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THE HISTOPATHOLOGY OF METHYL ALCOHOL POISONING*

Nerves other than the optic nerve - 318

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One of the earliest references to the toxicity of wood alcohol is in an article published by MacFarlan[14] between the years 1855 and 1856 in London. Approximately twenty-five years later a French investigator, Poincaré,[18] carried on experimental work upon the toxic effect of its vapors. From that time to the present literature contains many articles concerning the toxicity of this substance. As early as 1880 it was found to be toxic regardless of its portal of entry and also that the toxic manifestations were widespread throughout the body. Even Poincaré mentioned such changes in the liver, heart, kidneys, and lungs of his experimental animals. Holden[9] observed degenerations of the ganglion cell layer of the retina (with Nissl stain), and degenerations of the medullary sheath affecting some fibers of the optic nerve. These changes were accompanied by numerous hemorrhages into the meninges of the cord and brain.

Following the development of the ophthalmoscope, clinical observation of the eye grounds became more common, and the changes in this organ grew in importance until methyl alcohol became generally considered as a specific toxin for the retina and in particular for the optic nerve. This is exemplified in the statement of Wood and LaWall,[27] "that this predilection for the optic nerve is but a part of the general tendency toward nerve trunks," and that of Tyson,[23] who stated that while these toxic manifestations are most pronounced in the retina and optic nerve, possibly other cranial nerves are also affected.

The tissues forming the basis of the present study resulted from

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a series of experiments made by Dr. Carey P. McCord[15] in the Industrial Health Conservancy Laboratories of Cincinnati, Ohio, in which a careful study of the toxic effects of methyl alcohol following various methods of administration was made. A very brief summary of that work is as follows.

The animals used were thirty-one young rhesus monkeys, fifty-eight rabbits of four breeds, and 176 white rats. Of these the final number having tissues available for microscopic study were forty-one monkeys, twenty-six rabbits, and eighty-one rats. These animals were treated by skin absorption, inhalation, and ingestion. The materials used were various grades of natural and synthetic methyl alcohol, samples of which had been obtained both from the manufacturer and upon the open market. Details concerning the manner of application can be found in Dr. McCord's discussion.

PRESENT STUDIES

No animal was utilized for tissue study unless found before the body warmth had left the corpse. Autospies were performed immediately and portions of tissue preserved in the proper fixatives. The remainder of the organs was tested chemically for the presence of methyl alcohol or its decomposition products.

The eyes of all monkeys and all rabbits except albinos were examined at least once by a competent ophthalmologist.

Intoxication was evident following all methods of application. The first sign of intoxication was a dilatation of the pupils, which reacted slowly to light. This was followed by an illness which sometimes led to prostration and possibly to death. Recovery from the effects of methyl alcohol frequently took place even during sustained exposure. Animals which had been blind upon ophthalmoscopic examination frequently regained sight and a subsequent examination revealed no pathology in the eye grounds. The brand or purity of the alcohol seemed in no way to affect the pathological changes. Animals subjected to methyl alcohol have regularly shown the presence of this substance in the blood, urine, and tissues. Formaldehyde was never recovered in any appreciable amounts.

By inhalation the threshold of danger is well below 1000 p.p.m. of methyl alcohol vapor, while by skin absorption the threshold is near 0.5 cc. per kilogram of body weight applied four times daily. Individual animals vary greatly in susceptibility, black animals being extremely resistant. There is some species variation in that rats are most susceptible and rabbits most resistant.

The typical histopathological picture of the tissues of these animals following methyl alcohol poisoning varied more with the species of animal used than upon the method of administration. Upon repeated contacts of the skin to alcohol it showed evidence of irritation, which sometimes changed to actual ulceration and necrosis. Irritation of the skin was noted by Rosenau[20] in individuals poisoned by methyl alcohol. Dublin and Lieboff[4] mentioned inflammation of the throat and mucous membranes of the air passages among the clinical manifestations of the poisoning following inhalation of methyl alcohol fumes.

Following either method of administration the organs of the abdomen most constantly affected were liver, spleen, and kidneys. The reaction in the liver was practically always one of parenchymatous degeneration, which, in the more severe cases, had proceeded to focal necrosis. This change in the liver cord cells was much more constant than fatty degeneration spoken of by Poincaré in 1879, and since then by Dublin and Lieboff, Smith,[22] Weese,[26] and others. The almost constant change in the kidney was a parenchymatous degeneration of the epithelium lining the convoluted tubules. This finding was also confirmed by Poincaré, Weese, Smith, and by Isaacs.[10]

In the thoracic cavity both the lungs and heart showed rather constant evidence of pathological change. In some cases the lungs gave evidence of a terminal pneumonic consolidation as noted by Weese in mice. In the milder cases edema, congestion, and desquamation of alveolar epithelium was noted, as mentioned by Pierce and by Poincaré. These changes were observed more frequently in those animals subjected to inhalation of alcohol fumes than in those treated by either absorption or by oral administration. The earliest changes in the heart began as an edema and progress to granular degeneration, and in some in-

stances, to a final necrosis of the heart muscle fibers. These findings also confirmed those of Poincaré.

The hemopoietic system and blood showed interesting changes. The earliest reference found to any change in the blood and blood vascular system is in a paper by Buchner, Fuchs, and Megele,[2] published in 1901, in which they discussed the capillary engorgement produced by the external application of methyl, ethyl, and propyl alcohols. Twelve years later Miura[16] injected methyl alcohol into the blood stream of four rabbits and one dog. From his results he concluded that methyl alcohol is toxic to the blood-forming organs. The next year, after experimental poisoning by inhalation, Tyson and Schoenberg[25] stated they believed methyl alcohol to be a true hematoxic. All the degenerative changes observed in other tissues they explained on the basis that the interference with the circulation of the blood deprived them of of their nutrition and oxygen. In Smith's recent paper he mentioned splenic engorgement and phagocytosis.

In the present series the lymph nodes were frequently found to be hyperplastic and the spleen in many cases gave evidence of increased blood-forming activity. This phase of the toxic action of methyl alcohol opens a somewhat new and interesting field of investigation upon this subject and upon which we hope to make further report at an early date.

The influence of methyl alcohol upon the central nervous system was much the same as elsewhere in the body: capillary congestion, edema, and patchy degeneration in the neurones. This cellular degeneration occurred more often in the spinal cord than in the brain. Pierce recorded cerebral congestion occurring both in his own cases and in those of Strohmberg. Isaacs noted in his collection of human cases edema and congestion of the brain and meninges and an increase in the amount of spinal fluid. Rühle[21] found in dogs, scattered hemorrhages along the blood vessels in the pons, medulla, and cord. He also noted that the vascular endothelium contained large amounts of lipoid and that there was perivascular infiltration. This condition preceded the hemorrhages. In the experiment under discussion there was no evidence of either the perivascular infiltration or hemorrhages noted

by this investigator. Holden also described hemorrhages into the meninges, brain, and cords of dogs. He agreed with several other investigators that the alcohol causes pathological changes in nerves other than the optic nerve. He reported that the experimental dogs appeared partially deaf as well as blind before death. Both Rosenau and Tyson refer to hearing impairment in human cases. Tyson also cited one case of paresis of the left internal rectus muscle of the eye. Jelliffe[11] has noted other forms of neuritis than optic neuritis, citing a human case with neuritis of the upper extremities. McCord, in his clinical observations on the animals which comprise this study, noted evidence of such peripheral nerve involvement. These clinical observations were later confirmed in stained preparations of peripheral nerve of these animals.

In studying the eye and optic nerve constant changes were found 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 area of the retina but were scattered throughout. These retinal changes are quite similar to those found by MacDonald[13] in human cases, and by Smith, Weese, Holden, Friedenwald,[5] Tyson and Schoenberg,[24] and Birch-Hirschfeld[1] in experimental animals. Hale[6] discussed Moulton's two cases of complete optic atrophy without changes in the retina. On the other hand it seems not uncommon to find degenerations in the retina without any degenerative changes in the optic nerve. Birch-Hirschfeld definitely stated that degenerations in the optic nerve occurred in but one of his cases. MacDonald did not find any optic nerve pathology in his human cases. Weese and Tyson and Schoenberg fail to mention the optic nerve. Very few of our animals showed any change in the optic nerve although numerous specific neurological stains were used. The animal showing such changes most definitely was the monkey which was blind at death.

With these findings in mind the discussion arises as to whether the retina or optic nerve is affected first, or whether they might both be the result of the same change and occur simultaneously. Tyson believed that the loss of function is due to the affected nerve fibers first or at least coincidentally with the degeneration in the ganglion cell layer. However, our observations in the present study force us to agree with Birch-Hirschfeld, MacDonald, and Henderson and Haggard[7] in thinking that the degeneration of the retinal ganglion cell uniformly precedes any degenerative changes in the optic nerve.

The most important factor in this process is the direct action of the alcohol itself, while a contributing factor may be the accompanying edema. That such a rôle might be played by edema is suggseted in a bulletin published by the National Research Council of Canada.[19] Kasaas[12] believed that circulatory disturbances in the choroid and in the sheath of the optic nerve, together with edema, lead to degeneration of the retina. The author stated that the edema disappeared and visual power partially returned if collateral circulation be restored. In human cases of a chronic nature, several of recurrent transitory blindness with a gradual impairment of sight are reported in a bulletin issued by the New York State Department of Labor,[3] and in some animals of the present series blindness was apparently transitory. One monkey in particular was blind both clinically and upon ophthalmoscopic examination at one time during the experiment, but prior to death its sight was proved again normal by the same means. Histological examination of the eyes of this animal revealed no evidence of pathologic change. Such transitory blindness was not of uncommon occurrence among the animals reported by McCord.

There has been a gradually growing tendency to consider methyl alcohol as a specific poison to the optic nerve and retina. This concentration of attention upon one manifestation of a disease to the exclusion of its other less conspicuous lesions is not confined to this disease, however. Among rather numerous possible examples we may cite the fact that until the very recent careful observations of Herrick[8] the thought prevailed that the

pathology of meningococcic infection was limited entirely to the meninges. The proof that such infections are true cases of generalized septicemia has thrown new light upon this disease and explains the not infrequent overwhelming infections of this organism and sudden deaths occurring before meningeal pathology has developed. Other conditions in which a similar attitude has been assumed by the physician are the relationship of the kidney to hypertension, and also in the lesions of poliomyelitis. Similarly the lesions of the eye have been so conspicuous as to mask the other manifestations of the poison of methyl alcohol. The pathological conditions arising from these associated effects may be, however, just as constant and possibly more important than the changes taking place in the eye. Also it is possible that an individual may suffer from methyl alcohol poisoning in severe degree and still show no eye changes, just as meningeal lesions are no longer considered essential for the diagnosis of meningococcus infections.

SUMMARY

A histopathological study has been made of forty-one monkeys, thirty-six rabbits, and eighty-one rats which had previously been treated with methyl alcohol. The alcohol was administered by inhalation, by skin absorption, and orally. The method of application made no apparent difference either in the type of lesions or in their severity.

There is some variation in species susceptibility to methyl alcohol in the animals studied; rats are most susceptible to the alcohol and rabbits are most resistant. Individual variations in susceptibility to this toxin are very marked.

The characteristic pathological lesions of methyl alcohol poisoning are degenerative ones. Only the parenchymal tissues and neurones are affected. This granular degeneration of parenchymal tissue may proceed to necrosis. There is practically never injury to connective tissue and therefore seldom any fibrosis. These changes are accompanied by a generalized capillary engorgement and edema.

The pathological conditions in the eye are identical with those

found elsewhere in the body. The edema is most marked in the retina and optic disc. Degeneration of the ganglion cells of the retina is sometimes followed by degenerative changes and fibrosis within the optic nerve.

There may be multiple degenerations involving nerves other than the optic nerve.

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