

HEXAMETHYLENAMIN *

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Hexamethylenamin is widely used as an antiseptic to prevent and to combat various infections of the serous cavities and blood as well as those of the urinary tract, the wide range of application being due to the striking effects obtained in some cases of cystitis and allied conditions, as well as to the great penetrability of the drug, which after ingestion can be found in every fluid of the body.¹ These facts, as well as the possible liberation of free formaldehyd, to which the efficiency of the drug is usually ascribed, would seem to make it an ideal drug in infections, and great claims have been made for its efficacy. But the question arises: Is formaldehyd liberated, and if so, is it in sufficient amount to have an antiseptic action?

Hexamethylenamin is readily decomposed into formaldehyd and ammonia in acid solutions, less readily in neutral or slightly alkaline solutions, and not at all in a stronger alkaline medium. When injected intravenously it produces a temporary increase in the rate and depth of respiration which would indicate an ammonium action and a consequent formaldehyd liberation. In addition, formaldehyd is always found in acid urines after administration of the drug. These results might mean a liberation of formaldehyd in all parts of the body; but Hanzlik and Collins² and others have failed to find such a liberation in any of the body fluids except the gastric juice and urine. There is a possibility, however, that it is liberated and yet not detected, since one of us (McGuigan) has shown that small amounts of formaldehyd are oxidized in the blood so rapidly that it quickly escapes detection by the ordinary means, even that introduced into the stomach or liberated from hexamethylenamin by the gastric juice and subsequently absorbed. To meet this objection a new method is offered for the detection of free formaldehyd in the blood. This consists in dialyzing the normal circulating blood in animals through collodion tubes interposed between the carotid

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1. McGuigan, Hugh: *Jour. Biol. Chem.*, 1912, xi, 33, proceedings.

2. Hanzlik, Paul J., and Collins, R. J.: *Hexamethylenamin: The Liberation of Formaldehyd and the Antiseptic Efficiency Under Different Chemical and Biological Conditions*, *THE ARCHIVES INT. MED.*, 1913, xii, 578. This gives a complete review of the literature.

artery and the external jugular vein.³ The tubes are immersed in water or saline solution and the living blood is dialyzed during the action of the drug. If any formaldehyd is formed, part of it will rapidly pass into the dialysate, where it can be identified by the usual tests. The results show uniformly that hexamethylenamin is found in the dialysate in a few minutes after the injection, while free formaldehyd is not detected even after several hours of dialysis. The following protocol will illustrate:

Male dog. Ten kg. Ether anesthesia.

- 1: Collodion dialyzing tubes attached to the carotid artery and external jugular vein.
- 1:20: Dialysis commenced. Tests of the dialysate for hexamethylenamin and formaldehyd negative. 100 c.c. of 3 per cent. hexamethylenamin in 0.9 sodium chlorid slowly injected into the femoral vein in the next ten minutes.
- 1:40: Dialysate tests: Hexamethylenamin positive; formaldehyd negative.
- 2: Dialysate tests: Hexamethylenamin positive; formaldehyd negative.
- 4:10: Dialysate tests: Hexamethylenamin positive; formaldehyd negative. Urine strongly positive to free formaldehyd tests.
- 4:30: During the next ten minutes 40 c.c. 0.5 per cent. formaldehyd injected slowly into the femoral vein.
- 4:40: Dialysate test shows free formaldehyd.

In control experiments the injection of formaldehyd only always gave free formaldehyd in the dialysate. Some hexamethylenamin is also formed. The Jorrisen and Rimini tests were used for free formaldehyd, and Hehner's test for the combined form.

It is evident that formaldehyd is not liberated in amounts sufficient for detection with the phloroglucin or phenylhydrazin tests. Since these reagents will detect amounts far less than enough to have any antiseptic action, hexamethylenamin antiseptis, if any, cannot be due to decomposition products. But even though formaldehyd were liberated in minute amounts it would not have the reputed hexamethylenamin effect, since after injection small amounts of free formaldehyd are so rapidly oxidized that antiseptic action is improbable, while in larger amounts it is decidedly injurious.

Hexamethylenamin itself has no antiseptic action on yeast or bacteria outside of the body, but the possibility still remains that the mere entrance and exit of the drug may have a beneficial action when taken internally.

3. Abel, John J., Rowntree, Leonard G., and Turner, B. B.: Removal of Diffusible Substances from the Circulating Blood of Living Animals by Dialysis, *Jour. Pharmacol. and Exper. Therap.*, 1914, v, 275. This gives Abel's method without a coagulant. We were unaware of the priority of Abel in this field when the work was done.

SUMMARY

Since, after the administration of hexamethylenamin, free formaldehyd appears only in the gastric juice and acid urine, and not in other secretions or in the blood, even with dialyzing tests, the liberation results from the acid reaction only and not from cell action. Even if it were liberated in other locations it would probably exert no beneficial action because of its reconversion or rapid oxidation into injurious products. Combined formaldehyd as hexamethylenamin, does not decompose readily until an acid medium is reached, when the action is that of weak formaldehyd. The only apparent indication for the internal administration of the drug, therefore, is in infections of the urinary tract.