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

show the predominating picture of pathologic change.

It seems evident that the initial tissue injury is manifested ophthalmoscopically as an edema or hyperemia only, and that undoubtedly many retinal changes, not visible with the ophthalmoscope but none the less important, may not be observable.

Microscopic evidence found in the human eye

The following summary describes the significant changes observed in the cases reported in the literature:

In the autopsies reported by Pick and Bielschowsky,[12] the most interesting histologic findings appeared in the ganglion-cell layer of the retina, in comparison with which the other layers of the retina were only slightly altered. The tangible changes were demonstrable only in the inner granular layer where an agglomeration of the chromatin substance into coarse masses had taken place.

In the retrobulbar section of the optic nerve, changes were found which, however, in comparison with those in the retina, seemed trivial. In occasional medullary sheaths, a fine-grained fatty degeneration was found. There were to be noted, at some points, swellings and inflations in the axis cylinders. If all these findings in the optic nerve are taken together, we may say with certainty that an acute destruction of the nerve substance must have taken place.

In the central nervous system, there were both chronic and recent changes in all three cases. The chronic changes were no doubt due to a chronic alcoholism in each case. The acute changes were exclusively in the ganglion cells. Compared with the changes in the retina, these were only trivial, from a quantitative as well as a qualitative point of view.

Comment. These findings are significant because they describe in considerable detail the results as found in the retina, optic nerve, and the higher centers in three patients who died of acute methyl-alcohol poisoning. It is the most complete description of this situation in the literature and offers most significant data from which conclusions can be drawn. However, the question of post-mortem changes arises, and there is no way of determining its validity. It may be said that the described changes are very suggestive of post-mortem changes. This point is emphasized by study of the author's cases in which post-mortem changes occurred. These showed a striking similarity to those described by Pick and Bielschowsky.

The latter's statement that the most important changes occurred in the ganglion cells bears out the findings in animal experimentation. They also stress the observation that the changes in the optic nerves were slight by comparison. In spite of the fact that they minimize the optic-nerve changes, there is evidence of pathologic processes which should not be minimized. The degenerative changes in the medullary sheaths and the swelling of the nerve fibers are definite signs of optic-nerve injury.

In the central nervous system the finding of ganglion-cell destruction is significant and shows that the process is not confined to the eye.

The case reported by Rymowitsch[13] was that of a man who died of chronic methyl-alcohol poisoning. He noted hydropic and fatty degeneration of the retinal ganglion cells, varicose hypertrophy of the nerve fibers, and edematous saturation of the granular layers. No detailed account was recorded.

Comment. The report is much too brief to be of scientific value. It does, however, indicate changes in the retina that seem to be characteristic.

In Schwartz's[14] two cases in which death occurred from methyl-alcohol poisoning, the following facts were noted: There were no changes in the optic nerves; there were alterations, however,

in the vagus and phrenic nerves. Changes found in the retina accounted for the blindness.

Comment. The report is much too brief to be of scientific value. It is significant that no changes were found in the optic nerves. Unfortunately, the changes in the retina, vagus, and phrenic nerves were not described.

In MacDonald's[15] three patients who died as a result of imbibing methyl alcohol, the following changes were noted.

Case 1. The retina showed marked degeneration in the ganglion-cell layer. The vessels of the choroid were considerably congested.

Case 2. The ganglion cells were decreased in number and degenerated, and cystic spaces were seen throughout this layer. The vessels of the choroid were markedly congested.

Case 3. The retina showed marked changes. The ganglion cells were decreased in number, and cystic spaces were seen throughout this and the nerve-fiber layer.

In view of the well-known early post-mortem degenerative changes that take place in the delicate ganglion-cell structure, MacDowell could not say that his findings were of value; they suggest that the central scotoma and loss of vision were due to toxic degenerative changes that take place in the ganglion cells. He believed that the subsequent changes which result in optic atrophy are due to ascending degeneration of the nerve fiber following the damage to the ganglion cell. The optic-nerve changes, he believed, to be late, for no pathologic alteration could be observed in the optic nerves of any of his cases.

Comment. Without doubt, post-mortem changes account for some of these tissue changes, and it is difficult to evaluate the findings. The cases were so acute that the pathologic changes had not progressed very far. It is important to note the absence of signs of edema in the retina and the absence of signs of pathologic involvement in the optic nerves.

In Menne's[16] two patients who died of methyl-alcohol poisoning, the following points were noted.

Microscopically, there was little change in the optic nerves except edema and hyperemia and some patchy proliferation of glial cells. The most pronounced alterations were observed in the ganglion cells of the retinas, most marked nearest the disc. There were no noteworthy changes in the glial cells except for marked edema.

Comment. It is important to note the presence of edema of the optic nerve and the fact that the ganglion-cell layers again showed the greater change. Edema of the retina was also noted. It is unfortunate that more detail was not given so that a proper evaluation could be made.

The author's two cases were the result of methyl-alcohol poisoning with fatal outcome. The interpretation of the findings is as follows.

CASE 1, A. There appeared to be a small amount of papilledema. Disintegration of the elements was observed in the rods and cones, forming an albuminouslike precipitate. There was a wealth of ganglion cells and this layer showed no evidences of increased gliosis. However, practically all of the ganglion-cell nuclei were pushed to the extreme periphery of the cell. In many of the cells the Nissl substance was arranged in a peripheral ring, while in still other cells there was more advanced dissolution of the Nissl substance indicating chromatolytic changes. All the ganglion cells were distinctly swollen, including those in the macular region. This perhaps represents an early stage in a destructive process.

CASE 1, B. This eye was similar to the preceding one.

CASE 2, A. There was a definite edema of the nerve head, more marked than in the preceding eye. There seemed also to be

an increase in the glial elements in the nerve-fiber layer of the retina surrounding the disc and passing into the optic nerve. The rod-and-cone layer had undergone dissolution. The ganglion cells were quite plentiful, but there was an increased number of glial cells in this layer. The ganglion cells themselves were swollen. The nuclei tended to bulge peripherally from the cell body. The Nissl substance had disintegrated, and in some cells was placed peripherally; in others it had taken on a finely granular appearance; and in still others the cell had only a shadowy appearance. It seemed that many of the ganglion cells in the macular region were better preserved than those in the periphery.

CASE 2, B. This was similar to A. There was an occasional normal ganglion cell, however, and in places the retina was detached because of the great accumulation of debris from the disintegrated rod-and-cone layer.

The optic nerves in 58 A and B appeared to be normal; that of 59 B showed some pink-staining areas which had the characteristics of edema, but no change was apparent in that of 59 A.

Comment. In these cases there should have been obvious post-mortem changes in the retina because the specimens were not fixed in formalin until 12 hours after death. However, the material was refrigerated. Evidently some of the changes are *post mortem.* It is significant that they correspond very closely to the retinal changes reported as occurring in the other cases, and the question naturally arises as to how many of these are due to post-mortem changes.

In the author's cases the engorged choroidal vessels and some edema of the retina are worthy of note. Also of importance is the presence of optic-nerve changes in one case.

To draw conclusions from the preceding autopsy reports is difficult because: (1) there are not sufficient cases; (2) the reports are not complete; (3) there is a possibility that the tissues were not fixed immediately and that many of the findings are the result of post-mortem changes.

The findings that are most significant emphasize the retinal changes, which are chiefly in the ganglion layer. It should be borne in mind that post-mortem processes would cause alterations similar to these. Undoubtedly, some of the changes are the result of the toxic process, but, to be scientifically accurate, it is difficult to ascertain how many are actually due to this cause.

It is rather significant that there were few changes in the optic nerves. Although there were some changes that suggest a toxic process, many were undoubtedly *post mortem.*

If we can assume that the reported findings are not *post mortem,* we have indeed valuable data. We can then say with assurance that the retina suffers most from the toxic exposure and especially the ganglion cells. This would be expected because of their greater sensitivity to change. The presence of injury in the ganglion cells of the brain is proof that similar changes are found elsewhere in the body.

The presence of degenerative changes in the optic nerves in some of the cases shows that the process is not confined to the retina. Likewise, edema was present in both the retina and the optic nerve. The absence of pathologic changes in the optic nerve in many instances may be due to the acute process, the type of tissue arrangement where early changes may not show so readily, and the possibility of improper staining to show these early changes.

The presence of choroidal congestion appears to indicate that the vascular portion of the eye is involved. Some investigators claim that the entire process is a vascular one, but this does not appear to

be the case, judging from the description given. It must be admitted that the evidence of changes in the human eye is the most forcible argument that can be presented as to the pathologic process resulting from methyl-alcohol poisoning.

Animal experimentation carried out by other investigators to determine the effect of methyl alcohol on the ocular structures

The essential facts concerning these experiments are as follows:

In one dog Holden[17] found degenerative changes in the ganglion-cell and the nerve-fiber layers of the retina, and the medullary sheaths of the fibers of the optic nerve. The author concluded that the retina is affected primarily, and the change in the optic nerve represents a secondary stage of the process.

Comment. It is rather impractical to come to any conclusion after an investigation on one dog. Suspicion arises that post-mortem changes may have given rise to errors in evaluating the findings.

Birch-Hirschfeld[2] experimented with rabbits and chickens and made the following observations: The toxic effect first appeared in the ganglion cells of the retina. After this the inner granules degenerated, later the outer granules.

In only one case could distinct signs of degeneration of the nerve fibers be found, and these appeared in the animal which showed the greatest changes in the retinal layers—in a temporal wedge-shaped region of the cross-section beginning immediately behind the bulbus. There was distinct disintegration of fibers, extending posteriorly for about 5 mm., the remainder of the cross-sections showing fairly normal conditions. In the preparations no sign was found of round-cell infiltration even in the degenerated region, nor a noteworthy connective-tissue proliferation.

Birch-Hirschfeld further stated that without doubt the degenerative changes in the optic nerve were of a secondary nature. This is indicated by their absence in the other cases, where the toxic effect on the retinal cells was less pronounced.

Comment. This research is undoubtedly significant; that it has been recognized as such is evident from the repeated references to it in the literature. Critically considered, however, it should be borne in mind that these findings apply to rabbits and chickens and are not necessarily indicative of what may be found in the human eye. There is also the possibility that other factors enter into the situation which may produce some of the changes: (1) post-mortem changes which appear so rapidly in the retina; (2) trauma as the result of killing the animal; (3) imperfect staining and fixing.

If his work is scientifically accurate, his data do bear out his contention that methyl alcohol, even in small doses in the experimental animal (rabbit and chicken), in the first place appreciably injures the cells of the retina; and that only in secondary fashion can the degenerative processes occur in the optic nerve. There must have been some doubt in his mind as to the accuracy of this work because in 1920 he repeated it.

Friedenwald,[5] working on a rabbit, noted the toxic effect on the ganglion cells of the retina. The retinal ganglion cells showed marked degeneration, and the inner and outer nuclear layers were less affected.

Comment. The same criticism may be applied to this work that applied to Holden's. Insufficient data were presented to substantiate the conclusions.

Tyson and Schoenberg,[18] working with guinea pigs, rabbits, dogs, and a monkey, concluded that microscopic findings indicated an edema of the tissues with very early signs of beginning degeneration of the ganglion layer of the retina.

They found that the choroid gave the

impression of hyperemia. As to the retina, the rods and cones and the external nuclear layer were normal. The outer reticular layer was slightly edematous, the inner nuclear layer normal, the inner reticular layer also slightly edematous. The ganglion cells were swollen and surrounded by clear areas, the nuclei being displaced far toward the periphery. The inner layers of the retina showed some edema. The medullary sheath of the optic nerve took Weigert's stain rather weakly.

Comment. This work is especially significant because it confirms the findings of retinal degeneration with ophthalmoscopic evidence to support it.

The change in H-ion concentration of the aqueous and evidence of acidosis are suggestive of chemical changes in the eyeball that substantiate to a measure their theory as to the process leading to the retinal degeneration.

The evidence they obtained of the increased susceptibility of higher animals is valuable; of special significance is their contention that methyl alcohol is a true hematoxin and produces a degenerative change in all tissues.

Kazas,[19] in his work on the effect of methyl alcohol on rabbits, found that the general picture of changes in the retina, except the degenerative process, presented the phenomena of dropsical saturation. The degeneration was not always connected with dropsy. Changes in the retina were markedly expressed in all its layers including the layer of rods and cones. An adipose degeneration of high grade was noted, not only in the layer of nerve fibers but also in the ganglion-cell layer, in the cells proper, and in the inner molecular and nuclear layers.

Adipose degeneration was expressed in all optic nerves. A considerable increase of connective tissue was found. Adipose degeneration was markedly expressed in the N. oculomotorius and the chiasma.

He therefore succeeded in obtaining changes as follows: in the vascular membrane; in the membranes of the optic nerve; in the retina, beginning with dropsy and degeneration up to albuminuric retinitis; and in the optic nerve, beginning with parenchymatous degenerated neuritis up to axial atrophy.

Comment. The results of this investigation appear to confirm the previous research on this subject. The microscopic picture reported is in agreement with that observed by others, although this writer lays special stress on the independence of the degenerative changes and the dropsy changes. The finding of adipose degeneration in the optic nerve and the oculomotor nerve is especially important. The increase of connective tissue is significant. Important also is his contention that the affection of the nerves was independent of the retinal changes. His explanation of the pathologic process is worthy of thought.

Igersheimer and Verzar[20] attempted to determine whether the sense of light might be used as a clinical criterion of the toxic effect upon the retina. As experimental animals they chose chickens.

They concluded that the light perception was temporarily impaired three weeks after the beginning of the poisoning. There was then complete restoration; after four additional weeks of poisoning, the perception of light was again reduced. The retina showed no changes of note.

Comment. The significance of this research is that no pathologic changes were noted in the chickens' eyes. The technique of applying the drug was apparently correct, and the method of sectioning the eyes was apparently not at fault. The writers emphasize the point that acute intoxication was avoided, and it is possible that this avoidance may account for the absence of retinal pathology. The

fact remains that under careful experimental conditions the retina showed no evidence of pathology.

Schanz[21] believed that between the taking of the poison and the onset of blindness there is an interval in which light has a sensitizing effect which must be necessary before the poison can have its effect. As an experimental confirmation of this theory, he gave methyl alcohol to three rabbits, protected one eye from light, and exposed the other to the sun for a number of hours, five or six times in the course of several weeks. He considered the toxic amblyopia to be the result of a sensitization injury to the retina, which absorbed more light, especially short-wave rays, under the influence of sensitizers. In one of these experimental rabbits, killed on the nineteenth day after the last exposure, he found "rather large exudates in the lower half of the retina of the exposed eye, while the protected eye was free from every change."

In the eye exposed to methyl alcohol, he found a distinct diffuse degeneration of the entire cross-section of the optic nerve behind the point where the vessels enter the eyeball. The optic nerves of the eye kept in darkness were found to be normal.

Comment. This experiment proves nothing of note. The insufficient data do not allow conclusions to be drawn. The theory that light is a factor, acting in conjunction with the methyl alcohol to produce retinal changes, is a new approach but does not appear to have much basis for acceptance.

In 1920 Birch-Hirschfeld[3] repeated his experiments, using dogs and monkeys. He found that distinct signs of degeneration (analogous to those previously found in rabbits and chickens following the same form of intoxication) were present in the ganglion cells.

Extensive degenerative changes could be observed even in the beginning portion of the medullary optic nerve, immediately behind the lamina cribrosa. These changes did not appear in the entire cross-section. There were all stages of change ranging from beginning partial degeneration of individual fibers to practically complete disintegration of the entire bundle; but in the degenerated areas it showed distinct changes.

The primary change in the glial tissue rests upon a degenerative process; this degenerative process the author assumed to be due to edematous saturation leading to loosening and disintegration of the fibers.

He concluded that the degeneration of the nerve fibers in the optic nerve was not the result of pressure necrosis due to the proliferated septal tissue or similar tissue showing inflammatory infiltration.

In view of this, and of the normal macroscopic condition of the optic nerve with reference to size of the cross-section and consistency, the author assumed that the exudative processes in the nerve trunk had not yet fully developed.

Comment. This research confirmed Birch-Hirschfeld's earlier findings and in addition demonstrated their presence in higher forms of animals, such as the monkey. His conclusions concerning the optic-nerve findings seem to be more definite in this investigation, especially the changes in the nerve fibers.

He stresses the absence of inflammatory reaction and edema, although the nerve tissue showed extensive degeneration in areas. The degeneration also involved the glial tissue and suggests that it is the result of the direct action of the poison.

De Schweinitz[4] examined dogs which had been acutely and chronically poisoned by methyl alcohol and in no case did microscopic study reveal pathologic changes in the retina.

Comment. These findings are of special significance. Although the research is brief, it is, as is characteristic of this author's work, most reliable. The absence of positive findings is in wide variance with other similar work and leaves it all open to question.

Friedenwald and Felty[22] performed a similar set of experiments using rabbits, guinea pigs, and dogs.

They were unable to produce any retinal or optic-nerve lesions with methyl alcohol and concluded that the original reports of Birch-Hirschfeld in regard to alleged changes in ganglion cells were artifacts, since they could produce similar changes in material from normal animals by variations in fixation and embedding.

Comment. For scientific accuracy of comparison, it is of value to compare the methods used with those used by others who did find retinal changes. Friedenwald is an accurate observer and this adds weight to the importance of his findings.

Schwarzkopf[23] experimented with rabbits and dogs, and studied the effect of light in relation to ocular changes.

In the retina he found pronounced degeneration, chiefly in the ganglion cells. Inflation of the cell body and nucleus, to the point of obliteration of the cell boundaries, alternated with shrinkage processes and clumping of the chromatin. There was no edema. The vessels were normal. The inner granules presented indistinct chromatin structure, inflation, and chromatolysis.

In the optic nerve a bilateral diffuse degeneration was observed immediately behind the bulbus, almost to the point of entrance of the vessels. Enlargement of the septa and multiplication of nuclei occurred only in the anterior sections. There was inflammatory infiltration.

Comment. Schwarzkopf's anatomic investigations are a complete confirmation of the Birch-Hirschfeld results. In the retina, the ganglion-cell layer offered the first and most conspicuous changes. It is especially significant that he found degenerative changes in the optic nerves immediately behind the eyeball.

Scott, Helz and McCord[24] performed experiments on 31 monkeys, 58 rabbits, and 176 white mice.

Upon studying the eyes and optic nerves of these animals these investigators found constant changes both in retina and nerve. However the changes in the retina predominated and were uniformly of the nature of an acute toxic lesion. The vessels of the choroid were markedly congested. The entire retina was edematous, but especially the fiber and ganglionic-cell layers. The ganglion cells were degenerated. This degeneration was patchy in occurrence, normal areas being immediately adjacent to markedly degenerated ones. These degenerated areas were not confined to any one portion of the retina but were scattered throughout. These retinal changes were quite similar to those found by MacDonald in human cases, and by Holden, Friedenwald, Tyson and Schoenberg, and Birch-Hirschfeld in experimental animals. It seemed not uncommon to find degenerations in the retina in the absence of any degenerative changes in the optic nerve.

Comment. As in other works on animals the retinal changes seemed to predominate. The findings in this work were in accord with the changes found by other investigators.

To summarize the results of this experimental work: It is interesting to note that nine papers reported definite pathologic changes in the retina and optic nerve. The authors of three reports failed to find evidence of change.

In all nine instances the findings were in fair agreement. In describing the retina, it was common to find the changes

consisted of definite degenerative alterations in the ganglion cells and a change of less degree in the other layers. A typical statement reads as follows:

"The changes in the retina predominated and were uniformly of the nature of an acute toxic lesion. The vessels of the choroid were markedly congested. The entire retina was edematous, but especially the fiber and ganglionic cell layers. The retinal ganglion cells showed marked degeneration; the inner and outer nuclear layers were less affected. This degeneration was patchy in occurrence, normal areas being immediately adjacent to markedly degenerated ones. These degenerated areas were not confined to any one area of the retina but were scattered throughout."

As regards the optic-nerve changes, all nine authors found evidence of pathologic involvement, and it seemed common to find degenerations in the retina associated with the degenerative changes in the optic nerve. The retinal changes seem to predominate.

It is especially significant that degenerative changes in the optic nerves were found immediately behind the eyeball. Most of the writers agreed that the degenerative changes in the optic nerve were less conspicuous. The following quotations are characteristic:

"In cross-sections, extensive degenerative changes could be observed even in the beginning portion of the medullary optic nerve, immediately behind the lamina cribosa. These changes did not appear in the entire cross-section. There were all stages of change ranging from beginning partial degeneration of individual fibers to practically complete disintegration of the entire bundle; but in the degenerated areas there were distinct changes.

"In the preparations was found no sign of round-cell infiltration even in the degenerated region, nor a noteworthy connective-tissue proliferation.

"The primary change of the glial tissue rests upon a degenerative process; this degenerative process was assumed to be due to edematous saturation which leads to loosening and disintegration of the fibers. The degeneration of the nerve fibers in the optic nerve was not the result of pressure necrosis due to the proliferated septum tissue or similar tissue showing inflammatory infiltration."

It seems that the predominant finding in both the retina and the optic nerve was edema. This was associated with signs of necrosis or degeneration of all parts but especially the higher differentiated cells of the retina. There was no evidence of inflammatory infiltration nor of vascular engorgement except for a slight amount in the choriod.

Contrary to these findings are the negative results found in the work of de Schweinitz and Friedenwald. It is difficult to explain the difference in result. As the details of their experimental work were not published, it is impossible to make a fair analysis. It might be of value to mention that de Schweinitz must have been still in doubt, in spite of his experimental work, because he personally suggested to the author that this problem should be solved. The findings of two such reliable observers should be considered significant. The following statement by Friedenwald should be borne in mind in making a final decision:

"The original findings of Birch-Hirschfeld in regard to alleged changes in the Nissl bodies of the ganglion cells were artifacts, since he could produce similar changes in material from normal animals by variations in fixation and embedding."

(To be concluded)