THE PHYSIOLOGICAL EFFECTS OF EXTRACTS OF THE HYPOPHYSIS CEREBRI AND INFUNDIBULAR BODY.

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Injections of extracts of the hypophysis cerebri have been tested by Szymonowicz and by Oliver and Schäfer during the course of their well-known experiments upon the effects of extracts of the adrenal glands. Szymonowicz * states that in two experiments of this kind, made upon dogs, he obtained a slight fall of blood pressure and a quickening of the heart beat, just the reverse of the cardiac and vascular phenomena observed after injection of adrenal extracts. He concluded, therefore, that the physiological effects of extracts of the hypophysis cerebri are different from those caused by extracts of the adrenal glands, and, so far as can be gathered from his brief description, are much less marked. Oliver and Schäfer † obtained different results. In their hands extracts of the hypophysis caused usually a marked rise of blood pressure together with an augmentation of the force of the heart beat, results resembling those obtained from extracts of the adrenal body. There was, however, this difference, that the pituitary extracts, unlike the adrenal, caused no slowing of the heart beat. As these results are quite unlike those obtained from extracts of the thyroid body, the authors use them somewhat hastily, as appears from my experiments, to combat the prevalent view of a physiological relationship between the thyroid and the hypophysis cerebri. The contradictory results obtained by the investigators quoted suggested to me the desirability of making further experiments of the same nature upon this organ. The results of these experiments have been very uniform so far as the general effects of the extracts are concerned,

* Szymonowicz, Pflüger's *Archiv*, lxiv (1896).

† Oliver and Schäfer, *Journal of Physiology*, xviii (1895).

and in some respects are quite different from those referred to briefly above.

The hypophysis cerebri is usually described as consisting of two lobes. One, the large anterior lobe, is distinctly a glandular structure, as shown by its histological characteristics. Embryologically it is described as arising in part or entirely from the epithelium of the mouth cavity. According to Haller * it possesses an incomplete system of ducts that open between the meningeal membranes. Any secretion that it may form passes therefore, in part at least, into the cerebrospinal liquid contained between these membranes. Properly speaking the term hypophysis cerebri should be restricted to this lobe, and this significance is now given to it by morphological writers, although in human anatomy it is still commonly employed to include the so-called posterior lobe as well. The posterior lobe of human anatomy lies upon and is partially enclosed by the anterior lobe or hypophysis proper. It is connected by a stalk with the tip of the infundibulum, and embryologically it is to be regarded as an outgrowth from this part of the brain. It would seem more desirable therefore to speak of this body not as the posterior lobe of the hypophysis cerebri, but as the infundibular body, and this designation I shall use in this paper. The infundibular body is quite small as compared with the hypophysis. Its histological structure in the adult mammal has evidently not been studied very exhaustively. According to the older accounts it consists largely of a network of neuroglia, and it has been commonly regarded therefore as a rudimentary organ without distinct physiological value. Berkley † has studied its histology by means of the Golgi method and reports that its structure is complicated and somewhat curious. He finds in it numerous nerve cells belonging to several types, a cortical layer of ependymal cells, a network of neuroglia tissue, some peculiar structures resembling nerve end-organs, and lastly a quantity of glandular-like epithelial cells arranged in part to form tubes or closed vesicles, some of which contain a colloidal material. This rather complex structure indicates that the infundibular

* Haller, *Morphologisches Jahrbuch*, xxv (1896).

† Berkley, *The Johns Hopkins Hospital Reports*, iv (1895).

lobe is not merely a rudimentary organ, and the glandular tissue that Berkley describes suggests a secretory activity of some kind. This suggestion I may say at this point is corroborated by the physiological experiments described in this paper.

In my experiments extracts were made of both the hypophysis cerebri, or anterior lobe, and the infundibular body, and the effects of each were tested separately by injection into the circulation of anæsthetized dogs. The extracts in some cases were made from the dried tissue prepared according to the method described by Oliver and Schäfer. That is, the glands were pressed out as thin as possible and dried rapidly in a sulphuric acid chamber. The dry material when used was powdered and extracted with a few cubic centimetres of normal saline solution. In most cases, however, glycerine extracts were made from the fresh tissues. In making these extracts the two lobes were first separated, each was then rubbed to a creamy pulp in a mortar with a small quantity of glycerine, and the mixture was allowed to stand for several hours. Before using this extract it was diluted with a few cubic centimetres of normal saline solution and was filtered either at once or after standing an hour or two.

A few experiments were made with the hypophysis of the dog, but in most cases the gland from the sheep was used, since it is much larger and can be obtained easily from animals killed at the slaughter-houses. In the sheep the hypophysis and the infundibular lobe together make a structure of considerable size, lying in the sella turcica and nearly covered by a bony and membranous operculum. This position makes its removal a simple matter, since the brain may be removed rapidly in mass from the skull without disturbing the hypophysis, the only precaution to observe being to first cut the stalk connecting the infundibular lobe to the infundibulum. The size of the entire organ in the sheep is variable, being proportional apparently to the size of the animal; the weight is usually from 300 to 500 mgrms. The hypophysis proper is much the larger of the two lobes. It forms a firm reddish mass incompletely separated on the upper side into two lobes by a shallow longitudinal furrow. The infundibular body is a small whitish mass weighing about $\frac{1}{10}$ as much

as the hypophysis. It lies upon the upper surface of the hypophysis at its posterior angle, and the long stalk connecting it with the infundibulum runs in the shallow furrow that separates the two halves of the hypophysis. If this stalk is seized with a pair of forceps and dissected carefully backwards, it and the adherent infundibular body may be separated easily from their loose attachment to the hypophysis.

The extracts made from these two lobes were injected directly into the jugular or femoral vein of an anæsthetized dog by means of a fine-pointed hypodermic syringe, and as a rule 2 cc. of the extract were used for each injection. The effects obtained were as follows:

The extracts of the hypophysis alone caused little or no perceptible change in blood pressure or heart rate. In some cases the effect was entirely negative, in others a slight but inconstant effect upon blood pressure was noticed. Upon the whole it would seem that extracts of this body have no characteristic effect upon the circulatory or respiratory organs.

With the extracts of the infundibular body, however, the results were very marked and in their main features quite constant, although somewhat variable in detail and apparently slightly different according to the anæsthetic employed. The main effect upon an animal with its vagi intact was a pronounced slowing of the heart beat together with an increase in blood pressure; while upon an animal with its vagi cut or under the influence of atropin the effect consisted chiefly in a marked prolonged rise of blood pressure together with a slower and stronger heart beat. These two effects are illustrated in the accompanying illustrations (Figs. 1 and 2). The details of the curves obtained varied somewhat for each animal. In general the course of the curve when the vagi were intact was as follows: Within a few seconds (5-10) after the beginning of the injection the blood pressure rose to a variable extent; this was followed quickly by a temporary fall, which was also quite variable in amount. During this period the heart beat was somewhat slower and apparently more feeble, except in the case of peptone anæsthesia, in which on the contrary the heart rate was accelerated temporarily. The duration of the fall in pressure was also variable; in some cases it lasted for a few seconds

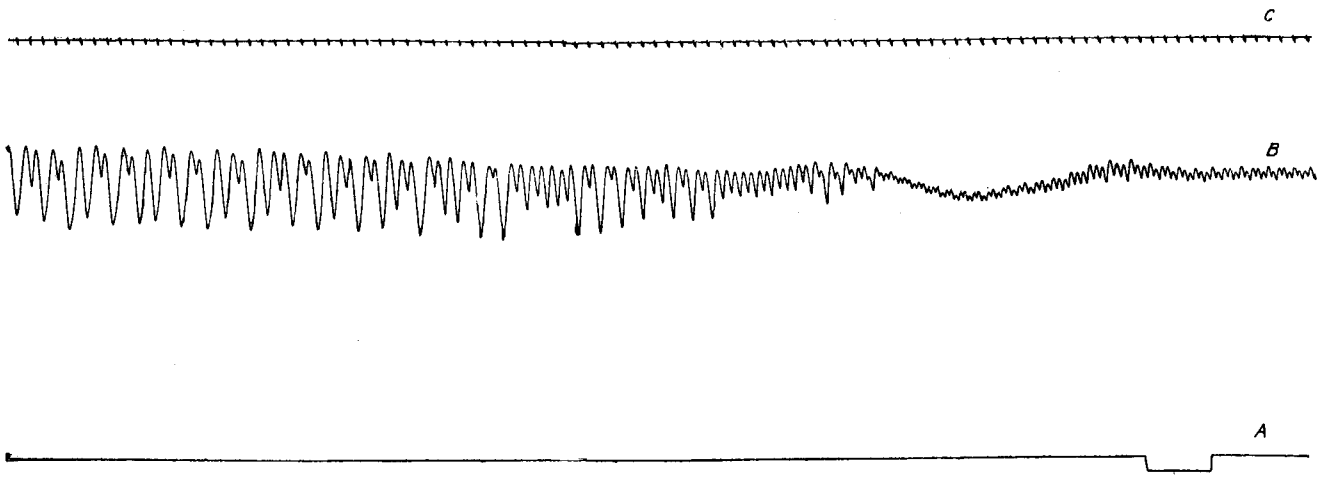

FIG. 1.

Tracing from a dog under peptone, showing the effect of extracts of the infundibular body upon the heart beat and blood pressure when the vagi are intact. The tracing reads from right to left and is reduced ½ in size. *A* is the base line. The depression in this line indicates the time during which the injection was made into the jugular. *B* is the blood pressure record; *C*, the time record in seconds. Before injection the blood pressure = 150 mms., the pulse rate = 144. During the first small fall in pressure the pulse rate = 165. At the end of the tracing the pulse rate = 55.5, and the maximal blood pressure = 163 mms.

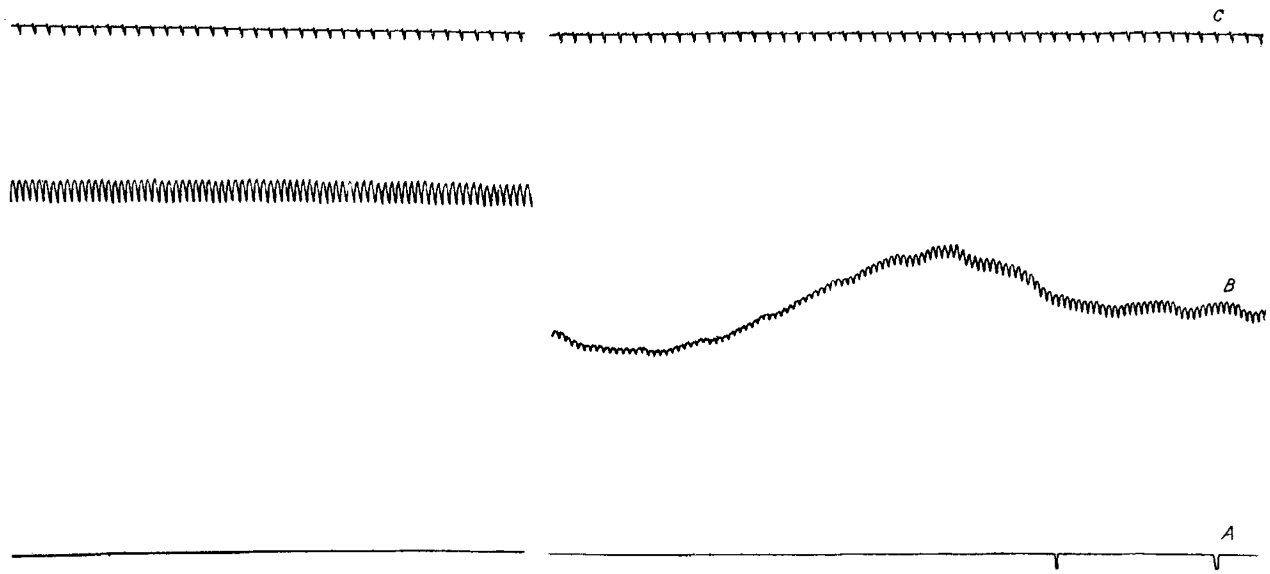

FIG. 2.

Tracing from a dog under morphia (and ether), showing the effect of extracts of the infundibular body when the vagi are cut. This tracing reads from right to left, and is reduced ½ in size. *A* is the base line; the injection of extract was made in the interval between the two marks on this line. *B* is the blood pressure record; *C*, the time record in seconds. Before injection the arterial pressure = 134 mms., the pulse rate = 151. The first rise of blood pressure reached to 162 mms., and in the succeeding fall the pressure sank to 108 mms., with a pulse rate of 147. At the end of the tracing the characteristic and constant effect of the extract is shown. The blood pressure here = 192 mms., and the pulse rate = 130.

only, while in one instance it continued for nearly a minute. This phase was then succeeded by the main effect, namely, a very marked slowing of the pulse rate that lasted for a long time, in some cases over half an hour. The maximum slowing was attained gradually, and the return to the normal rate was made still more slowly. During this period the maximum blood pressure first increased slowly, rising usually to a level above that prevailing at the time of the injection, and then slowly dropped back to normal. Roughly speaking the maximal blood pressure was reached at the time that the pulse rate was the slowest.

Some idea of the extent of these changes in pressure and pulse rate when the vagi are intact may be obtained from the following tabular statement of the results of some of the experiments:

Exp. 1. Dog under morphia (0.05 grm.) with a little ether.

Pressure before injection of extract of the infundibular body	= 109 mms. Hg.
Greatest pressure after injection of extract of the infundibular body	= 156 " "
Pulse rate per minute before the injection	= 134 beats.
Slowest pulse rate per minute after the injection	= 57 "

Exp. 2. Dog under morphia (0.05 grm.) with a little ether.

Pressure before injection of extract of the infundibular body	= 120 mms. Hg.
Greatest pressure after injection of extract of the infundibular body	= 160 " "
Pulse rate per minute before the injection	= 68 beats.
Slowest pulse rate per minute after the injection	= 33 "

Exp. 3. Dog under morphia (0.05 grm.) with a little ether.

Pressure before injection of extract of the infundibular body	= 124 mms. Hg.
Greatest pressure after injection of extract of the infundibular body	= 147 " "
Pulse rate per minute before the injection	= 122 beats.
Slowest pulse rate per minute after the injection	= 74 "

Exp. 4. Dog under morphia (0.05 grm.) with a little ether.

Pressure before injection of extract of the infundibular body	= 113 mms. Hg.
Greatest pressure after injection of extract of the infundibular body	= 148 " "
Pulse rate per minute before the injection	= 93 beats.
Slowest pulse rate per minute after the injection	= 40 "

Exp. 5. Dog under morphia (0.05 grm.) with a little ether.

Pressure before injection of extract of the infundibular body	= 120 mms. Hg.
Greatest pressure after injection of extract of the infundibular body	= 140 " "
Pulse rate per minute before the injection	= 100.5 beats.
Slowest pulse rate per minute after the injection	= 49.5 "

Exp. 6. Dog under peptone injected into the femoral artery, 1 dgrm. to 1 kilo.

Pressure before injection of extract of the infundibular body	= 87 mms. Hg.
Greatest pressure after injection of extract of the infundibular body	= 148 " "
Pulse rate per minute before the injection	= 144 beats.
Slowest pulse rate per minute after the injection	= 78 "

Second experiment upon the same animal:

Pressure before injection of the extract	= 150 mms. Hg.
Greatest pressure after injection of the extract	= 163 " "
Pulse rate per minute before the injection	= 144 beats.
Slowest pulse rate per minute after the injection	= 56 "

Exp. 7. Dog under ether alone.

Pressure before injection of extract of the infundibular body	= 144 mms. Hg.
Greatest pressure after injection of extract of the infundibular body	= 172 " "
Pulse rate per minute before the injection	= 142 beats.
Slowest pulse rate per minute after the injection	= 108 "

It will be seen from these figures that the injections increased the blood pressure from 9 to 42 per cent., while the pulse rate, omitting experiment 7, suffered a reduction of from 40 to 60 per cent. In experiment 7, in which the animal was deeply under ether, the reduction in pulse rate was only 24 per cent., a result approximating, as we shall see, that obtained from animals with the vagi cut. Deep anæsthesia with ether apparently suspended in part or entirely the normal irritability of the inhibitory centre. As compared with adrenal extracts the effect of extracts of the infundibular body is characterized by its long duration. The blood pressure rises more slowly to a maximum, remains above the normal level for a longer time and sinks quite gradually. The long continuance of the heart effect is even more marked, and it is curious that this effect should have been overlooked by previous observers. It is possible of course that in the experiments of Oliver and Schäfer and of Szymonowicz upon the pituitary gland, the extracts contained little or no material from the infundibular body, since no attempt was made in their experiments to distinguish between the effects of the two lobes. The slowing of the heart comes on somewhat later than the effect upon blood pressure; it increases to a maximum within one or two minutes after the injection, and then decreases

very gradually, the pulse rate returning to the normal at the end with some suddenness. The entire effect may last for twenty or thirty minutes or longer when the dose is a maximal one. If, however, repeated injections are given the effects caused by the successive injections may be much less marked or may fail altogether, the result depending upon the interval of time between the injections and also upon the strength of the dose used. The loss of reaction following upon repeated injections seems to be much more marked than in the case of adrenal extracts.

A typical example of the effect of repeated injections may be given in detail to illustrate the disappearance of the reaction even with maximal doses and with intervals of time sufficient or nearly sufficient for the effects of preceding injections to pass off. In Experiment 6 of the above summary the following results were obtained. Previous to the injection of peptone the blood pressure had been 144 mms., and the pulse rate 165.5 per minute. After injecting peptone rapidly into the femoral artery, one decigramme to a kilo of animal, the pressure sank rapidly to 28 mms., while the pulse rate rose to 216. An interval of half an hour was allowed, and at the end of this time the pressure was 87 mms., while the pulse rate was 144. Several successive injections of extracts of the infundibular body were then made.

The effect of the first injection:

The pressure was raised to 148 mms.
The pulse rate was slowed to 78 beats.

Twenty minutes after this injection the pressure was still at 150 mms., while the pulse rate had returned to 144.

Effect of the second injection twenty minutes after the first:

The pressure was raised to 163 mms.
The pulse rate was slowed to 55.5.

At the end of seven minutes the pressure had returned to 152.5 mms., and the pulse rate to 115.5.

Effect of the third injection seven minutes after the second:

The pressure was raised to 161 mms.
The pulse rate was slowed to 69.

At the end of four minutes the pressure had returned to 144 mms., and the pulse rate to 139.5.

Effect of the fourth injection four minutes after the third:

The pressure was raised to 148 mms.
The pulse rate was slowed to 102.

The effect in this case was quite transient, the heart rate and blood pressure returning to normal within one minute.

It would seem from this and similar experiments that the active substance of these extracts, as in the case of the adrenal extracts, is destroyed or neutralized in some way in the body so that its action is comparatively temporary. For this reason also injection of relatively large quantities of the extract when made subcutaneously fails to give any reaction upon the heart or blood-vessels, none, at least, sufficiently distinct to be detected with certainty upon the kymographic records. It would seem that an injection of this extract made directly into the circulation leaves the heart and blood-vessels in a condition of diminished irritability toward a new injection. This loss of reaction is certainly not due to a paralysis of the muscles of the circulatory organs or the nerves supplying them, since repeated injections of maximal doses cause no depression of vascular tone, nor removal of the normal tonic inhibition of the heart. The blood pressure and pulse rate in such cases simply return more or less completely to the normal, and new injections have either a negative result entirely or an effect more temporary than that of the preceding injections. It has seemed in some experiments as though repeated injections resulted in a permanent improvement of vascular tone and a slower and stronger heart beat, but as this effect, when observed, came on quite slowly, it was not possible to determine satisfactorily whether it was due to the injections. All that can be said positively is that the sudden reaction upon the pulse rate and blood pressure ceases after renewed injections, occurring at short intervals, without any appearance of fatigue or paralysis in the heart or blood-vessels. These organs, on the contrary, seem to acquire an immunity from the active substance of the extract. How long this immunity may last was not determined.

The effects of the injections when made upon animals with the vagi cut or under the influence of atropin differed from those described above in that the blood pressure was increased to a greater extent, while the slowing of the heart beat was much less marked. The fact that the heart rate was slowed at all under these conditions is very interesting and constitutes a marked difference between the effects of extracts of the infundibular body and the adrenal gland. This fact indicates moreover that extracts of the infundibular body affect the heart in part by acting on the cardio-inhibitory centre, and in part by a direct peripheral action exerted either upon the heart musculature directly or upon its intrinsic nerves. The general character of the results obtained when the connections of the heart with the inhibitory centre are removed may be illustrated by the following summary of experiments:

Exp. 1. Dog under morphia (0.05 grm.) with a little ether. Vagi cut.

Pressure before injection of extract of the infundibular body	= 92 mms.
Greatest pressure after injection of extract of the infundibular body	= 180 "
Pulse rate per minute before injection	= 148 beats.
Slowest pulse rate per minute after injection	= 93 "

Exp. 2. Dog under morphia (0.05 grm.) with a little ether. Vagi cut. Two previous injections with the vagi intact.

Pressure before the injection of extract of infundibular body	= 128 mms.
Greatest pressure after the injection of extract of infundibular body	= 145 "
Pulse rate per minute before injection	= 144 beats.
Slowest pulse rate per minute after injection	= 120 "

Exp. 3. Dog under morphia (0.05 grm.) with a little ether. Atropin injected, vagi cut.

Pressure before injection of extract of infundibular body	= 134 mms.
Greatest pressure after injection of extract of infundibular body	= 192 "
Pulse rate per minute before injection	= 151 beats
Slowest pulse rate per minute after injection	= 124.5 "

In these experiments the increase in blood pressure varied from 13 to 95 per cent. of the original pressure, while the reduction in pulse rate varied from 17 to 35 per cent. The comparatively small effect upon blood pressure in experiment 2 is probably due to the fact that

two injections of extract had been made before the section of the vagi, and, as was stated above, repeated injections are followed by a smaller reaction even when a considerable interval of time is allowed to intervene.

I have not in these experiments made any very thorough attempt to determine whether the extracts of the infundibular body affect the musculature of the heart and blood-vessels directly or act mainly upon the central nervous system. Two experiments, however, in this direction have yielded results that indicate that the active substances in these extracts, as in those of the adrenal glands, cause a rise of blood pressure by peripheral action upon the blood-vessels. In one experiment the spinal cord was cut below the medulla, and in addition most of the thoracic and lumbar cord was extirpated. After this operation the blood pressure had fallen to 23 mms. Hg, and the pulse rate per minute was 146. Injection of 2 cc. of an extract of the infundibular body caused the pressure to rise to 72 mms., an increase of 213 per cent., while the pulse rate fell to 91 beats, a reduction of 37 per cent. This experiment indicates that if the rise of blood pressure was caused by a peripheral constriction of the arteries, this constriction was not due to an effect upon the spinal centres, as claimed by Szymonowicz in the case of adrenal extracts, but to an action upon the arteries themselves. In a second experiment the kidney was placed in an oncometer and its changes in volume were recorded together with the kymographic tracing of the pulse and blood pressure. It was found that the volume of the kidney decreased as the blood pressure rose and vice versa; thus indicating that the increase in blood pressure is accompanied by and in part most probably caused by a peripheral constriction of the arteries.

At various times during these experiments I have tested the effect of glycerine extracts of different parts of the central nervous system, especially of the cerebral cortex, the medulla oblongata and the pineal gland. The extracts of the three last-named bodies have given inconstant results, which may be accounted for partly perhaps by the fact that the injections were made usually in the course of experiments upon the extracts of the infundibular body. In some cases the results

of these injections were negative or very slight, but at other times they caused a marked fall in blood pressure. Their effect certainly differed very greatly from the constant and characteristic reaction caused by the extracts of the infundibular body, and it seems quite evident that this structure contains a material distinct from anything occurring in other parts of the brain.

What this substance is I have not as yet attempted to determine. Its physiological effects resemble closely those caused by the active substance in adrenal extracts, but, as has been stated above, it differs from the adrenal extracts in the marked slowing of the heart beat that it causes after the two vagi have been cut, as well as in the longer duration of its action both upon the heart beat and the blood pressure. Moreover, the physiological reaction of the extracts of the infundibular body differs very distinctly from that caused by extracts of the hypophysis cerebi. This fact, taken in connection with the difference in structure of the two bodies and their difference in embryological origin, seems to indicate that physiologically as well as anatomically they are independent structures. The method of injecting extracts appears to teach us nothing with regard to the physiological activity of the hypophysis, it neither confirms nor disproves its supposed relationship to the thyroid body. On the contrary the marked influence of extracts of the infundibular body suggests that this organ may form a secretion of great importance to the functional activity of the circulatory organs. Certainly the effects caused by its extracts tend to disprove the prevalent view that this body is merely a functionless rudiment of an organ of primitive importance.

Haller,* in his interesting paper upon the development of the hypophysis, points out that in some of the lower vertebrates, the teleosts for example, a true glandular organ, the infundibular gland or saccus vasculosus, develops as an outgrowth from the infundibulum and maintains an open connection with the infundibular cavity. He concludes therefore that in these forms the gland opens directly into the cerebral ventricles. In the higher vertebrates, the mammals for instance, he

* Haller, loc. cit.

finds no trace of this gland, but instead a solid outgrowth, which he calls the processus infundibuli, attached to the tip of the infundibulum and apparently rudimentary in structure. This processus infundibuli corresponds apparently to the infundibular lobe, the effect of whose extracts has been described in this paper, and it seems possible that the solid process still retains the glandular structure of the primitive infundibular gland.