II. THE SIMILARITY IN THE RESPONSE TO POSTERIOR LOBE EXTRACT (PITUITRIN) AND TO PILOCARPINE WHEN INJECTED INTO THE CEREBRAL VENTRICLES

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In the preceding paper it was pointed out that the intraventricular injection of "pituitrin" has a profoundly different effect from that which follows its subcutaneous or intravenous administration. Instead of the customary pallor of the skin with evacuation of the bowels, there usually occurs a prompt cutaneous vaso-dilatation with an extreme sudorific effect, often with repeated vomiting and a considerable fall in body temperature.

This peculiar and striking response to pituitrin when put in the ventricles was so suggestive of the known pharmacological reaction to pilocarpine that it seemed advisable to make comparative studies of the effect of the extract and of this drug. Accordingly, in one of the patients who had shown at an earlier session a well-marked reaction to intraventricular pituitrin a test was first made with a subcutaneous injection of 12 mgm. of pilocarpine. This led to the familiar response characterized by moderate flushing, slight sweating with salivation and lachrymation, some intrabdominal uneasiness but no vomiting, a temporary increase of 20 points in the pulse rate but no change in blood-pressure or pupils, and an insignificant fall in rectal temperature of 0.8°F. A slight rise of 7 points in the basal metabolic rate was observed but this was considered to lie within the margin of error.

On the following day, less than half of this dose of pilocarpine, namely, 5 mgm., was introduced into the lateral ventricle. Almost immediately there was a rise in pulse rate of 20 points without appreciable alteration in blood-pressure or change in size of the pupils. In a few moments the patient had a sensation of warmth soon followed by a marked generalized flush, a drenching perspiration and excessive salivation accompanied by prolonged retching and vomiting. In the course of the next two hours the temperature dropped off two degrees, from 98.8° to 96.8° but with no change in the basal metabolic rate.

This reaction was more severe than had been anticipated and in the six other patients, on whom similar tests have subsequently been made, one-half of this amount of pilocarpine, namely, 2.5 mgm., has been introduced; but this smaller dose has elicited the same prompt and striking reactions in all instances but one. The exception was in a patient who had a glioma involving the tuber and in whom the intraventricular injection of one cubic centimeter of surgical pituitrin had likewise caused no appreciable effect.
To show how nearly comparable are the reactions to the two substances administered in this way the following protocols may be given side by side.

The patient, John S., was convalescing from an operation for the removal of a large glioma of the left temporo-occipital region unassociated with hydrocephalus. At the time the tests were made his wound was healed, there was no tension and he was wholly free from symptoms. A previous intraventricular injection of 1 c. cm. of surgical pituitrin in the ventricle had caused a definite though inconspicuous response leading to a fall of temperature of one degree only and, contrary to the usual rule, a rise in metabolism from +1 to +8. He was then given a test with 2.5 mgm. of pilocarpine which evoked such a marked reaction that on a subsequent occasion, for better comparison of the two effects, a dose of 1.5 c. cm. of pituitrin was injected. The protocols of these two injections are subjoined.

**REACTION TO PILOCARPINE (Cf. Chart I)**

| -1; weight 65.4 kgm. | +3; weight 66.4 kgm. |
| Blood: erythrocytes 5,010,000; sugar 0.124 mgm.; total lipoids 0.652. Pupils 5 mm. (unaffected throughout). | Blood: erythrocytes 4,290,000; sugar 0.098 mgm.; total lipoids 0.635. Pupils 4.5 mm. (unchanged throughout). |
| Rectal temp. 99°F.; pulse 65; blood-pressure 124/75. | Rectal temp. 98.9°F.; pulse 65; blood-pressure 124/76. |

10:30 Ventricular tap; 5 c. cm. fluid withdrawn.

10:38 Injection 2.5 mgm. pilocarpine with prompt slight enduring rise in blood-pressure to 156/95.

10:43 Borborygmi; nausea; vomiting; slight flush.

10:48 Continued vomiting; marked flush; free sweat.


11:10 Temp. begins to drop (32 minutes).

11:17 Retching; vomitus blood-streaked.

11:20 Blood: erythrocytes 4,950,000; sugar 0.160; total lipoids 0.685.

11:30 Sweat still profuse; retching less frequent.

11:30 Sweat still profuse; retching less frequent.

11:00 Marked flush; heavy sweat; nausea continues.

11:04 Temp. begins to drop (26 minutes).

11:31 Continued rapid fall in temp. to 96.4°; no vomiting.

11:47 Blood: erythrocytes 4,450,000; sugar 0.111; total lipoids 0.657.

12:10 Flush fading; cessation of sweat; temp. 93.8°.
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REACTION TO PILOCARPINE (CF. CHART I)  
(Continued)

12:20 Flush fading; skin drying; temp. 96.6°.

12:35 Reaction practically over. Temperature at lowest level, 96.4°.

1:00 Metabolism taken, +6. Weight 63.8 kgm.

1:20 Chart discontinued. Temp. at 97.2°. Blood-pressure remains slightly elevated. Rectal temperature subsequently taken half-hourly by thermometer; pre-injection temperature not regained until 3:30.

REACTION TO PITUITRIN (CF. CHART II)  
(Continued)

12:20 Reaction about over. Temp. at lowest level, 93°. Shivering though body and extremities warm to touch.

1:00 Metabolism +46 (shivering); weight 64.3 kgm.

1:20 Metabolism +23. Temp. 94°. Comfortable; no shivering.

2:20 Blood; total lipoids 0.686; metabolism +22; temp. 95°.


4:20 Metabolism +29. Temp. 97.8°. Weight 64.3 kgm. Chart discontinued. Subsequent rectal temperatures taken with thermometer half-hourly. Pre-injection temp. of 99° not regained until 7 P.M.

The similarities in the reactions to the given doses of pilocarpine and pituitrin noted in these protocols are possibly still more apparent from the plotted records which are here appended (Charts I and II). These charts show the prompt slight pressor response which endured throughout the period of reaction; the secondary slight slowing of pulse rate; and the downward chute in rectal temperature which began after the lapse of about half an hour. Both substances produced the same pronounced flush and drenching sweat which lasted approximately one hour and a half. There was no appreciable change in the size of the pupils with either injection.

The chief differences in the responses lay: (1) in the more marked vagal effect from pilocarpine with continued retching and vomiting until positive blood was shown by the guiac test whereas there was only a brief period of nausea with pituitrin; (2) in the far more pronounced and enduring fall in body temperature from pituitrin which persisted long after the cessation of the sweat, the normal rectal temperature not having been regained after the 2.6° drop due to pilocarpine until three hours had elapsed, and after the pituitrin test, with a 5.9° drop to its lowest level of 93°, not until the lapse of six and one-half hours.

One peculiarity in the reactions shown by this patient was the unexpected increase of 43 per cent in the basal metabolic rate which coincided with the lowest temperature caused by the pituitrin injection. For this astonishing reaction with the body temperature at 93° there is
no ready explanation unless it was that the patient was shivering. The finding was so contrary to the usual rule, it was repeated hourly for the next four hours, the rate as recorded in the protocol still remaining high though shivering had ceased; and on the following morning it was found to be still elevated at +13 though the patient was comfortable, composed and without fever.

![Chart I](chart.png)

**Chart I**

Showing the effect on pulse rate, respiration, blood-pressure and rectal temperature of an intraventricular injection of 2.5 milligrams of pilocarpine.

At an earlier session, as mentioned above, a cubic centimeter of pituitrin had given only a mild reaction, and it may be presumed, had we cared to subject this willing man to further tests, that a dose of pilocarpine larger than 2.5 mgm. would have given as striking an antipyretic response as the 1.5 cubic centimeter dose of pituitrin evoked. In the two patients in the series who had received 5-mgm. intraventricular doses of pilocarpine, one showed a fall of 2° in temperature in one and one-half hours and the other a fall of 4.5°. Personal idiosyncrasy doubtless is but one of many factors in the variability of the reactions; the remarkable thing
Showing (for comparison with Chart I) the effect of 15 cubic centimeters of salicyluric injected into the...

CHART II

Metabolism 96
Metabolism 76
Metabolism 22
Metabolism 86

Ventricular tap
Sodium injection
Blood pressure
Pulsus paradoxus
Deferent duct
is that the responses to the two substances, under the inexact circumstances of these observations, not only bear such a close resemblance but are chronologically and quantitatively so similar.

Just how and where pilocarpine and its allied drugs act upon the secretory glands seems to be not fully agreed upon by pharmacologists. They are supposed to have an excitatory effect on the peripheral nerve terminations in the various glands and at the myoneural junction of smooth muscle. And since the effect of atropine is antidotal to that of pilocarpine, it has been assumed to have a paralytic effect on the same terminal apparatus whether in salivary, gastric, pancreatic or sudoriferous glands or unstriated muscle. Some authors, indeed, have claimed that the action of muscarine and allied drugs is a direct one on the organs themselves and that the nerves are not in any way involved. However this may be, all authorities agree that the effect of these drugs on the circulation varies in different species, and so far as man is concerned neither has a haemodynamic response been observed nor any effect on the pulse rate in any dose that one would feel justified in administering.

Though the physiological action of pilocarpine is evidently expended somehow in stimulating the autonomic nervous system, the possibility that it might act on a higher center controlling the system rather than on the periphery does not seem to have been given due, if any, consideration. This may, indeed, be true of other drugs, the effects of which are similarly apt to be studied on anaesthetized animals or on pithed animals under artificial respiration.

Though the subject, whose tests have been cited in the protocols above, happened to be convalescent from an operation for a cerebral glioma which had been exposed from the side, the larger number of tests in the series have been made upon patients following frontal osteoplastic operations for pituitary adenomas. In the process of making the customary bone flap for all such procedures four or more preliminary perforations are made through the skull and these small holes make subsequent access to the ventricle by a needle even more simple than the performance of a lumbar puncture. The flap, moreover, is so outlined that its lower leg, for purposes of concealment, passes through the line of the eyebrow which necessitates division of the supraorbital nerves to the corresponding side of the forehead. Hence the scalp overlying the bone flap, though its blood supply is intact, is denervated and remains anaesthetic until, in the course of some months, the nerves reunite.

It has long been known to clinicians that paralysis of the peripheral nerves renders the corresponding skin field irresponsible to the sudorific effects of pilocarpine. This fact, utilized long ago by Victor Horsley to determine the upper level of a spinal cord lesion, has been more recently employed by Otfrid Foerster as a means of mapping out the dermatomes
after the surgical division of the spinal nerve roots. However, owing to overlap of the skin fields supplied by the spinal segments, the boundary of the affected area under these circumstances is less sharply demarcated than in the operations under consideration.

As shown in Miss Coddington’s color sketch (frontispiece), the perfectly healed flap remains pale and dry in striking contrast to the rest of the face and body which may be greatly flushed and dripping with sweat. With a sufficient dose, either of extract or drug, to give a marked reaction the contrasting color effect in the forehead is brought out by either interventricular pilocarpine or pituitrin and also by an intramuscular injection of pilocarpine. On the other hand, the intramuscular or intravenous injection of pituitrin, as already pointed out, causes a generalized pallor which affects the skin of both sides of the forehead alike. Since the circulation of the bone flap remains intact, this would appear to indicate that the effects both of pituitrin and pilocarpine introduced by way of the ventricle are not exerted on the sweat glands through the medium of the circulating blood or of sympathetic fibres which accompany arterial blood-vessels but must be produced by effector impulses which travel from some higher center by way of the peripheral nerves, presumably along certain sensory fibres, which, in their antidromic function, behave as part of the parasympathetic system.

Both of these substances, moreover, the drug as well as the extract, give reactions that suggest a parasympathetic (bulbar) rather than a sympathetic (thoroco-lumbar) stimulation; and whether it is justifiable to assume that these supposedly reciprocal systems, if they are actually separable, are each under the control of its own higher hypothalamic center further studies may possibly show. Unquestionably the action of other drugs, particularly those of the muscarine series, when introduced into the cerebral cavities is a matter that needs ventilation.

Conclusions.—Pilocarpine and pituitrin have a similar action in producing widespread vaso-dilatation, sweating, vomiting and lowering of the body temperature when injected into the cerebral ventricles. The effects suggest a central autonomic stimulation predominantly of the parasympathetic division.