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VISCERAL CHANGES IN WOOD ALCOHOL POISONING BY INHALATION.

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PART I. THEORETICAL.

1. *Introductory.*

VERY few investigations have been made of harmful effects of inhalation of methyl alcohol—I am referring to the work of Eulenberg (1), Poincaré (2), Tyson and Schoenberg (3), and Loewy and Heide (4) and Mueller (5). Of these only Poincaré and Tyson and Schoenberg have studied the histo-pathological changes. But these results, although not numerous, leave no room for doubt as to the extremely dangerous effects of inhalation of wood alcohol. To quote Tyson and Schoenberg: "There exists a striking similarity between the effects of ingestion and the inhalation of wood alcohol."

The work of Loewy and Heide is of very great importance and interest as they were the first investigators to study the question of the relation of concentration of methyl alcohol in the air to its absorption.

2. *Pharmacological and Chemical Data.*

In comparing the effects of ethyl alcohol with those of methyl alcohol one is confronted with the fact that a single dose of the former is more poisonous than the same dose of the latter.

As pointed out by Harnack (6), Fuehner (7) and others, the intensity of action (*Wirkungsintensitaet*) of equimolecular solutions increases with the increase of the number of atoms of carbon, as well as with the greater solvency for lipoid substances (Meyer Overton), and inversely as the surface tension of the solutions. (When, however, the number of carbon atoms reaches 7, *i. e.*, after heptyl alcohol is reached, these laws are no longer true since the higher alcohols, such for example as cetyl alcohol, are almost solid, insoluble in water and are as a rule non-absorbable.)

These investigators claim that ethyl alcohol, *i. e.*, its action, is from two to four times as strong as that of methyl alcohol in single doses,—for example, codeine (a methyl preparation of morphine) is much weaker than dionine (an ethyl preparation of the same alkaloid).

But Pohl (8) observed experimentally that while no bad effects followed immediately after the administration to an animal of a small dose of methyl alcohol, very serious results were noticeable a few days later, the experiment in many instances terminating fatally. If a small non-lethal dose be repeated a few times fatal issue occurs invariably, while ethyl alcohol, similarly administered, produces no such effects.

Vital info.

How are we to explain such paradoxical phenomenon? Why does a substance, non-lethal in a single dose, become lethal after a few repeated doses, and *vice versa?* The explanation as given by Pohl is as follows: Ethyl alcohol is very rapidly oxidized in the animal body, in fact so rapidly that over 90 per cent. of it is converted to carbon dioxide and water, whereas methyl alcohol is oxidized very slowly, with the formation of formaldehyde and then formic acid.

It is formic acid and its cumulative action that is responsible for the untoward effects of methyl alcohol, the variability of individual results depending on the individual power of oxidation, the action of wood alcohol thus becoming especially dangerous in those who are ill nourished.

Placet (9) constructed the following table showing the difference in the elimination—that is, the rate of elimination of the two substances.

In other words, the complete elimination of wood alcohol requires five times as much time as that of ethyl alcohol, and we are dealing here with a cumulative action.

In rabbits the elimination of wood alcohol while faster than in dogs is

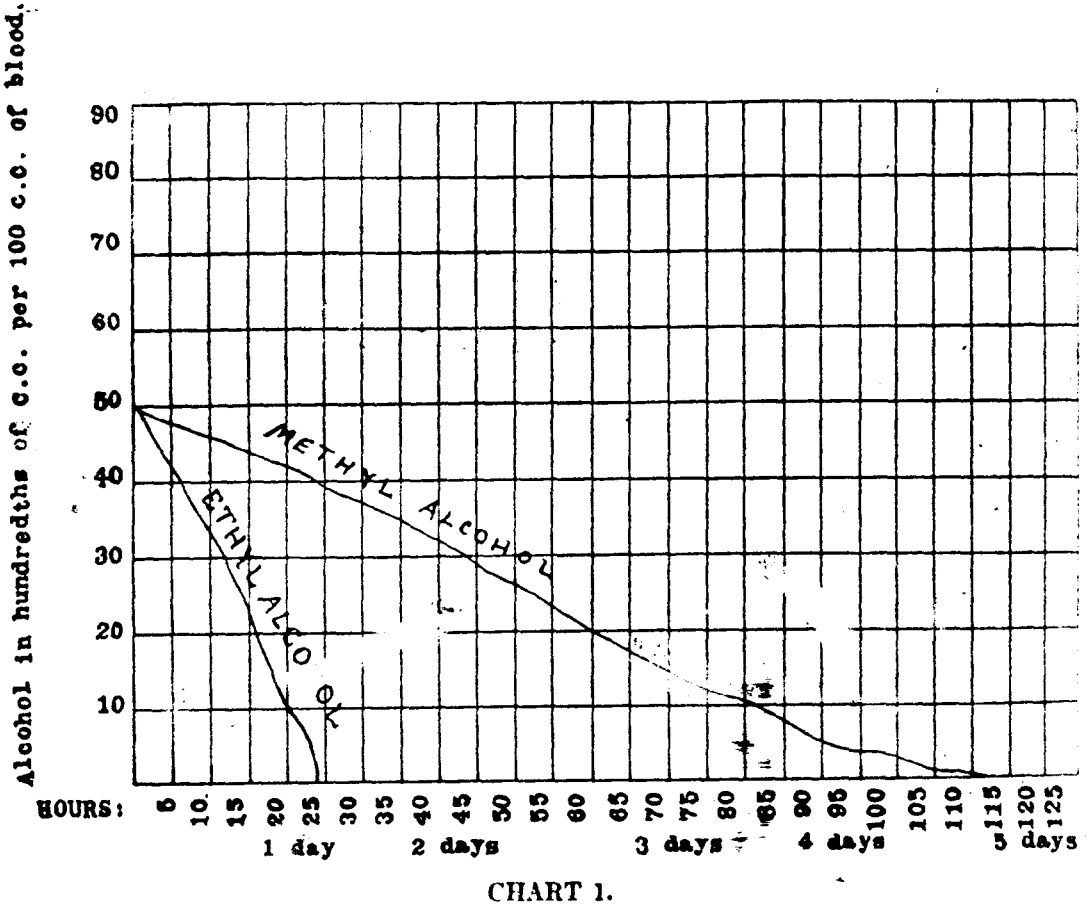

CHART 1.

The curves of elimination of ethyl and methyl alcohol after ingestion of 5 cc. of alcohol per kiloweight, in the form of a 10 per. cent solution. (Dog.)

three times as slow as that of ethyl alcohol. Because of the relatively more rapid elimination of wood alcohol in rabbits than in dogs I have chosen the former for my experiments since the results obtained with them will be at least as significant as those obtained with any other animals and I shall be spared a possible reproach for having used the animals in which the elimination was the slowest, and, *pari passu*, the pathological changes the greatest.

The histo-chemical investigations of Placet (9) show that the power of fixing methyl alcohol varies with the different tissues, the following organs being given in the order of their affinity: brain, liver, kidney and muscles. This statement of Placet finds abundant confirmation in the results of my experiments.

Possessing a marked affinity for certain tissues, methyl alcohol very slowly undergoes oxidation to formic acid which, as we know, has to be neutralized in one of two ways: either by protein-split ammonia if the animal has some stored protein for this purpose, such neutralization eventually leading to protein starvation, or by the alkalies of the blood (and this happens invariably when there is no ammonia), such neutralization leading to acidosis. These are the systemic effects, in addition to such well-known local manifestations of intoxication as optic neuritis, etc.

As to the various circumstances governing the inhalation and absorption of methyl alcohol, the questions which naturally suggest themselves are: What relations exist between the concentration of wood alcohol in the air and quantities which are inhaled into the lungs? How much time is necessary for the saturation of the body with it? For the production of harmful effects? What is the maximum quantity of wood alcohol inhaled which is still compatible with life?

Wood alcohol is very readily absorbed into the body from the pulmonary surface. Loewy and Heide have shown that inhaling the air in which wood alcohol is present in so slight concentration as 0.2 per cent. for two to eight hours leads to its accumulation in the animal body in the quantities varying from 0.32 to 0.55 grams per kiloweight, which means that if a person weighing 60 kilograms (about 150 lbs.) inhales the air in which wood alcohol is present in the proportion of 0.2 per cent for 8 hours, at the end of this period there will accumulate in this body about 25 grams of wood alcohol, which is a considerable amount bearing in mind the extremely slow oxidation of this substance. (See Chart 1.)

As to the rate of absorption, this depends entirely on that of diffusion, which is of course most rapid at the beginning of inhalation when the difference in the partial pressure of methyl alcohol in the air and that in the pulmonary blood is the greatest. When (and this happens very soon because of the slow elimination of wood alcohol) this difference is equalized, the rate of absorption will depend solely on the rapidity of elimination of wood alcohol by the animal body. In other words, absorption of wood alcohol is most rapid at first,

quickly becoming slower and slower until it becomes entirely dependent on the elimination.

Part II. Experimental.

Twelve rabbits, with controls, were used, one half of the animals being subjected to inhalation of Columbian Spirits, and the other to that of commercial wood alcohol (both brands were purchased from Eimer and Amend, New York).

It was of utmost importance to create atmospheric conditions as similar to those which prevail in ordinary workshops as possible, and with that purpose in mind a wooden box was built according to the specifications evolved by Tyson and Schoenberg, with suitable openings and mica valves, sufficient draught being allowed to insure a very fair ventilation, the temperature being about 68° F. throughout the entire length of the experiment, with hygrometric readings being invariably about 60 per cent.

The animals were very carefully looked after, and were placed under the best hygienic and sanitary conditions (thus having a decided advantage over the great majority of workers).

Both wood alcohol and Columbian Spirits were administered as follows: A piece of cotton large enough to soak up 1 ounce of either substance was suspended from a hook in the ceiling of the cage for periods of time varying from 15 minutes to one hour, three times.

In no case was it necessary to increase either the amount of the substances used or the frequency and the duration of exposure to inhalation. In fact, the first three animals died within 6–10 days after 15 minutes' exposure, three times a day, with one ounce having been used, when it became necessary to decrease the quantity of wood alcohol and Columbian Spirits to one-half of an ounce.

The animals—except those three which died within 10 days after the experiment had been begun, were permitted to live 2 months, 4 months, 6 months, 8 and 10 months, respectively.

The most striking observation was the uniformity of lesions (practically in every case the same organs, and those only, were involved), the extent of lesions varying with the duration of time exposure, thus the fatty degeneration of the cardiac muscle or destruction of the perenchyma cells of the cerebrum being more extensive in the rabbit which had been exposed for 6 months than in the one which had inhaled wood alcohol or Columbian Spirits for but 2 months.

Another interesting observation was the fact that neither macroscopically nor microscopically could there be detected the slightest difference between the effects of the "ordinary" commercial wood alcohol and those of "refined" or Columbian Spirits—in fact, should one be disposed to do so, he could properly maintain that the latter is, if anything, a more violent acting poison than the former, since the two most severe cases of destruction of the cerebral parenchyma were observed in the cases of inhalation of Columbian Spirits.

Of course, one might expect *a priori* that there would be no difference, since mere masking of the odor and

possible removal of certain impurities can in no way be expected to prevent or mitigate the physiological action of formic acid—the true *modus operandi* in the cases of poisoning by wood alcohol.

On what some of the manufacturers base their claims that the "refined" product is "quite harmless" is rather uncertain, I should think, unless they are of a very trustful disposition. One might as well try to "deodorize" and "refine" bromine and proclaim it, *eo ipso*, "quite innocuous."

Because of the striking uniformity of lesions it is unnecessary to go into each protocol or description of histological picture separately, a general discussion being sufficient, providing one bears in mind that the extent of the various lesions is directly in proportion to the length of exposure.

As noticed in the theoretical part of this study (Placet, Loewy and others), the central nervous system—notably the cerebrum—appears to bear the brunt of the attack, it being together with the optic nerve the most frequently as well as the most extensively involved organ. Next in frequency, but not necessarily in extent, of involvement are the kidneys, the liver, and the muscle—the latter again showing a very marked inequality of involvement, the cardiac muscle being affected in every case while the striated and the smooth muscle were involved but in 10 per cent. of the cases.

This limitation of lesions to the above organs brings us face to face with another deduction, namely that in so far as distribution of the lesions is concerned (and it will presently be shown that this applies to the nature of lesions as well), there appears to be no difference between the effects of wood alcohol when imbibed and when inhaled.

The lesions found in the various parts of the cerebrum, the cerebellum, the medulla and the pons consisted of different degrees of inflammatory and degenerative processes. Macroscopically the tissues appear yellowish, glistening; the line of demarcation between the gray and the white matter is not as sharp as in the control animals, in the more prolonged cases the gray matter appearing quite thinned—the entire picture being one of a non-specific atrophy.

Microscopically, the neurocytes are diminished, assuming a spindle-like shape. Nissl's granules also are diminished, with brownish pigment scattered here and there.

In the more severe cases the parenchyma cells are greatly reduced in numbers as well as in size. Thus, for example, the brain of the rabbit which had been exposed to the inhalation of Columbian Spirits showed practically nothing but neuroglia cells and no trace of parenchyma cells, the latter being represented by masses of granular debris and fat droplets, partly taken up by the so-called contractile cells, *i. e.* leucocytes, lymphocytes, and according to Birch-Hirschfield, endothelial cells.

The different stages of parenchymatous degeneration depend, of course, on the length of the exposure to which the animal has been subjected, the nuclear changes varying from the wandering of the nucleus to the

periphery of the cell to the total karyolysis.

My impression is that the apparent increase of the connective tissue is due not only to the fact that the parenchyma cells have disappeared, but to the actual proliferation of the fixed tissue cells, as seen by the very marked thickening of the adventitia and the media of the blood-vessels.

The entire microscopical picture corresponds very closely to Adami's "exhaustion" condition,* which is "anatomically recognized by the disappearance of cells and fibres and the secondary overgrowth of glial tissue filling in the space."

The lesions of the liver and the kidney present, both macroscopically and microscopically, the typical characteristics of albuminous degeneration (cloudy swelling) and fatty degeneration—the increased size of the organ, softened consistence, the tissue being almost friable (*etat crible*), glistening yellowish color, the protoplasm being uniformly dull-gray, the outline of the cells in most cases being altered or lost. The nuclei are much smaller than they normally are, lost in many cases, and appearing as vague, shadowy structures in others. The cell bodies are filled with granular, dust-like masses.

In cases of long standing, in addition to the above general appearance there is also a marked increase of the connective tissue, especially around the blood-vessels.

The muscle cells, especially the heart, present an appearance very similar to that of the liver and the kidney, as well as both fragmentation and segmentation, in some of the cases.

The lung shows in many cases patches of broncho-pneumonia, which, however, are not uniform, either in distribution or in extent.

*Adami and Nicholls, The Principles of Pathology, 1911, Vol II, p. 526.

Part III. Conclusions.

1. Wood (methyl) alcohol when administered by inhalation is as dangerous as if absorbed by ingestion.

2. The effects as revealed by the study of lesions depend primarily upon the concentration (which in its turn depends upon the ventilation), and the length and the frequency of exposure.

3. No appreciable difference has been noticed between the effects of the ordinary commercial wood alcohol and those of the so-called Columbian Spirits.

4. The results of the study are all the more significant because the animals used in connection with it (rabbits) probably are more resistant than any other to the effects of wood alcohol, owing to the rapid oxidation of the poison.

5. As in ingestion, so also in inhalation the real cause of the toxic effects of wood alcohol lies not in the toxicity of wood alcohol *per se*, but in its slow oxidation to formic acid which is very poisonous, acting as it does both as an acid and, during oxidation, as an aldehyde.

6. The danger to workers in industries in which they are exposed to the inhalation of wood alcohol—no matter in what form—may be partially, and only partially, obviated by

a most thorough ventilation; the most important consideration being allowed for each worker much more space than is usually alloted, in order to diminish the concentration of the vapor of wood alcohol.

7. The workers should be warned of the danger of the exposure.

8. Perfect health, *i. e.* perfect oxidation processes, is the best protection against the danger of the inhalation of wood alcohol, and whatever interferes with it (poor nutrition, loss of sleep, alcoholism) makes the individual all the more vulnerable.

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In Memoriam.

I have been denied the greatest pleasure a pupil is to know—to thank his teacher for the inspiration, encouragement and sympathy.

General G. M. Sternberg, Surgeon-General U. S. Army, Ret., under whose direction the work was done, has now been dead over a year, and it is but in revering his memory that I can do homage to the splendid man and the great scientist that he was.