CHAPTER XVI.

THE PITUITARY BODY AS GOVERNING CENTER OF VITAL FUNCTIONS.

THE PITUITARY BODY AS THE GOVERNING CENTER OF THE BODY'S IMMUNIZING FUNCTIONS.

An editorial writer[1] remarked recently: "It was not entirely poetic imagination that inspired Jacques Loeb to predict that through the oxidases one may, in time, be able to control life as the artist governs the keys of the piano. Not merely the normal course of life, but also that vast gamut of diseases characterized by metabolic derangements might be controlled if we only knew how to favor or retard the action of the oxidases." Four years ago I pointed out that these identical functions were carried out by the pituitary body.

In the first volume I contended that the anterior lobe of this organ contained sensory cells which had for their purpose to detect the presence of toxic substances in the blood. Considerable evidence was also submitted to show that these sensory structures could, in case of need, and through the intermediary of the adrenals, enhance the functional activity of the organism's defensive functions. As interpreted from my standpoint, therefore, the pituitary body should be considered as *an organ of special sense* provided by Nature to protect the body against the harmful effects of poisons of all kinds.

That such a protective function actually exists in man is further sustained by the fact that its presence is clearly discernible throughout the entire phylogenetic scale, at least down to and including mollusks. "Near the base of the stem of each ctenidium" [gill-combs], says Ray Lankester,[2] "is a patch of the epithelium of the body-wall, peculiarly modified and supplied with a special nerve and ganglion. This is Spengel's olfactory organ, which *tests* the *respiratory fluid*, and is persistent in its

[1] Editorial: Medical News, Dec. 24, 1904.
[2] Ray Lankester: Art. "Mollusca," "Encyclo. Britannica," ninth edition, vol. xvi, p. 636.

position and nerve-supply throughout the group Mollusca." To this group of cells Lankester gave the name *"osphradium."* Parker and Haswell[3] more specifically define the functions of this organ, viz., "to test the *purity* of the water entering by the respiratory current."

Ascending from the Invertebrates to the Vertebrates, we find this same organ in the lowest of fishes, the lancelet or amphioxus. In this lowly animal, the water, which enters the mouth and traverses the entire body, also subserves the respiratory function (Lankester).[4] "The mouth of Amphioxus would seem to be well guarded against the intrusion of noxious substances," writes Willey,[5] "everything entering the mouth

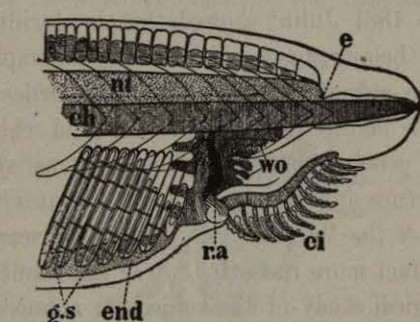

FIG. 1.—TEST-ORGAN IN AMPHIOXUS IN A YOUNG TRANSPARENT INDIVIDUAL. (*After J. Müller, slightly modified by Willey*).

wo, Ciliated epithelial tracts. *gs*, Gill-slits. *end*, Endostyle (the future thyroid). *ra*, Down-growth of Aorta. *nt*, Spinal cord. *ch*, Notochord. *e*, Eye-spot. *ci*, Cirri.

has to pass through a vestibule richly provided with sensitive epithelial cells." The relations of these cells are shown in Fig. 1. Lloyd Andriezen[6] likewise refers to sensory structures in amphioxus constituting "a nervous organ," which is "sensitive to the *quality* of the water which passes over it," and remarks that "this is no isolated phenomenon, for we find a striking analogy in the osphradial organ and ganglion of Mollusca, which is situated at the entry of the mantle or respiratory chamber, and serves to *test* the quality of the water which passes over the respiratory organ." We thus have clear evi-

[3] Parker and Haswell: "Manual of Zoölogy," p. 277, 1900.
[4] Lankester: *Loc. cit.*, vol. xiv, p. 258.
[5] Willey: "Amphioxus and the Ancestry of the Vertebrates," p. 19, 1894.
[6] Lloyd Andriezen: Brit. Med. Jour., Jan. 13, 1894.

dence to the effect that these lower forms, at least, are endowed with a specific apparatus, which, though primitive, has for its purpose to protect the *oxygen-bearing stream*, and, through the latter, the body at large.

A feature of great importance in this connection, however, is the evident presence of two structures fulfilling correlated functions. While Lankester refers to "a patch of epithelium" . . . . "*supplied* with a special *nerve* and *ganglion*," located at the base of the gill-combs in Mollusks, he includes all these structures in Spengel's "olfactory" test-organ. The importance of this lies in the fact that we have in this dual organ a counterpart of the pituitary body, which is composed, as is well known, of two lobes, one epithelial and the other neural. As far back as 1881 Julin[7] showed that in Ascidians, or sea-squirts, which belong to a subclass below amphioxus (the Urochorda), the *sub*neural gland, which underlies a ganglion embedded in the mantle of these animals (and which ganglion represents the general center of their nervous system), was similar in structure and relations to, and a counterpart of, the pituitary body of the Vertebrates. Lloyd Andriezen[8] not only confirmed this fact more recently, but as the result of comprehensive histological study of the subject in ammocœtes (larval petromyzon) and lower forms, affirmed the previously supposed two-fold function of this organ. "Even in the highest mammals and *man*," says this investigator, "it has a two-fold structure and represents a double organ."

The close relationship between the two organs is clearly shown in Fig. 2, a longitudinal section of the upper portion of a young clavelina, or sea-squirt, shortly after metamorphosis. Although drawn by van Beneden and Julin, the illustration is a part of one reproduced from Willey's treatise, and the lettering in the latter is intentionally preserved. The water enters *m*, the mouth, is tested by *hy*, the hypophysis, *i.e.*, the pituitary body, and the latter, as clearly shown, is in immediate contact with *g*, the ganglion.

This affords additional testimony in another direction. In the first volume I stated that the pituitary body was not only

[7] Julin: "Recherches sur l'organis. des ascidies simples," Archives de biol., vol. ii, pp. 59, 211, 1881.
[8] Lloyd Andriezen: *Loc. cit.*

connected with the adrenals, but also that the fibers from the former organ ultimately reached the latter by a direct nerve path, even though the adrenals were located in so remote a position as above the kidneys, *i.e.*, amongst the abdominal viscera. In Fig. 2, *vn*, the visceral nerve (which, with the ganglion, represents the animal's entire central nervous system), as may be seen, extends from *g*, the ganglion, to *int*, the intestines. Benedin and Julin allude to this nerve as the *cordon ganglionnaire viscéral*, or "visceral ganglionic cord," which starts "from the posterior end of the adult cerebral *ganglion*, and, proceeding along the dorsal side of the pharynx above the dorsal lamina, becomes lost among the viscera" (Willey[9]). Huxley and Martin,[10] moreover, refer to the "patch of sensiferous

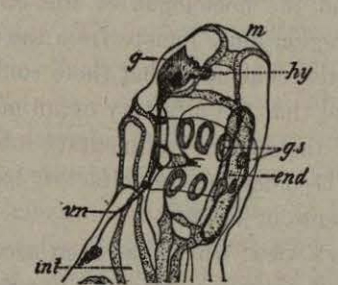

FIG. 2.—OSPHRADIUM OR TEST-ORGAN OF A YOUNG ASCIDIAN.

m, Mouth. *hy*, Hypophysis (Pituitary), the test-organ. *g*, Ganglion. *end*, Endostyle (future thyroid). *gs*, Future gill-slits. *vn*, Visceral nerve. *int*, Intestine. (*Drawn after van Beneden and Julin.*)

epithelium in the roof of the inhalant siphon" or test-organ (Lankester's osphradium) as being "immediately connected" with "the parieto-splanchnic ganglion." We have seen that the abdominal main path to the adrenals is the great splanchnic nerve. It is evident, therefore, that even in so low a group as Mollusca, which includes the bivalves, shell-fish, clams, oysters, mussels, etc., the univalves, snails, periwinkles, etc., and the cuttle-fishes, squids, octopi, etc., though supplied with very limited nervous systems, the fundamental nerve structure or cephalic ganglion is intimately connected with the hypophysis or pituitary body—an early prototype of the system I have traced in man.

[9] Willey: *Loc. cit.*, p. 224.
[10] Huxley and Martin: "Practical Biology," p. 312, 1892.

A confusing feature of the whole problem has served greatly, however, it seems to me, to obscure our knowledge of the functions of the pituitary body. We have seen that the osphradium, the patch of epithelial cells forming Spengel's organ, and to which water-testing functions have been ascribed, is referred to by various zoölogists as an *olfactory* organ. Again, the pituitary body, as we know, is connected with, and forms part of, the infundibulum in craniate Vertebrates. The uniformity of this anatomical relationship obviously suggests a functional connection between them, especially since, in the course of its embryological development, the pituitary becomes, in most forms, detached from the mouth to actually fuse with the infundibulum—evidently a purposeful step. Von Kuppfer[11] having found the homologue of the olfactory organ of Amphioxus in a region quite remote from the infundibulum in craniate Vertebrates, concluded that there could be no relation between them, and that the olfactory organ of Amphioxus was the homologue of the median rudimentary lobe of the embryo which ultimately becomes the true olfactory lobe, *i.e.*, that connected with the sense of smell.

Von Kuppfer's view, which has been accepted by a number of investigators, though apparently poised on a sound foundation, is invalidated by the fact that he *assumes* that there exists but one structure supplied with specific olfactory cells, whereas the nature of the functions of the osphradium in mollusks, and the corresponding test-organ in Ascidians, Amphioxus, etc., and other facts, clearly suggests that there may be *two*. This important question can only be settled by showing that in the higher mammals there exists, besides the olfactory lobe of the organ of smell, another region supplied with olfactory cells and intimately connected with the pituitary body. That such is actually the case is shown by the following facts:—

Nearly forty years ago, Peremeschko[12] described a transverse slit, or cavity, between the glandular elements of the anterior lobe of the pituitary and the partition which separates it from the posterior lobe. This cavity was found by him to be

[11] Von Kuppfer: Archiv f. mikr. Anat., Bd. xxxv, S. 469, 1890.
[12] Peremeschko: Virchow's Archiv f. Anat. u. Phys., Bd. xxxviii, S. 329, 1867.

lined throughout in man with *ciliated epithelium.* Wilhelm Müller[13] also found that the internal wall of this slit, forming part of the interlobular partition, was lined with this epithelium. Cadiat[14] and others have since confirmed these observations—all made, however, before the more advanced histological methods had been developed. Recently this region of the pituitary body was studied by Gentès,[15] by the Golgi method, in the higher mammals, namely, the cat and dog. He found that the anterior lobe was, in reality, composed of two parts, the glandular and neural, the latter forming the *inner* wall of the partition between the two lobes. The epithelium revealed by ordinary stains was shown, by the Golgi method, to contain interstices penetrated throughout by sensory cells, each cell sending broad processes to the free surface and into the depths of the epithelial layer. The latter's structure, he states, recalled exactly that of the *olfactory area of the nasal mucous membrane.*

The value of these observations is enhanced by the fact that Gentès does not refer to the researches of zoölogists, whose labors, of course, were beyond his normal field. We thus have, in his work, an independent confirmation of the existence in the pituitary body of the higher mammals, of a structure totally independent of the organ of smell, and which, even in the lowly mollusk, has been accorded the rank of a *protective* organ—precisely that recognized by Spengel in Ascidians, *i.e.,* to "test the respiratory *fluid.*"

One of the functions I have ascribed to the pituitary body of man is none other than this, namely: to detect any toxic substance that may be present in the blood, the organism's oxygen carrier and, therefore, its respiratory *fluid,* after the water-vascular system has become a blood-vascular system.

As we will see farther on, this harmonizes with the phylogeny and embryology of both lobes of the pituitary body.

Drugs, toxins, venoms, toxic physiological wastes, etc., assume, under these conditions, the position of foreign elements in the blood-stream. On the other hand, the presence in the human pituitary body of nerve-cells recalling those of an organ

[13] Wilhelm Müller: Jenaische Zeit. f. Naturw., Bd. vii, S. 327, 1873.
[14] Cadiat: "Anatomie Générale," cited by Guépin, Tribune médicale, Dec. 10, 1891.
[15] Gentès: C. r. de la Soc. de biol., T. lv, p. 100, 1903.

capable of reacting to innumerable kinds of odoriferous emanations and therefore to the immeasurably small particles of which they are composed, explains why the body responds actively to the influence of so many of these toxics and why so minute a dose of a given remedy, $^1/_{600}$ grain (0.0001 gramme) of aconitine, for example, or an equally diminutive quantity of vaccine virus can evoke, in the human organism, such marked phenomena as those observed.

It is evident, therefore, that we are dealing, in this connection, with the *foundation of the organism's auto-protective mechanism*—one indeed, as I have stated in the first volume (and as will be further emphasized in the present one), whose beneficial influence we can, through our remedies, govern at will. But I also pointed out therein that it was through the intermediary of the oxidizing substance—adrenoxidase—that this influence was exercised. How is the distribution of this all-important substance governed, *i.e.,* hastened or retarded? If, as I hold, the pituitary body is a structure through which disease may be controlled, what constitutes within its precincts the keyboard—using Jacques Loeb's comparison—which we, as artists, must utilize to attain this object?

The purpose of this chapter is to answer this question.

THE PITUITARY BODY AS A NERVE-CENTER.

In the first volume, I ascribed to the pituitary body the function of a general nerve-center. While urging that it was the anterior lobe of this organ which carried on the function referred to in the preceding section—that of "test-organ"—owing to its identity as the governing center of the adrenals, I held that the posterior or "neural" lobe, which is linked with the anterior, and connected by its pedicle with the base of the brain, was the primary source of certain motor impulses now thought to originate in the bulb or medulla oblongata. The anatomical relations of the two organs to which I attribute such commanding importance is well shown in the illustration on page 963, in the ascidian. The ganglion adjoined to the pituitary body *hy,* is not merely the cell-body of a neuron, as the term implies; as stated by Jacques Loeb:[16] "In ascidians the central

[16] Jacques Loeb: "Comparat. Physiol. of the Brain," p. 35, 1902.

nervous system *consists* of a central ganglion." It is, in other words, the source of *all* motor impulses transmitted to the various organs of these animals.

In the higher Chordata, which include all vertebrates—fishes, amphibians, reptiles, birds and mammals and, therefore, man—the anatomical relations remain the same as in the Ascidians. Thus, as stated by Parker and Haswell[17] in reference to the development of the pituitary is this phylum: "The floor of the diencephalon grows downward into a funnel-like prolongation, the *infundibulum:* with this the pituitary diverticulum of the pharynx comes into relation, and there is formed partly from the dilated end of the diverticulum, partly from the extremity of the infundibulum, a gland-like structure, the pituitary body or hypophysis, always situated *immediately in front of the anterior extremity of the notochord.*" In other words, from the lowly Ascidian, which represents one of the simplest organisms classed among the Chordata, up to man, the pituitary body is connected with, and forms part of, the upper extension of spinal cord in the base of the brain. Its infundibular extension, as is well known, is the *neural* or posterior lobe of the pituitary, which is separated from the anterior or "glandular" lobe by the partition in which the "test-organ" is embedded.

That the pituitary body fulfills important functions in the higher animals as well as in the lower forms is strikingly suggested by the results that follow removal of the organ, especially when it is fully developed, as in adult animals.

Marinesco[18] trephined the bone underlying the organ and destroyed the latter by cauterization in cats. Two died almost immediately; two twenty-four hours later, one lived four days, another five days, and the last eighteen days. No cause for death could be found other than the destruction of the pituitary. Dastre[19] performed similar experiments. All the animals died. Alluding to Marinesco's experiments and to others by Vassale and Sacchi,[20] Schäfer states that the symptoms observed were: "(1) diminution of the body temperature; (2) anorexia and lassitude; (3) muscular twitchings and tremors developing

[17] Parker and Haswell: "T. B. of Zoölogy," vol. ii, p. 96, 1897.
[18] Marinesco: Bull. de la Soc. de biol., June 4, p. 509, 1892.
[19] Dastre: Richet's "Dict. de physiol.," vol. i, p. 109, 1895.
[20] Vassale and Sacchi: Arch. ital. de biol., vol. xxii, p. 123, 1895.

later into spasms; (4) dyspnœa." In their original article, Vassale and Sacchi mention an instance in which the pituitary was only partially destroyed; although the characteristic phenomena followed and lasted about three weeks, the animal recovered and remained healthy eleven months. The incomplete destruction of the organ was then confirmed. They state that animals die promptly after a complete operation. Andriezen[21] says that destruction of the pituitary causes apathy and psychical depression, marked relaxation of the muscular system, and muscular spasm. Co-ordination and equilibrium are greatly impaired. The temperature becomes abnormally low; nutrition is reduced; cachexia supervenes and death follows. Caselli[22] after removal of the gland in young animals observed cachexia, glycosuria, and death. Pirrone[23] ascertained experimentally, among other facts, that "the results of the suppression of its functions are disturbances of mobility, great depression, rapid emaciation, cachexia and death." He was also led to conclude that "although the exact functional mechanism of this gland is not as yet well understood, it is evident that it is of the greatest importance to the economy," and furthermore, that "although a partial lesion is compatible with existence, its total removal irrevocably leads to death." Krönlein and Von Eiselsberg[24] destroyed the pituitary body in cats. The procedure invariably proved fatal. Friedmann[25] removed the organ from several kittens from 3 days to 10 weeks old. All died except one, which showed "an insignificant staggering" and lived two and one-half months. With Maas[26] the same observer also removed the pituitary in eighteen animals. Twelve died in from one to thirteen days; two died of complications; three which continued to live, were found still to possess a part of their organs; the remaining one, notwithstanding complete removal, lived three and one-half months; after which it was killed. Death might be ascribed, in these younger animals at least, to the severity of the operative procedure adopted, since, as I have stated in the first volume,

[21] Andriezen: Brit. Med. Jour., Jan. 13, 1894.
[22] Caselli: "Studii anat. e sperim. sulla fisio-pat. della glandula pituitaria," 1900.
[23] Pirrone: La riforma medica, Feb. 25, p. 205, 1903.
[24] Krönlein and Von Eiselsberg: Trans. German Surgical Assoc., Apr. 6, pp. 110, 111, 1904.
[25] Friedmann: Berliner klin. Woch., May 12, p. 436, 1902.
[26] Friedmann and Maas: *Ibid.*, Dec. 24, p. 1213, 1900.

the thymus fulfills to a certain extent the functions of the adrenal system until the organs composing the latter are developed. Very young mammals correspond with the lower vertebrates (toads, frogs, etc., for instance) in this particular, the morbid effects of removal growing in intensity as the higher mammals are reached.

The most decisive experiments, however, were performed by Masay,[27] whose object was to ascertain whether all the animals did not die owing to the severity of operation. After removing a disc of bone 6 millimeters in diameter from beneath the pituitary body of two dogs, he rapidly destroyed the organ with thermocautery. The next day both animals were profoundly asthenic and unable to stand, while spasmodic twitchings and "convulsive trembling" occurred. On the third day, these phenomena became more marked; coma supervened, and the animals died. The pituitary body was found cauterized in both animals and congestion of the nerve-centers was noted. In a third dog, the same procedure was resorted to, but in two stages. The pituitary body was exposed as in the two other instances, and the animal *allowed to recover.* Two secondary hæmorrhages and marked hyperthermia occurred, but a week later all signs of discomfort had disappeared. The pituitary was then destroyed with galvano-cautery. On the following day, the symptoms observed in the two other dogs appeared, viz., marked asthenia, with occasional paroxysms of muscular spasm or very violent convulsions, *hypothermia,* and "very rapid" heart beat. They became gradually more intense, and the lethal course observed in the other animals followed.

It is when the fatal influence of removal of the pituitary body is compared with the effects of removal of the *brain* that the functional importance of the former organ asserts itself.

Beginning with the lower vertebrates we have Wilber's frog,[28] which lived five years after removal of its cerebral hemispheres. "During all this period the animal never once showed signs of any initiative, its only movements being very slight and attributed to muscular ennui, like that of persons asleep. The eyes, optic nerves, and optic lobes of the brain were unin-

[27] Masay: Ann. de la Soc. roy. de sci. méd. et nat. de Bruxelles, T. xii, Fasc. 3, p. 1, 1903.
[28] Wilbur: Amer. Med., Jan. 7, p. 6, 1905.

jured, and the animal could evidently see, but without understanding. The most attractive frog food put before it was absolutely unnoticed, and it has been fed every day for five years by an attendant, who would open its mouth, and with force push a bit of fresh meat or fish far enough back into its throat to arouse the reflex mechanism of swallowing. If touched, it would move or leap; if placed in water, it would swim until some support was reached; if turned upon its back, it would promptly and vigorously right itself."

In a higher vertebrate, the pigeon, the results are the same. "The results of ablation of the cerebral hemispheres in pigeons," says Schäfer,[29] "have been described in great detail by Rolando, Flourens, Longet, Vulpian and others. A pigeon so mutilated continues able to maintain its equilibrium and to regain it when disturbed. When placed on its back, it succeeds in regaining its feet. When pushed or pinched, it marches forward. Should it happen to step over the edge of the table, it will flap its wings until it regains a firm basis of support. When thrown in the air, it flies with all due precision and co-ordination. Left to itself, it seems as if plunged in profound sleep. From this state of repose it is easily awakened by a gentle push or pinch, and looks up and opens its eyes. Occasionally, apparently without any external stimulation, it may look up, yawn, shake itself, dress its feathers with its beak, move a few steps, and then settle down quietly, standing sometimes on one foot and sometimes on both. Should a fly happen to settle on its head, it will shake it off. If ammonia be held near its nostrils, it will start back. Should the finger be brusquely approximated to its eyes, it will wink and retreat. A light flashed before its eyes will cause the pupil to contract; and if a circular motion be made with the flame, the animal may turn its head and eyes accordingly. It will start suddenly and open its eyes widely if a pistol be discharged close to its head."

In the higher mammals, the absence of the influence of the brain on the life processes is none the less evident. Goltz's world-renowned dog which lived eighteen months after its brain (including part of the optic thalami and corpora striata) had been removed piecemeal, affords a striking example of this fact.

[29] Schäfer: *Loc. cit.*, vol. ii, p. 700.

It walked about, curled itself up when about to sleep, reacted promptly to tactile impressions, thus showing that the sensory mechanism was not destroyed; it snarled and barked, withdrew its feet when these were placed in cold water, recovered its equilibrium when its feet were placed on the falling flap of a table; limped when one of its legs was accidentally hurt; rejected and showed dislike for meat rendered bitter with quinine, and refused more food when satiated.

Thus, in animals that live long enough after complete destruction of the pituitary body, morbid phenomena occur which point clearly to disturbance of cardinal vegetative functions, as shown by dyspnœa, hypothermia, rapid emaciation, asthenia, staggering, impairment of co-ordination and equilibrium, cachexia, spasms, convulsions and death. Removal of the hemispheres, on the other hand, disturbs in no way these functions—sensory or motor—thus showing that even in the higher mammals, all purely automatic functions, oxygenation, circulation, digestion, nutrition, locomotion, general sensibility, etc., are absolutely independent of the cerebrum. Indeed, Soury,[30] referring to the *cortex,* remarks: "The experiments of Steiner, Goltz, and Schrader show that the existence of this organ is not necessary in the performance of psychical functions considered in general as *inferior.*" . . . . "It is the organ for superior psychical functions termed memory, association of ideas, acquired experience and reflection."

That the pituitary body is the seat of functions now generally attributed to the cerebral cortex is evident.

While experiments in animals, clinical and post-mortem observations have shown the existence in the cortex of areas which have been called "motor" because motor effects were elicited on stimulating them, this term is used merely for want of a better one and is not regarded by physiologists as necessarily meaning that the impulses transmittted from the cortex are necessarily "motor" in the sense usually given this word. "The terms 'motor area' and 'motor center,'" says Schäfer,[31] "are here used to imply those portions of the cerebral cortex which are directly connected by efferent projection fibers with the lower

[30] Soury: "Système nerveux central," T. i, p. 635, 1899.
[31] Schäfer: *Loc. cit.*, vol. ii, p. 722.