Very good progress notes on clinical effects of pathological MeOH

THE OCULAR EFFECTS OF METHYL ALCOHOL POISONING:

Report of a Catastrophe Involving Three Hundred and Twenty Persons

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ON OCTOBER 20, 1951 a large quantity of bootleg whiskey containing 35 per cent methyl alcohol and 15 per cent ethyl alcohol was distributed in Atlanta, Georgia. During the succeeding seven days, three hundred and twenty persons sought emergency medical care at Grady Memorial Hospital because of symptoms attributable to the ingestion of this mixture. Twenty-four persons died before or shortly after reaching the hospital and thirteen died on the medical wards, making a total of thirty-seven deaths. A general report of these cases has been published elsewhere.[5]

Ophthalmic observations were made by one of the authors (Benton) on a large proportion of the patients immediately upon their acceptance to the hospital emergency room. Data were recorded concerning the amount of contaminated whiskey consumed and the date thereof, onset and character of symptoms, the vision, pupillary reaction to light, visual fields (confrontation method) and ophthalmoscopic appearance of the fundi. Every patient admitted to a hospital bed was examined daily until the time of his discharge and then at gradually longer intervals in the eye clinic. Measurements of visual acuity and central visual fields and observations of the ocular fundi were made at each visit during the eight month follow-up period. Patients who were never admitted to the hospital were asked to report to the eye clinic for examination. One hundred and twenty-three patients returned for re-examination.

The symptoms of acute methyl alcohol poisoning usually develop eighteen to forty-eight hours after ingestion, but in a few instances transitory symptoms were noted within one hour. The patients complained of visual disturbances, weakness, abdominal pain, nausea and vomiting, headache, dizziness, and shortness of breath. Some patients had consumed as little as 90 cc. of the alcoholic mixture and others had drunk as much as 750 cc. Within this range there was no close correlation between the severity of symptoms and the quantity of methyl alcohol consumed.

The initial visual symptoms ranged from spots before the eyes to complete blindness. Many patients complained of whitish or grayish misty vision. The visual acuity was either normal or markedly reduced. The patients with severe visual loss could count fingers only in the mid-periphery of their visual field. Three patients who were conscious had no light perception in either eye. Characteristically, the initially reduced vision showed an early recovery which was in some cases only transitory. Many patients experienced full return of vision

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during the first hour of treatment by intravenous alkaline fluids. All patients who regained and retained normal visual acuity did so within six days after treatment was begun. If the vision did not return to normal in six days, it invariably dropped again to a very low level. Only 3 patients, all nearly or completely blind at the time of hospital admission, failed to exhibit any permanent or temporary improvement in vision.

In the acute phase of poisoning, diminution of the pupillary reaction to light occurred in all patients with impaired vision and in many patients with normal vision. The degree of impairment of the pupillary light reflex proved to be of considerable prognostic value. Patients with dilated, fixed pupils usually died: if they recovered they always had severe visual damage. Lesser degrees of impairment in the pupillary response to light were indicative of a more favorable outcome and no patient with normally reacting pupils had permanent visual loss. These findings are illustrated in figure 1.

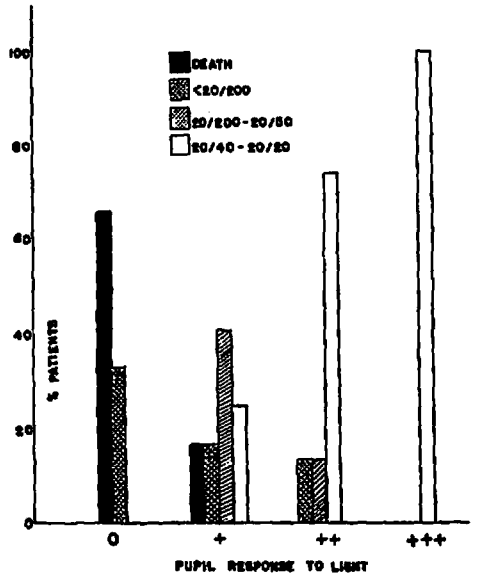

FIG. 1—Correlation of pupillary response to light with fatality and final vision (+++ equals normal reaction).

The ophthalmoscopically visible fundus changes were always identical in type and sequence of appearance and varied only in intensity from one patient to the next. A hyperemia of the optic disc could be seen at the time symptoms of visual loss developed. The reddish color of the papilla persisted from one to seven days. From six to twenty-four hours after the hyperemia became visible, there developed a whitish striated edema of the disc margins and adjacent retina. Edema was most extensive along the course of the major retinal vessels, and it persisted for ten to sixty days. The peripapillary retinal edema appeared to be chiefly in the nerve fiber layer. Engorgement of the retinal veins usually accompanied the retinal edema and followed a similar course. These characteristic fundus changes were seen in 87 per cent of patients with initial visual loss and in every patient who later showed permanent impairment of vision. Mild or moderate retinal edema was followed by complete recovery of vision in some cases, blindness in others. It was found, however, that all patients who had severe retinal edema and most patients with moderate retinal edema had some degree of permanent visual loss.

In patients with severe ocular damage an atrophy of the optic disc became visible in thirty to sixty days. Usually the optic nerve atrophy was identical in appearance to so-called primary optic atrophy, although occasionally a cupping of the nerve head that simulated glaucoma was seen.

In 5 patients there was a striking difference between the visual acuity of the two eyes, even though the ophthalmoscopic changes were always bilaterally equal. In 4 of the 5 such cases, the left eye was the most severely impaired. The shape of the scotomas offered the explanation of this difference in visual acuity. In the central field of the better

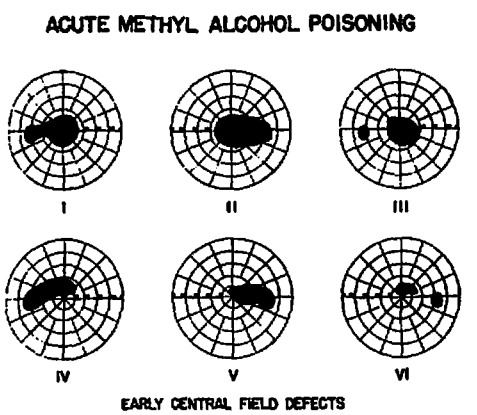

FIG. 2—Acute methyl alcohol poisoning. Early central field defects (5/1000 form).

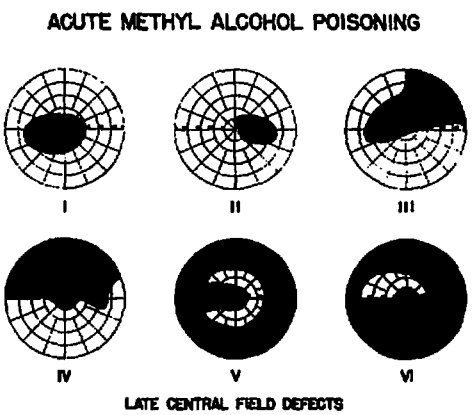

FIG. 3—Acute methyl alcohol poisoning. Late central field defects (5/1000 form).

eye, the scotoma extended from the blind spot like an open mouth preparing to engulf the fixation area. In the opposite eye a complete cecocentral scotoma obliterated the area of critical vision. After four to six months, the visual acuity in the better eye began to decline and approach the level of the other eye.

The typical alteration of the visual field was a cecocentral scotoma of considerable density. Frequently this type of scotoma was incomplete so that it arched above or around the fixation point and did not impair central visual acuity. A few patients had a pericentral or paracentral scotoma not connected with the blind spot (fig. 2). In only 2 patients was the peripheral field constricted in the early stages. After two to four months various and bizarre alterations appeared in the visual fields. Defects of the fiber-bundle type and peripheral constriction usually combined to eliminate all or most of the field of vision (fig. 3). The symptoms and signs described above are similar to those reported previously by other authors.[2,3,4,6,10,14,17,20,21]

Chemical studies revealed the presence of methyl alcohol in the blood, urine, spinal fluid, aqueous and vitreous humors of the eye. The concentration was always greater in the vitreous than in the aqueous of the eight eyes tested. A trace of formaldehyde was found in the vitreous of one eye. Formic acid was not detected in the aqueous or vitreous of either eye in one fatal case.

The most important alteration in the biochemical status of persons poisoned with methyl alcohol occurs in the carbon dioxide combining capacity of the blood. The blood carbon dioxide was measured on every patient immediately upon his acceptance into the emergency clinic. The degree of acidosis proved to be an invaluable guide to diagnosis, therapy, and prognosis. This point has been repeatedly stressed by Røe and others since 1943.[4,7,14-17] The blood carbon dioxide was normal (above 26 milliequivalents per liter, or 55 volumes per cent) in 188 patients. Not one patient in this group had genuine symptoms or signs of methanol poisoning and undoubtedly many of these patients drank none of the contaminated whiskey. No treatment was given any patient who had a normal blood carbon dioxide. Follow-up studies were done two to six months later on 94 or 50 per cent of this group of patients, and not one had evidence of any visual damage from methyl alcohol. The blood carbon dioxide was 25 milliequivalents per liter or below in the re-

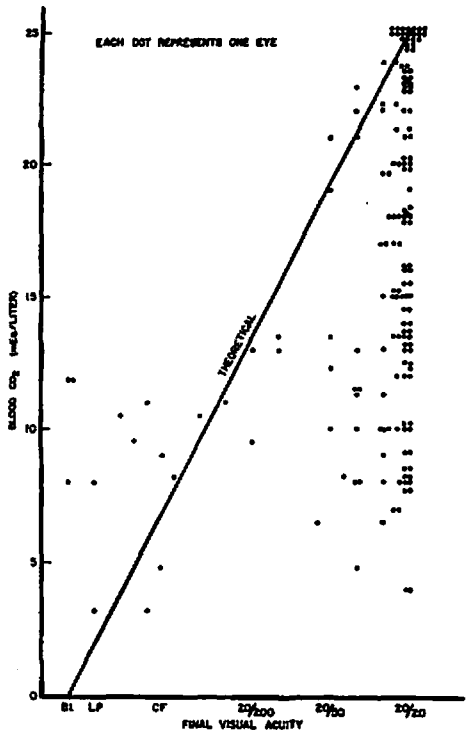

FIG. 4—Correlation of initial blood carbon dioxide with final visual acuity. (The wide scattering of the dots on the graph does not conform to the theoretical correlation as represented by the diagonal line.)

maining 132 patients. Thirty-seven of these patients died. All fatal cases had a severe acidosis with the blood carbon dioxide usually below 10 milliequivalents per liter. Death was always characterized by cessation of respiration from medullary paralysis. Convulsions were common. The heart usually continued to beat for several minutes after respirations stopped. When it was possible to obtain a history on the patients who died, it was learned that they were always blind or nearly blind before their final loss of consciousness. Ninety-five patients with a low blood carbon dioxide survived the poisoning. Sixty-two of these patients had visual symptoms. Objective ophthalmoscopic findings were present only in patients with visual symptoms, and occurred in 87 per cent of those. The relation of blood carbon dioxide before treatment to the final visual acuity showed that chances of restoration of complete vision was possible at almost any carbon dioxide level, but patients with a very low carbon dioxide level frequently had permanent loss of vision. No patient with a carbon dioxide level above 12 milliequivalents per liter had a final visual acuity worse than 20/200 in either eye. These findings are illustrated graphically in figure 4.

Treatment was directed toward the elimination of acidosis in those patients with a low blood carbon dioxide. Bicarbonate of soda was taken by mouth in patients whose symptoms were mild and whose blood carbon dioxide was between 20 and 25 milliequivalents per liter. Patients with a very low carbon dioxide and severe symptoms were given soda bicarbonate intravenously. The available supply of already prepared alkaline solutions for intravenous administration was quickly exhausted. New solutions were readily prepared by dissolving the dry powder from clean, previously unopened boxes of bicarbonate in flasks of sterile glucose, saline, or distilled water. Several hundred such solutions containing 25 to 50 grams of bicarbonate per liter were given intravenously with no ill effects. Symptoms of alkalosis rarely developed even though the blood carbon dioxide rose to 40 or 50 milliequivalents per liter in some patients. Because of the strong tendency for acidosis to recur, it was found that alkali therapy had to be continued for a minimum of three days, with constant check of the blood carbon dioxide or urine pH. This was strikingly demonstrated in 4 patients who were treated in the emergency clinic and failed to follow instructions to take soda bicarbonate orally at home. They were brought back the next day in severe acidosis and died.

Adequate correction of acidosis in patients with severe methyl alcohol poisoning will not invariably save life or vision. If the acidosis is severe or has persisted for several hours, death may result in spite of energetic treatment, or if the patient survives, he may have marked loss of vision.

Also, inadequate alkali therapy may result in a prolonged state of mild or moderate acidosis and permanent loss of vision. These observations can be illustrated by the following examples:

Cases 6, 7 and 8 demonstrated prolonged acidosis as the result of inadequate alkalinization.

Case 6. This Negro boy aged 19, had consumed a half pint of the methanol mixture two days before admission. Visual acuity was reduced to 20/200 in the right eye and finger counting in the left eye. The blood carbon dioxide was 9 milliequivalents (mEq.) per liter. Sixty grams of soda bicarbonate intravenously quickly elevated the blood carbon dioxide to 27 mEq. per liter, but the following day it had dropped to 17 mEq. per liter. The administration of 16 grams of soda by mouth returned the blood carbon dioxide to 28 mEq. per liter. The final visual acuity was O.D. 20/30 and O.S., fingers at 18 inches. A cecocentral scotoma persisted in the left central field whereas a pericecal scotoma in the right field spared the fixation area.

Case 7. This 26-year-old Negro male drank a half pint of the poisoned whiskey. Within 18 hours the vision became blurred. He did not seek treatment for another 18 hours, at which time his vision was reduced to finger counting at 10 inches. The blood carbon dioxide was 13 mEq. per liter. Fifty grams of soda bicarbonate intravenously elevated the blood carbon dioxide to 30.5 mEq. per liter. The following day the blood carbon dioxide had fallen to 16 mEq. per liter. Thirty-five grams of soda by mouth brought the blood carbon dioxide up to 22 mEq. per liter. The final visual acuity was O.D., 20/200 and O.S., 20/100.

Case 8. This 40-year-old Negro man had consumed a half pint of the methyl alcohol mixture. Dimness of vision was experienced after 12 hours. The blood carbon dioxide was 15 mEq. per liter. For four days the blood carbon dioxide remained below 20 mEq. per liter in spite of an initial dose of 50 grams of bicarbonate of soda intravenously followed by oral doses of 30 to 45 grams daily. Although this patient could count fingers accurately at 10 inches at the time of admission, he became and remained totally blind.

Cases 3 and 5 show the tendency for acidosis to recur after initial correction.

Case 3. This Negro woman, aged 34, became blind 48 hours after consuming a half pint of the contaminated bootleg whiskey. The initial blood carbon dioxide was 9 mEq. per liter. Soda bicarbonate was given intravenously in doses of 35 grams and later 20 grams. The blood carbon dioxide remained above 30 mEq. per liter the following 36 hours and then fell to 23 mEq. per liter. No further treatment was given. The final visual acuity was O.D., 20/200 and O.S., fingers at 6 inches. A cecocentral scotoma persisted in the left field whereas the right fixation area was spared by a pericecal scotoma.

Case 5. This 37-year-old Negro man drank "a little bit" of the methyl alcohol whiskey eight hours before being brought to the hospital. Amblyopia was severe and the blood carbon dioxide was 5 mEq. per liter. After 75 grams of soda intravenously the blood carbon dioxide became normal and remained so during the following day. Twenty-four hours later the blood carbon dioxide had dropped to 16 mEq. per liter but was again elevated to normal by the oral administration of 30 grams of soda. The final visual acuity was O.D., 20/40 and O.S., fingers at 18 inches. Again the difference in visual acuity between the two eyes was due to a cecocentral scotoma in the left eye and a pericentral scotoma in the right eye.

The poor vision in cases 2 and 4 is evidence that adequate alkali therapy will not always prevent blindness.

Case 2. This 43-year-old Negro man drank a moderate quantity of the poisoned whiskey over a two-day period. Blurred vision was experienced one day later. The patient was not brought to the hospital until the following day, at which time he was blind. The blood carbon dioxide was 8 mEq. per liter. One hundred and twenty grams of soda intravenously elevated the blood carbon dioxide to 50 mEq. per liter, where it remained for at least two

		CASES							
DAY		1 L.R.	2 D.N.	3 R.F.	4 L.S.	5 W.G.	6 R.H.	7 W.M.	8 W.R.M.
1	CO_2 Soda CO_2 Soda	4 100 gm. 42	8 120 gm. 52	9 35 gm. 30 20 gm.	3 40 gm. 33 30 gm.	5 75 gm. 26	9 60 gm. 27	13 50 gm. 30.5	15 50 gm. 22
2	CO_2 Soda	43	49	36	42	38	17 16 gm.	16 35 gm.	12 45 gm.
3	CO_2 Soda			23	45	16 30 gm.	28	22 20 gm.	19 30 gm.
4	CO_2 Soda					35			19 30 gm.
Final Vision	O. D. O. S.	20/20 20/20	L.P. Blind	20/200 C.F.	C.F. L.P.	20/40 C.F.	20/30 C.F.	20/200 20/100	Blind Blind

days. Inspite of this he gained only a little vision and then again became blind.

Case 4. A 47-year-old Negro woman drank a half glass of the poisoned whiskey. There was headache, nausea and vomiting in six hours followed the next day by blurring of vision. The blood carbon dioxide at the time of hospital admission was 3.2 mEq. per liter. After 40 and 30 grams of soda intravenously the blood carbon dioxide remained over 40 mEq. per liter for two days. The visual acuity improved in two months to O.D., 20/100 and O.S., fingers at 6 inches, then dropped to finger counting in the right eye and light perception in the left.

Normal vision may result even in the face of initially low blood carbon dioxide if treatment is prompt.

Case 1. This 20-year-old Negro girl experienced abdominal pain and poor vision 24 hours after drinking a half glass of the bootleg whiskey. The blood carbon dioxide was 4 mEq. per liter. After 100 grams of soda intravenously the blood carbon dioxide was well above normal for at least two days. The visual acuity quickly returned to normal in both eyes and has remained the same.

ACTH was given to four patients with no beneficial effect. Spinal fluid exchange therapy was carried out several times on 3 patients who had severe visual loss.[11,19] No improvement resulted from this treatment. Ethyl alcohol was given intravenously to only one patient. Although definite improvement was observed, this is not given here as evidence in favor of the belief that ethyl alcohol should be used in the treatment of methyl alcohol poisoning.[1,2,14-17]

Histologic examinations on six eyes removed six to eighteen hours after death showed degeneration of the ganglion cells of the retina, slight edema of the nerve fiber layer near the disc, some degeneration of the rod and cone layer with accumulation of a small amount of albuminous fluid under the retina near the disc. All these changes could have been the results of normal post-mortem degeneration, particularly since the changes were more prominent in those eyes removed at eighteen hours than in those removed at six hours after death. Other investigators have presented considerable evidence that degeneration of the retinal ganglion cells is a specific toxic effect of methyl alcohol.[6,8,14-17]

Other pathologic findings of interest were a mild to moderate edema of the brain and an acute pancreatitis. Studies of cerebral blood flow were done on five patients with severe poisoning. The average arterial oxygen saturation was 92 per cent. Cerebral blood flow was reduced 33 per cent and cerebral oxygen consumption was diminished 35 per cent. Serum amylase determinations on several patients showed moderate to marked high levels, therefore it was felt that acute pancreatitis was often the cause of the severe abdominal pains in these patients.[5]

Many theories have been advanced to explain the mode of toxic action of methyl alcohol in the human body.[6,9,13,14-18] It is unfortunate that laboratory animals do not respond to this agent in a manner similar to the human. Acidosis almost never develops and the animals do not often appear to go blind. Fink[6] and also McGregor[8] have described degeneration of the retinal ganglion cells in animals poisoned with methyl alcohol, but this has been denied by Røe.[14-17] Conclusions from experiments on animals should be applied to humans with great caution and reservation.

Again! Is anybody Listening OUT There!

Apparently methyl alcohol breaks down slowly in the body to formaldehyde and formic acid. It appears unlikely that any of these chemicals acts directly on the retina or other nerve tissue. Methyl alcohol is rapidly distributed throughout all body fluids but symptoms of poisoning rarely develop in less than eighteen hours after ingestion. According to the theory of Rohr,[13] methyl alcohol or one of its breakdown products

slowly combines with the iron catalyst of the oxydase system rendering it inactive and causing a tissue anoxia. This process is accelerated in the presence of acidosis.[14-17] Because the retina has the highest oxygen requirement per unit concentration of iron of any body tissue, it is not surprising that this delicate ocular membrane should be damaged in methyl alcohol poisoning. An indirect toxic action, as just described, offers a ready explanation for the parallelism of ocular symptoms and signs of methanol poisoning with the amblyopia of lead, arsenic, thallium, or carbon disulfide poisoning or even that of severe malnutrition.[12] Recently Potts and Johnson[9] found evidence that the proximal toxic agent in methanol poisoning may be formaldehyde, a potent inhibitor of retinal oxidation and glycolysis. The acidosis does not appear to be the cause of amblyopia but it does act as an accelerating force. If acidosis can be corrected before permanent ocular damage has resulted, a return of normal visual acuity can be expected. If retinal tissue hypoxia has existed long enough for irreversible degeneration of the ganglion cells to occur, treatment may prevent death but visual impairment will be permanent. Until a specific chemical is found that will prevent or release the combination of methyl alcohol or its products with the iron oxydase system, rapid, intense, and prolonged alkalinization appears to be the most important phase of treatment for acute methyl alcohol poisoning.

SUMMARY

Clinical and pathologic observations on a group of three hundred and twenty patients with acute methyl alcohol poisoning are reported. There were thirty-seven deaths.

Visual symptoms, occurring eighteen to forty-eight hours after ingestion of methanol, included blurred vision, loss of central vision and complete blindness. The pupils reacted sluggishly or not at all to light. Absence of the pupillary light reflex was a sign of poor prognosis for life or eventual restoration of visual acuity. The visible retinal changes were hyperemia of the optic nerve head and superficial edema of the papilla and surrounding retina, and later a simple atrophy of the optic nerve. All patients with severe retinal edema had some degree of permanent visual loss. The earliest central field defect was usually a cecocentral scotoma. Later more complex types of visual field defects appeared.

Acidosis was present in every severely poisoned patient. The degree of acidosis paralleled the severity of general and ocular symptoms.

Partial or complete recovery of the initially reduced visual acuity was observed in most patients. If the visual acuity did not return to normal within six days after treatment was begun, it invariably dropped again to a very low level. The final vision was 20/200 or less in both eyes of six patients and in one eye of three patients.

Histologic studies on six eyes enucleated after death revealed changes consistent with post-mortem degeneration.

On the basis of the results obtained in this series of cases, the most effective treatment of acute methyl alcohol poisoning consists of intensive and prolonged alkalinization.

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DISCUSSION

ALBERT M. POTTS, M.D., Cleveland, Ohio (by invitation): It is at once a great pleasure and privilege to be asked to discuss this report of Drs. Benton and Calhoun. They are without doubt the two living ophthalmologists with the greatest experience in clinical methyl alcohol poisoning and the observations which they made have the virtue of high significance because of the large number of cases observed.

The importance of methanol poisoning as an ever-present menace lies in the very fact that such a catastrophe as the one reported could occur within the past year. Its seriousness is underlined by the statistic that of all cases reported here showing any symptoms 28 per cent, or one for every three and one half patients, died (320 less 188 symptom-free = 132 cases of which 37 deaths = 28 per cent). Of the survivors an equal proportion had some measurable visual damage and 10 per cent of the survivors were made blind, retaining vision of 20/200 or less.

Although the number of individuals involved in this instance is an unprecedentedly high one, instances of smaller outbreaks of methyl alcohol poisoning are still not uncommon among the civilian population. In the Armed Forces, where access to ethyl alcohol is restricted, methanol is a constant hazard as some of Dr. Calhoun's earlier papers testify. In one series of World War II veterans, methanol poisoning accounted for 6 per cent of blindness from all causes and this may be considered a representative figure.

Wherever methanol poisoning appears one finds avarice and greed and the placing of

financial gain above human life itself. When methanol poisoning first became a problem at the beginning of the present century, this was manifest in the initial denial, then concealment, of the toxicity of methanol by its manufacturers. This phase of concealment is well illustrated by the slides of labels of methanol 1904 vintage published by Wood and Buller. I should like to ask if Dr. Benton can tell us briefly just what legal recourse was available to the surviving victims and what present legal measures exist to prevent recurrence of such mass destruction.

One is pleased to note that the authors devote much of their effort in applying their data to the central, threefold knotty problem of methyl alcohol poisoning. This central problem is constituted of these subdivisions: (1) the cause of death, (2) the cause of blindness, and (3) the role of acidosis. Some writers in the past with more assurance than evidence have asserted that the characteristic acidosis is the cause of both death and blindness. That it is a contributing and perhaps chief cause of death is substantiated by the extremely low values for carbon dioxide combining power and by the authors' successes with alkali therapy. This is in line with the findings of Røe, of Berger et al, and others. However, the essayists are careful to state that adequate correction of acidosis in patients with severe methyl alcohol poisoning will not always save life or vision. This statement in regard to life is quite in keeping with what we know of acidosis from other causes. Patients in diabetic coma for more than twelve hours have only a 30 per cent chance of survival. However, the authors state that "if acidosis is severe or has persisted for several hours, death may result in spite of energetic treatment." If by several hours the authors really mean two hours or less, this is unlike other types of acidosis and should be noted. Detailed figures on time and severity of acidotic coma would be highly desirable here.

The question of the connection between acidosis and visual loss is an entirely different matter. Although they do not directly say so there are several points at which the authors seem to imply a causal relationship between acidosis and blindness. The temporary improvement in vision during the early phases of alkali therapy is curious, but its significance is contradicted by the authors' scatter diagram (fig. 4). Here there is indeed more visual loss in patients who had a more severe initial acidosis, but there are cases with measurable loss of vision and nearly normal carbon dioxide combining power. Among the more severe cases of acidosis it makes little difference whether the initial carbon dioxide was 4 mEq. per liter or three times that much; the proportion of blindness is roughly the same. Similarly in the cases described in detail there is no correlation between treatment and blindness. This is exactly what we would expect if acidosis and loss of vision were parallel manifestations of a basic toxic mechanism but had no cause and effect relationship with each other. Most significant of all, we must bear in mind that in acidosis from other sources, such as diabetes, visual loss is not characteristic. The diabetics who survive extended coma with carbon dioxide values every bit as low as those typical of methanol intoxication show no characteristic decrease in visual acuity.

Work in our own laboratory in Cleveland with whole animals and surviving tissues, using radioactive methanol as an indicator shows that methyl alcohol is chiefly metabolized in the liver and the gastrointestinal tract. Most of the labeled carbon fixed in tissues occurs in the liver. Since only at a site where a compound is fixed in tissue is it likely to exert its toxic effect, we have begun to think of methanol poisoning as primarily a disease of the liver. The acidosis is conceivably the result of a perverted metabolism of this organ. The idea is further substantiated by the paper of Van Slyke and Palmer describing an unidentified organic acid excreted in extremely high quantities by a methanol poisoned patient. There was collected some 4 liters of tenth normal acid in 48 hours and the acid was shown to be neither formic, lactic nor acetoacetic acid. Work is in progress on monkeys with a view to isolating this acid. The chemical identification of the acid should throw much additional light on the mechanism of acidosis.

One area in which we must emphatically disagree with the authors is their discussion of the biochemistry of methanol poisoning. The theory which they present, that methanol or a breakdown product combines with the "iron catalyst of the oxydase system," was devised by Røe on the basis of no direct experimental evidence. Actual experiments with surviving retina, reported by us (Potts, Albert M., and Johnson, Lorand V.: Studies in the visual toxicity of methanol. I. The effect of methanol and its degradation products on retinal metabolism, Am. J. Ophth. v. 35, part II: 107-113 [May] 1952) show that the cytochrome system is relatively insensitive even to formaldehyde, the most potent inhibitory breakdown product of methanol. The succinoxidase system, one of whose components is the cyto-

chrome-cytochrome oxidase system, is much less sensitive to formaldehyde than is glycolysis. Subsequent work, as yet unpublished, shows that the hexokinase system which phosphorylates glucose is the actual site of inhibition. Thus the chemical site of action is actually at the beginning not at the end of the metabolic cycle. There is no evidence that retinal hypoxia is a feature of methanol poisoning.

The caution of the authors about the use of experimental animals is well taken. Methanol poisoning is obviously not the same in experimental animals as it is in humans. One need only examine the lethal dose for rats as compared to humans to realize that in grams per kilogram of body weight the dose to kill a rat is some ten times higher than that for man and that on this weight basis methyl alcohol is no more toxic to a rat than ethyl alcohol. Actually one must be observing a narcotic type organic solvent poisoning in the rat and a specific metabolic product poisoning in the human—two very different effects. Nevertheless opportunities to observe human cases as numerous as this series come once in a lifetime, and when they come they must be instantaneously used to advantage or the opportunity is forever lost. What is more, the pressure to institute life-saving measures is so great that controlled experimentation is out of the question. For this reason the Western Reserve laboratory has made every effort to locate a suitable experimental test object. This effort is being prosecuted in several directions. With the help of the electroretinogram a survey of visual methanol toxicity in lower animals is being made with particular emphasis on cone retinas and mixed retinas and the utilization of lower primates. In addition human biopsy and autopsy material is being employed for in vitro work. It is hoped that by some such approach the necessity of waiting for disasters may be short-circuited.

When such an event as the one under consideration does occur, we are most fortunate if we have individuals like the authors available to seize the opportunity and make the most of it. I believe that they should be congratulated for their handling of the situation and for extracting from it the data presented here.

F. PHINIZY CALHOUN, JR., M.D., Atlanta, Ga.: A catastrophe of this magnitude provides the chance of a lifetime to observe the acute and late eye manifestations of this condition. Dr. Benton was able to devote practically his full time to recording and evaluating the eye findings during the acute stages. The analyses given today, therefore, are the results of hundreds of eye examinations of these patients made during the acute and follow-up stages of the condition.

It may be worth while to mention the panic and terror which characterized the catastrophe. Among the consumers of so-called "alley" whiskey, hysteria mounted as news of the poisoning spread. The sidewalks outside the hospital became crowded day and night with worried relatives. The emergency clinic became swamped with victims, both real and otherwise, and some method of rapid screening of these patients became necessary. Although the commonest symptom was some disturbance of vision and the only useful physical signs in screening patients for treatment were the ophthalmoscopic findings of disc hyperemia and retinal edema, occasionally severely poisoned patients failed to show these changes. Fortunately there was at hand a new bedside method of determining the carbon dioxide combining power of the blood which required simple equipment and produced a highly accurate reading in a few minutes. This test then became a quick, reliable method of screening patients for treatment and of following therapy.

The actual poisoning agent and the significance of the acidosis in this condition are still unsettled problems. Although the acidosis may have nothing to do directly with the visual loss it remains a fact that in many cases, relief of symptoms with sodium bicarbonate therapy was prompt and satisfactory; with correction of acidosis, there was return of consciousness, disappearance of pain and nausea and improvement in subjective visual complaints. A few, however, despite return of the carbon dioxide combining power to normal remained comatose and died in a few days. It was the strong clinical impression that the massive alkalinization utilized in the treatment of this series of patients prevented a greater loss of life and vision than actually occurred.

Answering Dr. Potts' question, according to local newspaper accounts the offending bootlegger and plainly marked drum of methanol were soon found. The man was tried, convicted, sentenced to life, and is at present appealing for a retrial.

Figures of the time factors in the acidosis are given in the paper. We are well aware of Dr. Potts' recent beautiful work in this condition and believe that he is very close to a solution of the entire problem.