

THE PHYSIOLOGY OF THE PITUITARY GLAND AND THE ACTIONS OF ITS EXTRACTS.¹

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LODGED in the saddle of the sella turcica and shielded in a privileged manner from the traumatism of the outside world, lies a small body, the hypophysis cerebri, or pituitary gland, the function of which has always been, and still is, largely shrouded in mystery. Since Galen and Vesalius taught that it filtered mucus into the nose and pharynx, the functions attributed to this gland have varied from such vitalistic conceptions as a habitation for the soul or a stopper preventing the escape of vital spirits from the third ventricle, to the more lowly duties of an excretory organ for the brain, a lymphatic gland, etc. Obviously, no scientific conception of the organ's function could be formulated until its development and structure were understood and, consequently, the discovery of its dual origin in 1838 by Rathke² marks the time when a beginning could be made toward the unveiling of its true function. Since then a host of histological investigators, prominent among them, Stüda,³ Schönmann,⁴ Müller,⁵ Schwalbe,⁶ Berkley,⁷ v. Kölliker⁸ Paulesco,⁹ and Herring,¹⁰ have added in a material manner to a clear understanding of its structure and development.

HISTOLOGY AND EMBRYOLOGY. The pituitary body consists of a large pink-colored anterior portion, and a smaller pale posterior part. Developmentally considered, the posterior lobe arises as a downward growth from the midbrain, its cavity being continuous with the third ventricle. This part remains permanently connected with the brain by a stalk or infundibulum, the cavity of which, except in the cat, becomes obliterated by a growth of neuroglia tissue. The anterior portion arises as an upgrowth from the buccal ectoderm, which is cut off by the fusion of the sphenoidal cartilages. At first this cut-off mass exists as a hollow island of cells, but as the cells proliferate only a cleft remains. The cells on the posterior side of this cleft apply themselves to the posterior lobe, which they cover and invade to some extent, forming cut-off masses

¹ Presented before the Detroit Medical Club, June 2, 1910.

² Müller's Archiv., 1838, p. 482.

³ Ztschr. f. wissenschaft. Zoologie, 1868, xviii, 44.

⁴ Arch. f. path. Anat. u. Physiol., 1892, cxxix, 310.

⁵ Ztschr. f. Naturwissenschaft., 1891, vi, 354.

⁶ Referred to by Herring (Ref. 8).

⁷ Brain, 1894, xvii, 515; Johns Hopkins Hosp. Reports, 1895, iv, 285.

⁸ "Entwicklungsgeschichte," 1878.

⁹ Quoted by Parhon and Golstein, "Les Sécrétions Internes," Paris, 1907.

¹⁰ Quart. Jour. Exp. Physiol., 1908, i, 121.

of cells. The rest of the cells develop into the large anterior lobe, which becomes very vascular."¹¹

When fully developed, the posterior lobe is composed of neuroglia tissue, together with a few ependymal cells. Berkley believed he observed also nerve cells and fibers, but this has not been substantiated by subsequent investigators, and it seems probable, as Herring points out, that the cells described as nerve cells were in reality not such. The posterior lobe has an epithelial investment, first described by Pereineseliko,¹² in 1867, but more in detail by Paulesco, in 1906, and Herring, in 1908. According to this latter observer, the completeness of this epithelial covering varies in different animals. In the cat and dog the investment is complete, but in most mammals (man, monkey, ox, pig, rabbit) the epithelium does not entirely surround the posterior lobe, but is more particularly gathered toward its anterior part, forming the *pars intermedia* of the pituitary gland. A few gland cells are seen scattered here and there throughout the neuroglia tissue. This part is almost devoid of bloodvessels, and the colloidal secretion (or degeneration products?) of the epithelial cells is passed into the neuroglial tissue to be absorbed, by its lymphatic system, into the third ventricle.

The anterior lobe consists largely of differentially staining, granular cells, that are arranged in columns around thin-walled blood spaces. No evidences of glandular ducts are present. Haller¹³ claims that the anterior lobe is a tubular gland, discharging its secretion directly into the subdural space, but the evidence of other histologists appears against such a view, and indicates rather that these cells discharge their secretion directly into the blood spaces.

THE FUNCTIONS OF THE PITUITARY GLAND. One of the first questions of interest in studying a gland's function is its necessity to life. Physiologists and surgeons alike have attempted to answer this question by determining the effects of its removal. In 1892 Marineseo¹⁴ reported that removal of the pituitary gland in cats was fatal within one to eighteen days after the operation. Before death the animals showed signs of emaciation, a fall in temperature and heart rate. Vassale and Sacchi¹⁵ reported that the removal of the pituitary gland in forty animals (cats and dogs) resulted in death within five to seven days. The symptoms before death consisted in an accelerated respiration (amounting at times to dyspnoea), polyuria, polydipsia, vomiting, rigidity of the posterior limbs, fibrillary twitchings and clonic as well as tonic convulsions. Partial removal caused less pronounced symptoms, and occasionally the animal survived. Similar results have been reported by Casselli.¹⁶

¹¹ For excellent diagrams see Herring, *Quart. Jour. Exp. Phys.*, i, 121.

¹² *Arch. f. path. Anal. u. Physiol.*, 1867, xxxviii, 329.

¹³ *Morpholog. Jahrb.*, 1896, xxv, 101.

¹⁴ *Compt.-rend. Soc. de biol.*, June, 1892.

¹⁵ *Arch. Ital. de biol.*, 1893, xviii, 3.

¹⁶ Quoted by Parhon and Golstein (*loc. cit.*).

In 1900 Friedmann and Maas¹⁷ reported that extirpation of the pituitary gland was compatible with life. Lo Monneo and Van Rynberk,¹⁸ in 1901, Gaglio¹⁹ in 1902, and Pirrone²⁰ in 1903, also came to this conclusion. They admitted that serious symptoms and even death often followed its removal, but attributed these unfortunate events to cerebral traumatism or infections. The fact that some animals survived fifty to eighty days was advanced as proof sufficient that the gland was not of vital importance. In 1905 Fiehera²¹ found that partial removal of the gland in pullets caused, not death, but a stunted growth. He could not be certain, however, that the effects were not due to cerebral injury.

Experimenters were thus divided into two camps, the one group believing that the gland was of vital importance, suspicious of an incomplete removal in case death failed to occur; the other group holding that it was not necessary to life, attributed the symptoms and death to cerebral injury and infection. This was the state of affairs in 1906 when Pauleseco²² devised the technique for the temporal route of reaching the pituitary body, a method that possesses at least two advantages, viz.: it permits the removal of the gland *de visu* and minimizes the risk of infection or traumatism. Pauleseco²³ reported that complete removal by this method was invariably fatal, but that partial removal was compatible with life if the part remaining contained some of the anterior or epithelial portion. Cushing,²⁴ in this country, has been able by the use of this method to substantiate that ablation of the anterior lobe is always fatal in adult canines, but that removal of the posterior lobe is entirely without effect. Crowe and Cushing²⁵ point out, however, that young animals survive a total hypophysectomy longer than adult ones. Crowe, Cushing, and Homans²⁶ have strengthened these results by being able to ward off death and the serious symptoms caused by total extirpation of the gland, by its transplantation into the brain substance or the red bone marrow of long bones.

Not only is the gland necessary to sustain life, but clinical men and pathologists have also added evidence which indicates its importance to normal functions, for, when the anterior lobe becomes hypertrophied or atrophied (implying increased or decreased secretion), certain developmental disturbances apparently arise which vary in degree at least with the age at which they occur. Thus, a congenital hypertrophy of the pituitary gland is frequently asso-

¹⁷ Berl. klin. Wehnschr., 1900, p. 1213.

¹⁸ Quoted by Parhon and Golstein (loc. cit.).

¹⁹ Arch. ital. de Biol., 1902, xxxviii, 177.

²⁰ Quoted by Parhon and Golstein (loc. cit.).

²¹ Report at Acad. des sciences, June, 1907; "L'Hypophyse du Cerveau." 1908.

²² Loc. cit.

²³ Proc. Amer. Physiol. Soc., Amer. Jour. Physiol., 1908, xxiii, 23.

²⁴ Jour. Amer. Med. Assoc., 1909, liii, 247.

²⁵ Quart. Jour. Exp. Physiol., 1909, ii, 359.

²⁶ Ibid.

iated with a general overdevelopment of the body (giantism), whereas an hypertrophy occurring in adult life apparently gives rise to acromegaly, a condition characterized by greatly overdeveloped extremities. Congenital hyposecretion causes infantilism, whereas later in life it is followed by a loss of sexual characteristics. These altered states of secretory activity may be induced by various causes, some but imperfectly understood. The compression of the pituitary by tumors, the effect of blood supply and nutrition and of the products elaborated by other glands of internal secretion on the pituitary are still awaiting more detailed investigation and need concern us here no further.

The following facts, then, seem established: (1) The pituitary gland is necessary to life, and any diminution or increase in its function results in metabolic or sexual disturbances; and (2) this control over the body is probably exerted through an internal secretion elaborated by the cells of the anterior lobe.

NATURE OF THE INTERNAL SECRETION. Has the internal secretion been determined? What is its nature? Is it a single substance or does the gland secrete a number of substances? Answers to these and similar questions have been sought by studying the effects of injections of its extracts on the muscular and nervous functions, on nutrition and development, on the secretion and composition of urine, on the flow of the digestive juices, and on the cardiovascular system, this latter supplying the most productive field for research.

Experimentation has shown that by water, glycerine, or salt solutions, a substance may be extracted from either fresh or dried glands which resist boiling, and, when introduced intravenously or intraperitoneally, causes polyuria, slow or accelerated pulse, accelerated respiration, dyspnea and motor disturbances, such as ataxia and paralysis of the hind legs, symptoms, it will be noted, which are also characteristic of the removal of the gland. This substance is obtained only from the posterior lobe, however. The extracts thus far obtained from the anterior lobe are apparently inert even when injected in enormous doses.²⁷ This fact seems very peculiar since it is the anterior lobe which is composed of glandular tissue and which would, therefore, be expected to furnish the physiologically active principle, and the paradox becomes still more interesting when we consider that it is this portion alone which is of vital importance.

The fact may receive several interpretations. We may imagine that the active substance is secreted by the anterior lobe in an inactive form and that it becomes activated or chemically altered in some manner as yet not understood after reaching the posterior or neuroglial portion. Schäfer²⁸ apparently leans toward such a view. This hypothesis, nevertheless, requires a brave assumption, since,

²⁷ L'Hypophyse et la Médication hypophysaire, Paris, 1909.

²⁸ Philosoph. transact. B., etc. 1.

first, no proof exists that neuroglial tissue possesses such an activating or formative power; and, secondly, there is no evidence that the anterior lobe passes its secretion into the posterior lobe—in fact, histological evidence appears opposed to it. For this reason, it seems to me, we are not justified in assuming that the substance extracted from the posterior lobe is identical either in composition or action with that of the anterior lobe. Until further evidence is forthcoming, I prefer to believe that this lobe elaborates a secretion as yet unknown, which affects nutrition and is necessary to life, and that the posterior lobe either forms an additional secretion not of vital importance, or contains chemical substances which, though not normally secreted into the blood, when extracted and introduced, affect the body functions. The reasons for my belief, summarized, are: (1) The anterior lobe alone has an influence on growth, development and life, whereas the extracted substance is found only in the posterior lobe; (2) there is no evidence of the extracted substance in the normal circulation; and (3) injections of the extract do not neutralize the symptoms arising from extirpation of the gland, but, in large doses, they produce symptoms that simulate them.

For the present, then, it seems preferable to regard *extracts of the pituitary gland* rather as drugs which exert a characteristic action on the body than as physiological secretions—drugs whose therapeutic value consists of the effects they may produce on the heart, bloodvessels, kidney, etc., rather than of any hypothetical value they may possess in supplementing a deficient function of the anterior lobes.

THE ACTIONS OF PITUITARY EXTRACTS (SOME UNSETTLED PROBLEMS). A perusal of the literature indicates that the effect of pituitary extracts, even on the circulatory system, where it has been most extensively studied, is by no means universally agreed upon. To expedite an analysis of its action, I have summarized the literature on its circulatory effects and in the discussion propose to add a number of results that I have recorded while using pituitary extract in investigating other problems (Table I).

TABLE 1.—Summary, Circulatory Effects of Pituitary Extracts.

Investigator and date.	Portion used.	Solvent or extractive.	Effect on blood pressure.	Effect on heart rate.	Effect on amplitude of beat.	Action on blood vessels.	Remarks.
Oliver, Schäfer, 1892; Howell, 1898	Entire gland Posterior lobe Posterior lobe	Water, glycerine Water, glycerine	Increased No effect Increased	No slowing No effect Slowed	Increased (Increased or decreased) Increased	Constriction Constriction	Vagotomy unaltered slowing Vagotomy prevented slowing
Livon, 1898	?	Glycerine	Increased	Slowed	Increased	Vagotomy prevented slowing
Schäfer, Vincent, 1899	Anterior lobe Posterior lobe Posterior lobe	Saline Alcohol Saline	No effect Increased on 2d or 3d Injections decreased Increased	No effect No effect or slowed No effect	Increased Increased	Constriction Constriction	Vagotomy unaltered slowing
de Clyn, 1899-1900	Entire gland (?)	Alcohol Salt solution	Increased	Slowed; periodic rhythm Slowed	Increased Increased	Constriction Dilation	Slowing not entirely prevented by atropine or vagus section
Oshague, Vincent, 1900	Posterior lobe (outer part) Posterior lobe (inner part) Anterior lobe	Alcohol Salt solution Salt solution	Increased Negative Increased	Slowed or no effect Increased	Decreased
Hamburger, 1901-1910 Silvestrini, 1903	Anterior lobe Posterior lobe	Saline, alcohol, glycerine Salt solution Salt solution	Decreased Negative Temporary increase Later, decrease	Increased	Increased Later decreased
Garnier, Thoms, 1900	Anterior lobe Cultured at anterior	Salt solution Salt solution Salt solution	Negative Negative Increase Later decreased Negative	Slowed	Increased Weaker	Vagotomy prevented slowing
Schäfer, Herring, 1900	Posterior lobe Anterior lobe	Salt solution Saline	Increased Negative	Slowed	Constriction, later dilation Constriction
Huilton, Curran, 1907	Entire gland (?)	Saline	Increased	Slowed
Schäfer, Herring, 1908	Fathedral portion posterior lobe Neuroglial portion Same	Saline Saline Alcohol Alcohol	Increased Decreased on subcutaneous injection Negative Increased	Slowed or no effect Often temporary acceleration Slowed	Increased Increased	Slowing not abolished by vagotomy
de Bonis, 1908	?	Saline	Increased	No effect
Huilton, Curran, 1909	Posterior lobe (human pituitary)	Saline	Increased	No effect

Effects on Bloodvessels and Arterial Pressure. Experimenters are commonly agreed that pituitary extracts cause a rapid and pronounced increase in blood pressure, different from that of adrenalin in its longer duration. This rise is largely due to a constriction of the arterioles, for, as shown by Oliver and Schäfer,¹⁹ Howell,²⁰ and later by Schäfer and Vincent,²¹ the size of organs such as the intestine, spleen, and limbs diminish concomitantly with the elevation of pressure. The constrictor action is chiefly peripheral, for, as Oliver and Schäfer, and also Howell, have demonstrated, it occurs after destruction of the medulla and spinal cord. Furthermore, Oliver and Schäfer found that it decreased the flow through a perfused frog. More recently, Magnus and Schäfer²² have supplied evidence that not all the peripheral vessels are affected equally, and have pointed particularly to the frequent and prompt increase in size of the kidney when the pressure rises, an effect directly opposite to that produced by adrenalin. While investigating the relative value of vasomotor drugs in renal hemorrhage,²³ I had occasion to substantiate this fact, and further, to show that the venous outflow from this organ was markedly augmented after administration of pituitary extract. These results indicate either that the rise in pressure passively overpowers the local constriction or that the drug exerts a direct dilator action on the renal vessels as well. I have a number of times perfused the drug through the kidney of a dog and when thus tested invariably caused a constriction, as shown by a decreased outflow and an increase in the height of the oscillatory perfusion pressure. The constriction induced by the extract obtained from $\frac{1}{10}$ gram of fresh infundibulum corresponded in degree to that resulting from 1 c.c. of a 1 to 100,000 solution of crystalline adrenalin. From this it differed, however, by being of *shorter duration* and unmodified, as far as I have been able to determine, by a dose of apocodein or of ergotoxin sufficient to abolish completely the action of adrenalin. Should subsequent experiments corroborate this observation, it would indicate that the drug acts directly on the muscle and not on the nerve endings in the bloodvessels, as is the case with adrenalin. In a few cases the constriction induced by pituitary extract was followed by a dilation such as I have previously reported following the constriction of chloroform. Such a dilation has not only been obtained with the commercial preparation "Pituitrin," in which the chloretone preservative might possibly be suspected of being responsible for the dilation, but with a saline extract of the fresh infundibular portion containing no preservative. It is not impossible that a larger series of perfusion experiments

¹⁹ Jour. Physiol., 1895, xviii, 277.

²⁰ Jour. Exp. Med., 1898, iii, 248.

²¹ Proc. Physiol. Soc., Jour. Physiol., 1899, xxiv; Proc. of Soc., p. xix; Jour. Physiol., 1900, xxv, 87.

²² Jour. Physiol., 1901, xxiii; Proc. Soc., 9.

²³ Arch. Int. Med., 1910, v, 348.

on various organs may show this dilation frequently to follow the preliminary constriction thus indicating that the increase in the kidney volume observed in animal experiments is not entirely a passive affair. Sollmann has also shown that pituitary extract has a slight central dilator action, for when the spleen left in contact with the central nervous system was perfused, an intravenous injection caused a slight dilation of the splenic vessels.

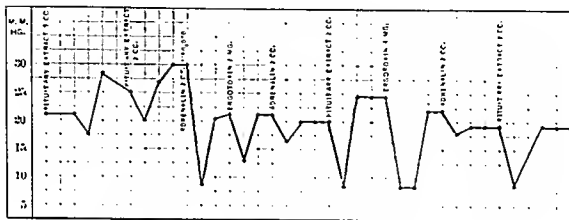


FIG. 1.—Plot showing action of pituitary extract and adrenalin when perfused before and after ergotoxin.

Action on the Heart. Most experimenters have come to the conclusion that pituitary extract slows the heart and increases the amplitude of its contractions, but the details are more or less at variance. Oliver and Schäfer³¹ in their first report observed no changes in heart rate, but Howell³² described a slowing which occurred synchronously with the main rise in pressure. Schäfer and Vincent³³ subsequently observed this slowing, but found it entirely absent in a certain number of cases. When it did occur, it was usually not coincident with the rise of pressure, but occurred after the pressure had passed the highest level. Not infrequently, too, it was preceded by a period of acceleration. Similar differences in results are also evident in the reports and curves of other investigators. In addition to a slowing, de Cyon³⁷ and Garnier and Thiaon³⁸ noted changes in the rhythm of the heart, the beats grouping themselves into periods of two or more.

The causation of the slowing is also unsettled. According to Livon,³⁹ Garnier and Thiaon,⁴⁰ and Schäfer and Vincent, it is apparently due to a stimulation of the cardio-inhibitory centre, since it is abolished by vagus section. According to Howell and de Cyon it is at least only partly due to this, for, while the cardiac action may

³¹ *Loc. cit.*

³² *Loc. cit.*

³³ *Arch. f. d. ges. Physiol.*, 1898, lxxiii, 339; 1900, lxxxi, 94.

³⁷ *Jour. de physiol. et de path. gén.*, 1906, viii, 251.

³⁸ *Jour. de physiol. et de path. gén.*, 1909, ix, 16.

³⁴ *Loc. cit.*

³⁹ *Loc. cit.*

be modified by the section of the vagi, or by injection of atropin, slowing is not prevented. They, therefore, concluded that pituitary extracts exert a direct effect on the heart as well. Support is given to this view by the fact that the same slowing occurs, as I have found, when the drug is perfused through a rabbit's heart isolated from all nerve centres. In such experiments the peculiar grouping of beats was also occasionally present.

As far as the effect of intravenous injections on heart rate is concerned, I find that my records of twenty-seven injections consist of a miscellaneous series of results corroborative of nearly every worker. The same pituitary extract (Pituitrin, P., D. & Co.) was employed in all of these cases.

TABLE II.—*Effect of Pituitary Extract on Rate and Contraction of Heart.*

Experiment.	Dose pituitrin.	Rate per 10 sec.			Amplitude in mm.			Remarks.
		Before.	During pressure rise.	1 minute after.	Before.	During pressure rise.	1 minute after.	
327	2 c.c.	21	..	17	18	18	17	
329	2 c.c.	17	..	15	11	12	9	
330	2 c.c.	18	..	15	16	16	14	
	4 c.c.	17	..	15	16	16	14	
333	2 c.c.	20	23	20	12	16	11	
335	2 c.c.	29	29	24	20	18	15	
334	2 c.c.	31	..	30	18	..	13	After hemorrhage
339	4 c.c.	31	30	21	24	26	9	Vigorous artificial respiration
341	2 c.c.	27	27	20½	10	12	11½	After hemorrhage
355	2 c.c.	18	17	18	22	20	19	
	3 c.c.	18	18	18	14	14	13	
	4 c.c.	16	17	16	14½	14½	14	
360	4 c.c.	16	15	15½	25	25	27	
361	3 c.c.	23	22	20	17	13	15½	
	3 c.c.	22	22	22	17½	18	18½	After atropine, 1 mg.
	4 c.c.	17	16	16	17	18	16½	
362	3 c.c.	18	21	14	20	21	19½	
	3 c.c.	19	20	14	20	18	16½	After previous dose of digitalis

Upon grouping these experiments, I find: (1) Cases in which no slowing follows the injection (cf. 335, 334, 333, 361); (2) cases in which an immediate slowing takes place which is usually continued (cf. 339, 355, 360, 361); and (3) cases in which the slowing is late in its onset and sometimes preceded by an acceleration (cf. 333, 362).

To explain and harmonize these results and the effects of vagus section on them, I have formulated the following tentative hypothesis, which fits in with the data so far in hand but which future work may not substantiate. *The slowing of the heart occurring synchronously with the rise in pressure is due to a stimulation of the cardio-inhibitory centre. The slowing which is late in its onset is due to a direct action on the heart.* Either, both, or neither of these

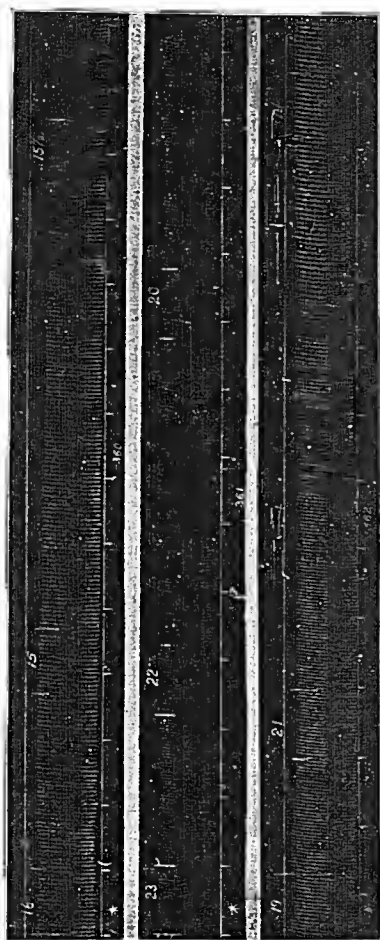


FIG. 2.—Three cardiographic tracings from different dogs, showing effect of 2 c.c. "pituitrin" injected at 4. Upper curve shows temporary increase in amplitude followed by decrease, slight left innominate slowing (vagus action?). Middle curve shows an early decrease in amplitude, systolic decrease, trans. increase. Slight early slowing (vagus action?), more than named later (direct cardiac action). Lower record shows very temporary increase in amplitude followed by a decrease. Heart rate first accelerated, later markedly slowed (direct cardiac action).

actions may follow the injection of pituitary extract, the factors determining the reaction being unknown. If both effects are present, vagus section will modify but not abolish the slowing. If the slowing is due to a vagus action alone, vagotomy will prevent the slowing, while, if late in its onset, and due to a depressing cardiac action, it will exert no influence.

It is quite generally assumed that pituitary extract increases the amplitude of contraction, an assumption which, in the majority of cases, it appears, is unfortunately based on no other evidence than the size of the oscillations of a blood pressure tracing which, of course, is no criterion of the strength of the beat. Oliver and Schäfer⁴¹ alone, so far as I have been able to discover, obtained myographic tracing of the heart. They concluded that these records showed an increase in the amplitude of contraction. Hebdorn and Cleghorn⁴² obtained, on perfusing the apex of a dog's heart with extracts of the posterior portion of the pituitary gland, only a decreased amplitude of contraction, which was the rule in my own experiments. The tracings published by Osborn and Schäfer likewise show clearly that the augmentation of ventricular contraction is rather fleeting and followed by decrease in strength. With this discrepancy in mind, I carefully analyzed my own curves of the ventricular contraction recorded by a cardiograph, and in a few instances by a cardiac plethysmograph. The results of a number of these experiments I have also incorporated in Table II. They show that in 85 per cent. of experiments a decrease in amplitude of contraction, similar to that observed in the perfusion experiments, occurred. It took place synchronously with the late slowing in both cases. I therefore believe that pituitary extracts exert a late depressing action on the strength of beat as well as the rate of the heart. In a number of experiments, 20 per cent., this depression (which I consider the characteristic cardiac action) is preceded by a brief period of strengthened beat, sometimes accompanied by a slight acceleration and occasionally by a slight slowing.

THE DISSIMILARITY OF ADRENALIN AND PITUITARY EXTRACT. Both adrenalin and pituitary extract cause a rise in blood pressure, and for that reason the statement is often made in pharmacological literature that the two substances cause similar reactions. My results indicate that such a statement is not warranted. The likeness of the two reactions ceases with the rise in blood pressure, and, as regards its other actions, no two drugs could be more dissimilar. A comparison of the reaction of the two drugs may be made from the following summary:

⁴¹ Text-book of Physiology, i, 947.

⁴² Scand. Arch. f. Physiol., 1897, viii, 163; Amer. Jour. Physiol., 1899, ii, 273.

	Adrenalin	Pituitary Extract
Blood pressure	Rapid rise Temporary	More gradual rise Prolonged
Heart rate (Vagus intact) (Vagus cut)	Slowed chiefly by vagus action Accelerated Rarely slowed	Slowed chiefly by direct depressing action Slowed Rarely accelerated
Heart strength (Intact or perfused)	Increased systole Decreased tonus Amplitude increased	Decreased systole Increased tonus Amplitude decreased
Renal vessels	Constricts only Abolished by apocodein and ergotoxin	Constriction may be fol- lowed by dilatation Not affected by either

NUMBER OF ACTIVE SUBSTANCES IN PITUITARY EXTRACT. Since the pituitary extracts affect gland, nerve, and muscle cells as well as the heart and bloodvessels, and since no single chemical substance has been isolated, as is the case with adrenalin, it is not impossible that they contain more than a single active substance. The first suggestion that pituitary extract contains more than one chemically active substance was made by Schäfer and Vincent. These investigators pointed out that, although the first injection induced a rise in blood pressure, subsequent doses are less and less effective and may even cause a fall. Hence, they concluded that pituitary extract contained a pressor and depressor substance having opposite effects on the bloodvessels; that, in the case of the first injection, the pressor substance overpowered the depressor and, as tolerance developed, the latter substance alone remained active. At first, these investigators believed that they were able to extract the depressor principle with alcohol and ether, but in his most recent publication Schäfer explains this result as due to an imperfectly absolute alcohol. The depressing principle suggests cholin as far as its action on the blood pressure is concerned, but, according to Schäfer and Vincent, this substance acts on the heart, while they apparently attribute the action of the depressing pituitary substance to a dilator action on the bloodvessels. As we seen the curves reproduced by various workers, we many times obtain a suggestion of a fall in blood pressure, especially when more than a single dose has been administered. This may be attributed to a depressor principle, but unless accompanied by cardiographic records, such curves are difficult to interpret. In some cases, where I obtained a similar diminution, this fall was clearly due to a depression of the heart by pituitary extract, and not a vasodilation. At first thought the dual action on the perfused renal vessels might seem to supply evidence of two substances—a constrictor and a dilator. Even if subsequent experiments should indicate that a large percentage of perfused kidneys give such a reaction, this assumption need not be made, for, as I have shown before, a single chemical substance like

chloroform may cause such a double action. Furthermore, the constrictor reaction of the perfused kidney does not diminish on subsequent injection, much less is it supplanted by a dilation. Hence, further evidence is demanded before we can assume the existence of two principles affecting the peripheral vessels.

A second suspicion of two substances in pituitary extract was voiced by de Cyon, who believed he had isolated a substance (hypophysine) in alcoholic and ethereal extracts which acted to slow and augment cardiac contractions, while the residue extracted with water caused no cardiac effect but constricted the bloodvessels. Schäfer and Herring, however, on repeating similar experiments could not find any active substance in alcoholic extracts, nor could they find any difference in activity between saline extracts from fresh glands and from the residue left after previous extraction with alcohol and ether. Thus, the proof of separate substances acting on the heart and on the bloodvessels does not seem clearly established.

More recently, Schäfer and Herring came to the conclusion that pituitary extract contained a substance with a specific action on the renal cells. They based their contention on the fact that, although repeated doses of pituitary lose their pressure-raising ability, they retain their ability of promoting urinary secretion. Houghton and Merrill,² however, were not able to satisfy themselves that any diuresis occurred which could not be satisfactorily explained by the blood pressure changes.

Similarly, Peimberton and Sweet³ believe that extracts of pituitary contain a substance capable of inhibiting the flow of pancreatic juice through action on the cells, but Edmunds⁴ maintains that no inhibition occurs except as it is induced by changes in the blood supply. It is evident, then, that more convincing work will be necessary before we may safely assume the existence of more than one principle in extracts of the pituitary gland.

SUMMARY. In conclusion, it may be well to recapitulate briefly the chief ideas that I have sought to bring out in this paper.

1. Developmentally and histologically, the pituitary gland is composed of an anterior or epithelial portion and posterior or neuroglial portion.
2. The anterior lobe evidently elaborates a secretion that is necessary to life and to normal metabolism and development.
3. This substance has so far resisted extraction by various solvents, hence its chemical nature and physiological properties remain unknown.
4. The posterior lobe, which is not of vital importance, contains or secretes a substance that may be extracted by water, glycerine, or

¹ Jour. Amer. Med. Assoc., 1908, II, 1849.

² Arch. Int. Med., 1908, i, 634.

³ Jour. Pharmacol. and Exp. Therapeut., Proc. of Society, 1909, i, 571.

salt solution, and resists boiling, but it has not been demonstrated that it is identical with the secretion of the anterior lobe or that it represents its vital principle.

5. These extracts constrict the peripheral vessels (probably by a direct muscular action), thus producing a marked rise of arterial blood pressure. This constriction is not equally pronounced in all organs, for the renal vessels are, at least passively, dilated during its action.

6. These extracts are generally stated to slow and strengthen the heart, but myographic tracings of the intact and perfused heart indicate a depressing influence to be the most constant and characteristic one, an increase in the amplitude being only exceptionally the case. The slowing, as well as depression, are largely attributable to a direct cardiac action, but the former may be augmented by a vagus effect.

7. Pituitary extract resembles adrenalin in its action only in that it causes a rise in blood pressure. The manner in which they affect the heart and bloodvessels, as well as the effects induced, are entirely different.

8. In addition to its cardiovascular actions, pituitary augments the secretion of urine and inhibits the flow of pancreatic juice, but it has not been definitely determined whether these varied reactions are due to separate substances, to a specific affinity of a single substance for different cells, or whether they are secondary to changes in the circulation.

STIFF AND PAINFUL SHOULDERS, WITH LOSS OF POWER IN THE UPPER EXTREMITY.¹

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Most physicians of experience have had patients with persistently stiff and painful shoulders and weakness of the arm, usually following some trauma to the shoulder, but sometimes without any history of such a cause, and they have been at a loss how to account for or to treat them. The complaints of the patients vary somewhat, but they are sufficiently similar to warrant the suspicion, at least, that most of them are due to a common cause, although some cases deviate from the usual type enough to raise the question of a common origin and to make the solution of the problem

¹ Read at a meeting of the Northwestern Medical Society of Philadelphia, September 5 1910.