THE PITUITARY GLAND AND THE MAINTENANCE OF BLOOD PRESSURE*

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The possible rôle of the pituitary gland in the maintenance of normal physiological activity of the cardiovascular system has often been discussed. Since the time of Marie[13], when acromegaly was identified as a distinct clinical entity, the accompanying changes in the cardiovascular system have been an object of special interest. The investigators[9, 10] of the later nineteenth century demonstrated anatomical changes in the heart and peripheral vessels, but they were hampered by the lack of instruments with which to measure the arterial tension. Since then numerous clinical observations have been made of the blood-pressure changes that accompany acromegaly and other disturbances of the pituitary gland. Patients with chromophobe adenomas of the pituitary, which lesion ordinarily destroys the gland without compressing the adjacent brain, have a relatively low systolic pressure (below 100 in 11 per cent, and below 110 in 46 per cent of 200 cases; 2 had hypertension[6]). Patients with craniopharyngiomas which serve to compress the base of the brain as well as the stalk of the pituitary have an even lower pressure. Even "in adults a systolic pressure of 90 is common and the registration of 85/60 in a patient of 21, and 60/50 in a patient of 23, and of 80/60 in a patient of 30 occur in the hospital series"[6]. Cases with eosinophilic tumors, presenting the clinical picture of acromegaly, have a blood-pressure below 120 in 30 per cent[8] of the cases. The incidence of hypertension in acromegaly is still an unknown quantity. Patients with basophilic adenomas of the pituitary present, as an invariable symptom, hypertension ranging between 180 to 250 systolic and 110 to 180 diastolic. Thus, the blood-pressure in pituitary disease varies from a frank hypotension to a severe grade of hypertension, depending on whether the pituitary gland is hypoactive, due to the presence of a destructive tumor, or hyperactive as the result of the oversecretion of an active adenoma.

In seeking an explanation of the above facts, laboratory workers have demonstrated the presence of a pressor principle in the posterior lobe of the pituitary. Here, however, we are confronted with an inconsistency: for pituitary tumors involve the anterior lobe

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while the pressor principle is confined to the posterior lobe. In order to cast more light on this problem experiments were performed in which posterior lobe extracts were introduced directly into the third ventricle and the blood-pressure changes noted. There is some evidence that posterior lobe extracts administered in this manner may directly affect the diencephalic nuclei via the spinal fluid[6]. The results are of a preliminary nature, so that it seems justifiable to review briefly the clinical and the pharmacological evidence that forms the background for the present conception of this problem.

A Review of the Clinical Literature

Eosinophilic tumors of the pituitary. In acromegaly, symptoms referable to functional disturbances in the cardiovascular system are the rule. Palpitation, dyspnea, arrhythmias, syncope, cyanosis, cardiac enlargement, atherosclerosis and cardiac failure are common manifestations[8]. The blood-pressure may or may not be changed. In a hospital series of 100 cases, Davidoff[8] noted that the pressure was below 120 in 30 per cent. Very low pressures have been recorded[2, 12]. In such a series as that reported by Davidoff, one might well expect to find low blood-pressures, since patients are hospitalized only after a number of years of their disease have passed. In many cases pituitary insufficiency had probably intervened. Hypertension has also been noted, but there is no statistical survey of its incidence. Alessandri[1] reported a case with a pressure of 250 mm. Phillips[17] studied a case with a pressure of 170 mm., while Packard's[15] patient had a pressure of 185 mm. Payenneville and Cailliau[16] reported a patient with a pressure of 168 mm.; Yater[18] a case with a pressure of 182/115; Cushing and Davidoff[7] two cases with pressures of 190/130 and 170/130; Ironside[11] one with a pressure of 220/165; and Claude[4] and Claude and Boudouin[5] reported two more cases with pressures of 280 and 240 mm. In those reported by Cushing and Davidoff[7], Ironside[11], Yater[18], Claude[4], and Claude and Boudouin[5] an enlargement of the thyroid was also present. In the case studied by Claude during life[4] and after death[5] a hyperplasia of the adrenal cortex and medulla was found. This tends to indicate that the hypertension present was probably the result of a secondary hyperactivity of the adrenal gland.

The single record of a high or a low blood-pressure does not,

however, indicate the true state of affairs in regard to cardiovascular function. Only continuous observation over a period of years can elicit the answer to this, as to many of the problems that confront the endocrinologist. The following case taken from the records of the New Haven Hospital[14] illustrates the paroxysmal character of the hypertension that may be present.

F.B., male, aged 49 years, was admitted to the hospital with the symptoms of diabetes mellitus. His pressure was recorded as 158/110 and 152/96. On examination he was found to present the characteristic features of acromegaly. His diabetic symptoms were controlled and he was discharged one month later. He remained sugar-free without insulin for the next 2½ years. Two and one-quarter years after his hospital admission he was again seen following three attacks that suggested coronary occlusion; at this time his pressure was 170/110. In the intervals between the two attacks of hypertension his pressure remained quite constantly at 140/80-90.

Thus, either a high or a low blood-pressure may be found in acromegaly, depending in part on the stage of the disease during which the pressure is taken.

Basophilic adenomas of the pituitary. While the pressure in cases of chromophobe adenoma is usually low, and the pressure in cases of eosinophilic adenoma either low or high, the pressure in cases of basophilic adenoma is strikingly high and constantly present. A hypertension existed in the 13 of the 16 cases reported by Cushing[6] in which the pressures are recorded, as well as in an additional case studied by Bishop and Close[3].

The blood-pressures are tabulated below.

No.	*Case*	*Sex*	*Age*	*Systolic*	*Diastolic blood-pressure*
1	1	F	23	180	110
2	2	F	20	185–200	——
3	3	F	23	185	——
4	5	F	12	190	130
5	6	F	28	205–230	——
6	8	M	19	198	110
7	11	M	30	178	100
8	12	M	24	190	170
9	13	F	36	175–185	110–120
10	14	F	44	190–230	——
11	15	F	15	140	110
12	16	F	12	130–150	80–95
13	B & C	F	22	250	180
			23.7	188.5	126.6 average

The above figures are quite remarkable. They leave little room for doubt concerning the potentialities of the pituitary gland to influence the blood-pressure level. The blood-pressure is uniformly high in all the cases in which it is recorded, falling below 175 mm. systolic in only two cases (11 and 12). The diastolic pressure is quite as much elevated, averaging 126 and falling below 110 in only cases 7 and 12. Case 12, however, is a female of only 12 years of age. The blood-pressures are even more remarkable in the light of the average age of the patients when seen, namely, 23.7 years. The oldest patient is a female of 44; her blood-pressure 190-230 systolic. The highest pressure is recorded in the case of Bishop and Close at 250 systolic and 180 diastolic.

Case 1 and case 11 are of unusual interest in that the blood-pressure level fell; in case 1 the pressure gradually declined from about 180/140 to "normal" over a period of 19 years; in case 11 the pressure fell from about 178/100 to 134/86 following radiation of the pituitary, either post hoc or propter hoc.

In six of Cushing's cases the adenoma was found at post-mortem examination (cases 3, 6, 7, 10, 13, 14). The tumor was also discovered in the case of Bishop and Close. The tumor was located in the anterior lobe in all the cases, and no invasion of the posterior lobe by basophilic cells was noted except in case 10 where the tumor almost completely replaced the posterior lobe. No blood-pressure is given, unfortunately. The tumor is usually minute and sharply deliminated from the rest of the pituitary body. In case 6 the tumor measured 3 by 4.5 mm., in case 7 it was 2.5 mm. in diameter; in case 13 it was "minute"; and in case 14, 2 mm. in diameter. On X-ray there was some slight evidence of an intrasellar growth in cases 1, 5, 10, and 11 as revealed in the faintness of the posterior clinoids and in a suggestive enlargement of the sella; but certainly not sufficient to indicate any degree of increase in the intrasellar pressure. Hence, we can rule out of consideration indirect pressure upon other cellular elements of the pituitary as the cause of the hypertension. In the light of the pharmacological evidence to be presented later, that the posterior lobe extracts are the only component parts of the pituitary to elevate blood-pressure in the experimental animal, attention must be drawn to the fact that we are dealing here with a very small adenoma of anterior lobe basophilic cells having no demonstrable anatomic connection with the posterior lobe.

Previous Experimental Studies

Extracts of the posterior lobe. The first demonstration of a pressor substance in the pituitary was made by Oliver and Schafer in 1895[53]. Three years later Howell[44] defined this principle as belonging to the posterior lobe. In the following 15 years many investigators dealt with this problem and proved beyond doubt that the posterior lobe contained some substance, on extraction, which caused a prolonged rise in pressure in the anesthetized laboratory animal. Halliburton, Candler and Sikes, in 1909[36], showed that this was also true for the human pituitary. The injection of similarly extracted anterior lobes was without effect on the pressure[29, 40, 41, 44, 54, 60, 62]. Hamburger[37], however, felt that the anterior lobe did contain a small amount of pressor substance. Howell and others[59, 60] also pointed out that the response to successive injections is less and less until it disappears entirely. This "inhibitive" effect persists for about 1½ hours[42]. Abel and his coworkers, using unaltered extracts[19], an extract purified by precipitation with mercuric chloride[20], and a highly purified tartrate[21] found that, although the response to a single dose was a rise in pressure, the response to a second or successive dose might actually be a fall. This "inversion" effect had been noted by earlier workers but was attributed to contaminating substances. The persistence of the effect with the purified extracts led Abel to believe that it was an intrinsic part of the hormone. Geiling and Campbell[30] arrived at a similar conclusion. Hogben and Schlapp[42], Schlapp[61], Vincent and Curtiss[65], and Stehle[63], were unable to demonstrate the inversion effect. Gaddum[28] felt that the high titer of oxytocic principle in Abel's extracts accounted for the fall in pressure, since he could demonstrate such a fall in the cat and fowl.

The response in unanesthetized animals. The response to pituitary extracts in the unanesthetized animal differs in certain respects from that in anesthetized animals. The administration of pituitrin to trained dogs produces a fall in the systolic and a rise in the diastolic pressure[46]. A sharp precipitous fall in pressure may be induced by a single dose[33]. The type of response appears to depend on the size of the dose administered[34, 56]. With small doses a pure pressor response may be induced, while, with larger doses a combined pressor-depressor response results, the curve taking a sharp precipitous drop and then rising above the baseline for a considerable

period. However, there is no essential difference between the types of response in unanesthetized dogs and anesthetized animals (more frequently the cat has been used). Raginsky, Ross and Stehle[56] noted that ether and luminal have a tendency to augment the depressor response; chloretone has no such effect.

The action on the heart. It was appreciated, very early in the course of the work with pituitary extracts, that a slowing of the artificially perfused heart[24, 38, 39, 50] and a decrease in the cardiac output[24] results from the addition of extract to the perfusate. Tigerstedt and Airila[64], in 1913, were the first to demonstrate the reduced cardiac output in the intact animal. This they accomplished by introducing a stromuhr into the aorta of their rabbits. Constriction of isolated strips of coronary arteries was also demonstrated[23, 24, 26, 50, 55]. Similarly, the cardiac output and rate is decreased in the unanesthetized dog[46]. A consideration of the EKG[31, 57] led Geiling to the conclusion that pituitary extracts acted directly on the heart muscle as well as on the vagus. He calls attention to the similarity of the action of the extracts and of anoxemia. Gunn[35] noted that the coronary output of the artificially perfused heart decreased 30 per cent on the administration of extract diluted 1:400. Ross, Dreyer and Stehle[58], working with the Starling heart-lung preparation, found that the coronary output of the cat's heart decreased markedly with the addition of extract to the perfusion fluid. The coronary blood flow diminished, depending on the dose given, from a normal value of 80-150 cc/min. to as low as 0-20 cc/min.; a decrease of from 75 to 100 per cent. The cardiac output follows the coronary output by a small fraction of time and decreases proportionately. Melville and Stehle[51] added a bit more evidence of a similar nature. They noted that the total response to pituitrin plus adrenalin (or ephedrin), the latter drug given with or just previous to the pituitrin, is greater than the sum of the responses of both when given singly. They also found this effect was not present in a cat with an artificial heart and intact peripheral circulation, but was present in a heart-lung preparation. The authors[32, 51] believe that the cardiac inhibition resulting from the pituitary extracts explains the depressor responses that are obtained in the intact animal. The interesting curve obtained in our unanesthetized dog bears out this theory. The pressure resulting from the intracardiac administration of 20 units of pitressin alternated sharply between rises and falls. Each change in pressure

followed a marked alteration in the pulse rate; when the rate fell the pressure fell and vice versa.

Intraventricular pituitrin. In contrast to the voluminous literature on the effects of pituitary extracts injected peripherally are the few observations dealing with the responses to intraventricularly injected pituitrin. In light of the knowledge of the hypophyseodiencephalic relationships it is somewhat surprising that the stimulus comes from the clinic rather than the laboratory.

In a series of recent papers, Cushing[6] studied the effects of injecting pituitrin "S" into the lateral ventricles of human subjects. In the first case he reports that the injection of 1 cc. of pituitrin was followed by a slight temporary fall in pressure from 130 mm. to 110 mm. at the end of 12 minutes and then by a rise in pressure to 140 mm. The pulse slowed from 80 to 60 beats per minute. In three other patients the pressure also rose; in one, from 124/76 to 150/90; in another from 110/60 to 130/80; in the third the pressure is not given. These cases had intact diencephalons although operated upon for one type or another of cerebral neoplasm. They all presented the usual response to intraventricular pituitrin, intense flushing, profuse salivation and perspiration, retching and sometimes vomiting, and a marked fall in the basal and in the body temperature. In one case, a woman with a tumor of the third ventricle, there were no metabolic responses to the pituitrin, but the pressure rose from 110/65 to 140/85. In two cases with destructive lesions of the diencephalon due to metastatic tumor and to hydrocephalus there was no change in the pressure upon intraventricular pituitrin.

In the above seven cases, five responded with a rise in pressure while two did not. These latter had destructive lesions of the diencephalon. Of peculiar interest is the fact that Cushing was able to inhibit completely the responses to intraventricular pituitrin by the simultaneous administration of atropin either into the ventricular system or into the systemic circulation. Were it not for this the elevation in pressure that occurs may very well be the result of the absorption of the drug into the peripheral circulation. Grollman[32] and Geiling injected pitressin intramuscularly into patients in 0.4 to 0.8 cc. doses, half those used by Cushing, and found that the pressure rose within a few minutes and remained elevated for several hours. The increases were of the same order as those following intraventricular injection. In one case where whole pituitrin was used a fall occurred instead of a rise.

Light and Bysshe[49] investigated this problem in the monkey (*Cercocebus aethiops*). They found that the introduction of 1 cc. of pituitrin "S" into the lateral ventricle produced a slowing of the pulse of from 30 to 50 beats; the slowing beginning at 3 to 5 minutes and reaching a maximum in 15 minutes. The pressure fell 15 to 30 mm. This response is exactly that obtained with a similar dose administered under the skin. On the other hand, vasodilatation began after a latent period of only 45 seconds. They also used extracts derived from pituitary powder and from material furnished by Parke, Davis and Company, with similar results. The effect on the vascular system varied only with a change in the pressor content of the extracts used.

The following experiments were performed on anesthetized cats and on one unanesthetized dog. The pitressin was injected directly into the third ventricle after the performance of a craniotomy. In this manner the drug is applied directly to the third ventricle without the possibility of peripheral effects due to the absorption of the drug into the systemic circulation. In the experiment performed on the unanesthetized dog, the pitressin was injected into the lateral ventricle through a burr hole in the skull, made at a previous operation.

The Present Experiments

Method. Cats under anesthesia were used in seven experiments performed. The last experiment was performed on a dog under no anesthesia. In experiments 1, 2, 3, and 4 intraperitoneal chloralose, 1 per cent, in doses of 10 cc. per kilo body weight, was used as the anesthetic. In experiments 5, 6, and 7 ether anesthesia was employed. In these cases the animals were anesthetized by being put in a crock filled with ether fumes; this permits a slow but certain method of anesthetizing the animal. In the cases where chloralose was used, the animal was permitted to walk about while the intraperitoneal injection was made. The cat is usually unaware of the procedure. The following procedures were then adopted and carried out consistently on all the cats. The cat, after being completely anesthetized, is placed on its back on the table and a midline incision is made in the neck. The trachea is then cannulated and the right carotid artery is exposed and ligated. The animal is then turned over on its abdomen and the head clamped to an

upright. A craniotomy is then performed exposing the right hemisphere, but the dura is left intact. The wound is temporarily closed; the animal placed on its left side and the right carotid artery cannulated and connected to a mercury manometer for the recording of the blood-pressure. The dura is now incised and turned back to the midline. Light traction on the right hemisphere exposes the corpus callosum through which a needle may be passed with ease into the third ventricle. The cats as a rule withstand the procedure well; but in an occasional case the blood-pressure falls to shock levels—these cats are discarded.

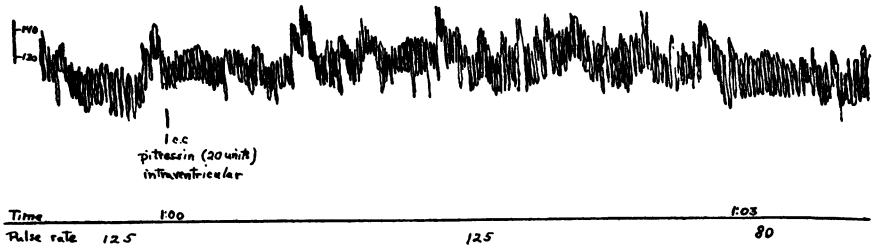
The procedure in experiment 8 on the dog differed from that followed in the case of the cats. A preliminary operation was performed some weeks before the actual experiment, at which time a burr hole was made in the skull over the left occipital region and the left carotid artery was sutured over the sternomastoid muscle just under the skin. The dog received very little training previous to the experiment, but he was a docile animal and did not object strenuously to the manipulations. At the time of the experiment the left carotid artery was exposed under local anesthesia and connected to the usual mercury manometer, the system containing sodium citrate 5 per cent.

In the first 7 experiments on the cats pitressin (10 pressor units/cc.), and pituitrin (10 pressor units/cc.) were used. In experiment 8, pitressin of 20 pressor units/cc. strength was employed as well. The extracts contained 0.5 per cent chloretone as preservative. In experiments 6 and 7 the chloretone was boiled off in order to eliminate this factor, the strength of the extract being checked by intravenous injection subsequently on the same animals.

At the end of each experiment the animal was subjected to post-mortem examination and the brain subjected to gross inspection in order to determine the position of the needle and the presence or absence of trauma to the walls of the third ventricle. In experiment 6 methylene blue was injected through the needle used and was found staining the walls of the third and the fourth ventricles. There was no trauma found on gross examination of the third ventricle except in experiment 7 where the needle had penetrated the base of the brain and caused hemorrhage which had filled the cavity of the third ventricle. We are well aware that gross examination is not entirely satisfactory in determining damage to the brain tissue. In experiment 8 the brain of the dog was carefully removed and the

puncture wounds of the cortex traced into the brain substance. We were unable, however, to determine accurately where the needle had entered into the ventricular system. But, since the needle had evidently entered the brain tissue, and we were able to secure spinal fluid, we feel reasonably sure that the needle was in some part of the ventricular system. A small amount of carmine was injected through the needle about 10 minutes before death. It was not detected at necropsy even on serial section of the brain; evidently it had been diluted and diffused throughout the spinal fluid.

Results. The injection of pitressin into the third ventricle of cats under anesthesia (experiments 1-7) and into the lateral ventricle of the unanesthetized dog (experiment 8) was without appre-



ciable immediate effect on the blood-pressure or pulse rate. Two exceptions were found, experiments 1 and 7, which will be discussed later.

Discussion

The most consistent feature of the experiments is the absence of an immediate response to the intraventricular pitressin. In 11 injections in 5 of the 7 experiments performed on the anesthetized cats and in the experiment on the unanesthetized dog, there was no response to the drug. In experiment 1 the injection of 0.3 cc. of pitressin caused a fall in pressure of 32 mm. which persisted for a period of 6 minutes. Evidence of injury to the brain was not found on gross examination, but there appears no other way to account for this unusual result. In experiment 7, the injection of 0.1 cc. of pituitrin (chloretone-free) occasioned a rise of 16 mm. Here, however, there was gross evidence of damage to the base of the brain for the needle had penetrated the floor of the third ven-

tricle and the circle of Willis producing hemorrhage into the third ventricle.

In the first 7 experiments the problem arose as to the possibility of the anesthetic depressing the diencephalon and preventing any response. The ether and chloralose used are known with a fair degree of certainty not to depress the basal nuclei. What is more significant is that, in these experiments, the diencephalon reacted to mechanical stimulation of the needle on the ventricle. In experiment 1 (with chloralose) the introduction of the needle caused a rise in pressure of 8 mm., in experiment 3 (chloralose) movement of the needle caused a fall in pressure of 24, 20, and 20 mm. respectively, in experiment 4 (chloralose) movement of the needle produced a fall in the pressure of 10 mm., and in experiment 5 (ether) moving the needle caused a rise of 24 mm. Thus, mechanical stimulation of the walls of the third ventricle may cause either a rise or a fall in pressure depending, no doubt, on the portion of the wall touched by the needle. The anesthetic, moreover, has no relation to the character of the response. The final proof, however, resides in experiment 8 where no anesthetic was used.

This experiment differs in several respects from the previous ones, namely, in the absence of anesthesia and in that the cerebral spinal-fluid circulation was intact, permitting absorption into the systemic circulation of the drugs introduced into the cerebral ventricles. The injection of 20 units of pitressin into the ventricle of the dog gave no immediate response; there was no flushing reaction detectable, no change in blood-pressure or in pulse rate. Five minutes after the injection the pulse rate slowed from 125 beats/minute to 80 beats/minute; the blood-pressure did not undergo any alteration. Twenty minutes later, when the pulse had risen to 100 beats/minute, 20 units of pitressin were again injected with a similar negative response except for a slowing of the pulse after a period of about five minutes. A subcutaneous injection of 20 units yielded no appreciable reaction, no doubt due to the inhibitory effect of the previous two doses. The same dose was then injected into the heart. The pressure rose immediately about 40 mm., then began to oscillate sharply between this level and the normal level. The pulse alternated between 56 beats/minute and 120-150 beats/minute, preceding the changes in pressure. This experiment illustrated the dependence of the blood-pressure on the events taking place in the heart.

In experiments 1, 2, and 6 pitressin in doses of 0.1 to 0.3 cc. was injected into the central end of the unligated carotid, hoping in this way to bring the drug into direct contact with the diencephalic nuclei via the blood stream. It is sufficient to say that in no case could any significant difference be detected between the response to the drug given in this way and the response to intravenous injection.

The above results, especially those obtained with the unanesthetized dog, are similar to those of Light and Bysshe. They noted that the blood-pressure and pulse rate in their monkeys began to fall 3 to 5 minutes after intraventricular injection, reaching its height in 10 to 15 minutes. The flushing reaction occurred immediately. In our dog there was no flushing reaction or sweating of the foot pads detectable. However, this is difficult to recognize in dogs, as shown by Lawrence and Dial[47].

Summary and Conclusions

1. In six experiments performed on 5 cats under anesthesia and on one dog under no anesthesia, there was no change in the blood-pressure following intraventricular injection of varying doses of pitressin.

2. In one experiment there was a fall of 32 mm., and in another a rise of 16 mm. The latter case was possibly due to trauma of the base of the brain; the former was not.

3. Review of the clinical literature strongly suggests the intervention of the anterior lobe in the regulation of blood-pressure.

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