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AN UNUSUAL FACTOR INFLUENCING ACTION OF SOME DRUGS ON SMOOTH MUSCLE.

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INTRODUCTORY.

The study of the action of a drug from a broad pharmacological point of view is vastly more complicated than is generally appreciated by the clinical practitioner and even by specialists in other fundamental medical sciences. One of the most important phases connected with a complete pharmacological study of the drug is the necessity for the investigation of various *conditions* affecting the action of such a compound. The conditions influencing the action of drugs are of a three-fold nature. They may depend upon the drug itself, as for instance the dose of the reagent administered, its concentration, its method of administration, etc. Again they may depend upon the patient or animal to which the drug is administered. Thus for instance, the age of the animal may play an important rôle apart from the dosage; the condition of the subject whether normal or pathological may make a great difference in its reaction to the drug, etc. Not only may the action of a drug vary with individual subjects but even various organs and indeed parts of the same organ may respond differently to one and the same pharmacological agent. Thus Young and Macht have shown that the smooth muscle tissue of the *trigonum vesicae* responds very differently to certain sympathetic and para-sympathetic drugs from the smooth muscle of the fundus of the same bladder (1). Again the difference in response between pathologic and normal tissues has been well illustrated by the researches of Macht and Ting who found that the bronchi of pigs respond differently to Epinephrine, Pilocarpine, Atropine and the other pharmacological reagents when the animals suffer from bronchial pneumonia as compared with the response of the bronchial muscle from normal pigs' lungs (2). Finally, in the third place, the action of drugs may be profoundly influenced by certain external conditions. For instance, the room temperature may markedly affect the action of a drug as is the case with injections of Colchicine in frogs; ultraviolet rays increase the potency of Quinin and Quinidin Sulphate injections in rats as shown by Macht and Teagarden (3), and polarized light was found by the present author to affect the convulsions produced by camphor to a greater degree than non-polarized light of the visible spectrum of exactly the same intensity (4). All these various factors concerned in drug action have been discussed by the author elsewhere (5). The present note is intended

to give another remarkable illustration in regard to the effect of certain conditions on the action of drugs.

STUDIES ON THE VAS DEFERENS.

The author and his assistants in this laboratory have been accustomed, among other routine procedures in connection with the examination of drugs, to test the activity of Corpus Luteum preparations on the contractility of the isolated *vas deferens* of rats. This reaction was first described by Matsumoto and Macht in their studies concerning the response of various genito-urinary organs to treatment with all kinds of endocrine and other glandular products (6). These authors noted that the *vas deferens* of rodents and more particularly of the guinea-pig and rat was extremely sensitive to the treatment with extracts of the Corpus Luteum of various animals. Even a very small quantity of Corpus Luteum extract introduced into a chamber containing an isolated vas caused a marked contraction of the organ and such a contraction was not produced by equivalent quantities of other gland extracts, with the exception of Epinephrine.

The method of study has been described elsewhere and consists of suspending a healthy *vas deferens* freshly dissected from a rat, in oxygenated Locke's solution at 37° to 38° C. and recording its normal contraction upon a kymograph. The vas is then tested as to its activity with a small dose (0.1 milligram of Adrenalin) in 50 cc. of Locke's solution and, after washing the organ, it is again tested with a glandular product and the degree of contraction is compared with the standard contraction of Epinephrine.

In connection with such routine examinations of glandular products by means of *vas deferens* it was noted that the *vasa deferentia* of certain rats were less sensitive to the effects of Epinephrine and Corpus Luteum extracts than the *vasa deferentia* of other rats; that is the absolute height of contraction obtained with some vas preparations was much greater than the height of contraction obtained with other vas preparations although a comparison of the activity of Corpus Luteum and Epinephrine always gave the same ratio. In seeking for an explanation of the above phenomenon attention was called by the author's technician, Charles Kamphaus, to the fact that some of the male rats were completely isolated while other male rats were kept in close proximity to female rats. Accordingly careful and extensive observations were begun in order to ascertain whether sexual excitement had any bearing on the height of the contraction exhibited in the isolated vas by various drugs. A group of white rats were kept in clean cages completely isolated and far away from any female rats, and another group of rats of exactly the same stock and pedigree were kept in another cage which was placed next to a third cage containing females of the same species. All the animals were fed on exactly the same rich diet of Prof. McCollum with an abundance of vitamines, and all other conditions were maintained the same in both groups of rats. It was found that the male animals, kept in proximity to the females showed definite signs of sexual excitement, and it was found almost invariably when such rats were killed and their *vasa deferentia* were used for testing drugs, that their response was much greater than the *vasa deferentia* obtained from the group of rats which were kept isolated and kept entirely apart from any female rats. This difference in the degree of contractility of the *vasa deferentia* was not due to any macroscopic difference in

the length or thickness of the vas examined but seems to be due to a greater sensitiveness of those organs in the one group of animals. The subjoined illustrations, Figs. 1 and 2, give an excellent idea of the results obtained. In Fig. 1 are shown the contractions obtained with *vasa deferentia* excised from segregated male rats. It will be noted that these preparations showed normal rhythmic contractions of the organs and gave a definite response to Epinephrine (Ep.) and various Corpus Luteum extracts (179–180). On the other hand in Fig. 2 are shown *vasa deferentia* excised from male rats belonging to the "promiscuous" stock and in this case it will be noted that the contractions obtained with exactly the same quantity of Epinephrine and Corpus Luteum extracts were much higher than in the preceding. The same was found true of male rats which were kept together with females in the same cage. We do not think that the difference is an accidental one because these observations have been carried on for a long time and were repeatedly found to hold good. It would seem that sexual excitement of the male kept in proximity to the female renders *vas deferens* more sensitive to certain drugs.

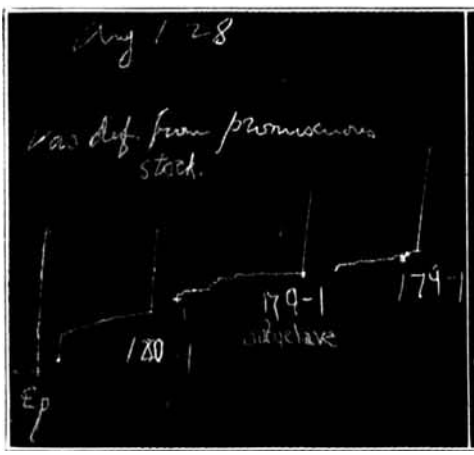

Fig. 1.—Response of normal vas deferens of segregated rat to Epinephrine 0.1 milligram in 50 cc. of Locke's Solution and Corpus Luteum Extract 1 cc. in 50 cc. of Locke's Solution.

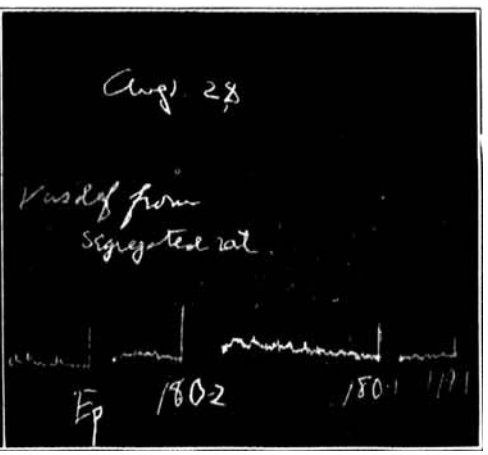

Fig. 2.—Response of normal vas deferens of promiscuous stock to Epinephrine 0.1 milligram in 50 cc. of Locke's Solution and Corpus Luteum 1 cc. in 50 cc. of Locke's Solution.

CONCLUSION.

The evidence adduced seems to point to the conclusion that the *vasa deferentia* of rats kept under continuous sexual excitement and activity are more sensitive to Epinephrine and Corpus Luteum extracts than the *vasa deferentia* of control male rats kept isolated and apart from proximity of any female animals.

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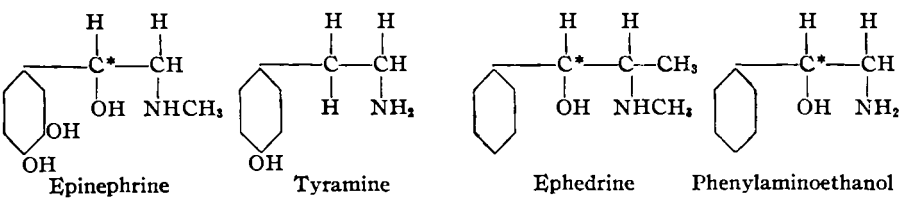
CHEMICAL EXAMINATION OF α-PHENYL-β-AMINO-ETHANOL SULPHATE.*

BY SAMUEL M. GORDON.

The varied therapeutic uses of epinephrine have created for it a demand that has led manufacturers and others to find in place of it compounds, either natural or synthetic, with variations within the molecule. Some of the variations have already found wide use; namely, ephedrine, isolated from Ma-Huang and tyramine, originally isolated from Ergot, but now prepared synthetically. Recently, a substance closely related to the three preparations described above has been described in the medical literature. More recently, a report detailing the clinical application of phenylethanolamine sulphate was submitted to the *Journal of the American Medical Association.*[1] As is the custom with papers dealing with new therapeutic agents the Council on Pharmacy and Chemistry was requested to make a preliminary report on the drug. In this connection, the Chemical Laboratory of the American Medical Association was asked to investigate the chemical constitution and character, and to elaborate standards for the drug.

Alles[2] has recently reported on the physiologic action of phenylethanolamine, or more specifically α-phenyl-β-aminoethanol. The compound has been previously described by others, notably by Mannich and Thiele,[3] who also prepared a number of derivatives and homologues of the compound.

A comparison of the structural formulas of epinephrine, ephedrine, tyramine and phenylaminoethanol[4] will serve to bring out the similarities and conversely the differences in their chemical nature.



Epinephrine Tyramine Ephedrine Phenylaminoethanol

It will be noted that the side chain of ephedrine contains three carbons, while the other three contain two; the former being a derivative of propyl benzene; the other three being derivatives of ethyl benzene. Epinephrine and tyramine both contain hydroxyl groups in the nucleus, hence may be expected to be more prone to oxidation, a serious objection pharmaceutically and therapeutically. Ephe-

* Contribution from the American Medical Association Chemical Laboratory.

[1] *J. A. M. A.*, 91 (1928), 1033.

[2] *J. Pharmacol.*, 32 (Dec. 1927), 121.

[3] *Archiv der Pharmazie*, 253 (1915), 181.

[4] The Council on Pharmacy and Chemistry of the American Medical Association has suggested that α-phenyl-β-aminoethanol sulphate be referred to as phenylaminoethanol sulphate. *J. A. M. A.*, 91 (1928), 1037.