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BIOCHEMICAL STUDIES IN A FATAL CASE OF METHYL ALCOHOL POISONING*

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MONTREAL

It is not sufficiently appreciated that methyl alcohol is very toxic. For economic reasons, methyl (wood) alcohol is employed as a substitute for ethyl (grain) alcohol, in what may be termed comparatively innocent products, such as perfumes, hair tonics, skin lotions, polishes, varnishes, etc. Government analysts, not infrequently, find it employed in the manufacture of various extracts for the flavoring of food products. Since prohibition has come into force, pure methyl alcohol, being somewhat similar in odor and taste to ethyl alcohol, has been employed in the preparation of various alcoholic beverages. This in great part is due to ignorance and has resulted in many deaths.

The literature, both experimental and clinical, on this subject shows a preponderance of papers relative to the effects of this drug on the central nervous system, especially the brain and optic nerves, and little reference has been made to lesions elsewhere in the body. More recently the importance of an acidosis as the cause of the more general signs and symptoms in methyl alcohol poisoning has been emphasized.

Little consideration has, however, been given to the changes which may occur in the kidney and other functions which may be manifested by variations from the normal chemical composition of the blood. In the following case special attention was given to this.

REPORT OF CASE

History (Hosp. No. 4937/21).—A female, aged 70 years, was admitted to the medical wards of the Montreal General Hospital, into the service of Dr. H. A. Lafleur, with a history of having taken, with suicidal intent, Oct. 24, 1921, one drinking-glassful of wood alcohol. There was a history of vomiting prior to admission, but no vomiting occurred while she was in the hospital, a period of five days. On admission, the patient was drowsy and very much confused, so that it was not possible to obtain a detailed history.

Physical Examination.—The patient was a white female apparently of the stated age. There was slight cyanosis. The right pupil was larger than the left. Both reacted to light and accommodation. The tongue protruded in the midline with a slight tremor at the edges. There was a slight sweetish (acetone) odor to the breath. Physical examination otherwise was negative, with the exception of the fundi oculi. There was a slight effusion into the retina.

Course.—From the time of admission the patient grew progressively weaker. The respirations, at first of the Kussmaul (acidosis) type, became very

* From the Department of Metabolism of the Montreal General Hospital.

Hypersglycemia

pp 823

incontinent

pp 822

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Schiff Base 825

Methanol
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Acidosis explained

shallow during the last two days. October 29 the cyanosis became more marked and there was clinical evidence of bronchopneumonia.

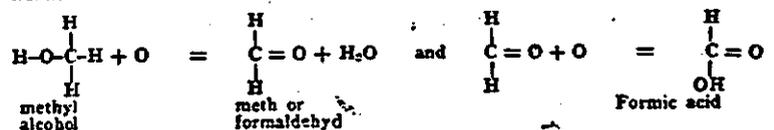
The patient was incontinent throughout her stay in the hospital, and it was not possible to obtain a specimen of urine at proper periods for chemical analysis. This was unfortunate as no examination could be made of the excretion of organic acids. A single specimen obtained by the house physician at the time of admission showed a clear urine, specific gravity 1.018, albumin 7.8 gm. per liter, many hyalin and granular casts, a few blood cells, and a trace of acetone. The accompanying table shows the combined results of the blood examination made every twelve hours during the patient's illness.

CHEMICAL ANALYSIS OF THE BLOOD

Date	Milligrams per 100 C.c.					CO ₂ Volume	Per Cent.			Venous Oxygen	
	Uric Acid	Urea N	Creat- inin	Sugar	Phos- phorus		Hb.	mHb.	Con- tent	Capac- ity	Un- satura- tion
Oct. 26, p.m.	3.1	42	1.6	46
Oct. 27, a.m.	5.3	102	2.3	39
p.m.	7.6	116	3.6	1822	5.6	39
Oct. 28, a.m.	5.4	130	4.0	223	11.2	34
p.m.	9.2	129	4.4	226	10.8	30	94	0	7.8	16.9	9.1
Oct. 29, a.m.	9.0	66	4.0	226	5.6	30
p.m. (3:30)	9.3	144	4.5	226	9.9	26	60	0	2.6	16.5	14.2
4 p.m. died											

DISCUSSION

It has long ago been demonstrated¹ that the difference in the character and degree of intoxication between ethyl and methyl alcohol is due to the fate of these substances following their administration. Ethyl alcohol is oxidized into easily excreted products, carbon dioxide and water. Methyl alcohol is, however, only partially oxidized. The products of this incomplete oxidation being meth or formaldehyd and formic acid.



These partially oxidized substances are very toxic. It has been found² that formic acid is six times as toxic, and formaldehyd² is thirty-three times as toxic as methyl alcohol. Thus, from the oxidation of a toxic substance, products may result which are many times more toxic. This has an important bearing in the interpretation of the blood analysis.

1. Hunt, R.: The Toxicity of Methyl Alcohol, Johns Hopkins Hosp. Bull. 13:2, 213, 1902.

2. Gettler, A. O., and George, A. V. St.: Wood Alcohol Poisoning, J. A. M. A. 70:145 (Jan. 19) 1918.

KIDNEY FUNCTION

In experimental work with methyl alcohol changes in the kidney have been noted. Tyson and Schoenberg³ in work on dogs found at necropsy dark purple and congested kidneys. Gettler² in one case, found marked parenchymatous degeneration of the kidneys. An analysis of the chemical findings of the blood in our case with reference to the urea nitrogen, uric acid, creatinin and phosphorus shows that rapid changes occurred in the kidney function. The uric acid content increased from 3.1 to 9.3 mg. per hundred c.c. in less than six days. The urea nitrogen content increased from 42 to 144 mg. per hundred c.c., and the creatinin content from 1.6 to 4.5 mg. per hundred c.c. blood in the same period. The acid soluble phosphorus varied from 8. to 11 mg. per hundred c.c. blood calculated as phosphorus (P). So far as we know only one other case has been studied from this viewpoint, that of Harrop and Benedict.⁴ Their findings differ entirely from ours. These authors found that the urea content of the blood was normal at one period, but remarkably low at another, 0.091 gm. per liter. This would correspond to 4.2 mg. urea nitrogen per hundred c.c. blood, which is exceedingly low. The blood phosphorus in their case was normal (3 mg. per hundred c.c. blood). Their patient recovered.

could be formic

The initial high findings in our case may have been due to a previously existant chronic nephritis. There can, however, be no doubt that the rapid changes noted daily were due to the action of the poison. Such findings suggest a complete "renal block," and correspond to those occasionally found in the acute retention as seen in hypertrophy of the prostate, or the anuria of mercuric chlorid poisoning. That the kidney function was practically nil is also supported by the rapid increase in the uric acid and creatinin content of the blood. The patient took no food during these few days of illness. It may, therefore, be assumed that all the uric acid found was of an endogenous origin. If it is assumed that the average daily excretion (endogenous) of uric acid is between 100 and 200 mg., and that this amount is not excreted but is distributed throughout the blood, it will account for the daily increase noted. The anatomic findings appear to corroborate this view.

BLOOD SUGAR

Hyperglycemia was present throughout the course of the disease. The lowest concentration of sugar, found at the first examination, was

3. Tyson, H. H., and Schoenberg, M. H.: Experimental Researches in Methyl Alcohol Inhalation, J. A. M. A. 63:915 (Sept. 12) 1914.

4. Harrop, G. A., and Benedict, E. M.: Acute Methyl Alcohol Poisoning Associated with Acidosis, J. A. M. A. 74:1 (Jan. 3) 1920.

0.182 per cent. This gradually increased to 0.228 per cent. These findings seem difficult to interpret. Apparently, they can be attributed to the impairment in the kidney function, for such findings are not infrequent in advanced cases of chronic nephritis. It might, however, be assumed that the figures do not represent glucose, for the reason that on theoretical grounds methyl alcohol is oxidized to formaldehyd, and the latter is a reducing agent. Part of the reduction of the cupric oxid in the test might therefore be attributed to the presence of this agent. Virtually, however, it does not seem that this occurred. The studies of Denis and Aldrich,⁵ who employed liquor formaldehyd for the preservation of blood specimens, show that the addition of this drug in certain amounts does not alter the results obtained in blood sugar estimation. Even if we assume that all the methyl alcohol taken by this patient was completely oxidized to formaldehyd and distributed throughout the body, its concentration in the blood would not reach the percentage that these authors found could be added to blood without interfering with the chemical estimation of sugar. An interesting observation of these same authors is that liquor formaldehyd prevents glycolysis for at least ninety-six hours in vitro. That this should occur in vivo is only conjectural. The impairment of the kidney function seems sufficient to account for the hyperglycemia noted.

ACIDOSIS

The plasma carbon dioxid combining power on admission was 46 volumes per cent. It eventually fell to 26 volumes per cent. Other factors which may lower the carbon dioxid combining power of the blood, such as increased pulmonary ventilation having been excluded, it may be assumed that an acidosis existed. An acidosis has previously been demonstrated⁶ in the study of methyl alcohol poisoning.⁶ It has, however, been attributed to the failure of the body to completely oxidize methyl alcohol with the production of formic acid. The acidosis has been found⁷ to be associated with an increase in the excretion of organic acids, lactic and formic. In our case the retention of phosphates in the blood would also explain part of the acidosis.

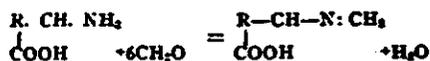
It does not appear to be unreasonable, on theoretical grounds, to suggest that the acidosis may, in large part, be due to the formation in the body of methylene derivatives, from the action of the formaldehyd on the amino-acids present. These derivatives are more

5. Denis, W., and Aldrich, M.: Note on the Preservation of Specimen of Blood Intended for Blood Sugar Estimation, *J. Biol. Chem.* 44:203 (Oct.) 1920.

6. Haskell, C. C.; Hileman, S. P., and Gardner, W. R.: The Significance of the Acidosis of Methyl Alcohol Poisoning, *Arch. Int. Med.* 27:71 (Jan.) 1921.

7. Van Slyke, D. D.: Studies of Acidosis, *J. Biol. Chem.* 41:567 (April) 1920.

strongly acid in reaction owing to the destruction of the basic properties of the amino group, and, therefore, should effect the acid base equilibrium of the blood. Such a reaction is readily demonstrated in vitro. The Henriques-Sørensen formol titration of amino-acid nitrogen is based on this principle⁸ as is shown in the following equation:



Also the production of free acids from the action of liquor formaldehyd on neutral ammonium salts in the body does not seem unreasonable and may explain part of the acidosis, as is shown in the following equation:



An interesting observation along these lines is that of Gregnolo who found after the injection of methyl alcohol there was an increase in the hydrogen ion concentration of the serum.

CYANOSIS

From the time of admission to the hospital the patient exhibited a definite cyanosis. This was very slight at first, but became more marked during the progress of the disease. Very little reference to biochemical studies could be found in the literature on the relation between methyl alcohol poisoning and cyanosis, although this relation has frequently been noted clinically. An effort was made to determine the cause in our case. An analysis was made of the oxygen content, oxygen capacity and oxygen unsaturation of the blood.

It might be recalled that the oxygen content represents the total oxygen combined with hemoglobin, and otherwise, circulating in the blood at the moment and site of withdrawal. The oxygen capacity represents the total oxygen the blood could hold if it were completely saturated with oxygen. The oxygen unsaturation⁹ represents the difference between the oxygen capacity and content. The method employed for the estimation of the oxygen was that of Van Slyke.¹⁰ It has been shown¹¹ that if the blood is completely saturated with oxygen in the lungs, the oxygen unsaturation of the venous blood may increase from 13 to 14 volumes per cent. before cyanosis appears. If it appears at less than this figure arterial unsaturation may be assumed. It will be noted in the chart that at the first estimation the oxygen

8. Hawk: Practical Physiological Chemistry, Ed. 6. Philadelphia, P. Blakistons Sons Co., p. 526.

9. Lundsgaard, C.: Studies of Oxygen in Venous Blood. J. Biol. Chem. **33**:133, 1918.

10. Van Slyke, D. D.: Gasometric Determination of the Oxygen and Haemoglobin of Blood, J. Biol. Chem. **33**:127, 1918.

11. Lundsgaard, C.: Studies on Cyanosis, J. Exper. M. **30**:271 (Sept.) 1919.

unsaturation was 9 volumes per cent. Assuming, therefore, that arterial unsaturation may have existed, the cause of this under the circumstances (poisoning) was problematic.

An analysis of the daily clinical notes showed that no gross changes occurred in the respiratory or circulatory systems. Although no gross clinical changes need be evident, and still certain conditions may exist which prevent complete oxidation of the blood, it seemed important to determine whether any chemical alteration had occurred preventing the blood from taking up its normal load of oxygen. Stadie¹² pointed out that there are many substances which in vitro readily produce methemoglobin. These include certain oxidizing agents, reducing agents, organic bases, salts and bacteria. It will be noted in the chart that during the first examination of the blood for methemoglobin none could be found. The method employed was that of Stadie.¹³

The cyanosis gradually became more marked, and on the following day definite changes (bronchopneumonia) were found clinically in the lungs. The blood examination one half hour before death, at which period there was a very marked degree of cyanosis, also did not show the presence of methemoglobin. At this time the oxygen capacity was practically normal. It may, therefore, be assumed that in the case studied either no methemoglobin was formed, or that it was eliminated as rapidly as it was formed and played no important part in the production of the cyanosis.

REPORT OF POSTMORTEM EXAMINATION

Pathologic Report.—Acute parenchymatous nephritis; cloudy swelling of the heart and liver; bronchopneumonia.

DETECTION OF METHYL ALCOHOL IN THE BODY TISSUES

Experimentally it has been found that when methyl alcohol is given per rectum it is excreted by the stomach. It has also been demonstrated that the stomach may excrete methyl alcohol unchanged for a considerable time. It has been assumed¹⁴ that the alcohol has a selective action for brain tissue. The brain in every one of six cases analyzed by this author was found to contain this alcohol. For these reasons both the brain and stomach tissues were analyzed in our case.

After a critical study of the fifty-eight methods proposed for detecting methyl alcohol, Gettler¹⁴ classified them in order of their

12. Stadie, W. C.: Studies on Blood Changes in Pneumonococcal Infections, *J. Exper. M.* **33**:627 (May) 1921.

13. Stadie, W. C.: A Method for the Determination of Methaemoglobin in the Blood, *J. Biol. Chem.* **41**:237 (Feb.) 1920.

14. Gettler, A. O.: Critical Study of Methods for the Detection of Methyl Alcohol, *J. Biol. Chem.* **42**:311, 1920.

efficiency. Those accepted as reliable, extremely sensitive, and involving little technical difficulty were employed. The method employed in this case is based on the oxidation of the methyl alcohol into formaldehyd and the detection of the latter by various color reactions. Potassium bichromate and concentrated sulphuric acid was used as the oxidizing agent. In detail the method was as follows:

Method.—In order to preserve the stomach contents the stomach was tied off at the cardiac and pyloric ends and removed in toto. This was then passed through a meat grinder and minced to a fine pulp. This pulp was then placed in an 800 c.c. Kjeldahl flask to which was added 400 c.c. water and sufficient concentrated sulphuric acid until a distinct acid reaction was obtained. This was then distilled and 200 c.c. of the distillate was neutralized to phenolphthalein with tenth normal sodium hydroxid and acidified with 5 c.c. of concentrated sulphuric acid, cooled, and 0.1 gm. potassium bichromate added and dissolved. This was then redistilled. To this final distillate the various color tests were applied.

1. To 3 c.c. distillate was added 5 c.c. concentrated sulphuric acid. This was cooled. The addition of a few milligrams morphin sulphate yielded a violet color. Test positive.

2. Test 1 was repeated with the morphin replaced by apomorphin. A violet color resulted. Test positive.

3. To 3 c.c. of the distillate were added two drops of a 2 per cent. solution of phenol. This was stratified on a layer of concentrated sulphuric acid. A red ring was noted at the junction of the two fluids. Test positive. Methyl alcohol was thus detected in the body tissues six days after its ingestion.

SUMMARY

In a fatal case of methyl alcohol poisoning changes had occurred in the renal and other functions as evidenced by variations from the normal chemical composition of the blood. These, in themselves, disregarding other well known factors, may account for the actual cause of death. Methemoglobin played no important part in the production of the cyanosis noted. Methyl alcohol could be detected in the tissues examined six days after the ingestion of the drug.

268) Rabinovitch, MD IM.

Biochemical Studies in a Fatal Case of Methyl Alcohol poisoning.
Archives of Internal Medicine, Chicago. 1922;29:821-827.

METHANOL

/HUMAN

/METABOLISM

ACIDOSIS

The methylenation of amino groups in amino acids and proteins
has been suggested as a factor in the development of acidosis.