and histological investigations—and those contributed by Gentès, harmonize therefore in attributing to the anterior pituitary body—including its posterior wall—besides the functions its epithelial elements subserve, the rôle of a sensory organ. It is evident, therefore, that my opinion that the purpose of this organ is to afford some form of protection to the organism, harmonizes fully with the teachings of several branches of biological science.

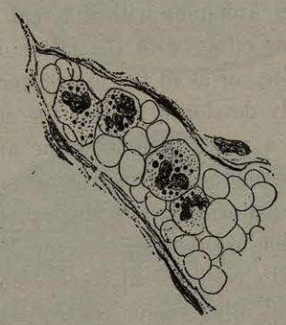
In the higher animals, however, we are no longer dealing with a structure which, as in the sea-squirt, the mussel, the lancelet, etc., tests in-going sea-water; and as their "respiratory fluid" is the blood, it follows that whatever protection the test-organ affords in these higher vertebrates, including man, must have for its purpose to counteract the effects of poisons brought thereto by the blood. Indeed, as stated by Claude Bernard, the blood of vertebrates "is an internal medium in which the anatomical elements live as fishes do in water."[29]

Again, the protection afforded by the test-organ in the invertebrates is far-reaching not because the oxygen derived from their respiratory fluid is materially reduced when noxious materials are present in it, but because this fluid also brings them their food. Thus, Amphioxus buries its body in the sand, the mouth and its cirri protruding in the water above. The latter, which supplies it with its oxygen, also brings microscopic plants and débris, which pass downward into the slimy secretion of its pharynx, while the water passes out again through the gill-slits, the respiratory organs. The test-organ is so situated, however, that any noxious substance entering either the respiratory or digestive apparatuses of the animal comes into contact with it. It is evident that the purpose of the test-organ is not so much to protect the animal against toxic agents that compromise the purity of the water as a respiratory fluid but as a nutritional medium.

This apparently militates against the fact that in the higher animals the blood replaces the sea-water as regards its functional relations with the test-organ of the pituitary body, since, in the light of the views I have advanced, it is not the

[29] Claude Bernard: "Leçons sur les propriétés des tissus vivants," pp. 55 to 58, 1866.

plasma which contains proteids and other food-stuffs, but the leucocytes. The situation would seem further complicated by the fact that, as shown in the preceding section, poisons as well as foods are absorbed in the intestinal canal and in the blood by these cells, and distributed by them throughout the organism. If, as in the invertebrates or ancestral vertebrates provided with a test-organ and a water vascular system, poisons must come in contact with the test-organ, in the higher vertebrates provided with a blood vascular system, the leucocytes would have to *enter* the pituitary body and secrete their toxic principles therein. That these cells, *i.e.*, leucocytes laden with poisons, food-products, etc.—can penetrate into the anterior pituitary is shown in the annexed illustration of a section of



POLYNUCLEAR LEUCOCYTES IN THE INTRAPARENCHYMATOUS CAPILLARIES OF THE ANTERIOR PITUITARY. (*Launois.*)

this organ, borrowed from a very able work by Professor P. E. Launois, of Paris,[30] and intended to show the presence of fat globules (a normal result, from my viewpoint, of the fact that they ingest fats in the intestinal villi) in what he describes as "polynuclear leucocytes of the blood in the intra-parenchymatous capillaries." It is obvious, therefore, that at least some of the leucocytes whose function it is to absorb food-substances, poisons, etc., anywhere in the body enter the anterior pituitary body.

What is the nature of their relationship with the test-organ? How can this structure become influenced by the rela-

[30] P. E. Launois: "Recherches sur la glande hypophysaire de l'homme," Paris, 1904.

tively small number of peptone- or poison-laden leucocytes which, merely as casual cellular constituents of the blood, happen to circulate in this organ? Before these questions can be answered, certain features of the prevailing views concerning the functions and histology of the anterior pituitary body require attention.

The anterior pituitary is now considered as a secreting gland, capable, as are the thyroid and adrenals, of furnishing a secretion to the blood. In the light of my views, however, this rôle no longer belongs to the pituitary body in all animals provided with adrenals, since I regard these organs as offshoots, so to say, of the anterior pituitary, which assumed at a given time in the animal scale all the secretory functions of the latter. Whether the adrenals, as in Sauropsida, be closely connected with the gonads, in Amphibia with different parts of the mesonephros, in Teleosts either with the latter or with the degenerate pronephros, etc., or as in the higher vertebrates, including man, with the fully developed kidney, the adrenals are invariably connected by a nerve path with the anterior pituitary—through, we have seen, the posterior or neural lobe, with which it becomes merged during embryological development. The purpose of this union asserts itself in view of the fact—pointed out in the preceding chapter—that the neural lobe is the seat of the sympathetic and other motor centers which have as their purpose to connect the test-organ with the nerve-center through which its defensive functions (as regards the body at large) can be carried out, namely, the adrenal center.

These facts suggest and additional evidence will show, (1) that the anterior pituitary body is not a secretory organ, and (2) that its function, as previously emphasized, is to test the quality of the blood circulating through it and awaken, if need be, a defensive reaction throughout the body. Such being the case, the supposed "secretory" elements of the anterior pituitary cannot be such. This is further suggested by the arrangement and structure of the epithelium.

If the organ were a gland, its secreting elements should be arranged in regular rows as in other glands, but such is not the case. As is well known, the anterior pituitary is made up of convoluted tubes or alveoli. In these structures, the cells,

Fig. 1.

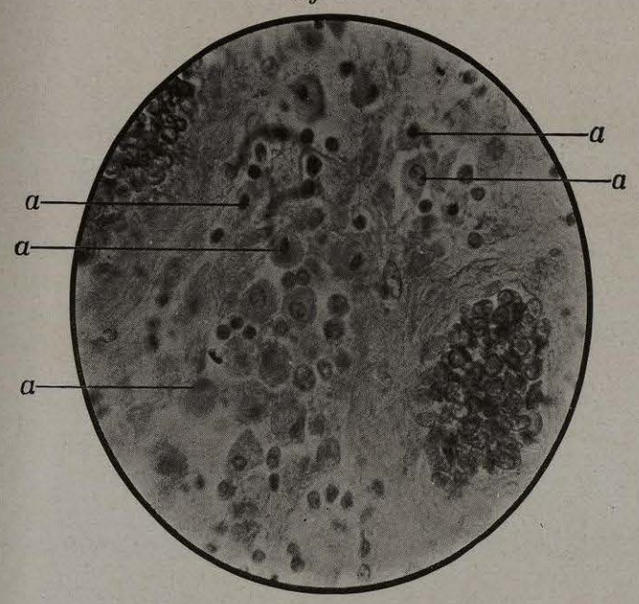
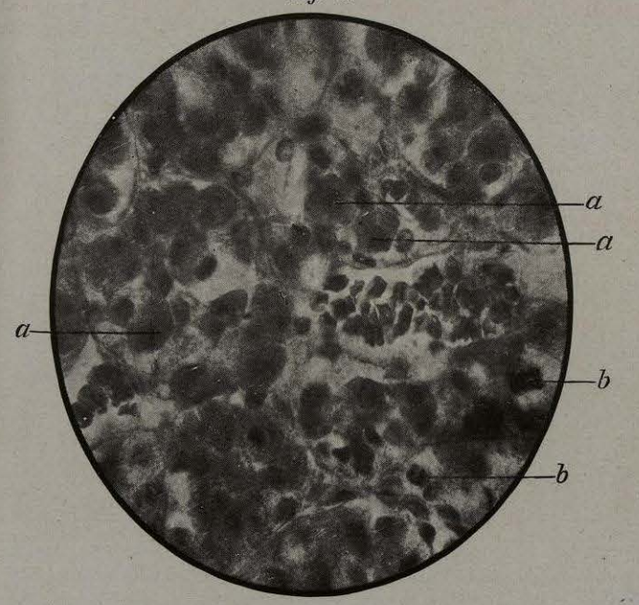


Fig. 2.



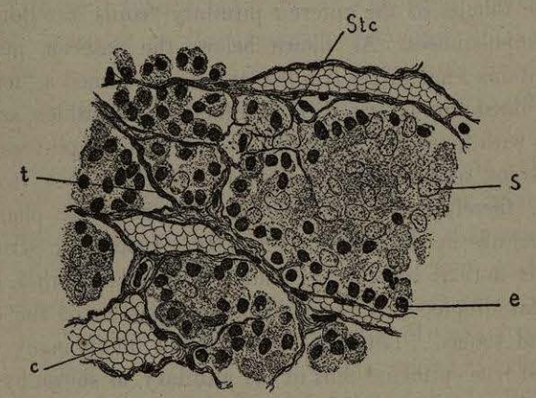
THE EPITHELIUM OF THE ANTERIOR PITUITARY AS PARTLY COMPOSED OF PHAGOCYTIC EPITHELIOID CELLS. *[Sajous.]*

Fig. 1, Epithelioid cells in a tuberculous lymphatic gland a.

Fig. 2, Normal tissue of anterior pituitary. Phagocytic epithelioid cells a.

although here and there arranged in order, owing to the contiguity of their tubular walls or stroma, are massed promiscuously. This is made clear by the cut reproduced below, from a paper by Launois and Mulon,[31] which shows according to their description, "siderophile" and "eosinophile" cells. In fact, Launois specifically states that they are simply groups of cells between which a secretion is formed. The microphotograph opposite page 1046 likewise emphasizes this important fact.

On the other hand, there is a striking resemblance between the large mononuclear cells which constitute the supposed gland-



IRREGULAR AND PROMISCUOUS DISTRIBUTION OF CELLS IN THE STROMA.
Stc, Intercellular stroma. *t*, Offshoots from the stroma. *c*, Blood capillaries. *s*, Siderophile cells. *e*, Eosinophile cells.

ular epithelium of the organ and the phagocytic endothelioid cells found, for instance, in the mesenteric lymph-glands. To emphasize this resemblance I submit herewith two microphotographs, one of an aggregate of such lymphatic endothelioid cells from a case of tuberculosis of the peritoneum (Fig. 1); and one of normal tissue from the anterior pituitary (Fig. 2). Indeed, the morphological structure of the pituitary is such as to have caused it to be compared to a lymph-gland by the older investigators, Monro, Müller[31a] and others. Nearer, however, to my own interpretation, is that of Charles Robin,[31b] who, in 1860,

[31] Launois and Mulon: Annales de gynéc. et d'obstet., Jan., 1904.
[31a] Müller: Jenaische Zeitsch. f. Naturw., Bd. vii, S. 327, 1873.
[31b] Charles Robin: "Dictionnaire Encyclo. des Sc. Méd." art. "Lymphatiques," 1860.

specified that the pituitary body did not actually form part of the lymphatic system, but that it was a lymphoid organ.

From my standpoint, however, this applies only to the anterior lobe. As is well known, it is bean-shaped and the posterior lobe is incorporated into its hilum. Böhm, Davidoff and Huber[31c] state, referring to lymph-glands, that "in shape they are much like a bean or kidney and the indentation on one side is known as the hilum." Both the anterior pituitary and the lymph-gland have a fibro-elastic capsule, septa which divide the organ into a multitude of compartments to which the above-named histologists refer as "medullary cords" (just as Launois calls the tubules of the anterior pituitary "cords"). Both contain lymph-sinuses. As shown below, the anterior pituitary also contains what in the lymph-gland Toldt termed a "terminal sinus," lined throughout with endothelial cells, which are continuous with those of the afferent and efferent lymph-vessels,"—the afferent vessels being omitted in the pituitary. It is not strange, therefore, that we should find the great phagocytic mononuclears in the anterior pituitary. Lymphatic structures are their normal habitats. Finally, we have seen that Reuter found fat droplets "in the lymphatic corpuscles of the diffuse lymphoid tissue." Launois likewise found fat in many of the supposed true epithelial cells of the pituitary, as shown by staining reactions, osmic acid, etc.

The function of these cells in the anterior pituitary likewise assumes a normal aspect, since it is essential that broken-down cells, including the leucocytes which have secreted their products into the organ, should be promptly eliminated. This is essentially the rôle of the mononuclears, acting as Metchnikoff's macrophages, *even when epithelioid, i.e.,* when forming part of an epithelium from which they can free themselves and migrate away. Thus, as stated by Ziegler,[31d] "proliferating tissue can produce cells which appear very like the larger forms of mononuclear leucocytes." Hektoen,[31e] on the other hand, states that "in typhoid fever a marked proliferation occurs in the endothelial cells of the lymph-follicles of the intestine, mesenteric lymph-nodes and spleen; and the new cells acquire marked

[31c] Böhm, Davidoff and Huber: "T. B. of Histol.," p. 197, 1905.
[31d] Ziegler: "General Pathology," p. 269, 1898.
[31e] Hektoen: "Amer. Text-book of Pathol.," p. 149, 1901.

phagocytic properties." Or, instead of migrating from the organ, these mononuclears may combine to form a giant cell. Referring to the formation of tubercle, for instance, Metchnikoff[31f] writes: "It is composed of a collection of phagocytes" . . . . . "which move towards the spot where the bacilli are situated and englobe them. The phagocytes retain their condition of epithelioid cells, or are transformed into giant cells." All this illustrates mononuclears in the act of apprehending pathogenic elements, detritus, broken-down cells, etc., of some kind, though forming part of the organ's parenchyma, and applies as well to the anterior pituitary as to any other lymphatic organ. Interpreted from my standpoint, therefore, *what is now regarded as the glandular epithelium of the anterior pituitary is mainly composed of promiscuously distributed epithelioid mononuclear macrophages, which carry on therein, as elsewhere, their function of general scavengers.*

Although he does not in any way refer to cells of the anterior pituitary as leucocytes—regarding them, in accord with all other investigators, as true epithelial cells, Launois's description of these elements clearly points to them as leucocytes, including the large mononuclears and giant cells referred to above. Thus, he refers to three types of cells found in the gland, judging, he says, "from their tinctorial affinities," as *"acidophiles," "basophiles"* and *"chromophobes."* Indeed, some cells, he says, recall when stained "the *neutrophile* granulations contained in certain leucocytes." Now, in Figure 1, we saw that "polynuclear" leucocytes are present, while the cells just referred to are "neutrophiles." Moreover, as I have previously shown, these are precisely the nutritional leucocytes which I traced from the intestinal canal to the tissues.

Launois refers also to the "acidophiles" as "siderophiles." We have seen in Gulland's plate opposite page 668 (first volume) that corresponding leucocytes also take the iron-hæmatoxyline stain and are colored black by it. The mitoma or networks present in these cells are also observable in the supposed epithelial cells, for Launois refers to the presence of a "reticulum." The basophiles likewise correspond tinctorially

[31f] Metchnikoff: "Lectures on the Comparative Pathol. of Inflam.," Starling's transl., 1893.

with leucocytes; they stain violet-blue with hæmatoxyline, pink with hæmatin-eosin, orange-yellow with hæmatin-eosin orange —even though there is good reason to believe that as soon as they enter the organ—or rather its anterior lobe—leucocytes promptly secrete their granules and thus lose their main staining affinities. This accounts—only from my viewpoint, of course—for the presence in the organ of the cells to which Launois refers as "chromophobes" (Comte), *i.e.*, cells which have but slight affinity for stains.

Regarded as leucocytes, and as I interpret their function, these "chromophobes" are merely depleted leucocytes. Thus, Launois refers to them as "still containing" *very few* "acidophile," "basophile" or "siderophile" granulations. They are found disseminated among the other elements of the organ and aggregate in clumps, the periphery of which is alone stainable. At first the granules accumulate in masses, which Launois connects "intimately" with the secretory process of the organ considered as a gland; interpreted from my standpoint, however, these granules are the identical granulations which leucocytes secrete elsewhere, and that are here used by the organ as a secretion. Indeed, Launois refers repeatedly to the presence of "granulations." In the basophile cells, for instance, he found the protoplasm rich in granulations "which have an elective affinity for basic dyes." In fact, he actually mentions the escape of granulations in the neighboring fluids and their dissolution therein. Scaffidi[32] also observed recently that the cells of the anterior pituitary shed their granules, and that when this is accomplished, the cytoplasm is disposed closely around the nucleus. Such cells are shown in the plate opposite page 1050.

All this explains why supposed "glandular cells" are so promiscuously distributed in the organ. Thus, Launois states that the distribution of these cells is very irregular, some "cords" being composed of eosinophiles, others of basophiles only, but that in general the different types are met with "in the one cord." At times the cells are distributed equally in all regions of the gland; at others, certain territories are richer in basophiles, others in acidophiles. There is as to this, he remarks, no fixed rule.

[32] Scaffidi: Arch. f. mikros. Anat., Bd. lxiv, S. 235, 1904.

Briefly, besides the great mononuclears, which are probably evolved *in situ,* since small mononuclears are also present in great numbers, and giant-cells, all of which are described by Launois under the belief that they are true epithelial cells, the organ contains the more familiar blood leucocytes, *i.e.*, neutrophiles, basophiles and acidophiles.

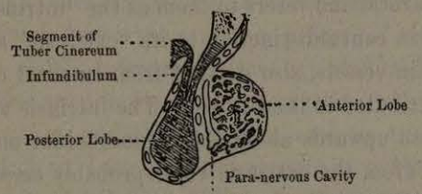
Before the details of the functional mechanism of the anterior pituitary, as interpreted from my standpoint, can be submitted, a few anatomical facts must be reviewed.

The leucocytes, as we have seen, are present not only in the tubules of the organ, but also in its capillaries, which are, according to all classics, very abundant. These are, as shown by Obersteiner,[33] the continuation of a number of vessels which pass from the base of the brain to the anterior lobe along the anterior surface of the infundibulum. Launois traced them to the internal carotid and refers to them as the "intrinsic" vessels of the organ, in contradistinction to its "extrinsic" supply, *i.e.*, two sets of thin vessels, also derived from internal carotid but which are distributed to the surface. The intrinsic veins of the organ also pass upwards along the infundibulum and meeting those derived from the extrinsic veins probably empty, according to Launois, in the deep sylvian vein. Both the intrinsic arteries and veins, according to Berkley,[34] "directly pass" into the anterior lobe "from the substance of the infundibulum." He speaks of a "large number of vessels" in this connection, a fact which accounts for the very rich supply of capillaries throughout the organ and between the tubules, which, as stated by Gray,[35] are united together by a very vascular connective tissue." It is apparent that leucocytes can readily enter the anterior pituitary with its arterial blood, and penetrate to every part of this organ.

That it is possible for the leucocytes to circulate freely in these parenchymatous capillaries and also to migrate through their walls, is shown by the fact that Obersteiner[36] found the vessels which pass between the cellular tubes "numerous and large" and their walls "remarkably thin"—so much so, indeed,

[33] Obersteiner: Soury, "Système nerveux central," vol. ii, p. 794, 1899.
[34] Berkley: Brain, Winter, p. 517, 1894.
[35] Gray: "Anatomy," p. 656, 1901.
[36] Obersteiner: *Loc. cit.*

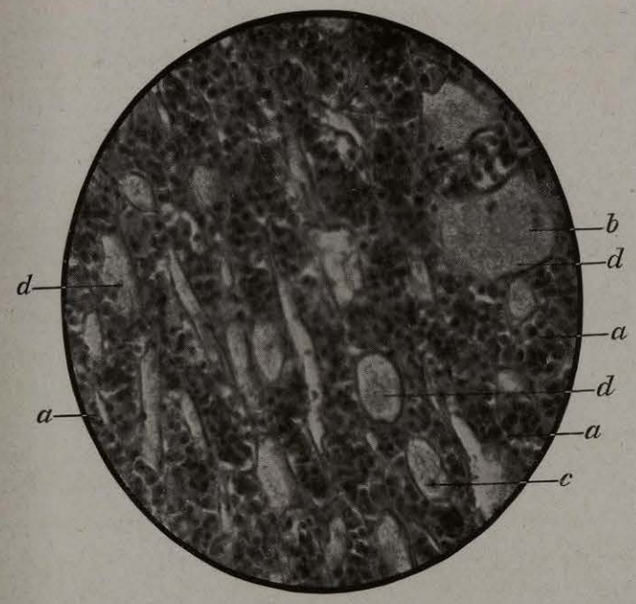
that Launois observed actual tears in the capillary walls of overactive organs which afforded a free communication with the tubules. The annexed microphotograph, in which leucocytes are present among many red corpuscles, clearly suggests, in fact, that the connective tissue walls of the tubules and capillary walls are one, and that, as elsewhere in the body, leucocytes laden with food-products, drugs, poisons, etc., can readily enter the tubules. Such leucocytes are plainly shown in the tubules in the same illustration. Here they evidently secrete their contents, for, as Comte has suggested, and as Launois was able to show by staining methods (although of course unaware that he was dealing with leucocytes), "two secretory products, one *basophile* and the other *acidophile*," are secreted, while the "intermixture of the cells which elaborate them indicates that these two products are themselves mixed before being eliminated from the parenchyma."



PERPENDICULAR ANTERO-POSTERIOR SECTION OF THE PITUITARY BODY OF A HUMAN EMBRYO OF FOUR MONTHS. (*Edinger.*)

Interpreted from my standpoint these are all very important features of the question in point. The leucocytes, containing as they do whatever they may have absorbed in the intestinal canal or in the blood, are distributed, we have seen, throughout the entire organism. What proportion of these cells happens to penetrate into the pituitary to form the supposed secretion is, as it were, a *sample of the food-elements and any noxious substance that they may contain, which are being distributed broadcast.* The blood as the bearer of leucocytes thus laden, fulfills the rôle that sea-water does in lower forms.

In these lower organisms, however, we have seen that the "respiratory fluid" and the food materials it contains are brought into contact with the center of their auto-protective mechanism, their "test-organ" or "osphradium." How is the corresponding process carried on in the anterior pituitary of the higher animals, including man?



PROMISCUOUS DISTRIBUTION OF CELLS IN THE ANTERIOR PITUITARY. *[Sajous.]*

a, Large epithelioid phagocytes. b, Neutrophile-nutritional-leucocytes. c, Basophile leucocyte. d, Capillaries.

Between the anterior lobe and the partition separating it from the posterior lobe is a transverse space, the "para-nervous slit" or pocket, which Haller, Parameschko, Cadiat and others regarded as an excretory canal, but which in reality is closed on all sides. It varies greatly in shape: it may be broken up by projections that unite the two surfaces, or form a relatively spacious vesicle; it may also appear closed, the two walls being almost in contact even though their cellular elements are different in nature. Thus while the surface forming part of the anterior lobe is lined with ciliated epithelium, that of the partition proper is composed of the sensory epithelium which, as shown below, forms the test-organ. Now, this cavity doubtless fulfills some important function: "The cavity proper of the para-nervous slit, the capacity of which varies," writes Launois, "contains a peculiar substance, the quantity of which is itself subject to the greatest fluctuations. This substance, which is apparently elaborated by the epithelial elements of the walls, is a mixture of *acidophile*, *amphophile* and mucoid secretion. While it recalls the materials we found in the parenchyma of the pituitary, it differs from it in being more *granular*, less homogeneous, and less compact. Staining methods show, moreover, that this substance is subject to currents, whirlpools and localized accumulations". . . . "and afford a new proof of the diversity of secretions of which the pituitary may be the source."

In the light of my views, these substances are not glandular secretions, which, as we will see, do not exist, but waves of a colloid compound of dissolved granules derived from food-products, normal or toxic physiological wastes, drugs, poisons, toxins, etc., that the leucocytes have brought to the sponge-like parenchyma of the organ and which the latter—probably owing to rhythmic contractions of its capsules—projects towards the "para-nervous" cavity.

That the anterior lobe is a contractile organ is suggested by the structure of its capsule, the currents and whirlpools, and by the fact that delicate nerve-fibers are distributed throughout its parenchyma—doubtless the terminals which Ramon y Cajal traced to the great nucleus in the third ventricle. Berkley[37]

[37] Berkley: *Loc. cit.*, p. 517.