level centers (spinal cord, bulb and midbrain) from which impulses *producing* voluntary muscular action emanate." Again, "the application of the terms 'motor' and 'sensory' must be used rather *for purposes of convenience* than with a view to a rigid definition of function."

Foster[32] says, however, in this connection: "The simplicity of the electrical phenomena resulting from cortical stimulation which we described, might at first sight lead us to conclude that the whole matter was fairly simple; and indeed, some writers appear to entertain the conception that in a voluntary movement such as that of the fore-limb, all that takes place is that the 'will' stimulates certain cells in the cortical area, causing the discharge of *motor* impulses along the pyramidal fibers connected with those cells, and that these impulses travel straight down the pyramidal tract to the motor fibers of the appropriate nerves, undergoing possibly some change at the place in the cord where the pyramidal fiber makes junction with the fiber of the anterior root, but deriving their chief if not their whole co-ordination from the cortex itself, that is to say, being co-ordinated at the very starting-point." He characterizes this view as "untenable," and the simplicity of the electrical phenomena as "misleading."

This obviously suggests that voluntary impulses are not themselves motor impulses, but stimuli which awaken such impulses in the spinal system. Indeed, referring to the experimental removal of both hemispheres in pigeons, Foster remarks:[33] "In this warm-blooded animal, as in the more lowly cold-blooded frog, the parts of the brain *below and behind the cerebral hemispheres* constitute a nervous machinery by which all the ordinary bodily movements may be carried out. The bird, like the frog, suffers no paralysis when its cerebral hemispheres are removed." The pituitary body evidently forms part of this region: "Until recently," writes Willey,[34] "it was generally thought that the infundibulum [the pedicle of the pituitary body] represented the anterior end of the brain, which had become bent downward and backward. Kuppfer has brought forward weighty reasons for doubting this. According to him,

[32] Foster: *Loc. cit.*, p. 680.
[33] Foster: *Loc. cit.*, p. 641.
[34] Willey: "Amphioxus and the Ancestry of the Vertebrates," p. 283, 1894.

the infundibulum is essentially a down-growth or evagination from the *floor* of the brain, occurring *behind* the anterior terminal extremity of the brain."

The functional relationship between the brain proper and this region below it is clearly defined in Foster's statement[35] that "on these the [cortical] motor area must have its *hold as on the spinal mechanisms.*" M. Duval[36] also identifies the character of the antero-lateral tracts themselves as extensions of the brain *per se* when he says: "When the antero-lateral columns are alone severed, *voluntary* action is abolished in the portion of the cord below the section. Evidently," he adds, "the antero-lateral columns serve at least in great part to transmit the *orders of the will;* they establish a communication between the cerebral centers and the *gray substances of the spinal cord.*"

The limits of this gray substance are apparently restricted to the spinal cord, judging from Duval's conclusion; but he gives the organ its true functional field when he also says:[37] "While the anatomist locates the upper limit of the spinal cord on a level with the occipito-atloidean articulation, for the physiologist it extends into the interior of the cranium . . . . about up to the sella turcica"—the bony pedestal, we know, of the pituitary body.

These facts plainly suggest (1) *that the pituitary body fulfills in the higher mammals as important functions as a nerve-center as the central ganglion does in the lower Chordata;* (2) *that it influences very markedly all the cardinal functions: respiration, oxygenation, nutrition, metabolism and locomotion;* and (3) *that it is the source of automatic motor impulses now believed to arise from the cerebral cortex.*

NERVE-PATHS FROM THE PITUITARY TO THE SPINAL CORD.

The evidence submitted in the foregoing section indicates that the pituitary body must be connected with the spinal cord by nerve-paths. As the spinal cord was shown to extend up to, and include, the infundibulum, which in turn terminates as the neural lobe of the pituitary, it becomes only a question whether the portion of the cord which extends above the bulb or medulla

[35] Foster: *Loc. cit.*, p. 688.
[36] Duval: "Cours de physiologie," seventh edition, Paris, 1892.
[37] Duval: *Ibid.*, pp. 40 and 78.

oblongata contains such paths. Not only has their presence in this location been ascertained by various investigators, but it has been shown that the basal structures to which they are distributed are connected directly with the pituitary body by nerves, both of its lobes receiving an abundant supply.

Over twelve years ago Andriezen[38] referred to the posterior or neural lobe as "little beyond a neuroglia remnant." I have since pointed out[39] however, that neuroglia is not a mere reticulated framework of connective tissue, as now believed, and have adduced evidence showing that it differs from the latter both in its origin and chemical properties; that it originates from blood-vessels and penetrates into nerve-cells. Andriezen himself[40] described neuroglia-cells connected with blood-vessels, *i.e.*, "ensheathing the vessels of the brain"—the purpose of these cells being, in his opinion, to prevent undue expansion of the cerebral vessels. The view of Golgi, Clouston and others that neuroglia supplies nutrition to the nerve-cells; the many allusions to the "chromatin," "pigmentation," "granules," etc., of these elements, now found in the literature of the subject; Bevan Lewis's belief that neuroglia-cells are "lymph" channels, further sustain the view I advanced four years ago, viz., that while *neuroglia fibers are minutes capillaries* (which do not stain like ordinary vessels, owing to their covering) that carry plasma laden with oxidizing substance (adrenoxidase) to the neurons, their terminals in the latter being the neuro-fibrils which penetrate the cell-body by way of its dendrites, the *neuroglia-cells govern the quantity of this substance* admitted into the true nerve-"cells," *i.e.*, the neurons.

Interpreted from this standpoint, the wealth of neuroglia and neuroglia-cells in the posterior pituitary indicates, not that it is practically a useless and vestigial organ as Andriezen and others believe, but precisely the opposite, viz., that it is a *very highly differentiated organ*. This accounts for the fact that Berkley,[41] referring to the prevailing view that the true nervous elements almost entirely disappear in the neural lobe of the adult mammal, remarks, after examining about 2500 slides

[38] Andriezen: *Loc. cit.*
[39] *Cf.* vol. i, pp. 539 to 590, incl.
[40] Andriezen: Intern. Monats. f. Anat. u. Physiol., vol. x, p. 532, 1893.
[41] Berkley: Brain, vol. xvii, p. 515, 1894.

of this lobe: "After reading these statements, it was something of a surprise to find the above-described beautiful specimens of several types of ependymal neuroglia-cells, extending *from all portions of the middle and inferior regions of the cavity of the third ventricle.*" He also found in the posterior lobe itself, an array of nerve-cells of various types, some of which are very complex and evidently specific to the organ, being found nowhere else in the body. Many of these are reproduced and described in the first volume (opposite pages 495, 496 and 498).

It is not only the neuroglia-cells that communicate with the third ventricle, however. As stated above, each lobe is supplied with true nerve-fibers which connect it with the basal structures.

Several older anatomists, Sappey, Luschka, Müller, etc., refer to the presence of longitudinal nerves on the surface of the infundibulum, the pedicle of the pituitary, which nerves were found to extend up to the third ventricle; but it was only when the Golgi silver stain methods were introduced that this question could be studied satisfactorily.

Ramon y Cajal,[42] who studied the subject in the mouse, traced a direct communication between the basal tissues and the *anterior lobe*. In the basal tissues, the cell-bodies were found in a "*mass of gray matter behind the optic chiasm*," *i.e.*, in the anterior extremity of the third ventricle, while their neuraxons passed downward towards the pituitary. Van Gehuchten[43] says in this connection, referring to Cajal's researches: "These fibers represent the axis-cylinders of a group of nerve-cells situated behind the optic chiasm. Several of these fibers end in the thickness of the pituitary's pedicle; others penetrate between the *epithelial cells* of the anterior or glandular portion of the pituitary." Berkley[44] also found nerves in this lobe, the fibers among the epithelial cells ending, as shown in the illustration opposite page 498 (vol. i, figure *l*) in the shape of small knobs. Andriezen's researches, as had those of Cajal, showed that the *anterior* lobe had "anatomical connection with the brain floor," and that the "development of a small *specialized* group of nerve-cells in the *basal* part of the brain cavity (thalamocoel) with

[42] Ramon y Cajal: Anales de la Soc. española de hist. nat., 2a Ser., vol. xxiii, p. 214, 1894.
[43] Van Gehuchten: "Anat. du système nerveux," vol. ii, p. 239, 1900.
[44] Berkley: *Loc. cit.*

which the subneural gland [the anterior lobe] came into relationship. The central canal of the spinal cord, traced forward into this region, was seen to undergo dilatation into a distinct ventricle." The far-reaching meaning of this statement asserts itself when it is recalled that Andriezen's researches include the whole of the animal scale from amphioxus, the lowest of vertebrates, to man. They indicate that simultaneously with the evolution of the *pituitary* there occurred not only that of the *special group of cells* intended to connect the organ with the base of the brain, but also that of *the third ventricle.*

Ramon y Cajal found that the *posterior* or *neural lobe* of the pituitary was filled with a close and thick plexus of fine varicose fibers, which ramified among the nerve-cells. Longitudinal sections showed that these fibers were "terminal arborizations of a bundle which passes *downward* into the infundibulum." Other fibers were observed to pass *upward* from the organ by way of its epithelial *walls* and to terminate in *a mass of gray matter* located behind the optic chiasm." "Downward" and "upward" obviously suggest the presence of sensory and motor paths to and from the neural lobe.

Of particular interest in this connection is a set of nerves shown to exist by Gentès.[45] This observer, who found that the partition between the two lobes contained a layer of cells histologically similar to the olfactory area—which layer I assimilate to the test organ—recently studied this structure anew with a view to tracing its connections. He was again led to the conclusion that it was an epithelial structure "in no way glandular and the nervous end-organs of which were sensitive or sensory," as to histological structure. In a still more recent study, Gentès[46] traced these connecting fibers from the sensory organ referred to, up to the tissues of the base of the brain. He says, in this connection: "Originating by free end-organs in the epithelial juxta-nervous layer [the sensory organ], they reach the sub-epithelial layer. They then *enter the neural lobe* and run through it in every direction. Following an *ascending direction* they go towards the organ's pedicle and soon form part of it; they can be followed up to the level of the *tuber cinereum,*" *i.e.,* the tissues that form the floor of the third ventricle.

[45] Gentès: C. r. de la Soc. de biol., T. lv, p. 336, 1903.
[46] Gentès: *Ibid.*, p. 1560.

This affords a clear idea of the connection between the sensory structure (or test-organ) in the partition between the anterior lobe and how the impulses it awakens pass up to the third ventricle.

We thus have clearly defined paths from each pituitary body to tissues of the base of the brain: (1) the fibers from the anterior or glandular lobe communicating with the "mass of gray matter behind the optic chiasm;" (2) one set of fibers from the posterior or neural lobe communicating also with this mass of gray matter; and (3) the fibers from the neural lobe derived from the test-organ which pass up to the tuber cinereum forming the floor of the third ventricle.

The structures in the base of the brain with which the pituitary is connected by these nerve paths are themselves the source of large numbers of fibers, a large proportion of which pass posteriorly to the midbrain, a region which, as stated by Edinger,[47] is "occupied mostly with longitudinal bundles, tracts, and fasciculi to the spinal cord and to the cerebellum." This applies especially to the "mass of gray matter behind the optic chiasm" which receives fibers from both lobes—an important feature of the third ventricle in all vertebrates. Lying immediately above the infundibulum, and therefore just above the pituitary itself, it is termed by comparative anatomists, the "giant-celled supra-infundibular nucleus." In amphibians, reptiles and birds, it extends on each side of the ventricle, and fibers derived from it (the supra-infundibular decussation) project posteriorly, *i.e., towards the bulb.* In mammals, the supra-infundibular nucleus is likewise the starting-point of various bundles, *e.g.,* Meynert's commissure, for instance, which does not degenerate when the cortex is removed but the destination of which is unknown; Gudden's commissure, the fibers of which pass to the posterior corpora quadrigemina; the cerebellum, etc. It is also connected with structures anterior to it by motor and sensory fibers in Teleostei, as shown by Van Gehuchten recently. It projects two prominent bundles which spread out on the walls and floor of the third ventricle, thus contributing to the formation of the "central gray matter" of the base of the brain, a region which Foster[48] characterizes as "a bed for the develop-

[47] Edinger: "Anat. of Central Nerv. System," Amer. edition, p. 124, 1899.
[48] Foster: *Loc. cit.*, pp. 635 and 636.

ment of the nuclei of the cranial nerves" and a continuation of the tegmental region, which he says "may perhaps be regarded as a more or less continuous column of gray matter, comparable to the gray matter of the spinal cord," and which "serves as *a sort of backbone to the rest of the central nervous system.*"

The fibers traced by Gentès from the area of sensory cells—in the anterior pituitary which I assimilate to the "test organ" of lower forms—to the posterior lobe and thence to the tuber cinereum, are likewise merged with fibers which are projected to this "bed for the development of nuclei," since the tuber cinereum is necessarily traversed by fibers which Andriezen,[49] using the silver chromate method in fœtal and newborn kittens, traced *"directly from the posterior pituitary to far back towards the pons,"* which lies immediately above the medulla oblongata and contains the nuclei referred to. Whether originating from the anterior or posterior pituitary, therefore, the nerves which connect these organs with the base of the brain find therein both indirect and direct paths capable of transmitting their impulses to the spinal cord.*

Still, as is well known, the pons is a bridge for the passage of impulses, afferent and efferent, which travel between various parts of the nervous system, including the cerebrum. Motor impulses projected by the nerve paths from the pituitary should not only persist after removal of the brain (a fact already ascertained), but if the pituitary body is a motor center (as the effects of its removal indicate), removal of the structure above the mesencephalon (which contains the bed of nuclei and all pontine structures) quite beyond the crura cerebri which carry the impulses from the brain should, in the higher mammals (in which the fibers from the pituitary were traced), impair motility. Christiani[50] not only found this to be the case, the power of progression being annulled in the experimental ani-

*When I wrote the first volume, experimental stimulation of various parts of the cervical sympathetic by Cyon and others had led me to conclude that the impulses from the pituitary body to the adrenals passed down this nerve to reach the sympathetic chain below, and finally, the splanchnic. I have found since, however, that the nerves stimulated in the neck were branches which excited the thyroid gland and only indirectly, therefore, the adrenals. All the efferent nerves from either lobe of the pituitary body thus pass to the spinal cord.

[49] Andriezen: Brit. Med. Jour., Jan. 13, 1894.
[50] Christiani: Arch. f. Physiol., S. 465, 1884.

mals (rabbits), but a phenomenon which promptly follows removal of the pituitary also appeared: tetanic spasm—due as we will see, to the accumulation of toxic wastes in the blood, the result in turn of impaired metabolism.

Another phenomenon which follows removal of the pituitary, we have seen, is hypothermia. Now, irritation of the structures of the third ventricle in the path of the nerves from the pituitary causes the opposite condition, hyperthermia. Isaac Ott, who, in 1884, began a series of studies having for their object to determine the location of heat-centers, found, among others, one located in the *anterior portion* of the *floor* of the third ventricle, and another in the *tuber cinereum*. The former region is precisely where all the fibers sent off posteriorly by the large gray nucleus to which Cajal traced afferent and efferent fibers from the anterior pituitary (a fact confirmed by Andriezen as to the presence of connecting fibers) originate, while the tuber cinereum contains those traced from the posterior lobe thereto by Gentès, and the fibers traced by Andriezen to the region of the pons. Ott and Harris[51] state that Ott's results were confirmed by von Tangl in the horse, and that the procedure mentioned causes a "great rise of temperature." These observations were also confirmed by Sakowitsch,[52] who found that puncture of the tuber cinereum raised both the *internal* and *peripheral* temperatures, the latter reached 43° C. (109.4° F.) six hours after the lesion was produced. Ott and Harris conclude that this is not due to division of fibers "coming from the corpus striatum, because a puncture through the mouth of the rabbit produces the same result, although only the lower surface of the *tuber* has been punctured with a needle."

This thermogenic function is evidently independent of the brain. "Fredericq[53] found," says Pembrey,[54] "that removal of the cerebral hemispheres in pigeons caused practically no difference in the daily curve of their rectal temperature. This observation has been confirmed by Corin and Van Beneden,[55] who have, in addition, shown that the pigeons without their cerebral hemispheres produce the same amount of carbon dioxide and

[51] Ott and Harris: Therap. Gaz., June 15, 1903.
[52] Sakowitsch: Neurol. Centralbl., Bd. xvi, S. 520, 1897.
[53] Fredericq: Arch. de biol., T. iii. p. 747, 1882.
[54] Pembrey: Schäfer's "T. B. of Physiol.," vol. i, p. 864, 1898.
[55] Corin and Van Beneden: Arch. de biol., T. vii, p. 265, 1889.

heat as do normal pigeons. The rapid rise in temperature which occurs when a hibernating marmot awakens is not prevented by removal of the cerebral hemispheres." On the other hand, while the region punctured is clearly traversed by the fibers from the pituitary body, there is no organ anterior to it to give rise to thermogenic impulses. This affords additional evidence to the effect that the pituitary body is connected by nerve-paths with the spinal cord.

This raises the question as to whether the areas punctured by Ott, von Tangl, Sakowitsch and others, can be considered at all as heat "centers." The fact that several such "centers" have been discovered suggests that the thermogenic impulses evoked are merely due to the irritation, *i.e.,* congestion of areas containing thermogenic nerve-paths. Schäfer[56] writes in this connection: "It is, however, very doubtful whether the facts observed warrant the assumption that the parts in question, which are apparently irritated by the lesion, are specific centers to determine the production of heat. For when the experiments on this subject are examined, it is found that the results are closely dependent upon the establishment of an irritative lesion in parts which are either directly in, or in close proximity to, the path taken by motor impulses." In view of the foregoing evidence this indicates that *the pituitary body is the general heat center.* I will adduce considerable additional evidence to this effect.

The fact that injuries or experimental lesions of the cortex, corpus striatum and crus cerebri can likewise cause a rise of temperature does not militate against this conclusion. They merely irritate areas that normally do not awaken thermogenic impulses but which, when artificially stimulated, do so by transmitting violent motor stimuli (*quasi* voluntary) to portions of the spinal system in which the nerve-paths of the thermogenic mechanism occur.

To poise these statements, and particularly the conclusion that the pituitary body is connected with the spinal system by nerve-paths on a solid foundation, however, it is necessary to show (1) that, irrespective of the brain, motor impulses can be provoked by irritating the paths of the nerves from the pituitary,

[56] Schäfer: *Loc. cit.,* vol. ii, p. 717.

i.e., the walls and floor of the third ventricle, (2) that the pituitary body itself can likewise evoke motor phenomena, and (3) raise the temperature of the body at large. The first line of evidence will alone be considered in this section, the two others being considered in succeeding sections.

Flourens, Bechterew, Weber, Ferrier and others obtained muscular movements by exciting the walls of the third ventricle, which contain, we have seen, fibers from the gray nucleus connected by nerves with the pituitary. As these might be ascribed to the cortex through sensory impulses carried by the optic thalamus, they will not be taken into account. Magnan,[57] however, caused epileptic seizures *after* removing the hemispheres. Vulpian[58] was also led to conclude by experiments that the center for epileptic convulsions was located at the base of the brain. Ziehen[59] caused prolonged tetanic spasm in rabbits by irritating the basal tissues after removing both hemispheres. Hering[60] found it impossible to inhibit tonic spasm in 20 monkeys in which the pyramids had been severed, thus disconnecting what is generally believed to be the path for voluntary impulses to the spinal cord. Prus,[61] moreover, showed that after division of the pyramids, the spasmogenic impulses passed by way of the base, *e.g.,* the tegmentum and pons, and his results were confirmed by Bischoff,[62] Hering[63] and others. Finally, Nino Samaja[64] after an elaborate experimental study of the question concluded that in the higher mammals tonic spasms were "exclusively" due to impulses derived from the base of the brain. The most violent kinds of muscular contractions are readily produced, therefore, irrespective of any brain action, by stimulating structures that contain nerve-paths from the pituitary body. This evidence shows also why removal of the pituitary is followed by such marked muscular weakness and relaxation, and by hypothermia: as the general center of all vegetative functions it governs the heat mechanism, *i.e.,* general oxygenation, and there-

[57] Magnan: Arch. de physiol., T. v, No. 5, p. 115, 1873.
[58] Vulpian: C. r. de l'Acad. des sciences, Apr. 27, 1885.
[59] Ziehen: Deut. med. Woch., Bd. xiv, S. 604, 1888.
[60] Hering: Wiener klin. Woch., Nu. 33, S. 831, 1899.
[61] Prus: *Ibid.,* Bd. xi, S. 857, 1898.
[62] Bischoff: *Ibid.,* Nu. 39, S. 960, 1899.
[63] Hering: *Loc. cit.*
[64] Nino Samaja: Rev. Méd. de la Suisse Romande, Mar. 20, 1904.

by the intrinsic functions of the muscular system—as additional testimony will demonstrate.

Pending this evidence the following conclusions are submitted: (1) *the neural or posterior lobe of the pituitary body is not, as generally believed, a functionless organ, but a highly organized nerve-center containing several types of nerve-cells;* (2) *both lobes are connected with the overlying third ventricle by nerve-paths which, through nerves from the giant-cell supra-infundibular nucleus and in the tuber cinereum, extend posteriorly to the midbrain—a continuation of the spinal gray matter which contains the nuclei of the cranial nerves;* (3) *the nerves that connect the pituitary body with the spinal cord passing posteriorly in the gray substance of the walls and floor of the third ventricle, various experimental phenomena now ascribed to "centers" in these structures, are in reality due to irritation of these nerves and to the artificial production of manifestations normally evoked by the pituitary body as a motor and heat center.*

THE NEURAL LOBE OF THE PITUITARY AS THE SEAT OF THE SYMPATHETIC CENTER.

In many invertebrates, two ganglia preside over the entire nervous system, the supra- and sub-œsophageal. If in the snail, for example, as shown by Vulpian[65] the upper (cerebral) ganglion is removed, the animal lives several weeks, but it remains absolutely motionless. If, on the other hand, the inferior ganglion is removed, the animal dies within twenty-four hours. Again, galvanic excitation of the cerebral ganglion produces no appreciable effect; similar excitation of the lower ganglion, however, provokes violent muscular movements, and if prolonged, often "arrests the heart in dilatation and diastole as is the case when the pneumogastric is stimulated in the neck of vertebrates"—in other words, inhibits it. Now, physiologists teach, although as stated by Langley[66] they "are still far from any real knowledge of the processes involved in inhibition," that it is a physiological function, and that the slowing of the heart's action which attends stimulation of the vagus in the neck exem-

[65] Vulpian: cited by Letourneau: "La Biologie," p. 389, 1891.
[66] Langley: Schäfer's "T. B. of Physiology," vol. ii, p. 674, 1900.

plifies the process. This is, in my opinion, a baneful conception; one indeed which has misled clinicians in their interpretation of several heart disorders and their treatment, and which, as I will show, has perpetuated our ignorance of the manner in which many of the most violent poisons cause death.

In the first volume I adduced evidence showing that the inhibitory phenomena and cardiac arrest caused by passing a current from the nose to the bulb were due to excitation of the pituitary body neural paths. In an article published since the first volume appeared[67] I emphasized the fact that inhibition was *not* a physiological function, and that it was due to a *morbid vasomotor constriction of the coronary arteries,* which slowed the heart because it deprived it of blood.

That the pituitary body contains a center capable of influencing the entire vascular system is demonstrable experimentally.

Cyon[68] observed, in the course of experiments on a large number of animals (carried on to study the relations between the thyroid and the pituitary), that any pressure, even the slightest, upon the pituitary body at once gave rise to a sudden variation of the blood-pressure, and to a marked reduction in frequency of the heart beats. He then applied the electric current to the exposed pituitary and found that an extremely weak current produced the same effects but to a much more intense degree. Not only was the increase of vascular tension general, but the suddenness with which the pressure rose could only be caused by a sudden constriction of the arteries.

Cyon's observations have been fully confirmed recently by F. Masay[69] and amplified in such a manner as to locate distinctly in the pituitary body the origin of the phenomena witnessed. His investigations showed that mechanical and electrical excitation of this organ caused a marked and immediate rise of blood-pressure—from 81 mm. Hg. to 200 in one instance—and that this effect was not prevented by section of both vagi. After splitting the soft palate longitudinally, a delicate electric trephine was used to remove a disk of bone imme-

[67] Sajous: N. Y. Med. Jour., May 14 and 21, 1904.
[68] Cyon: Archives de physiol., vol. x, p. 618, 1898.
[69] Masay: Ann. de la Soc. roy. des sci. méd. et nat. de Bruxelles, T. xii, Fasc. 3, 1903.