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Limiting Content of Theophylline Necessary to Prevent Local Toxic Action of Mercurial Diuretics.

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In a previous paper[1] it has been shown that theophylline greatly diminishes the toxicity of Mercurin* and Salyrgan at the site of intracutaneous injection. The beneficial action of theophylline in enhancing absorption after intramuscular injection has also been demonstrated[2] and it was found[3] that one mole equivalent (3.88% of theophylline monohydrate) produces the maximum effect. Since this and other data[3] are strongly suggestive of compound formation between theophylline and mercurial diuretics of general structure $NaOCO\text{-}R^{II}\text{-}HgOH$ it seemed advisable to determine the limiting amount of theophylline necessary to prevent local toxicity.

The experimental procedure was the same as that described before[1] and consisted in the intradermal injection into the abdomen of the rabbit of 0.05 cc. of Mercurin and Salyrgan to which varying amounts of theophylline had been added. Each solution was prepared to contain 39 mg. of mercury per cc. (about 0.2 M) and its pH was accurately determined with the glass electrode.

In the accompanying photograph, taken 24 hours after injection, the mole equivalents of theophylline and pH values for each of the 7 solutions are shown adjacent to the corresponding sites of injection. In all 5 rabbits were injected in this way for Mercurin and 3 for Salyrgan. The results for the 2 drugs are very much alike and were found to be so consistent that only one photograph is shown. It will be seen that the local toxicity decreases in proportion to the amount of theophylline present and in the case of the solutions containing 1, 1.25, and 1.5 mole equivalents, so little reaction was produced that it is difficult to locate exactly the sites of injection.

1 DeGraff, A. C., and Batterman, R. C., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1546.

* The sodium salt of N(γ-oxymercuri-β-methoxypropyl)-d-α-camphoramic acid. Mercupurin is a 10% solution of this salt which is also 5.35% with respect to theophylline monohydrate. The Mercurin used in suppositories contains 20% of the free acid.

2 DeGraff, A. C., Batterman, R. C., and Lehman, R. A., *J. Pharm. Exp. Therap.*, 1938, **62**, 26.

3 Lehman, R. A., and Dater, A., *J. Pharm. Exp. Therap.*, in press.

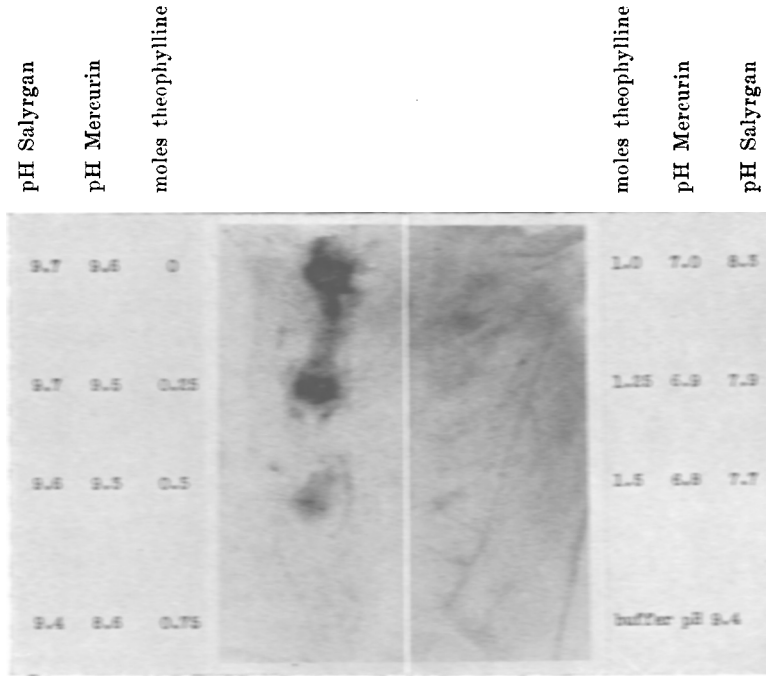

FIG. 1.

Photograph showing the influence of increasing amounts of theophylline upon the local lesions produced in the skin of the rabbit by Mercurin and Salyrgan.

Since theophylline reduces the pH of these solutions of diuretics a buffer was also injected as a control but in no case was an appreciable reaction observed.

One mole equivalent has been found to be the limiting amount of theophylline necessary to prevent the local toxic reaction to Mercurin and Salyrgan. The results are in agreement with other evidence pointing to compound formation between theophylline and mercurial diuretics.