

## Section on Scientific Papers

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### THE PHARMACOLOGICAL ASSAY OF PITUITARY PREPARATIONS.

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The function of the hypophysis cerebri or pituitary body continues to be more or less of a mystery notwithstanding the wide investigation which has been conducted. It has been conclusively shown, however, that the posterior lobe of the gland contains physiologically active substances, which are of considerable therapeutic importance. In addition to the marked increase in blood pressure which follows an intravenous injection of the infundibular extract, and which will be discussed later in this paper, the drug is known to have a strong stimulating action on the muscular fibers of the uterus, bladder and intestinal tract. This phase of its physiologic action has led to the extensive use of preparations of this gland in various obstetrical and surgical clinics, in dealing with uterine insufficiency and post-operative and puerperal atonic conditions of the bladder and bowels. The drug has also a diuretic action and, as recently shown (Otto, Schafer and Mackenzie) is an active galactagogue.

In very large doses and when administered over a long period of time, certain untoward results, as disorders of carbohydrate metabolism, motor disturbances, aberrations of the circulatory and respiratory systems may occur. However the amount of pituitrin required to produce such disturbances is so far in excess of the therapeutic dose that they can be ignored in considering the therapeutic action. The above symptoms are practically those which are characteristic of the extirpation, or atrophy of the gland. This is exactly the reverse of the results to be expected, since, in general, gland extracts, or the dried gland, administered to animals in which the gland is absent or inactive will partly or wholly compensate for the deficiency.

This gland presents another anomaly which may in part explain the peculiar action of its extracts. Of the two parts, the anterior and posterior, or infundibular portion, only the former is of vital importance, while only the latter contains a substance having a recognizable physiologic action when hypodermically administered.

With the importance of this gland in medicine, however, this paper is not concerned, but only with means of standardizing preparations obtained from it.

The drugs which are of value in medicine are scrutinized with great care, especially those which are powerful in their reaction. Wherever possible they are assayed with minute exactness. Many of the most valuable remedial drugs contain principles which are either known in a pure state, or of such complex composition

as to defy the skill of the analyst. For such drugs it is customary to make use of some constant and typical reaction which the drug has when administered to an animal.

This method known as the pharmacologic assay depends for its adaptability on the sharpness of the reaction and its sensitiveness to changes in the quantity injected.

Reviewing the typical effects of preparations of the pituitary gland, that on the kidneys causing polyuria seemed to meet the requirements for an assay process particularly logical if this effect were, as stated by Prof. Schafer, "essentially due to the glandular cells of the organ being stimulated to activity by the agency of a specific hormone."

Houghton and Merrill (Jour. Am. Med. Ass'n. Nov. 28, 1908) failed to convince themselves that this hypothesis is correct finding that the reason for the increased urinary flow is chiefly, if not entirely, dependent on the increased blood pressure. Neither is this reaction typical of this drug alone, since others which affect the blood pressure have a similar effect on the kidneys.

McCord (Archives of Internal Medicine, November, 1911) found that when the isolated kidney is perfused with Locke's solution containing active pituitary extract 92% of the experiments caused typical constriction and no fatigue of the organ was evident even after 20 injections. He suggested that this might be used as a means of standardizing preparations from the gland.

This method has not been given a conclusive trial since it has certain features which would tend to interfere with its quantitative exactness. It may, however, have undeveloped possibilities and when carefully followed up be found applicable to the problem.

Most investigators of this interesting body agree that the intravenous injection of extracts of the gland into dogs is followed by an increase in blood pressure, which is both rapid and pronounced. It resembles in some respects the change in blood pressure which follows the administration of adrenalin, both being caused by a constriction of the arterioles.

The resemblance between the actions of the two glandular extracts ceases with this, however, since the duration of the increased blood pressure due to pituitary extracts greatly exceeds that from adrenalin, and according to Cushney, Wiggers and others, is probably caused by direct action on the muscle instead of on the nerve endings.

The action of pituitary extracts on the blood pressure of dogs differs from that on rabbits and cats in the fact that the depressor action is not so quickly evident. Various workers, Schafer, Cushney and others, have noted that with animals other than dogs the second and subsequent injections of equal quantities of an active preparation of the gland bring about progressively smaller increases in pressure until a point is reached where no pressor but only a depressor effect follows. When large doses are used or when the injections are frequently made for a long period this action would vitiate the results even with the dog; but under the conditions of the test very little evidence of it appears.

This, then, is a typical reaction and while other effects are of more importance in therapeutics, no other lends itself more readily to measurement. While there is much to be desired in sensitiveness of the reaction to changes in the quantity

injected, the change in blood pressure is fairly constant and until a more accurate method has been evolved this can be used with confidence as a means of comparing the activity of one extract of the gland with that of another. When one of the two is a standard the assay is quantitative.

The method as now followed for determining the activity of extracts of this gland resembles in many of its details that used for standardizing extracts of the suprarenal gland or specifically for the assay of adrenalin. It depends on the fact that consecutive injections of a certain quantity of the active constituents of the gland under rigidly defined conditions increase the blood pressure of an anaesthetized dog to the same degree.

If the circulatory system be connected from an artery to a kymograph, tracings can be obtained which show this action of the extract and illustrate its applicability to the purpose.

The dog should be one of approximately 10 kilos weight.

It is best anaesthetized by an intraperitoneal injection of chloretone in oil (0.3 gm. per kilo).

The injections can be made most conveniently into a femoral vein and the blood pressure recorded from the carotid artery by means of a mercury manometer.

The amount of the active principle which is found best for injection is that contained in 0.02 gm. of the fresh, or 0.001 gm. of the desiccated, defatted gland, the increase in blood pressure resulting from an injection of this quantity being very nearly the same as that from 0.00001 gm. adrenalin, although no such comparison can be made use of in standardization work.

The preparation used for the standard is the dried, defatted, powdered gland, which is a stable product. Of this powder 0.001 gm. corresponds to approximately 0.02 gm. of the fresh gland. The solution for injection is made by rubbing 0.1 gm. of the powder in a mortar with successive portions of acidulated water until the yield is 100 cc. This solution should be either decanted or filtered from the sediment. One cc. of this solution contains the standard test dose. The reason for choosing this quantity is that the dog is more sensitive to small changes from this amount, that is, to variations in the quantity of active constituent which is contained in the solutions being assayed.

In making an assay the normal height of the dog's blood pressure is to be recorded first, then the height to which the standard test quantity will increase this pressure. After two or more injections of the standard are made, to determine the average increase in blood pressure, that quantity of the unknown sample which is supposed to contain an equal quantity of the active substance is injected.

If the rise in blood pressure from the injection of the sample is different from that produced by the test dose of the standard the amount of the sample used is varied accordingly until an amount which has a reaction equal to that from the standard test dose is found.

From this we can deduce the activity of the sample, since the same amounts of active substance must have been present in the two quantities which, when administered in the same manner consecutively, induce the same rise in blood pressure.