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On the relation of the chemical structure of the opium alkaloids to their effect on smooth muscle and on the discovery of a new therapeutic agent as a consequence thereof.

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In a paper dealing with the effect of opium alkaloids on the ureter,[1] the author has shown that the opium alkaloids in respect to their action on that organ can be divided sharply into two classes: the pyridin-phenanthrene group, of which morphin is the principal member on the one hand, and the benzyl-isoquinoline group, of which papaverin is the principal representative, on the other. The author showed that morphin and all its derivatives, with the exception of peronin or benzyl-morphin, all stimulate the contractions of the ureteral rings and increase their tonicity, while all the members of the papaverin group, namely, papaverin, narcotin and narcein inhibit the contractions of the ureter and lower its tonus.

In a subsequent paper[2] the author further analyzed the action of the opium alkaloids on the ureter and also studied a large number of other alkaloids and chemical compounds allied to them and was led to conclude that, as far as the stimulating action of the

[1] *Jour. Pharmacol. and Exp. Therap.*, 1916, IX, 197.

[2] *Jour. Pharmacol. and Exp. Therap.*, 1917, IX, 287.

morphin group on the ureter is concerned, that stimulating effect is to be ascribed to the *pyridin* part of the morphin molecule. Furthermore, the author showed that the inhibitory and tonus-lowering action of papaverin and its allied alkaloids appeared to be due to the presence of the *benzyl* grouping in the papaverin molecule. The skeleton structure of the morphin alkaloids and of the papevarin alkaloids is represented by the following structural formulæ:

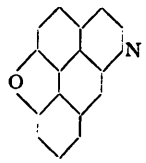

FIG. 1. Pyridin Phenanthrene Skeleton.

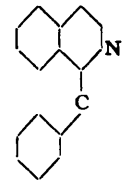

FIG. 2. Benzyl-Isoquinoline Skeleton.

It was further shown that when a combination of various opium alkaloids is used, the effect of the benzyl-isoquinolin members predominates in most cases. This explains also the anomalous effect of peronin or benzyl-morphin which, unlike all other morphin alkaloids, inhibits the contractions of the isolated ureter.[1]

Following the studies of the effect of the opium alkaloids upon the smooth muscle of the ureter, the author investigated the action of the same alkaloids upon other kinds of smooth muscle. The results of these investigations have in part been already published[2] and in part are to appear later. The smooth muscle structures which the author studied were the following: intestine, uterus, gall bladder, urinary bladder, biliary ducts, vas deferens, excised bronchioles, and arterial smooth muscle. As a result of these investigations, the author is led to conclude that the action of the opium alkaloids upon all smooth muscle is the same as that described in connection with the ureter, namely, that the morphin alkaloids *stimulate* contractions and increase tonus while the papaverin alkaloids *inhibit* contractions and lower tonicity, and furthermore, the experiments seemed to indicate especially in connection with the papaverin group that the inhibitory and tonus-

[1] *Jour. of Urology*, 1917, I, 201.

[2] *Jour. Pharmacol. and Exp. Therap.*, 1916, IX, 121; *Jour. Pharmacol. and Exp. Therap.*, 1917, IX, 473.

lowering action resides in the benzyl part of the papaverin molecule.

These observations and conclusions logically led the author to surmise that possibly the inhibitory and tonus-lowering effect of papaverin might be produced by the exhibition of a benzyl grouping in a simpler form. Accordingly a search was made for simple non-alkaloidal and non-narcotic compounds containing the benzyl radical which could be administered to animals without toxic results. Two such bodies were discovered. They were the well-known esters, *benzyl-benzoate* and *benzyl-acetate*. Inasmuch as these esters are practically insoluble in water, their pharmacological action could not be studied on excised tissues, but experiments on intact animals revealed the fact that both of these esters actually produced the same pharmacological effects as those given by the opium alkaloid papaverin, on the one hand, and that these esters were much less toxic than papaverin, on the other. Metabolic studies in connection with these experiments showed that the benzyl group of benzyl-benzoate and benzyl-acetate is in a large measure converted into hippuric acid in the body and is excreted as such in the urine. The comparatively very low toxicity of benzyl-benzoate and benzyl-acetate for animals and their striking papaverin-like effects on various viscera led the author to try their action upon himself and as no untoward or even disagreeable symptoms followed the ingestion of these drugs by mouth, it was deemed justifiable to administer these agents to suitable patients with their consent.

The conditions in which the benzyl effect was anticipated to produce pharmacological result, were those exhibiting either *excessive peristalsis* or excessive *spasm* of smooth muscle. It would take too much space in this preliminary communication to describe in detail all the cases in which benzyl-benzoate for the most part and benzyl-acetate to a lesser extent, were tried. The author need only state in this place that the oral administration of these esters was followed by remarkable pharmacological and therapeutic results of a beneficial character in the following conditions: (1) Excessive peristalsis and colic of the intestines, namely, in cases of diarrhea and dysentery. (2) Spasm and colic of the ureteral smooth muscle, that is, "renal colic." (3) In

"biliary colic " or spasmodic contractions of the gall bladder. (4) In uterine colic or spasmodic contractions of the uterus. (5) In vesical colic or spasmodic contractions of the urinary bladder. (6) In one case of spastic constipation with powerful tonic spastic contraction of the intestine. (7) In a few cases of pylorospasm. (8) In a large number of cases of arterial spasm or hyper-tension. (9) Lastly, one of the most striking of all the effects, in cases of bronchial spasm or true asthma. Administration of these drugs by injection has also been tried. A complete pharmacological study together with further therapeutic observations on the action of the above benzyl-esters and benzyl-alcohol will be published in due time in the Journal of Pharmacology and Experimental Therapeutics. This preliminary announcement, however, is made in this place because it is deemed that a sufficient number of observations, both pharmacological and clinical, have already been recorded by the author and a number of physicians who have kindly collaborated with him, to indicate that the benzyl-esters promise to become useful therapeutic agents.

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Studies in calcium and magnesium metabolism. Further observations on the effect of acid and dietary factors.

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Givens and Mendel[1] have found that "Administration of hydrochloric acid produced no significant effect upon the balance of N, Ca, and Mg in the dog." Stehle[2] has stated that "the administration of hydrochloric acid by mouth to the dog causes an increased excretion of calcium and magnesium as well as of sodium and potassium." New experiments have been conducted on two dogs which received a diet poor in lime, consisting of meat, cracker meal, lard, and agar. During two long periods each animal received daily 2 gm. hydrochloric acid. The results with

[1] Givens, M. H., and Mendel, L. B., *J. Biol. Chem.*, 1917, XXXI, 421.

[2] Stehle, R. L., *J. Biol. Chem.*, 1917, XXXI, 461.