diately beneath the pituitary body. Through this opening, two needle-like, perfectly insulated electrodes could easily be introduced. The variations of blood-pressure—the kymograph being connected with the carotid—and pulse-rate are clearly shown in the tables reproduced below. They indicate the comparative effects of excitation of the tissues around the opening, of the pituitary proper, and of the same organ after section of both vagi.

Exp. I.—Young Dog; Weight, 3.30 Kilog.	Blood-pressure.
Prior to excitation	63 mm. Hg.
Excitation of neighboring structures	63
After	63
Excitation of neighboring structures	63
After	63
Excitation of pituitary body	108
Immediately after	63
60 seconds after	63

Exp. V.—Dog; Weight, 2.6 Kilog.	
Prior to excitation	81 mm. Hg.
1st excitation of pituitary body	144
Immediately after	90
2d excitation of pituitary body,	
15 seconds	200
30 seconds	190
2 minutes	170
Immediately after	90

Exp. IX.—Dog; Weight, 5 Kilog.	
Both vagi cut.	
Prior to excitation	162 mm. Hg.
Excitation of pituitary body,	
first 15 seconds	280
second 15 seconds	270
Immediately after	225
1 minute later	156
2d excitation of pituitary body	252
" " " " " (close)	214
Immediately after	144
1 minute later	154

These striking effects speak for themselves. The blood-pressure was raised instantly, precisely as when the lower segment of the transected spinal cord is stimulated, in accord with Cyon's observation. Misled, however, by the prevailing view that the posterior lobe is a vestigial organ and the belief that the anterior lobe is a secreting gland, Masay attributed tentatively these effects to this "secretion." Not only, as I will show, is neither lobe of the pituitary a secretory organ, but it is evi-

dent that the rise of pressure throughout the whole organism could not have been produced instantaneously with the distribution of such a secretion as a preliminary feature of the process. As we will see presently, in fact, he produced similar effects by stimulating the medulla oblongata, with which, in the light of the facts submitted in the preceding section, the pituitary body is connected by nerve-paths.

This direct connection between the pituitary body and the bulbar centers accounts—in the light of my views—for an observation made by Masay, viz., that "during excitation [of the pituitary] the power of the heart beats is *diminished,* while immediately after, it increases very greatly and becomes greater than normal." We have here, in my opinion as previously stated, an example of *inhibition,* a *morbid process* due to excessive vasomotor contraction of the coronaries, as shown by the following evidence.

Brown-Séquard over fifty years ago[70] observed that stimulation of the lower end of the cut vagus, in the neck, caused *contraction* of the coronaries—a fact which led him to conclude that the vagus was the vasomotor nerve of the heart. In 1895, W. T. Porter[71] concluded that the vagus contained vasoconstrictors, a current of defibrinated blood passed at a constant pressure through the coronaries of an isolated heart being materially reduced in volume by excitation of this nerve. Maas[72] confirmed Porter's results. Heymans and Demoor[73] then found histologically that the muscular coat of the coronaries contained a rich network of vasomotor fibers. My own study of the subject showed that the cardio-inhibitory impulses transmitted to these vessels by the vasoconstrictor fibers *in* the vagus were derived from the *vasomotor center.*

A phenomenon, the mechanism of which had never been explained, *i.e.,* cardiac inhibition, thus readily accounts for the diminished cardiac action noted by Masay on stimulating the pituitary body. He produced an effect identical to that obtained by the brothers Weber[74] when, in 1846, they passed a current

[70] Brown-Séquard: "Experimental Researches Applied to Physiology and Pathology." New York, London, Paris, 1853.
[71] W. T. Porter: Boston Med. and Surg. Jour., Jan. 9, 1895.
[72] Maas: Pflüger's Archiv, Bd. lxxiv, Hft. 7 u. 8, S. 281, 1899.
[73] Heymans and Demoor: Mémoires de l'Acad. roy. de méd. de Belgique, T. xiii, 5me Fasc., 1895.
[74] Weber Brothers: "Handworterbuch d. Physiologie," Bd. ii, S. 42, 1846.

from the intranasal surfaces to the spinal cord, viz., he inhibited its action by reducing the caliber of the coronaries and reducing the quantity of blood supplied to the heart-walls.

The inhibitory effect of excessive constriction of the coronaries has been demonstrated by several investigators. Chirac[75] found that the beats of a dog's heart were soon arrested when one of the coronaries was tied. Erichsen[76] observed a similar result after tying these vessels. Leonard Hill,[77] referring to the investigations of Cohnheim and Schulthess-Rechberg,[78] McWilliam,[79] Bettelheim,[80] and others, also states that "ligaturing one of the largest branches only is frequently sufficient to cause arrest." Again, Sée, Bochefontaine and Roussy[81] observed that substances capable of plugging the coronaries—lycopodium spores, for instance—also caused cardiac arrest. Porter[82] plugged the left coronary artery in nineteen dogs and says that "the closure of the artery was always promptly followed by arrest." As the result of closure by ligation in sixty-seven dogs, he reached the deduction that "the frequency of arrest is in proportion to the size of the artery ligated." As cardio-inhibitory impulses transmitted through the vasoconstrictors of both vagal trunks probably influence *all* the coronary vessels simultaneously, the ease with which the heart's action can be arrested by exciting the bulbar center is easily accounted for. Finally, Kolster,[83] Porter,[84] and others have shown experimentally that the part of the heart supplied by an infarcted coronary artery degenerates.

Yet, if the vasomotor impulses inhibit the heart by causing excessive constriction of the coronaries, the effects on the heart wall should coincide with those resulting from deprivation of blood. Such is undoubtedly the case: E. Weber[85] observed that during partial inhibition the cardiac contractions were weakened, while Schiff[86] found that the muscular elements of

[75] Chirac: "De Motu Cordis," p. 121, 1698.
[76] Erichsen: London Hospital Gazette, vol. ii, p. 561, 1842.
[77] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 1, 1900.
[78] Cohnheim and Schulthess-Rechberg: Virchow's Archiv, Bd. lxxxv, Hft, 3, S. 503, 1881.
[79] McWilliam: Jour. of Physiol., Vol. viii., p. 296, 1887.
[80] Bettelheim: Zeitsch. f. klin. Med., Bd. xx, S. 436, 1892.
[81] Sée, Bochefontaine and Roussy: C. r. de l'Acad. des sci., T. xcii, p. 86, 1881.
[82] Porter: Jour. of Exper. Med., vol i, p. 46, 1896.
[83] Kolster: Skandinav. Archiv f. Physiol., Bd. iv, S. 1, 1893.
[84] Porter: Pflüger's Archiv, Bd. iv, S. 366, 1893.
[85] E. Weber: *Loc. cit.*
[86] Schiff: Archiv f. physiol. Heilk., 9ter Jahrgang, S. 22, 1850-51.

the entire organ responded less or not at all to stimuli. François-Frank, Fischel,[87] and others observed that the cardiac walls were softer than usual. Foster[88] states that when the interrupted current is used to stimulate the vagal trunk, the heart remains in diastole, motionless and flaccid. When, however, the current is weak, the beats are only slowed and weakened. Coats[89] ascertained manometrically that the contractions were markedly reduced in force. Gaskell[90] and Stefani[91] found that the ventricular tonicity was reduced. Muskens[92] also found that stimulation of the vagus lessened the force of the contraction in the frog.

Gaskell[93] characterizes as "most striking" the attending *depression of activity*. Still, there is no loss of inherent muscular irritability, since, according to Foster,[94] a pin prick in the heart during inhibition may cause a beat; the morbid phenomena are, therefore, the result of a deficient supply of the nutrient components of the blood. Porter[95] states that "but little is known as to the constituents of the blood which are essential to the life of the mammalian heart," and that "an abundant supply of oxygen is certainly highly important." The manner in which the deficiency of these blood constituents causes the inhibitory effects is suggested in the following lines of Langley's:[96] "The decrease of rigidity in the inhibited muscular tissue shows that inhibition is not caused by the development of a contractile force, acting in a direction opposed to the normal one and overpowering it. We are then brought to the conclusion that certain nerve impulses—the inhibitory nerve impulses—are able to *lessen* or to *stop* the chemical change *in the tissue* which leads to contraction."

It is evident, therefore, that even the diminution of the heart-beats which Masay observed *during* excitation is likewise due to vasomotor constriction.

Any doubt that may remain as to the influence of stimula-

[87] Fischel: Archiv f. exp. Path. u. Pharm., Bd. xxxviii, Hft. 3 u. 4, S. 228, 1897.
[88] Foster: "T. B. of Physiol.," sixth Amer. edition, Phila., 1895.
[89] Coats: Bericht d. k. Sachs. Gesellsch. d. Wissensch., S. 360, 1869.
[90] Gaskell: Philosoph. Trans., p. 1019, 1882.
[91] Stefani: Archives ital. de biol., T. xxiii, p. 172, 1895.
[92] Muskens: Pflüger's Archiv, Bd. lxvi, Hft. 5 u. 6, S. 328, 1897.
[93] Gaskell: Schäfer's "T. B. of Physiol.," vol. ii, p. 169, 1900.
[94] Foster: "T. B. of Physiol.," sixth Amer. edition, 1895.
[95] Porter: "Amer. T. B. of Physiol.," vol. i, second edition, p. 148, 1900.
[96] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 674, 1900.

tion of the pituitary body on the vascular system is removed by the fact that all of Masay's experiments indicate (1) that the rise of the blood-pressure and pulse occurred concurrently and fluctuated with the mechanical or electrical excitations of the exposed pituitary, and (2) that the recession of pressure, *i.e.*, the resumption by the arteries of their former caliber, occurred immediately after each excitation ceased. The following table illustrates forcibly the suddenness of the fluctuations under the influence of excitation:

Exp. IV.—Dog; Weight, 3.8 Kilog.	Blood-pressure.
Prior to excitation	81 mm. Hg.
Mechanical excitation of pituitary	98
Immediately after	36
Electrical excitation	100
Immediately after	72
Electrical excitation	100
Immediately after	72
Electrical excitation	100
Immediately after	81

This sudden elevation of pressure whenever the organ was stimulated occurred repeatedly until a clot prevented further work. An additional feature of these results is that the animal had been given morphine and curare, so that the rise in pressure represents an excess over that already caused by these drugs. Were it not for this, the difference between the pressure before and during excitation would have been much greater.

Still, if Masay actually inhibited the heart when he observed that excitation of the pituitary diminished cardiac power, and the brothers Weber produced the same effect by passing a current from the nasal mucous membrane posteriorly, removal of the pituitary body should prevent the phenomena caused by nasal excitation. Cyon[97] found that the inhibitory slowing of the heart obtained by stimulating the nasal mucous membrane and the reflex phenomena caused by the same procedure could no longer be obtained immediately after extirpation of the pituitary body. Even the most active stimulants, ammonia, for instance, applied directly to the nasal mucous membrane, failed to elicit the least response. "The beneficial influence of reflex action on the heart obtained by stimulating the nasal mucous membrane in *syncope,*" says this physiologist, "must react,

[97] Cyon: Archiv f. d. ges. Physiol., Bd. lxxi, S. 431; and Bd. lxxii, S. 635, 1898.

therefore, indirectly upon the cardiac nerves through the intermediary of the pituitary body"[98]—a true statement when, in the light of my views, the reflex effect is ascribed to constriction of the cardiac arteries, which are dilated (their muscular layer as well as the skeletal muscles being relaxed) during syncope.

This beneficial action of reflex contraction of the coronaries exemplifies clearly how the heart may be inhibited. In syncope the dilated vessels are restored to their normal caliber; in inhibition, excitation decreases their caliber until the streams of blood supplied to the heart are totally inadequate to sustain the functional activity of the organ. *Experimental inhibition,* therefore, *is an artificial process and does not, as physiologists teach, exemplify a normal function.*

All this has served further to show, not only that the coronaries are supplied with vasomotor nerves, but also that the pituitary body is *a* vasomotor center. Indeed, the latter feature, and the fact that, as believed by Masay, it is not a problematical secretion which causes the rise of blood-pressure, are placed on a solid basis by the experimental demonstration that stimulation of the pituitary body and of the bulbar vasomotor center produce similar effects. This is brought out in two of Masay's tables. The conditions presented here are such as to insure as much as possible correspondence in the strength of current used, the duration of stimulation, etc.

Exp. V.—Dog; Weight, 2.6 Kilog.	Blood-pressure.
Prior to excitation	81 mm. Hg.
1st excit. of pituitary body	144
2d " " " " first 15 seconds	200
2d " " " " after 30 "	190

Exp. II.—Dog; Weight. 5.5 Kilog.	
Prior to excitation	90
1st excit. of bulb	136
1st " " " after 30 seconds	154
2d " " " " " "	126

The needle-electrodes were merely thrust into the medulla oblongata from the front, instead of into the pituitary. The recession of the blood-pressure after stimulation was immediate in both instances, thus showing that the region stimulated in the bulb was *a* vasomotor center.

[98] Richet's "Diction. de physiol.," vol. iv, p. 131, 1900.

All this evidence emphasizes another fact, viz., that among the paths from the pituitary body to the spinal cord referred to in the preceding section, there are fibers that are capable of conducting vasomotor impulses at least as potent in their influence upon the general vascular system as those transmitted along the familiar paths of the spinal cord by the bulbar centers. That the impulses derived from the pituitary reach the peripheral vessels by way of the bulb and its spinal vasomotor pathways is self-evident, since there is no ground for the assumption that the pituitary body has an autonomous set of fibers for this purpose.

The presence of such an autonomous set of vasomotor fibers between the posterior pituitary and the bulbar vasomotor center, however, recalls vividly the relationship of the spinal cord below the bulb with the great sympathetic, and suggests an important question: may the vasomotor impulses not be sympathetic as to their distribution? Excitation of the bulbar vasomotor center causes, as stated by Winfield S. Hall, "general contraction of all the arteries," while paralysis of this center "causes *general* dilatation." Sympathetic vasomotor action, on the other hand, is a restricted one; thus, Howell, after showing the influence of stimulation and section of sympathetic paths, writes: "From these and numerous similar experiments, we may conclude that normally the arteries—*that is, the arterioles*—are kept in a condition of tone by impulses received through the vasoconstrictor fibers,"—evidently sympathetic constrictors. Now, the manner in which Masay's results could have been awakened through sympathetic fibers from the posterior lobe to the bulbar vasomotor center, and thence down the cord to the origin of the sympathetic nerves, the ultimate nerve-path to the tissues, is suggested by another quotation from Howell's work: "When vasoconstrictor fibers are stimulated, there is a *rise of pressure* in the artery supplying the organ and a fall of pressure in the veins emerging from the organ. This result is what we should expect if the constriction takes place in the region of the *arterioles*." As these terminal vessels are governed by sympathetic fibers, stimulation of the pituitary must either have raised the pressure by constricting the arterioles through these fibers, or by stimulating

the bulbar vasomotor center, thus causing constriction of all arteries. Which of the two processes is the true one?

Experimental evidence shows clearly that it cannot have been merely because the impulses excited the vasomotor center. As is well known, Ludwig and Owsjannikow, who established the limits of the latter, found that when the midbrain *above* the bulb was cut through, the blood-pressure was not materially influenced, and that it was only when the bulb was cut across or below the now recognized location of the center that paralysis of the vessels was complete. It is evident, therefore, that the vasomotor center is not located above the bulb.

Such is not the case, however, with what I will hereafter designate as the "sympathetic center."

In the twentieth chapter I will submit evidence to the effect that antipyrin and other coal-tar products and drugs produce their antipyretic and analgesic effects precisely by causing constriction of the arterioles supplied with the sympathetic vasoconstrictors to which Howell refers. Now, Sawadowski[98a] found that when the tissues of the base of the brain were cut through, "the cut being made through the thalami optici or the corpora striata," antipyrin and other antipyretics were no longer active. The section being far above the bulb, though immediately below the pituitary body, the fibers severed were those which transmitted Masay's blood-pressure raising impulses. The fact that these sympathetic vasoconstrictor fibers influence only the arterioles, the smallest arteries, explains also why Ludwig and Owsjannikow did not affect the vascular tension markedly by dividing the same nerves.

Again, the basal structures severed by Sawadowski—at least the walls of the third ventricle to which Cajal, Van Gehuchten and others have traced nerve-fibers from the pituitary—give passage to typical sympathetic fibers. Referring to this region, Edinger[98b] says: "The inner side of the thalamus is separated from the ventricle by a uniform layer of gray matter. This is called the central gray matter of the middle (third) ventricle, and consists of a tissue rich in cells, and traversed in all directions by numerous *fine, medullated* nerve-

[98a] Sawadowski: Centralbl. f. d. med. Wissen., Jahrgang xxvi, pp. 145, 161, 1888.

[98b] Edinger: "Anat. of Central Nerv. System," American edition, p. 260, 1899.

fibers." Now, the identity of such fibers is well known. "A striking feature of the *sympathetic* system," says Langley,[98c] "is the predominance of *small medullated* fibers in it. This was pointed out by Bidder and Volkmann in 1842. The great majority of its medullated fibers vary from 2μ to 3.5μ in diameter. . . . . Very large medullated fibers, 15 to 20μ, which are common in the roots of the spinal nerves, do not occur in the sympathetic system." Kölliker[98d] also teaches that "the neuraxes of sympathetic neurons become invested in many cases with a thin medullary sheath, thus forming very fine medullated fibers, which, on account of their small size, can be differentiated from the smallest cerebro-spinal fibers."

Cyon and Masay, in the light of this evidence, therefore, stimulated the *sympathetic center*, the marked elevation of blood-pressure provoked (and which receded instantly when the excitation ceased) being due to *constriction of all the arterioles* and the resulting accumulation and pressure behind the vascular obstruction.

This obviously liberates the bulbar vasomotor center of the functions ascribed to the sympathetic system, and endows the latter with autonomous functions. That such is the case is sustained not only by the foregoing evidence, but also by the anomalous rôle which the bulbar vasomotor center is inferentially made to play according to prevailing teachings (in view of the fact that experimental work on the sympathetic is used to exemplify vasomotor action, constriction and dilation) not only as the regulator of vascular tonus, but also, through its connection with the sympathetic, of functions of different kinds, secretory, motor (peristalsis) and inhibitory. Although, as will be shown in the twentieth chapter, the latter are, in reality, nothing but what might be termed "experimental" pseudo-functions, the fact remains that as stated by Hall in reference to the sympathetic system: "The importance of this system in the control of the vital functions of the body can hardly be overestimated." That it should be provided with its own center—though closely related with bulbar vasomotor center through its fibers thereto, which, as we have seen, are of the special sympathetic type—is, therefore, only logical.

[98c] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 648, 1900.
[98d] Kölliker: Cited by Huber: Jour. of Compar. Anat., Sept., 1897.

This involves the conclusion that the large vessels, as well as the arterioles, are supplied with vasomotor nerves, the former being governed by the bulbar vasomotor center. This is in accord with the more recent teachings of histology. Joris,[98e] in a comprehensive review of the subject, and after considerable histological work, using the Golgi and Ehrlich methods, concludes with the remarks: "A fact which we must consider as established is that all arteries and all veins are provided with intrinsic nerves. Their existence in the nerve-centers is not as yet established, notwithstanding the researches of Obersteiner, Morisson and Huber. But these negative results depend certainly upon the technical difficulties." To emphasize his statements, Professor Joris adds: "I said intentionally all the *arteries* and all the *veins*" . . . . . "blood-vessels are supplied with nerves, because their walls contain muscle-fibers." This can also be said of veins, among which he enumerates, besides the smaller veins, the "venæ cavæ, jugulars, iliacs, etc."

As to the distribution of these nerves and their function, Joris writes: "All the nervous branches which surround and accompany the blood-vessels do not ramify in the thickness of their walls. Many of them follow only momentarily the path of the vessels and terminate in other organs. These are the satellite nerves. The true vascular nerves are quite distinct from the satellite nerves." . . . . . "These [true vascular] nerves form, by their anastomoses, a perivascular plexus. Finer branches, differing structurally and having different functions, emanate from this plexus. Some are destined for the smooth fibers of the tunica media (*motor fibers*); the others are sensory (*sensitive fibers*)." All these nerves are evidently vasomotor, since they "end absolutely in the thickness of the vascular walls. Their anastomoses are mutual and never with neighboring nerves, muscular, glandular, etc." . . . . . "The perivascular plexus is clearly isolated; the aggregate of fibers which compose it form an independent exclusively vascular apparatus." As to the sensitive fibers, "they sink into the depth of the tunica adventitia as do the motor fibers, but do not anastomose with them."

[98e] Joris: Bull. de l'Acad. roy. de med. de Belgique, iv série, T. xx, p. 502, 1906.

If, as I hold, the larger vessels are governed by the vasomotor (bulbar) center, while the arterioles are controlled by the sympathetic (posterior pituitary) center, the nerves supplied to the latter vessels should be those of the sympathetic type, *i.e.*, the fibers of Remak, the small, supposedly "nonmedullated" fibers referred to a few pages back: "Vascular nerves are formed of nonmedullated and medullated fibers," writes Joris; "the latter are numerous on the surface of the vessels, the caliber of which exceeds 80 microns. They become gradually more scarce, and disappear completely along the more delicate vessels. None but nonmedullated fibers remain when the caliber of the vessel is approximately 50 microns." This diminutive size is quite compatible with the anatomical relationship of the arterioles as I interpret this term, *viz.*, the more or less elongated terminals of all arteries—which open directly into the capillaries, including the so-called "precapillary vessels.

The location of the neural lobe of the pituitary at the head of the spinal structures that project into the base of the brain; its identity as a highly differentiated structure; and the fact that in a large group of animals, either as the "sub-œsophageal ganglion" of various invertebrates, or as the "central ganglion" of the lower chordata, it is the general center of the nervous system, and the experimental evidence submitted clearly points to this organ as the seat of a center, such as the sympathetic center, which, as I will show, takes part in a function which far exceeds in importance that of preserving the vascular tonus—the only rôle fulfilled by the bulbar vasomotor center.

Summarized, all this evidence seems to me to have shown: (1) *that the neural or posterior lobe of the pituitary body contains a center which governs the great sympathetic system, including its vasoconstrictor nerves to the arterioles;* (2) *that this center is connected by nerve-paths with the medulla oblongata and spinal cord through which it transmits its impulses;* (3) *that the bulbar vasomotor center does not maintain the tonus of the arterioles, as now taught, but solely that of the veins and larger arteries;* (4) *that the center in the posterior or neural lobe of the pituitary which governs the caliber of the arterioles, should be termed the "sympathetic center."*

THE NEURAL LOBE OF THE PITUITARY AS THE SEAT OF COMMON SENSIBILITY AND AS A GENERAL MOTOR CENTER.

The pituitary body remained whole, of course, in the decerebrated animals referred to in a foregoing section, and the paths to the spinal cord likewise. Foster,[99] referring to such animals, states that they "may be kept alive *and in good health* for a long time," and they exhibit "a spontaneity obviously betokening the possession, not merely of a *conscious volition,* but of a certain amount of *intelligence.*" Now, there is no structure in the base of the brain that is endowed with such an attribute. The optic thalami and corpora striati are the only organs to which such an important rôle might hypothetically be ascribed; but we have seen that in Goltz's dog, destruction of these organs did not prevent its remaining "alive and in good health for a long time," and that all its functions were performed normally. The posterior pituitary alone is capable of playing such a rôle: not only does it contain highly differentiated nervous elements, various types of highly organized nerve-cells, but even its outer layer was found by Luschka,[100] Müller,[101] who studied the pituitary from myxine to man, and others, to be composed of gray substance recalling that of the cerebral cortex.

The neural lobe thus presents structural features which indicate that it is fully able to carry on functions of the highest order, and in which co-ordination is blended with enough conscious volition to account for the manifestations of intelligence to which Foster refers. As we will now see, it can not only generate motor impulses, but also receive sensory impulses and impressions—the products of sensual perceptions—of various kinds, and co-ordinate a group of motor impulses adapted to the needs of the moment—not mere manifestations of reflex action, but complex combinations. Even this represents but a refinement of functions which the neural lobe alone governs in the primitive chordata. Thus Loeb[102] states that Ferrier "mentions the one ganglion of the Ascidians as illustrative of the

[99] Foster: *Loc. cit.*, p. 643.
[100] Luschka: "Der Hirnanhang und die Steidrüse des Menschens," 1860.
[101] Müller: Jenaische Zeit. f. Naturw. Bd. vii, S. 327, 1873.
[102] Loeb: *Loc. cit.*