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Action of cocaine on pupil compared with action on other structures containing smooth muscle.

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The mydriatic effect of cocaine is regarded by some to be due to a stimulation of the peripheral sympathetic nervous mechanism supplying the radial muscle of the iris. By others it is regarded as the result of a direct weakening of the circular muscle of the iris.

The first group of experiments here reported were performed in an attempt to demonstrate by actual measurements such a weakening of the circular muscle by cocaine. Accurate pupillary measurements were obtained by measuring the image of the pupil on a scale in the eye-piece of a measuring telescope. Series of measurements made in this way were employed for the plotting of curves showing the development of drug effects.

Albino rabbits were the animals employed. In the study of cocaine, two drops of a four per cent solution were placed in one eye only. After five to ten minutes there was placed in each eye a definite amount of solution of physostigmine sulphate. Frequent measurements were made of both pupils, and curves were plotted to show the effect exerted by the cocaine on either the degree of the physostigmine effect or on the rate of its development.

Thirty-six experiments were carried out, some on animals from which the superior cervical sympathetic ganglion on one side had been removed, and some on animals on which this operation had been performed on both sides. A few experiments were on unoperated animals. This work gave no evidence of a weakening of the circular muscle of the iris by cocaine.

The second group of experiments is a study of the effect of cocaine on the isolated sphincter muscle of the iris, mounted in Locke-Ringer solution for the recording of its muscular activity as a kymographic tracing. Steers and large dogs were used.

Cocaine in 1:10,000 concentration produced no effect. This failure to obtain any effect with cocaine is not due to a loss of

the activity of the muscle, for it still contracts in the usual manner after applying physostigmine, and relaxes after the use of adrenalin or atropine. Cocaine in concentrations of 1:1,000 or stronger caused some relaxation of the muscle. Such concentrations are, however, too high to represent the concentration of cocaine which reaches the iris in clinical ophthalmologic use. This is indicated by the observation that while 1:1,000 cocaine readily produces an anesthetic effect, anesthesia of the iris does not occur after the usual clinical instillation into the conjunctival sac. The severe pain felt by the patient when the iris is cut during an operation for cataract is an evidence of this.

The third group of experiments is a study of the effects of cocaine on isolated tissue from certain other structures containing smooth muscle having a sympathetic nerve supply. This was done in a search for evidence as to whether cocaine may stimulate the sympathetics in smooth musicle other than the iris. The uterus of the rabbit, both pregnant and non-pregnant, was always markedly stimulated by cocaine (1:10,000). Both rate of contractions and tone are increased. The pregnant guinea pig shows a similar effect. Tracings showing the action of cocaine in these experiments are almost duplicates of control tracings made at the same time, using adrenalin (1:1,000,000) on a similar piece of tissue.

The uterus of the non-pregnant cat, in which the sympathetics are inhibitory, responds to cocaine (1:10,000) with a complete and rather prolonged inhibition of contractions. There is a primary rise of tone followed by a prolonged, marked relaxation. Adrenalin controls showed a similar effect, but much shorter in duration and without the primary rise in tone.

Isolated segments of small intestine show an inhibition of contractions and a loss of tone after the use of cocaine. There is a following rise in tone during which the contractions remain inhibited as to amplitude.

The evidence of these experiments has all pointed towards a stimulation of sympathetics rather than to a weakening of smooth muscle by cocaine in dilating the pupil. There was found:

1. No measurable weakening of the circular muscle of the iris by cocaine in the intact animal.

2. No relaxation of the isolated sphincter of the iris by cocaine in 1:10,000 concentration.

3. Isolated smooth muscle of uterus and intestine gave evidence of stimulation by cocaine, 1:10,000, in tissues where the sympathetics are motor. Where the sympathetics are inhibitory, on the other hand, an inhibition of rhythmic contractions was always obtained following the use of 1:10,000 cocaine. The tonicity of the muscle in the latter case showed a phase of inhibition and a phase of increased tone.

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Comparative metabolism of hydantoin and beta-methyl hydantoin.

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In previous experiments[1] it was pointed out that when beta-methyl hydantoin is given subcutaneously to dogs only fifteen per cent of the compound reappears unchanged in the urine. A similar amount is excreted as methyl hydantoic acid. But while all of the nitrogen of the compound was excreted, the remainder was unaccounted for in the nitrogen partition. Immense amounts of oxalic acid were found in the urines during experimental days, and this suggested hydrolysis of methyl hydantoic acid to methyl urea and glycollic acid, with oxidation of the latter to oxalic acid. Supplementary experiments have thrown doubt upon excretion of a large amount of methyl urea, hence the possibility of origin of the oxalic acid found from a substance such as methyl parabanic acid, in the method of determination, is being considered.

Experiments have also been carried out in which hydantoin and hydantoic acid were administered. In keeping with the findings of Lewis[2] no evidence of urea or ammonia formation was obtained. When hydantoin was given there was, however, an increase in organic acid excretion corresponding to elimination,

[1] Gaebler, O. H., *Proc. Am. Soc. Biol. Chem.*, 1925, lvii, 55.

[2] Lewis, H. B., *J. Biol. Chem.*, 1912-13, xiii, 347.