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CHAPTER 15

The Aliphatic Alcohols

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A. General

What may be called the "organic solvent properties" of the aliphatic alcohols manifest themselves in higher animals in narcosis and, eventually, death. These properties become more manifest with increasing length of the aliphatic chain (VON OETTINGEN 1943; MARDONES 1963). In this series ethanol has a special place. Its relatively high ratio of lethal to pharmacologic dose has led to its use and abuse throughout recorded history (cf. Gen. 9.20–21). Only with ethanol has reliable investigation been done on human subjects. Extensive studies of sublethal dose effects have been recorded. It has become clear that the organic solvent properties which ethanol shares with the other aliphatic alcohols and many other small organic molecules is the ability to act selectively on the central nervous system.

The physicochemical mechanism of this action still escapes us, but not from lack of attention to the problem. Pharmacologists concerned with the mechanism of anesthesia have done much experimentation with small organic molecules. Ethanol has frequently been included in the series of test substances. For relatively current work on anesthetics see the review of ROTH (1979). The review of KALANT (1971) deals with ethanol itself.

Some aspects are fairly well worked out. The postsynaptic membrane appears to be the only site where ethanol and anesthetics block neurotransmission at concentrations comparable to those that are attained after pharmacologic doses. It requires higher concentrations to block axonal conduction. Beyond this point all postulated mechanisms are speculative. There is no lack of speculation, but firm experimental evidence awaits the creative investigator.

Since so much of the central nervous system is dedicated to the eye and visual function, it is not astounding that there is a sizable catalog of effects of ethanol on the eye and vision. Since we are necessarily dealing with complex systems in the absence of a unifying theory, we must be content with a catalog only.

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B. Ocular Effects of Single Doses of Ethanol in Nonhabituated Individuals

I. Muscle Balance

The consensus is that at least for distance experimental doses of ethanol in humans cause esophoria (Powell 1938; Colson 1940; Brecher et al. 1955). One of these workers (Powell 1938) found exophoria for near vision, but this was not confirmed by the others. They agree with Charnwood (1951) that there is no vertical phoria induced by ethanol.

In the experiments of Brecher et al. (1955), blood alcohol levels were raised as high as 200 mg%. By the time these levels were reached, most of the subjects could not accomplish the fusion task no matter how much time was allowed. This explains and confirms the subjective diplopia reported by intoxicated individuals.

The experiments of Cohen and Alpern (1969) were directed toward the more complex measurement of the accommodative convergence/accommodation ratio (AC/A). They found a uniform increase in tonic convergence agreeing with the esophoria reported by earlier workers above. They further found a decrease in AC/A ratio with increase in blood alcohol level. Since the conditions of the experiment fixed the ammount of accommodative stimulus, this means that accommodative convergence for any given accommodative stimulus must be less under the influence of alcohol than in the normal. This lower response to an accommodative stimulus is not the same physiological entity as the esophoria measured at a fixed distance by previous investigators, and is therefore not paradoxical.

II. Extraocular Muscles in Action

Still another task in which the extraocular muscles participate is the fixation of a moving target. If the motion of the target is rapid, the eye must make a rapid motion (saccade) to fix the target in its new position. If the target is moving slowly enough, it may be tracked by a smooth following movement. On the basis of measurement of velocity and acceleration patterns, there is reason to believe that saccadic and smooth following movements are mediated by different neural mechanisms.

A special situation in which both smooth following and saccadic movement play a role is optokinetic nystagmus. Unlike vestibular and other forms of neurogenic nystagmus (see Sect. B.III), optokinetic nystagmus is partially under voluntary control. In the most common testing situation, a striped drum is rotated relatively slowly before the eyes of the subject. The cooperative subject will fix a stripe on the drum and follow the stripe until it disappears around the edge of the drum (slow following); he will then rapidly refixate a new stripe (saccade) and follow it until it disappears. By measuring optokinetic responses to a series of stripe velocities, this system, whose final pathway is also the extraocular muscles, can be explored.

The literature contains studies of ocular motility influenced by ethanol under very specialized conditions, but all these studies are consonant with one another. Drischel (1968) recorded the ability of the eye to follow a horizontally oscillating (projected) checkerboard target whose velocity changed sinusoidally. Over the

frequency range 0.3–4 Hz the eyes of the subject could track easily at lower frequencies but were unable to track at the high-frequency end of the range. When amplitude versus frequency and phase angle versus frequency were plotted before and after administration of alcohol, it was found that amplitude decreased and phase-angle separation increased even at blood alcohol levels (BAL) of 30 mg%. At 90 mg% both effects were much more marked.

MIZOI et al. (1969) used optokinetic nystagmus elicited by a set of stripes whose speed accelerated $1°/s^2$ over 125 s, i.e., during the test time the rate of the stimulus increased from 0° to 125° per second. The slow phase of optokinetic nystagmus was measured electrically, and it was found that in the normal subject the total breakdown of ability to perform the task was preceded by a set of responses where the velocity of the slow phase fluctuated widely. The beginning of this phenomenon was taken as the point of measurement. The velocity of the eye in the slow phase at this point was reduced by 28% in 24 subjects who had BAL of 41–89 mg%.

Both smooth following movements (pendulum moving through 45° of visual angle) and maximum saccadic velocity were investigated by WILKINSON et al. (1974). With their doses, maximum BALs reached 80 mg% (average six subjects), and peak saccadic velocities were reduced by 20% in relation to controls. Errors on smooth following movements were scored for the pendulum task, which could be performed flawlessly before alcohol. Blood alcohol levels of 100 mg% made subjects commit large numbers of errors.

The task posed in the experiments of FRANCK and KUHLO (1970) was simply to look back and forth between targets placed 10° each side of primary position (straight ahead fixation position). This required a saccade of 20° of visual angle, which reached a maximum velocity in control trials of 460°–338° per second. At BALs of 60–120 mg% there was an average decrease in velocity of 24%.

An earlier report by MILES (1924) required a saccade of 40°. Both adductive and abductive saccades were slowed by a significant amount at a fixed time after a standard dose of alcohol in five subjects.

Still another parameter of saccadic movement was explored by LEVETT and HOEFT (1977). These researchers measured the latency between stimulus and response in a saccadic task. One might regard this as ocular reaction time. Once more, in six subjects whose BAL reached 108 mg% on average, there was a mean latency increase of 21%. The authors attribute this to effects on higher centers than the ocular motoneuromuscular system.

In each of the entities examined in this section (smooth following of sinusoidal motion, smooth following in the slow phase of optokinetic nystagmus, maximum saccadic velocity, and the latency of saccadic responses), efficiency of accomplishing the task was impaired by ethanol. The falloff in maximum saccadic velocity could be postulated to be located in the ocular motor nucleus-extraocular muscle system; but when one considers the earlier breakdown of optokinetic tracking (MIZOI et al. 1969), the breakdown of smooth tracking into fragmented saccades (WILKINSON et al. 1974), and the increase of latency of saccadic responses (LEVETT and HOEFT 1977), one is inevitably led to higher centers. The physical location of the necessary servomechanisms to coordinate eye movement is still unknown, but the need for them is real (see, e.g., BACH-Y-RITA et al. 1971), and the participation of cortical vision immediately moves them from brain stem to cortex. The effect

of ethanol in lowest concentrations on other cortical functions makes this entirely believable.

III. Nystagmus

"Neurogenic" nystagmus, as differentiated from optokinetic nystagmus on the one hand and pendular nystagmus on the other, is a complex subject. Any competent treatment of the anatomy and physiology involved is well beyond the scope of this review. We must circumvent this complex area by simply defining neurogenic nystagmus as spontaneous rhythmic movement of the eyes, usually bilateral, usually synchronous, usually (but not invariably) horizontal, and exhibiting a fast and a slow component.

It has been known for more than 150 years that alcohol administration can cause this type of nystagmus. For a review of the early literature see Aschan et al. (1956a). The finding is real and it is inconstant. Howells (1956) found nystagmus in 4 of 12 subjects given alcohol (1–1.4 ml/kg). He did not measure BALs. Levett and Hoeft (1977) mention in passing (Fig. 3) the spontaneous nystagmus recorded in one of their six subjects at a BAL of 120 mg%.

Two patients have been reported by Bender and Gorman (1949) and one patient by Kroll (1969) who had spontaneous vertical nystagmus. They all had oscillopsia (the sensation of the world moving) as well. All three patients experienced relief of symptoms after receiving generous doses of alcohol. However, the two patients of Bender and Gorman were confirmed severe alcoholics with encephalopathy. The patient of Kroll disclaimed heavy drinking but required one-half to a whole pint of 80°–90° proof liquor to get relief from his nystagmus for a few hours. He had noticed this effect 4 months prior to his clinic visit. If his drinking was truly of only 4 months' duration, he could not be considered an alcoholic. One can go no further with this paradoxical effect at present.

Most curious of all is the well-authenticated entity, positional alcohol nystagmus. For an adequate exposition of this entity see the work of Aschan et al. (1956 a, b). An individual with medium BALs may show no nystagmus in primary position with eyes open. However, with eyes closed or with occlusive lenses, the act of turning from supine to lateral position induces horizontal nystagmus. Early after ingestion of alcohol the nystagmus has its fast component downward-turned (called "PAN I" by the Aschan group). Some 4 h after ingestion there is a period of inconstant response that lasts an hour or so; then the direction of the nystagmus reverses and the fast component is now upward (PAN II). PAN I appears within 30 min of ingestion at BALs of as little as 38 mg%. PAN II appears on the descending arm of the BAL curve and appears at an average BAL of 20 mg%. PAN II lasts after there is no detectable blood alcohol. Indeed, Hill et al. (1973) report than PAN II can last 15–16 h after the ingestion of 2.5 ml/kg of 100 proof liquor, which attained a maximum BAL of 90–100 mg% at 1 h. By their alcohol dehydrogenase determination, BAL was undetectable at 24 h. However, in some subjects they found some PAN I response at 24–32 h.

Clearly we have here one of the most sensitive physiological responses to alcohol intake. de Kleyn and Versteegh (1930) showed by ablation experiments that PAN in rabbits was dependent upon the presence of the labyrinths, not the sac-

cules. This suggests that there is a vestibular stimulus via the median longitudinal fasciculus to the brain stem nuclei controlling the oculorotatory muscles whenever a head turn occurs. Under normal circumstances this stimulus, which must be a weak one, is counteracted by the stronger stabilizing forces of vision and of unidentified cortical centers. When vision is nullified by closing the eyes and when the unspecified cortical centers are inhibited by ethanol, the vestibular message can elicit a response. The idea that the alcohol effect can persist long after alcohol has disappeared from the body is truly impressive. It makes one wish to philosophize on the mechanism of this minihangover. One must take note of the opinion of MONEY and MYLES (1974), based on their findings with heavy water, that PAN is entirely due to density changes of the endolymph in relation to the cupula. They suggest that the cupula is more dense than the endolymph after the ingestion of heavy water and less dense after the ingestion of ethanol. This difference in density allows gravity to activate the labyrinth.

IV. Intraocular Muscles

1. The Iris

The relatively meager work on alcohol and pupil size is all based on low BALs. SKOGLUND's (1943) four subjects received 15 ml 50% ethanol. Moderate dilation of the pupil measured from 16-mm frames was reported. However, BROWN et al. (1977), who raised BALs to 60 mg%, found no effect on pupillary size in their patients. In SKOGLUND's studies, even though there was modest pupil dilation there was no effect of alcohol on the rate of response to light for that pupil size.

2. Accommodation

The experimental data available on the effect of alcohol on accommodation are confined to the time required to accommodate or relax accomodation by 2 diopters (LEVETT and KARRAS 1977). Objective measurement (presumably of the third Purkinje image) showed slowing of the time required; the higher the BAL, the greater the slowing.

V. Electrophysiological Measurements

By employing electrophysiological methods, we are making use of precision instruments, but the biological interpretation of results leaves something to be desired. The a wave of the electroretinogram (ERG) does precede the optic nerve discharge (OND), but it requires stimuli at least 3 log units more intense than the dark-adapted threshold to allow it to be recorded. What is triggering the optic nerve through those 3 log units? The b wave of the ERG peaks long after the OND has passed; thus the b wave can only be an after potential reflecting some aspects of the retinal response. The c wave of the ERG is intimately connected with the direct current potential across the eyeball. It is elicited only by stimuli of long duration 0,5–1 s).

An early and frequently quoted report is that of BERNHARD and SKOGLUND (1941). However, this work was done on the open eyecup of the frog, and 10%

ethanol gave the best effect. Such a concentration is two orders of magnitude higher than the 100 mg% BAL which produced the effects we have been discussing until now. This must necessarily be ignored. In a similar preparation, 200 mg% ethanol in the excised opened frog eyecup decreased lateral inhibition of the receptor field of individual ganglion cells to microelectrode recording. The latency of the response was increased (Bäckström 1977).

A single dose of 15 g·ethanol per kilogram given by stomach tube caused rapid coma in cats and rabbits and eventual death, but at 2 h the b wave (200 μV at zero time) was abolished (Praglin et al. 1955).

When the test object was the dark-adapted sheep and the stimulus 5 log units above b-wave threshold, BALs had to be raised to 140 mg% before a 15% decrease in a-wave and b-wave amplitude was observed. A BAL of 200 mg% caused a 22% decrease in a-wave and b-wave amplitude (Bernhard et al. 1973).

van Norren and Padmos (1977) recorded the ERG in the monkey and paid particular attention to the first component – the cone contribution – of the b wave. The large effects of ethanol at 300 mg% (estimated) and of a number of inhalation anesthetics were to increase the latency of the cone component.

It is the consensus that alcohol increases the amplitude of the c wave of the ERG in sheep (Knave et al. 1974) and increases the amplitude of c wave oscillations with time in humans (Skoog 1974), as well as the low-amplitude components of the off-effect (Skoog et al. 1978). One must take cognizance of the report in one of the above papers (Skoog 1974) of a moderate increase in b wave amplitude after alcohol in man with no change in a wave. However, the author is vague about correlating these effects with BALs. This finding agrees with that of Ikeda (1963) and partially with that of Jacobson et al. (1969), who found an increase in amplitude of both a wave and b wave, and is contrary to the sheep data of Bernhard et al. (1973) above.

The visually evoked response (VER) is recorded from the occipital scalp or from occipital-parietal scalp electrodes. Adequate stimuli are flashes of light, or checkerboard or bar patterns that reverse black for white and vice versa. Because each response is of the same order of magnitude as the ongoing electrical noise, it is usual to summate 100–200 responses synchronously with the stimulus, using a special-purpose or general-purpose computer. The summated response is easily read. If one considers the response to a full-field flash, perhaps 50% of the amplitude is due to the fovea centralis and the surrounding 1° of macula. Thus the VER with proper stimuli can be an adequate objective measure of visual acuity. Optic nerve disease causes increased latency of the occipital response. A great obstacle to widespread use of the VER for objective measurements is the wide variation between individuals in amplitude and configuration. If one wishes to compare a hypothetically injured eye to a fellow eye known to be normal, one is on safe ground. When both eyes are in question, the usefulness of the VER drops precipitously. However, in human experiments where each subject is his own control, as before and after alcohol administration, valid conclusions should be attainable.

The earliest report on alcohol and the VER after Ikeda (1963) used visual summation on a storage oscilloscope is that of Müller and Haase (1967). Blood alcohol levels were not measured but peak time of the major response was nearly doubled, so it is reasonable to believe that the finding is valid even with the

inadequate instrumentation. Using summation of 100 responses of nine subjects to full-field flash on a PDP-9 computer, LEWIS et al. (1970) showed diminution in amplitude of the major components. This required 85 ml 95% ethanol, which produced blood levels of 70–100 mg%. This was confirmed by RHODES et al. (1975).

Only VAN LITH and VIJFVINKEL-BRUINENGA (1978) used alcoholics with initially subnormal VERs to a reversing-pattern stimulus as subjects. These individuals had further decrease in amplitude as well as increase in latency after 200 ml 35% ethanol.

It would seem that in normals the decrease in amplitude of the major components of the VER is a repeatable finding.

VI. Miscellaneous Measurements of Visual Function

One must deal here with the report of NEWMAN and FLETCHER (1941), who measured seven aspects of visual function in 50 subjects before and after alcohol administration. Blood alcohol levels ranged from 58 to 218 mg%. Neither investigator was an ophthalmologist. The tests and results follow:

1. Visual acuity (Keystone Telebinocular): 22% of subjects showed a drop of 20% or more in acuity after alcohol.
2. Depth perception (Keystone Telebinocular): 12% of subjects showed a 20% or more decrease in depth perception.
3. Distance judgment (Howard-Dohlman test): 18% showed 25-mm error in rod positioning after alcohol.
4. Lateral visual field (Brombach Perimeter). Used 20-mm white target. Only one subject showed 10° (?) narrowing of field.
5. Eye coordination (Keystone Telebinocular). "Used experience and judgment." Eighteen percent of subjects were judged to have major changes in this parameter.
6. Glare resistance (special apparatus from University of California, Berkeley): 12 of 50 subjects showed major changes.
7. Glare recovery (another special apparatus from University of California, Berkeley): 20% of subjects had major adverse changes.

The problem with this report is that there is no correlation between positive findings and BAL for the subject. Further, there is no tendency for a particular subject to have many changes and another subject to have few. Changes are scattered at random in relation to subject and in relation to BAL. For visual acuity decrease it was more than twice as likely for one eye to be affected as for both eyes. One is therefore likely to be dealing with some effect other than alcohol in this report. It is profitless to speculate at this distance on what the factor might be.

There is some confirming evidence on items 1 and 7. BRECHER et al. (1955) mention that 3 of 14 subjects showed decrease in visual acuity at higher alcohol levels. In their case this was 160–200 mg%.

The decreased visual acuity after alcohol in two subjects reported by MILES (1924) was small enough to be of questionable significance. At least it was in the same direction as the other reports.

Of the two more recent reports on glare recovery, one reports a glare recovery time shortened at BAL 21–142 mg% (TIBURTIUS et al. 1966). The second report de-

scribes glare recovery lengthened after ethanol dose that raised BAL to 60 mg% in 1 h (Adams et al. 1978). One can hardly draw conclusions on the data available.

In the same miscellaneous category is the light threshold increase of 30% in four subjects described by Lange and Specht (Jellinek and McFarland 1940) and the 50% decrease in the threshold for intensity discrimination (same authors).

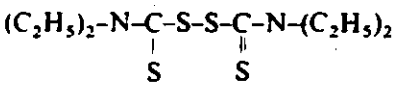
Goldberg (1943) described an alcohol effect on flicker fusion. At a constant frequency a brighter light was needed for fusion after alcohol. At constant brigthness a lower frequency was needed.

VII. Intraocular Pressure

The only firmly established fact is that alcohol does lower the intraocular pressure. All authors are in agreement on that subject (Peczon and Grant 1965; Houle and Grant 1967; Ramos et al. 1969; Ostbaum et al. 1973; Leydhecker et al. 1978; Giurlani et al. 1978). It also appears that whereas BAL peaks 30–60 min after a single oral dose, the maximum intraocular-pressure-lowering effect is manifest 1–3 h after alcohol. Beyond this there is no agreement on mechanism of action or dose-dependence of action.

C. The Special Case of Disulfiram (Antabuse)

The principal pathway for the metabolism of ethanol is oxidation to acetaldehyde and thence to acetate. The first oxidation is catalyzed by alcohol dehydrogenase with NAD as cofactor. The second step is catalyzed by aldehyde oxidase and NAD is again the coenzyme involved. Inhibitors of aldehyde oxidase allow the accumulation of acetaldehyde in someone who has imbibed ethanol, and marked symptoms can result. Headache, flushing of the face, hyperventilation, increase in pulse rate, and fall in blood pressure are some of these. For a survey of the types of compounds that have this effect see Maling (1970). The substance that has been utilized in the therapy of alcoholism is tetraethylthiuram disulfide (disulfiram, Antabuse).



introduced by the Jacobsen group (Hald et al. 1948; Hald and Jacobsen 1948a; Jacobsen 1952).

The ocular effect described following the use of alcohol by an individual who has taken disulfiram is scleral injection resulting in a bovine appearance (Hald and Jacobsen 1948b).

D. Chronic Alcoholism and the Eye

In chronic alcoholism there are two major ways in which the eye is affected. The first of these is the complex constituting the ocular consequences of Wernicke's encephalopathy. The clinical findings include nuclear ocular palsies, internal oph-

thalmoplegias, ptosis, and nystagmus (DUKE-ELDER and SCOTT 1971). The histopathological findings are multiple hemorrhages with glial reaction, particularly in the gray matter surrounding the third ventricle (DE WARDENER and LENNOX 1947). Although the condition was originally ascribed to the direct toxicity of ethanol, it is now agreed that the proximal cause is thiamine deficiency (PHILLIPS et al. 1952; DREYFUS and VICTOR 1961). Such an indirect effect need not be considered further.

The second entity is alcohol (tobacco-alcohol) amblyopia. It is universally recognized that some chronic alcoholics present clinically with blurred or decreased central vision; that the chief additional finding is central or cecocentral scotoma in the visual field examination; and that beyond a certain point temporal pallor of the optic nerve head sets in, and the loss of central vision is irreversible. For multiple case histories see VICTOR et al. (1960). Histopathological examination shows loss of the papillomacular bundle, beginning with the perifoveal ganglion cells and traceable through optic nerve and chiasm to the lateral geniculate nucleus (VICTOR et al. 1960; VICTOR and DREYFUS 1965). Amblyopia in chronic alcoholics had been accepted as a phenomenon of alcohol toxicity until relatively recently (GALEZOWSKI 1978; DE SCHWEINITZ 1896; LEWIN and GUILLERY 1913). Only with the work of CARROLL (1944) has strong clinical evidence been produced which places tobacco-alcohol amblyopia in the category of nutritional deficiency diseases. For more recent publications see the review by POTTS (1973) and the paper of VICTOR et al. (1960). The weight of evidence is tipping strongly toward B_{12}-deficiency as the direct cause for the appearance of the symptom complex in alcoholics. The indirect cause is the deficient diet which alcoholics get. When most of their calories are supplied by alcohol, vitamin intake is insufficient. Thus this second eye disease seen in alcoholics is also not a direct pharmacologic effect of ethanol and need not be treated further.

E. Methanol

Methanol, the one-carbon member of the aliphatic alcohol series, has organic solvent properties as do the other members. One pharmacologic measure of this is systemic toxicity in mice. The LD_{50} is 11 g/kg in white mice. At this dosage level deep narcosis (another organic solvent property) is observable within a few minutes of injection. When 2 g ethanol per kilogram is added to methanol dosage, the LD_{50} for methanol is reduced to 5 g/kg. The more toxic and higher-molecular-weight ethanol lowers requirements for LD_{50} from 343 mmol/kg for methanol alone to 199 mmol total alcohols per kilogram when ethanol is added (GILGER et al. 1952).

When one considers methanol toxicity in humans and other primates, the picture is complicated by the fact that there are two additional and potentially lethal mechanisms at work. One of the two is systemic acidosis, which is a constant factor. Part of the acidosis is attributable to formate production, but calculation shows that even if 100% of a lethal dose of methanol were converted to formate, there would not be enough acid to reach the levels observed. There must be additional metabolic acidosis at work (VAN SLYKE and PALMER 1920; POTTS 1955).

The second additional factor is the effect on the central nervous system. This is seen in the effect on the retina, which is manifested in early retinal edema and early nerve head edema (ophthalmoscopy), and in late optic atrophy. A further ef-

fect on the central nervous system is necrosis of the caudate nucleus and putamen, described in humans by Orthner (1950) and in monkeys by Potts et al. (1955).

The existence of these facts makes the conditions for the investigation of methanol effects very different from those for ethanol. The organic solvent effect with methanol is much weaker than that for ethanol, so quite large doses are required to demonstrate it (recall the LD_{50} for mice of 11 g/kg). The additional effects mentioned above (metabolic acidosis and central nervous system damage) are obtainable with considerably lower doses of methanol. Since both effects are potentially fatal, there is in actuality little possibility of studying the effect of methanol in humans. In cases of accidental poisoning the saving of life is the first consideration. Thus there has been no opportunity to study subtle effects of methanol on the human eye such as those reported for ethanol. However, with the introduction of the monkey as a test animal (Gilger and Potts 1955), it became possible to study methanol toxicity in primates with the triple ramifications outlined above. All evidence presented so far suggests strongly that there is direct parallelism between methanol poisoning in the monkey and in man and that this parallelism does not exist between man and subprimates. The very confusing older literature on subprimates is reviewed in detail by Gilger and Potts (1955). For these reasons much of the unequivocal information on methanol poisoning in primates comes from experiments on monkeys, not from experience with humans, but there is enough observation of human disease to confirm that each of the clinical features observed in monkeys has been seen in man.

To go into somewhat greater detail, susceptibility to the organic solvent properties of methanol is shared by primates and nonprimates. If the dose is large enough the animal becomes semicomatose within 30–60 min after an oral dose and never recovers consciousness. Doses that cause this type of death are 11 g/kg parenterally for mice (LD_{50}); 4.75 g/kg orally for rats (LD_{70}); 9–10 g/kg orally für dogs; and 8 g/kg orally für monkeys (*Macaca rhesus*) (Gilger and Potts 1955).

Oral doses of less than half the above (3 g/kg) are fatal for monkeys because of systemic acidosis. The clinical findings in monkeys on 3 g/kg or more were characterized by early transient intoxication, followed by a latent period of almost 24 h during which symptoms were minimal. Then came the onset of dyspnea, asthenia, and collapse. These clinical findings were correlated with a sharp drop in CO_2-combining power of plasma and a rise in urinary output of organic acid. If the acidosis is untreated, death results (Gilger and Potts 1955). The finding of acidosis was confirmed in rhesus and pigtail monkeys by McMartin et al. (1975) and by Clay et al. (1975); only Cooper and Felig (1961) were incapable of reproducing these results.

It is possible to titrate the acid production in a monkey by administering base intravenously. With a little care, blood pH and CO_2 capacity can be maintained within normal limits (Potts 1955). Despite the lack of acidosis the central nervous system sustains damage which is manifested in at least two sites. Early damage is seen ophthalmoscopically as retinal edema and nerve-head edema (Potts 1955). The late manifestation of this same damage is optic atrophy (Potts et al. 1955). Relatively early cogwheel pupil contraction and dilated pupils unreactive to light are observed. Other central nervous system damage seems concentrated in the basal ganglia. It is manifested early in symptoms such as tremor, apraxia, and in-

coordination of limbs. Later anatomic findings are observable and appear as necrosis in the putamen and caudate nucleus.

The treatment of methanol poisoning is based on human and animal findings. RÖE (1950) and BENTON and CALHOUN (1953) used bicarbonate to combat the acidosis in methanol poisoning. WOOD and BULLER (1904), AGNER et al. (1949), and RÖE (1950) advocated the use of ethanol in methanol poisoning. In rhesus monkeys GILGER et al. (1956) and GILGER et al. (1959) demonstrated ethanol to be life-saving and to prevent central nervous system involvement. The laboratory support for these findings lies in the in vitro demonstration by ZATMAN (1946) and the in vivo demonstration by BARTLETT (1950) that ethanol inhibits the oxidation of methanol. An alternative method of prevention of oxidation of methanol is peritoneal dialysis or hemodialysis. Isolated reports (PFISTER et al. 1966; WENZL et al. 1968) and a review (WINCHESTER et al. 1977) report successful use of dialysis in human methanol poisoning.

It is clear on the basis of the above that methanol must be oxidized to exert its toxic effect. What is still quite unclear is the mechanism by which the toxic effects of methanol are mediated. From studies on in vitro inhibition of retinal metabolism (POTTS and JOHNSON 1952) and studies on the effect of disulfiram on methanol toxicity (GILGER et al. 1952), as well as studies on the electrophysiology of the eye (PRAGLIN et al. 1955), it was demonstrated that of the two oxidation products of methanol, formaldehyde and formate formaldehyde was clearly the more toxic. Free formaldehyde has not been isolated in the tissues of experimental animals, but this is not surprising because a highly active toxic agent might well react with tissue before being detectable chemically. However, the demonstration of formaldehyde in brain tissue by the Falck-Hillarp method has proved equivocal (A.M. POTTS unpublished work). This leads one to ask whether in the oxidation of methanol free formaldehyde ever exists, or whether this oxidation stage is always bound to normal carriers. Further, there have been claims that formate given to monkeys can produce optic nerve edema and dilated fixed pupils (MARTIN-AMAT et al. 1978). No reports of basal ganglion damage have appeared. MARTIN-AMAT et al. (1978) invoke the inhibition of cytochrome oxidase by formate at $10^{-2}M$ levels (NICHOLLS 1975) as a possible mechanism. MAKAR and TEPHLY (1977) can produce acidosis and increase in formate levels in the methanol-treated rat by rendering the animals folate-deficient.

To summarize, methanol has a unique toxic action in humans at a dosage level so low that the effects described above for ethanol never come into play. Methanol can cause blindness and death through several pathological modalities including metabolic acidosis, optic nerve atrophy, and basal ganglion necrosis. The biochemical mechanism for these manifestations is far from clear.

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