THE OCULAR PATHOLOGY OF METHYL-ALCOHOL POISONING*

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INTRODUCTION

Methyl-alcohol poisoning in relation to the eye is of interest not only because it is clinically important, but also because the resulting pathologic processes in the eye are not fully known.

Whoever studies the literature on the subject must be impressed with the lack of uniformity of opinion as to the effects of methyl alcohol upon the ocular structures. Opinions concerning the toxicologic process are also at variance. Most of the opinions are based upon conclusions drawn from clinical observation, autopsy reports, and the results of experimental work in animals.

The literature is practically devoid of reports of studies upon pathologic specimens from the human eye. In most instances the reports were incomplete, and the material was not immediately fixed, thus allowing post-mortem degenerations to ensue. It is well known that the retina, even though refrigerated, immediately disintegrates, causing an appearance that may be interpreted as a pathologic change resulting from methyl alcohol. Another criticism of the early autopsy findings is that the fixing and staining process used was not adequate to show minute changes accurately. It seems, therefore, that whatever evidence may have been adduced as the result of human autopsy should be held in question.

Considering the ocular findings as the result of animal experimentations, doubt again arises. The fact impresses us that many of the conclusions reached concerning the effect of methyl alcohol on the human are based upon the results of experimental work on animals by H. Holden[1] in 1890 and Birch-Hirschfeld[2] in 1900. We must be skeptical of such conclusions, for Holden's work cannot be considered scientifically accurate. Likewise, Birch-Hirschfeld's work in 1900 should not be considered too seriously; he must have had some serious doubts as to its accuracy since he repeated it in 1920.[3] Doubt of the accuracy of the positive findings in this animal experimentation is also strengthened by the critical work of de Schweinitz,[4] who was unable to reproduce their results. Jonas Friedenwald[5] likewise obtained negative results and concluded, like de Schweinitz, that the previous work was probably in error. That such an error is possible is evident when we consider how very rapidly post-mortem changes occur in the retina. Also we must consider artifact and defective staining technique. It is entirely possible that the negative findings of de Schweinitz and Friedenwald are correct, and that animal experimentation is of no value in solving the problem. It is well known that animal tissues do not always exhibit the toxic effects of drugs that are manifested in the tissues of the human body.

The pathologic effect of methyl alcohol on the human being should be considered not only as to its effect upon the eye but also on the whole body, since its effect is widespread and not confined to a specific action on the retina, as some authors would have us believe.

Because of the uncertainty which apparently exists concerning these questions, further study of the subject seems

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indicated. The following investigation was undertaken to obtain more concrete information and thus establish a more definite conception of the ocular changes that are present in these cases.

Toxicity of Methyl Alcohol

The cause of the peculiarities of methyl-alcohol poisoning has not been satisfactorily explained. There is a paucity of facts regarding the actual behavior of methyl alcohol in the animal organism, so that the underlying causes of its extreme toxicity are by no means clearly understood. Certain facts, however, have been determined by animal experimentation and clinical observations which aid materially in drawing conclusions. These are:

Methyl alcohol may develop its lethal action through three different avenues of entrance into the system; namely, ingestion, inhalation, and cutaneous absorption.

The presence of various impurities does not influence the toxic action, and it is generally believed that the effect is due to a property incident in the methyl alcohol itself.

Methyl alcohol is a poison in which idiosyncrasy plays an important part, some persons being greatly affected by doses that would not harm the majority of people.

There is no evidence to show that a tolerance to methyl alcohol can be developed.

Man appears to be relatively more susceptible to a poison like methyl alcohol than is the dog or the rabbit, for it seems that poisons which powerfully affect the highly differentiated nerve structures are proportionately more dangerous the more highly developed the nervous system.

The fate of methyl alcohol in the human body is not definitely known. There is evidence suggesting that it is not the methyl alcohol itself but some of the chemical by-products of incomplete oxidation that originate these poisonous effects. It appears that formaldehyde and formic acid are the chief toxic agents, although there may be others. The toxic effect is thought to be due to the circulation of these toxic combinations in the blood and their coming in direct contact with the tissues.

It has been demonstrated that the difference in the character of intoxication between ethyl and methyl alcohol is due to the fate of these substances following their administration. Whereas ethyl alcohol is oxidized into easily excreted products, carbon dioxide and water, methyl alcohol is only partially oxidized and the products of this incomplete oxidation are formaldehyde and formic acid. Some explain this difference in the fate of the two alcohols by the difference in their rate of oxidation. Methyl alcohol in slow oxidation makes formic acid, while in rapid oxidation it forms carbon dioxide and water; hence, when it rapidly oxidizes it is comparatively harmless, while in slow oxidation, which usually occurs in some people, it is exceedingly toxic. The variation in effect on individuals therefore may be partly explained by the rate of oxidation which takes place in the person.

If this transformation of methyl alcohol into formaldehyde and formic acid takes place, we have an example of a poisonous compound forming two intermediate compounds which are much more toxic than the original. It has been estimated that formaldehyde is about 30 times and formic acid 6 times more toxic than methyl alcohol.

In considering formaldehyde as the intermediate product of oxidation it must be conceded that from a chemical standpoint such formation is possible; but upon surveying the experimental evidence, very little is found to substantiate the claim.

Most evidence points against its presence in the tissues and the only positive evidence found was given by Pohl,[6] who failed to find support for the view that any "considerable quantities" of formaldehyde are formed, but "it may be that formaldehyde is formed and that it is quickly converted into formic acid."

It must therefore be concluded that if formaldehyde is present it is present but a short time, which may, however, be sufficient to produce a toxic action.

In considering the presence of formic acid in the body there is indisputable evidence that it is present, for it is excreted in the urine, but when it is formed and how much is formed is not known. In many instances it is apparently the final oxidation product, although some individuals may have the power to decompose the methyl alcohol further to carbon dioxide and water. That formic acid is not present in the tissues to any degree is evident if tissue analysis can be depended upon as a criterion. Pohl thought it probable that all the methyl alcohol administered is converted into formic acid, that part of the latter is then oxidized to carbon dioxide. As he did not find it in the tissues to any degree he concluded that very probably either methyl alcohol itself or one of its derivatives is retained in the body and is then slowly converted into formic acid. Bongers[7] on the other hand, asserts that after the administration of methyl alcohol considerable quantities of methyl alcohol are excreted in the urine. It would seem from this that not all the methyl alcohol is converted into formic acid.

Varied tests made upon the distillates from tissues appear to establish the fact that methyl alcohol and not formaldehyde and formic acid is the principal recoverable toxic substance. Very rarely have even traces of formaldehyde and formic acid been detected. It therefore seems evident that methyl alcohol itself is retained in the body for some time and is apparently excreted unaltered or as formic acid which apparently is slowly formed.

It seems that the human body in many instances has great difficulty in oxidizing methyl alcohol. It has been stated that but 3 percent of the body metabolism can be attributed to the methyl alcohol, which seems to be conclusive evidence of the inability of the body to cope with it.

In the opinion of certain investigators, there is a more profound disturbance of the metabolism than is indicated by the simple failure of the body properly to oxidize methyl alcohol. Observations support the view that acidosis plays an etiologic role in the production of the symptoms following methyl-alcohol poisoning. As in a variety of other pathologic states where there is a reduction of the reserve alkali of the blood, the exact significance of this reduction is not clearly understood. There is evidence strongly suggesting that the disturbance of the acid-base balance may, in itself, cause definite anatomic changes. It must be conceded that acidosis might be an important factor in producing the poisonous action of methyl alcohol. Harrop and Benedict[8] were the first to treat a patient on this assumption. In the case reported by these authors there was a definite reduction in the reserve alkali and there was also the characteristic air hunger.

A highly significant feature of this phase of the problem is the slow elimination of the methyl alcohol or its conversion products from the organism, which leads to a subtle danger in the form of accumulated toxic products. Investigators have indicated that the probable explanation of the unduly pronounced poisonous character of methyl alcohol is not only the failure of combustion but also the delay in elimination. According to Henderson and Haggard,[9] more than a week

is required to eliminate the methyl alcohol acquired by a single large absorption. If the exposure is repeated before the elimination is completed, a cumulative effect results; the amount absorbed at each exposure is added to that which remains uneliminated. A toxic concentration is thus gradually built up in the blood as a result of repeated exposure to concentrations that do not cause an appreciable effect on a single exposure. Placet[10] has shown that the complete elimination of wood alcohol requires a period of time five times as long as that of ethyl alcohol.

It therefore appears evident that the toxicity of methyl alcohol may to some degree be attributed to the fact that it remains for a long period of time in the animal organism where it has time to produce varied and grave changes of a chemical and chemicophysical nature.

Most evidence points to the fact that the methyl alcohol is distributed very rapidly to all tissues and fluids of the body. There is practically no lag in the methanol-water concentration of the blood behind that found in any tissue at a particular instant regardless of whether the animal was accumulating methanol, was in a steady state, or was eliminating methanol following exposure. Consequently, all kinds of tissue or body cells are exposed to practically the same methanol-water concentration, there being no selective accumulation, retention, or predilection. The results also show that the amount of methyl alcohol in the body or in a particular tissue can be estimated from a determination of the methyl alcohol in any tissue or fluid.

It seems, therefore, that once consumed or inhaled, methyl alcohol quickly disperses to all tissues of the body, having no selective affinity but apparently injuring by direct action the more highly specialized tissues of the retina, brain, kidneys, and liver and to a lesser extent the other tissues. Experimental data confirm this fact as regards the eye because it has been demonstrated that the substances produced in the body by poisoning with methyl alcohol penetrate the eye readily.

On the other hand, there is some evidence to prove that methyl alcohol has a marked selective affinity for the most highly differentiated nerve elements of man. According to this evidence, the various organs do not show identical findings in the fixation of methyl alcohol; the brain and other nerve tissues exhibit a decided electivity for this substance, and contain the largest quantities of it. Liver, kidney, and muscles then show decreasing proportions of it. The specific affinity is in accord with that which might be expected from its lipoid make-up. This is explained by the fact that the alcohols, like ether, chloroform, and other volatile narcotics, are notably soluble in lipoids such as those characterizing the nervous system. With equal concentration of ethyl and methyl alcohol, methyl alcohol has the greater effect of modifying the lipoid content of organs. It should also be noted in this connection that there is a considerable increase in the fatty-acid and cholesterol content of the blood serum, resulting from acute experimental poisoning with methyl alcohol.

Furthermore, experimental evidence indicates that there is a greater absorption of methyl alcohol in the retina than there is of ethyl alcohol.

It is of importance to trace the ultimate fate of methyl alcohol in the body. Whereas ethyl alcohol is eliminated from the body chiefly through the lungs and, to a far greater extent, through oxidation in the tissues, methyl alcohol is also eliminated through the lungs, but is only to a small extent oxidized in the tissues. It is stated that only about 10 percent of the total amount of ethyl alcohol which dis-

appears from the body is eliminated in the expired air. Of methyl alcohol, on the contrary, more than 70 percent of the amount that disappears from the body appears in the expired air.

Voltz and Dietrich[11] found that after administration of 2 c.c. of methyl alcohol per kilogram of the body weight of a dog, 24.3 percent was excreted in 48 hours, of which 21.5 percent was in the expired air, and 2.18 percent in the urine. As 36.7 percent was found in the body, it follows that only 39.0 percent was oxidized in the body. If the caloric value of the methyl alcohol oxidized is calculated, it will be found that this represents only about 3 percent of the total metabolism of the body. These results are in marked contrast to those obtained in studies of ethyl alcohol under analogous conditions. It seems evident therefore that the bulk of poison is eliminated through the lungs, skin, and kidneys.

Comment. To draw conclusions from the data available is difficult. We must keep in mind that most of the positive evidence is the result of animal experimentation and may not hold true for man. It is to be regretted that so little effort has been made to obtain toxicologic data from the bodies of people who die as the result of methyl-alcohol poisoning. In a few instances the tissues were analyzed for methyl alcohol only, but nothing has been done that can be called conclusive. Considering the number of fatalities, from this form of poisoning the thoroughness of our scientific work leaves much to be desired. It is therefore evident that we are obliged to a great extent to draw conclusions on suppositions based mainly on theory and animal experimentation.

It seems evident that methyl alcohol cannot be oxidized readily by some individuals and consequently acts as a poison. It is most probable that the toxic substances remain in the system as such and are distributed to all of the tissues. Because of their prolonged contact with the tissues they cause pathologic changes, but to a greater degree in the highly specialized tissues such as the central nervous system, kidney, liver, and other organs. It is possible that the more highly developed tissues of the central nervous system are most affected because of their chemical structure and the resulting disturbance in their nutrition.

In review of the evidence at hand it does not seem logical to conclude that one specific substance causes the change. It would appear instead to be due to several factors. A profound change in the chemistry of the body caused by a lack of chemical balance such as is seen in instances of acidosis might be a factor. In addition to this, there could be a direct chemical action of methyl alcohol itself or in combination with the products of oxidation.

The degree of these reactions would naturally vary with the individual tolerance or the ability to cope with the drug.

It is significant that the patient in most of these cases does not experience an immediate toxic effect. It seems logical that if methyl alcohol were the only toxic agent, the patient would evince the profound toxic effect immediately upon taking the alcohol, for it is known that the latter is absorbed and circulates in the blood, almost immediately coming in contact with sensitive tissues. Instead, toxic symptoms in most cases are manifested many hours later. This would point to the fact that the pathologic changes occur after some drastic chemical upheaval has taken place in the chemistry of the body, such as is seen in acidosis or as the result of oxidation.

Just what action is responsible for the pathologic change it is difficult to state. The presence of methyl alcohol has been demonstrated in the tissues, but there is

no definite evidence to prove the presence of formaldehyde or formic acid in the tissues. That formic acid is formed in the body is proved by its excretion from the kidneys. The fact that it is excreted for such a long period suggests that the transformation into formic acid is a very gradual process. The exact period of time during which the formic acid remains in the body is probably of little significance, for a chemical of this degree of toxicity need act but for a moment to produce pathologic changes.

Admitting that methyl alcohol has an effect, the presence of its by-products is strong presumptive evidence that these are additional toxic elements which either alone or in combination with the alcohol cause a profound alteration in the chemistry of the body cells. This change in the body chemistry could produce an acidosis which in combination with the other factors causes pathologic manifestations in all tissues and especially in the tissues of lipoidal structure such as the retina and brain. We know that these highly specialized tissues are always more sensitive and will show degenerative changes even in a temporary upset that interferes with the normal metabolism of its cells.

From the data available, it may be stated that some chemical combinations are not tolerated by the body so readily as are others. Perhaps one of those most poorly tolerated by a large percentage of people is methyl alcohol. Although some individuals have the metabolic ability to cope with this drug, the greater number do not, and when it is taken into the body the abnormal metabolic processes that do occur produce chemical compounds that tend to act as poisons and alter the normal chemical balance so necessary to physical well being. It is generally known, and confirmed by the author's experiments on animals, that one of the oxidation products—namely, formic acid—can cause changes similar to those produced by methyl alcohol alone. It would be incorrect to state that because formic acid is known to be present in the body during the time of the toxic effect, it alone is the causative agent; but rather that formic acid is a factor and very probably acts in conjunction with methyl alcohol and other oxidation products to produce the pathologic changes. There is no conclusive proof that methyl alcohol alone is responsible, and until further proof is available the aforementioned statement may stand as a possible deduction.

Subjective ocular symptoms

VISUAL ACUITY

Fairly characteristic changes in the visual acuity are found in cases of methyl-alcohol poisoning.

In acute cases, the changes are sufficiently constant to be diagnostic. The characteristic visual change is first of all a sudden diminution of vision which may be of marked degree. This is followed by a gradual improvement in a few weeks, but is followed later by a gradual loss of vision which may progress to total blindness.

Comment. It is fairly accurate to assume that the initial loss of vision may be caused by the action of the chemical on either the ganglion cells, the nerve fibers, or both. Its sudden onset, followed in a few weeks by a return of vision, suggests that there is at first an edema of the tissues. Not necessarily all the tissue cells are involved. Microscopic study shows that the cells may be destroyed in patches, with some fairly normal cells between the areas of destruction. It is conceivable that the edema which undoubtedly results would for the time being inhibit the action of these undestroyed nerve cells, temporarily causing the total or almost total loss

of vision. The edema may be localized in the nerve, the retina, or both, but, judging from the ophthalmoscopic pictures, it is most frequently seen in the region of the papilla. When the ophthalmoscope does not show changes referable to edema, the latter may be retrobulbar. It is also possible that a retinal and choroidal edema may be present but not evident under the ophthalmoscope.

After a few weeks, the edema subsides and the ganglion cells that were not previously destroyed again function so that a certain degree of vision returns. Because of the disturbed nutrition resulting from the toxic effect on the cell and the edema during the acute process, many of these partially affected cells may die; this would account for the gradual second reduction in vision. The final vision depends upon the number of cells that survive. In the final stage, only a few cells may remain sufficiently normal to function, and the vision may be practically gone. In other cases, in which there is but a slight permanent loss of vision, only a few cells have been destroyed.

In order to appreciate these statements recourse must be had to a study of microscopic slides. In the retina may be seen a total destruction of ganglion cells, and adjacent to these cells ranging from normal to complete destruction. The edema is also definitely present and must inhibit the metabolism of the still undestroyed cells.

In the chronic cases, the gradual loss of vision follows the same process to a less degree. There is no sudden death of the ganglion cells and very little edema, but rather a gradual loss of vitality due to the altered metabolism of these highly sensitized cells.

PERIMETRY DATA

The perimetry findings are not characteristic. Scotoma are the most frequent finding and may be single or multiple. A central scotoma is the most constant finding. There is frequently a peripheral contraction of the field which varies greatly in degree and position.

Comment. From this observation, it is evident that the toxic effect is diffuse and variable. The constant occurrence of scotomata suggests that the effect varies in intensity, some areas being profoundly affected. The frequency of the central scotoma suggests the papillomacular bundle as an important point of involvement.

Because the ophthalmoscopic picture so frequently indicates a retrobulbar involvement or an involvement of the optic disc with little or no visible change in the retina, it would seem logical to conclude that the scotomata are the result of an optic-nerve edema. It is not certain, however, that they are not the result of localized involvement of the retina also. The variability of the perimetry findings over a period of time is in keeping with the visual acuity, and can be attributed to the same process.

It seems evident that with regard to the perimetry findings, a rule as to the exact structure affected cannot be established. Undoubtedly, both the retina and the nerve are involved in all cases; in some, however, one or the other may show the predominating change. From the perimetric evidence alone, one is inclined to consider the optic nerve as the portion chiefly affected, because the perimetric changes are more characteristic of this type of involvement.

Objective ocular findings

EXTERNAL

The objective findings give evidence of a disturbance in the pupillary and accommodation reflex arcs. That the involvement is variable is shown by the variable pupillary and accommodative reactions.

The symptom of ocular tenderness, both on pressure and on movement of the globe, is evidence of an ocular or retrobulbar congestion or edema. The picture

can be described as comprising phenomena which accompany an acute edema.

Comment. As to the localizing value, the objective findings suggest an involvement of the entire nerve and vascular elements of the eyeball, together with certain suggestions of retrobulbar involvement. There are also findings which prove that the reflex arcs of the pupil and accommodative mechanism are affected, pointing to a central involvement. The presence of ptosis and the involvement of certain extraocular muscles suggest a diffuse affection of nerves other than the optic and in all probability located in the higher centers.

OPHTHALMOSCOPIC DATA

From a study of the various ophthalmoscopic reports, it is evident that in the acute stage, the optic nerve is the most frequently involved part of the eye.

The process may at first involve the retrobulbar portion of the optic nerve only, or it may spread forward to include the papilla. It may involve the papilla from the onset. Most reports make little or no mention of the retina except the portion surrounding the papilla.

There are indications of circulatory disturbance with edema. The picture varies from a congestion of the nerve head to an intense edema. Mention is made of the dilated retinal vessels.

The optic atrophy that follows is proportional to the primary nerve involvement.

Comment. It seems evident from these data that the optic nerve is the portion of the visual apparatus primarily affected, and the process suggests an edema that may vary in degree. At least this would be one explanation for the ophthalmoscopic description given in the various cases reported. In the greatest number of these it is noted that the optic papilla shows signs of congestion or edema at various stages of severity; retinal edema is present but gradually diminishes in degree away from the disc. The retina not adjacent to the disc may show no signs of pathologic change except for hyperemia.

It is difficult to understand this picture when the microscopic descriptions emphasize so strongly the retinal phase of the change and show so little evidence of optic-nerve disturbance. It is, of course, possible that the retinal edema by comparison appears insignificant and gives the impression of a mere congestion when, in reality, it is quite severe. In other words, the marked optic-nerve involvement as seen with the ophthalmoscope does not preclude edema or destruction of the retinal elements. The absence of definite choroidal changes would tend to minimize the retinal ophthalmoscopic picture.

One may venture the opinion that in cases where the optic-nerve change is the predominating factor, a similar involvement occurs in the retina and choroid that is not shown ophthalmoscopically except for what appears to be hyperemia. The direct action of the toxemia in the retina may cause necrosis, but with little reaction visible ophthalmoscopically.

Undoubtedly, some cases are more definitely retrobulbar than others, whereas others show more intraocular changes. It seems that all of them on examination will exhibit some signs of involvement of both elements.

Another factor which indicates a more general involvement than merely the optic nerve is the postneuritic atrophy that develops. In these cases, reports show the presence of retinal atrophy as well.

It therefore seems plausible to conclude that the ophthalmoscopic evidence bears out the contention that the entire nerve structure of the eye is involved, including the retina and optic nerve. In addition to this there is a choroidal disturbance. The process is not always uniformly the same; instead, one part may