkey survived an

extended exposure (exact time not reported) of 5,000 ppm while another died "promptly" upon exposure to 1,000 ppm. The average rabbit was said to be far more resistant to methyl alcohol vapor than the average monkey. McCord stated that it was not unusual to observe monkeys which were totally blind, as determined by both general observation and ophthalmoscopic examination, recover their sight and display no signs of intoxication. Corneal opacity in both rats and rabbits occurred early in the clinical manifestations of poisoning, presumably in contrast to the slower development of blindness in monkeys. As a result of the incomplete reporting of quantitative results in this study, it is difficult to assess the validity of the author's inference that the vapor from 1 ounce (approximately 30 ml) of methyl alcohol even over a period of 2-3 days constitutes a threat to human life.

In 1961, Cooper and Felig [48] described a study in which methyl alcohol was administered to rhesus monkeys of both sexes. The expressed purpose of this study was to identify the organic acid or acids believed to appear in increased amounts in the urine of monkeys and humans as a result of methyl alcohol poisoning. Unfortunately, no human material was available during the course of this study. Twelve monkeys were used in this experiment with 8 being reused from 1-5 times. After oral administration of the methyl alcohol, the monkeys were observed at frequent intervals for spontaneous activity, maintenance of equilibrium, resistance to handling, and response to visual and other stimuli. Twenty-four hour urine samples, collected both before and after administration, were analyzed for organic acids. Serum bicarbonate levels were determined as a measure of metabolic acidosis.

The results of this study [48] were unexpected in that the monkeys used did not respond to methyl alcohol intoxication like humans or like the monkeys in the study by Gilger and Potts. [42] In the first place, all monkeys receiving methyl alcohol at doses of 6 g/kg or less survived; the LD50 was found to be in the range of 7-9 g/kg. Secondly, the clinical course of fatal poisoning was narcosis followed by death with no asymptomatic latent period. Thirdly, only one monkey displayed a transient blindness 4 days after receiving 9 g of methyl alcohol/kg. Finally, only one out of three monkeys appeared to develop a definite metabolic acidosis. This animal, however, failed to demonstrate an increased excretion of urinary organic acids as did all the other monkeys in this experiment. The authors suggested that the monkey was an animal model intermediate between nonprimates and humans as it demonstrated characteristics similar to both nonprimates and humans. The original expressed purpose of this study was to identify the acids found in the urine of humans following methyl alcohol poisoning using rhesus monkeys. Cooper and Felig, [48] however, found no significant increase in urinary excretion of organic acids 24-72 hours following ingestion of methyl alcohol.

A series of normal aliphatic alcohols were tested for comparative irritant potential in 4 rabbits by Renkonen and Teir. [49] Methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, and octyl alcohols in doses of 10 and 35 mg dissolved in water or paraffin oil at a constant volume dose were injected intracutaneously, and the animals were observed for skin reactions. Measurements of skin reactions were performed 24 hours after injection of the alcohols. At 10 mg of methyl or ethyl alcohol in water, no skin reactions were seen. The other alcohols, however, all elicited a

skin reaction. At 35 mg of the alcohols in water, methyl alcohol elicited a 9-sq mm skin reaction, ethyl alcohol a 47-sq mm skin reaction, and propyl alcohol a 75-sq mm skin reaction. At least on the basis of tests on rabbits, it would appear that methyl alcohol is not a significant skin irritant.

In a range-finding test designed to show the potential for chemical substances to produce chemical burns of rabbit corneas, methyl alcohol was classified as grade 3 by Carpenter and Smyth. [50] The total grading scale ran from 1 to 10. An example of compounds in grades 1, 5, and 10 are ethylene glycol, acetone, and sodium hydroxide, respectively.

The remaining studies discussed in this section explore the enzymatic pathways of methyl alcohol metabolism in the animal systems studied and show that the primary pathway of methyl alcohol metabolism (although not the products) is different in nonprimates and primates.

In 1964, Tephly et al [51] studied the effect of ethyl alcohol and 1-butanol on the metabolism of 14C-labeled methyl alcohol in rats. The rats were given 1 g/kg of 14C-labeled methyl alcohol ip and monitored in metabolism cages. Methyl alcohol was oxidized at a constant rate of 24 mg/kg/hr for the first 28 hours. At the end of 36 hours, 77% of the methyl alcohol had been converted to 14C-labeled carbon dioxide and 24% of the administered dose was excreted unchanged. Approximately equal amounts were excreted unchanged by pulmonary and combined urinary and fecal routes. When an equimolar amount of ethyl alcohol was injected with the 1 g/kg 14C-methyl alcohol, there was a 55%-decrease in the amount of total 14C-labeled carbon dioxide excreted in the first 90 minutes following administration. The authors concluded that the enzyme systems responsible for the

metabolism of methyl alcohol were inhibited by ethyl alcohol, but a more likely interpretation is that ethyl alcohol preempted the metabolic activity of this enzyme system. The authors cited previous in vitro studies which indicated that the isolated catalase-peroxidase system had an equal affinity for methyl and ethyl alcohols whereas the affinity of the purified alcohol dehydrogenase system was 10-50 times greater for ethyl alcohol than for methyl alcohol. The authors [51] considered this to be evidence that the catalase-peroxidase system was primarily responsible for methyl alcohol metabolism in rats. At a molar ratio of 8:1 methyl alcohol to ethyl alcohol, there was no inhibition of ethyl alcohol metabolism. The authors concluded from this that the metabolic pathway for ethyl alcohol oxidation plays an insignificant role in the rat for the oxidation of methyl alcohol.

Additionally, 1-butanol was studied for its effect on the oxidation of 14C-ethyl and 14C-methyl alcohol. [51] In vitro studies cited by the authors indicated that 1-butanol had a greater affinity for ADH than ethyl alcohol; however, 1-butanol was a poor substrate for the catalase-peroxidase system. The in vivo experimental results revealed that 1-butanol was a potent inhibitor of ethyl alcohol metabolism and a poor inhibitor of methyl alcohol metabolism. Furthermore, the authors studied the effect of 3-amino-1,2,4-triazole (AT), an inhibitor of catalase, on the oxidation of 14C-methyl alcohol and 14C-ethyl alcohol. Pretreatment of rats with 1 g/kg AT ip 1 hour prior to methyl alcohol administration decreased methyl alcohol oxidation by about 50%. AT had virtually no effect on ethyl alcohol oxidation. In summary, the authors concluded from the results of all these studies that the catalase-peroxidase system in the

rat played a major role in the oxidation of methyl alcohol and was not primarily responsible for the oxidation of ethyl alcohol.

In 1968, Makar et al [52] published a comprehensive study on the mechanism by which methyl alcohol is metabolized by monkeys in vivo. Six young rhesus monkeys were used repeatedly throughout the study. They received 14C-methyl alcohol injected ip. The monkeys were divided into 2 groups. In order to determine the effect of dose size on oxidation, one group received 1 g/kg and the second group received 6 g/kg. At the 1 g/kg dose, 14C-methyl alcohol was oxidized at the rate of 37 mg/kg/hour between the first and the fourth hours. During this period, the rate of 14C-labeled carbon dioxide formation was linear. The animals receiving 6 g/kg oxidized the alcohol at a rate of 47 mg/kg/hour during the same time interval. Thus, the oxidation rates of the 2 doses were significantly different. In the animals receiving the higher dose of 14C-methyl alcohol, 49% of the methyl alcohol was oxidized to 14C-carbon dioxide, 35% was removed by pulmonary excretion as unchanged methyl alcohol, and 16% was removed via the kidneys as unchanged methyl alcohol.

The effect of ethyl alcohol on 14C-methyl alcohol oxidation and methyl alcohol on 14C-ethyl alcohol oxidation in monkeys was also studied. [52] Varying amounts of ethyl alcohol were injected with a constant dose of 14C-methyl alcohol (0.5 g/kg), and 14C-labeled carbon dioxide was collected at intervals over a 4-hour period. When equimolar quantities of the 2 alcohols were used, methyl alcohol oxidation was reduced 90% throughout the entire period of observation. These results are in contrast to the results of Tephly et al [51] in rats as described above where an equimolar dose of ethyl alcohol caused a 55%-reduction in methyl alcohol

metabolism. The results of the equimolar doses of the alcohols indicated that the peroxidative system is not the primary metabolic pathway for methyl alcohol in the monkey. If it were so, inhibition of methyl alcohol oxidation should have been around 50%. These findings suggested that the alcohol dehydrogenase system, or possibly a system other than the peroxidative system, was responsible for methyl alcohol oxidation in the monkey.

In another study, [52] the effect of 1-butanol on 14C-methyl alcohol metabolism in the monkey was observed. In vitro studies cited by the authors showed that, compared with ethyl alcohol, the reactivity of 1-butanol was greater for the alcohol dehydrogenase system. Moreover, 1-butanol was less reactive with the perioxidase system than either ethyl or methyl alcohol. With a molar ratio of 14C-methyl alcohol to 1-butanol of 1:0.5, the oxidation of methyl alcohol was inhibited 63% during the first 90 minutes following dosing. This finding is in contrast to the results of the rat experiments described earlier [51] where 1-butanol did not noticeably affect methyl alcohol metabolism. This again supported the view that for monkeys the alcohol dehydrogenase, or some system not involving catalase, is the primary metabolic pathway for methyl alcohol oxidation.

Makar et al [52] referred to one of their earlier studies in which the effects of inhibition by AT on hepatic catalase in the rat were examined. Intraperitoneal administration of AT to rats was shown to reduce the oxidation of methyl alcohol by 50% in vivo. However, in this study, [52] when 5 monkeys received AT prior to 14C-methyl alcohol there was no significant drop in methyl alcohol metabolism. This suggested to the authors that the catalase peroxidase system was important in the oxidation

of methyl alcohol in the rat but did not play a significant role in the monkey.

Clay and coworkers [53] administered methyl alcohol to rats, rhesus monkeys, and pigtail monkeys. Acidosis developed consistently in pigtail monkeys (at 2-4 g/kg ip) but in only 1 of 4 rhesus monkeys (at 4 g/kg ip) and not at all in rats. Using the pigtail monkey as the animal model of choice for other experiments, several studies were performed. Blood ions and pH were measured in pigtail monkeys injected ip with methyl alcohol 4 g/kg as a 20% solution in physiological saline. Blood bicarbonate (pCO2 and total CO2) and pH decreased over the period 7.5-21 hours, glucose increased moderately and formate increased markedly. There were also significant increases in lactate, alpha-hydroxybutyrate, beta-hydroxybutyrate, alpha-ketobutyrate, acetoacetate, p-hydroxyphenylacetate, and p-hydroxyphenyllactate; however, these increases accounted for only a small part of the increases in blood anions, with formate constituting the major, almost total, constituent replacing blood bicarbonate. In another experiment, a specific inhibitor of hepatic alcohol dehydrogenase, 4-methylpyrazole (50 mg/kg by vein) was administered 30 minutes prior to methyl alcohol (4 g/kg ip) and every 6 hours thereafter. Under these circumstances, there were no significant decreases in blood pH or other signs of toxicity during the 48-hour observation period. These experiments give additional support to the evidence that methyl alcohol in primates is primarily metabolized by alcohol dehydrogenase and then further oxidized to formate which is the principle cause of acidosis.

The well-designed studies of Tephly et al, [51] Makar et al, [52] and Clay et al [53] present strong evidence that different enzyme systems are

primarily responsible for the oxidation of methyl alcohol in rats and monkeys and that the pathway in monkeys more closely resembles the pathway in humans as previously discussed in this chapter. The cited evidence also indicates that the nature of methyl alcohol poisoning in monkeys more closely resembles that in humans than in nonprimates. It is tempting to speculate that this similarity is a result of the similar metabolic pathways in these species. No direct evidence supporting this speculation has been found, however, and the exact reasons why humans are affected differently by methyl alcohol than nonprimates remain unknown.

Correlation of Exposure and Effect

Well-documented studies that correlate environmental levels of methyl alcohol with observed toxic effects have not been found in the literature, nor have any long-term epidemiologic studies of chronic low-level occupational exposure been found.

Effects seen from either of the 2 most common routes of occupational exposure (inhalation and percutaneous absorption) include: headache [14,16,17,39]; dizziness [13,19]; nausea [16,17,26]; vomiting [17]; weakness (unspecified) [16]; vertigo [17,26]; chills [13]; shooting pains in the lower extremities [13]; unsteady gait [17]; dermatitis [14]; multiple neuritis characterized by paresthesia, numbness, prickling, and shooting pain in the back of the hands and forearms, as well as edema of the arms [15]; nervousness [19]; gastric pain [19]; insomnia [19]; acidosis [19]; and formic acid in the urine. [26] Eye effects, such as blurred vision, [16,17] constricted visual fields, [17,19,25] blindness, [13,25] changes in color perception, [17] double vision, [19] and general visual

disturbances [17] have been reported. Eye examinations have shown sluggish pupils, [13,17] pallid optic discs, [13] retinal edema, [17] papilledema, [26] hyperemia of the optic discs with blurred edges and dilated veins. [17]

The study by Bennett et al [40] showed similar symptoms resulting from ingestion. These are acidosis, headache, visual disturbances, dizziness, nausea and vomiting, severe upper abdominal pain, dilated and nonreactive pupils. Eyeground examinations showed hyperemia of the optic discs and retinal edema. The eyeground changes were almost always found in acidotic patients. This finding is suggestive of a correlation between acidosis and visual disturbances. However, a number of patients with and without acidosis complained of visual disturbances. Additionally, blood tests showed elevated serum amylase levels in 14 of 21 patients. This finding in conjunction with complaints of upper abdominal pain and pancreatic necrosis seen at autopsy led the authors [40] to conclude that hemorrhagic pancreatitis resulted from acute methyl alcohol intoxication. However, reports of acute hemorrhagic pancreatitis by parenteral routes have not been found.

Direct skin contact with methyl alcohol has been said to cause dermatitis, [14] erythema, and scaling. [27] The reported variability in susceptibility [14] is probably largely because of variations in time of contact with methyl alcohol; it is evident that sufficient dermal contact with any lipid solvent such as methyl alcohol has the potential for causing skin irritation.

Direct contact of methyl alcohol with the eyes resulted in chemosis and superficial lesions of the cornea which were rarely of a serious

nature. [24] This conclusion was supported by the findings of later studies on rabbits, [50] which showed that methyl alcohol was a mild eye irritant.

Many of the signs and symptoms of intoxication attributed to either the ingestion, inhalation, or percutaneous absorption of methyl alcohol are not specific to methyl alcohol. Thus, for example, headache, dizziness, nausea and other gastrointestinal disturbances, weakness, vertigo, chills, behavioral disturbances, and neuritis can be caused by a wide range of chemical and physical stresses on the organism. Therefore, these signs and symptoms may be of little use in diagnosing methyl alcohol poisoning. The characteristic signs and symptoms of methyl alcohol poisoning in humans, then, are the various visual disturbances and severe metabolic acidosis which appear to result from overexposure to methyl alcohol by any route. Chronic exposure at relatively low levels of methyl alcohol may have effects other than those resulting from acute exposure; however, no studies have been found that would support this speculation.

The presence of a characteristic asymptomatic latent period following ingestion of methyl alcohol, prior to the development of acidosis and/or visual disturbances in humans and in some nonhuman primates, suggests that these effects are caused by a metabolite of methyl alcohol rather than by the alcohol itself. Evidence for a metabolite of methyl alcohol acting as the proximal toxic agent is the fact that toxic manifestations can be attenuated by the administration of ethyl alcohol, [29] a compound that has been shown to inhibit the oxidation of methyl alcohol in vivo. [30,31,37]

As a result of the critical role which the metabolism plays in the course of human methyl alcohol intoxication, it is clear that factors which

affect that metabolic pathway will also affect the severity and course of the methyl alcohol intoxication. The amelioration of methyl alcohol poisoning by ethyl alcohol [29] is one example. The individual variations in activity of the alcohol dehydrogenase systems probably account for the variation in the individual responses observed with methyl alcohol poisoning. In their study of an epidemic of methyl alcohol poisoning, Bennett et al [40] noted what they called an extreme variation in individual response to a given amount of methyl alcohol in that one individual died after ingesting approximately 15 ml of a 40% methyl alcohol solution and another survived after ingesting 500 ml of this same solution. This wide variability in individual susceptibility to ingested methyl alcohol has also been noted by others, [11] and reviewed by Cooper and Kini. [44]

Although not as clearly documented, there appears to be a similar individual variability among persons exposed to methyl alcohol by inhalation or percutaneous absorption, both in the type of symptoms manifested and in their severity. For example, Wood [18] described the cases of 4 men who were employed together as varnishers of beer vats. One felt dizzy after the first day and could not continue past the second day. Another did not develop symptoms until the third day. The remaining 2 worked through the third day but subsequently died without returning to work. In Tyson's study of the pencil-varnishing operation, [17] all the women in the room presumably had similar exposures but only 2 sought medical treatment for visual disorders. The results of one inhalation study [47] using rhesus monkeys revealed individual susceptibility differences in that one animal died during exposure to 1,000 ppm methyl

alcohol whereas another survived an exposure to 5,000 ppm.

Quantitative data are not available which might indicate at what concentration in the air methyl alcohol constitutes a threat to human life. McCord [47] reported that exposure of one monkey to methyl alcohol at 1,000 ppm for an unspecified length of time was lethal, but the lack of reported experimental detail leaves this result open to question.

Humperdinck [25] described a case in which an employee experienced diminution of vision which was associated with chronic exposure in the workplace to concentrations of methyl alcohol in the range of 1,600-10,900 mg/cu m (1,200-8,300 ppm).

Leaf and Zatman [30] reported that when human volunteers were exposed to methyl alcohol concentrations of 650 to 1,430 mg/cu m (500-1,100 ppm), 3-4 hours of exposure were all they could reasonably tolerate. The authors did not make it clear, however, whether further exposure could not be tolerated because of the direct effect of methyl alcohol vapor or because of the conditions of the experiment.

Kingsley and Hirsch [39] reported that the frequency and severity of persistent headaches in employees of the Sandia Laboratories appeared to be a function of the proximity of their workplace to direct process duplicating machines which used methyl alcohol-based duplicating fluid. Air samples in the vicinity of the duplicating machine operations in the workers breathing zone revealed concentrations of methyl alcohol ranging from 15 to 375 ppm (20-490 mg/cu m), while air samples 10 feet from the machines revealed concentrations of approximately 100 ppm (130 mg/cu m). As stated by the authors concentrations were usually in excess of 200 ppm (260 mg/cu m) and less than 300 ppm (490 mg/cu m).

In 1917, the New York State Industrial Commission [14] made a survey of the artificial flower industry, in which methyl alcohol was used as a dye solvent. In one factory, the airborne level of methyl alcohol was found to be 200 ppm W/V. In many instances, the odor was noticeable at a distance of 75 feet from the dipping and drying operation. Exposure to methyl alcohol in this environment was said to result in dermatitis, anemia, nearsightedness, and conjunctivitis. As previously discussed in the section on Epidemiologic Studies, it seems doubtful that exposures at 200 ppm of methyl alcohol were responsible for the effects noted.

Greenburg et al [38] reported on the health effects of 19 men employed in the fused-collar industry for a period of 9 months to 2 years. The airborne concentrations of methyl alcohol and acetone to which these workers were simultaneously exposed were 22-25 ppm and 40-45 ppm, respectively. Physical examination including ophthalmoscopic examination performed on these men revealed no significant findings which might be related to methyl alcohol exposure.

Chao Chen-Tsi [22] stated that airborne methyl alcohol at a concentration of 3.3 mg/cu m (2.5 ppm) caused a diminution of light sensitivity in the most sensitive human subjects whereas methyl alcohol at a concentration of 2.4 mg/cu m (1.8 ppm) had no such effect.

Ubaydullayev [23] indicated that airborne methyl alcohol at a concentration of 3.5 mg/cu m (2.7 ppm) caused a change in one human subject's sensitivity to light during dark adaptation whereas a concentration of 3.1 mg/cu m (2.4 ppm) had no effect. In addition, all 6 human subjects exposed to airborne methyl alcohol at a concentration of 1.5 mg/cu m (1.1 ppm) showed changes in the alpha-rhythm amplitude of their

EEG's, whereas 1.0 mg/cu m (0.77 ppm) was a no-effect level.

Unfortunately, it is difficult to assess the validity of the results reported both by Chao Chen-Tsi [22] and by Ubaydullayev [23] since neither author provided any specific information as to the source and purity of the methyl alcohol used, how the subjects were exposed to methyl alcohol, how methyl alcohol concentrations were determined, how the human responses were measured, and what statistical methods were used to treat the experimental data. Moreover, even if adverse effects do occur at relatively low concentrations of methyl alcohol, it has not been clearly established whether subtle changes in EEG patterns or light sensitivity can be classed as adverse health effects. As discussed in the section Effects on Humans, it seems doubtful that these represent adverse changes of exposure at low concentrations of methyl alcohol.

Chao Chen-Tsi [22] and Ubaydullayev [23] reported odor thresholds for methyl alcohol which also were studied by Scherberger et al [20] and May. [21] Ubaydullayev [23] reported a minimal perceptible concentration of methyl alcohol of 3.4 ppm while May [21] reported an odor threshold of 5,900 ppm. May's study has the advantage of being thoroughly described; it used a relatively large number of subjects. If, in fact, the odor threshold for methyl alcohol is in the neighborhood of 5,900 ppm, it is clear that methyl alcohol may not be detectable by odor at concentrations which might pose a threat to human health.

A summary of available data would seem to indicate that chronic exposure to air concentrations of methyl alcohol in a range of 1,200-8,300 ppm can lead to impaired vision. [25] Concentrations probably in excess of 200 ppm may lead to persistent, recurring headaches. [39] On the other

hand, occupational exposures at air levels of 25 ppm [38] during an 8-hour working day apparently may be endured without harmful effects.

No human or experimental mammalian studies have been found to evaluate the possible mutagenic, teratogenic, or carcinogenic effects of methyl alcohol. In a study [54] in grasshoppers, Oxya velox Fabricius, 0.3% methyl alcohol injected in the vicinity of the testes produced an incidence of 3.5% chromosomal aberrations in testicular tissue, but examination of the stages of spermatogenesis was not performed.

No aberrations were observed in grasshoppers injected with distilled water. Saha and Khudabaksh [54] did not report any evidence for the induction of permanent aberrations in germ cell lines or for the inheritability of the observed abberations. In view of the fundamental differences in genetic mechanisms, the utility of the grasshopper in quantitatively predicting inheritable germinal or somatic mutations in humans is questionable.