III. THE ACTION OF ATROPINE IN COUNTERACTING THE EFFECTS OF PITUITRIN AND OF PILOCARPINE INJECTED INTO THE CEREBRAL VENTRICLES

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In the two preceding papers it has been shown: (1) that the intraventricular injection of pituitrin leads to a striking response characterized by nausea and vomiting, flushing, sweating and a marked fall in body temperature usually though not always accompanied by a drop in the basal metabolic rate; and (2) that a reaction of surprisingly similar type promptly follows the intraventricular injection of pilocarpine.

Since we have in atropine an effective antidote to pilocarpine, it was felt that should the reaction of pilocarpine by way of the ventricle be checked by atropine, we might expect the pituitrin reaction to be similarly checked if the two substances, the drug and the extract, in the production of their similar effects, actually operated through the same and probably central nervous mechanism.

On one or two occasions when the reaction to pituitrin had been more marked than expected and the subject was rendered unduly uncomfortable from the recurrent retching and vomiting, it had been observed that an injection of 1 mgm. of atropine and 5 mgm. of morphia effectually checked the reaction. Under this suggestive lead, the matter was first put to test as follows:

A patient, convalescent from a highly successful operation for a chromophobe adenoma, had shown on October 14, 1930, a typical, moderately severe response to the intraventricular injection of 1 c. cm. of pituitrin with sweating, vomiting and a fall of temperature of two degrees in two hours accompanied by a drop in the basal metabolic rate from \(-11\) to \(-18\). On repeating the test four days later, with the coincidental subcutaneous injection of 1 mgm. of atropine, there was no discernible response.

Another patient, likewise convalescent from a similar operation for the same malady, had shown on October 16, 1930, a somewhat tardy (30 minutes) but typical response to 1 c. cm. of pituitrin intraventricularly with moderate sweating, flushing and vomiting over a period of two hours and a drop in temperature of 1.2°F. Eight days later, 5 mgm. of intraventricular pilocarpine provoked a prompt and vigorous reaction with vomiting, sweating, flushing, lachrymation and salivation, and a drop in rectal temperature of 4.4° in 90 minutes, the basal metabolic rate remaining unchanged. After an interval of three days, on October 27, 1930, the intraventricular injection of 1 c. cm. of surgical pituitrin, when repeated with the coincidental subcutaneous injection of 1 mgm. of atropine, caused no appreciable reaction apart from a subjective dryness of the mouth, a possible slight temporary contraction of the pupils, a trifling increase in pulse rate and a moderate pressor response.

It remained to be seen whether atropine would have an inhibitory effect on the response to pituitrin as well as to pilocarpine when coinci-
dentally injected into the ventricle. A favorable opportunity to make the test occurred in the following case:

The patient, a woman 56 years of age, had been operated upon November 10, 1930, for a fairly well encapsulated left parasagittal glioma which was easily removed, apparently intact. From this operation she made an excellent recovery with perfect wound healing and no febrile reaction at any time until the 17th postoperative day when for the first time, following a series of x-ray treatments, she showed a slight wave of pyrexia reaching 102°F.

Having already come to realize the possibility that the temperature-lowering effect of intraventricular pituitrin might be utilized to combat the neurogenic hyperthermias which sometimes occur after serious operations for tumours,* though there was no reason for suspecting that this patient's mild fever was of this type, it at least gave an opportunity of seeing what would be the effect of the injection as an antipyretic.

Accordingly on November 28th at 4:25 P.M., the rectal temperature being 102.4°F., 1 c. cm. of surgical pituitrin was introduced into the ventricle with the usual, though in this instance only a moderately striking reaction, which was somewhat delayed in onset and occurred without appreciable change in pulse rate or blood-pressure. After an interval of 10 minutes there was nausea, lachrymation and salivation; in 15 minutes, the temperature had begun to drop (101.7°F); in 35 minutes sweating and flushing were first definitely noted; after 60 minutes there was a copious evacuation of the bowels (temp. 100.8°F); in 1 hour 20 minutes there was an initial attack of vomiting followed by other similar attacks during the course of the next two hours by which time the reaction was over, though the rectal temperature continued to fall until 8 P.M. when it was at its lowest point of 98.4°F., a drop of 4 degrees.

Four days later, December 2, 1930, with the rectal temperature at 99.8°F, she was given at 9.40 A.M. an intraventricular pilocarpine test (2.5 mgm.) which gave a typical reaction as follows: There was a prompt pressor response from 110/70 to 140/80 which endured throughout the test; at the end of 5 minutes she experienced abdominal uneasiness followed by nausea and retching; after 9 minutes, first appearance of sweating, flushing and salivation soon becoming excessive; 11 minutes, an explosive, copious bowel movement;** 16 minutes, owing to patient's agitation the reaction was checked by a hypodermic injection of morphia 5 mgm. and atropine 0.5 mgm. This injection promptly quieted her and within 5 minutes, though the flush continued, the sweat had ceased together with the salivation, leaving her with a dry mouth. Periodical vomiting nevertheless recurred during the next hour and a half, the last specimen showing a positive guiac test for blood. The rectal temperature slowly dropped in the course of two hours from its initial 99.6°F to 97.1°F, its lowest level.

This patient, therefore, having shown a moderate reaction to an intraventricular injection of 1 c. cm. of surgical pituitrin and an unduly exaggerated one to the intraventricular injection of 2.5 mgm. of pilocarpine, permitted us to try the effect of the preliminary intraventricular injection of atropine on these responses. Accordingly, on December 4, 1930, 0.5 mgm. of atropine was introduced in the ventricle without any appreciable

* These hyperthermias are more commonly observed in children after the radical removal of median cerebellar tumours which lead to the abrupt collapse of the secondary hydrocephalic distention of the ventricle.

** It will be observed that both intraventricular pituitrin and pilocarpine in this case had an unusually definite effect on the sacral autonomic.
effect other than the sensation of dryness of the mouth and questionable slight increase in the diameter of the pupils. Thirty minutes later, one c. cm. of surgical pituitrin was introduced without any subsequent subjective effect or objective reaction whatever on the part of cardiovascular, gastrointestinal or thermo-regulatory mechanisms.*

On December 8th at 11.25 A.M., again after the usual preliminaries, another 0.5 mgm. of atropine was injected into the ventricle, the same subjective sensation as before of dryness in the mouth being produced, but there was no determinable pupillary change. Thirty minutes later 2.5 mgm. of pilocarpine was introduced, and though the tongue appeared to become somewhat more moist there was, apart from this, no observable effect of the drug whatsoever.

Whereas, after the typical response to pituitrin or pilocarpine given alone, this patient, as has been true of other subjects similarly tested, showed for some hours inappetence due to subdiaphragmatic uneasiness with waves of nausea, on the conclusion of each of the tests which were counteracted by atropine she eagerly ate a hearty lunch.

Atropine, in the opinion of pharmacologists, exercises a paralytic effect, like curare, at the peripheral nerve termination of the glands as well as at the myoneural junction of involuntary muscle. In other words, the drug supposedly acts at the same peripheral points at which pilocarpine causes its excitatory effects, the two drugs being peculiarly antidotal. These observations herein reported if correctly interpreted would seem to suggest that both drugs may act centrally as well, and if this is so they must probably operate through some diencephalic center where parasympathetic impulses may be discharged or inhibited.

**Conclusion.**—Atropine whether given subcutaneously or previously introduced in the cerebral ventricles appears completely to counteract the customary effect both of pilocarpine and of pituitrin when administered by way of the ventricles.**

* Whether the atropine served to check the usual oliguric effect of the extract unfortunately could not be determined.

** In the succeeding papers an explanation of certain negative responses to the intraventricular injection of pituitrin and pilocarpine will be offered, and the possible method of action of these substances so introduced will be more fully discussed.