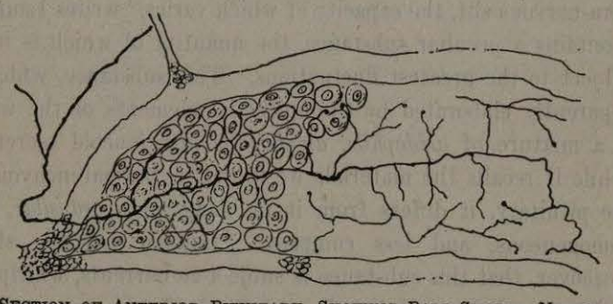
describes these fibers as "bundles of small nerves following the course of the arteries" and from which "come off, at irregular intervals, single fibers, or branches from the main stems, which pursue a very irregular course through the glandular substance, crossing over or accompanying the large venous channels in the septa, and finally being distributed upon the coils of the epithelial cells forming the follicles." His drawing of a set of these fibers, including their ball-shaped terminals, is reproduced below. These ball-shaped endings recall strikingly the sensitive terminals found elsewhere in the œsophagus, larynx, bladder, etc. If they are sensory, their purpose suggests itself: to provoke reflex dilatation of the blood-vessels through which the organ relieves itself of the blood which has



SECTION OF ANTERIOR PITUITARY, SHOWING BALL-SHAPED NERVE TERMINALS AMONG CELLULAR ELEMENTS. (*Berkley.*)

caused it to dilate. The capsule of the anterior pituitary, containing as it does "a fine network of elastic fibrils" (Launois), dilates when the organ is hyperæmic—as shown by the enlarged appearance often witnessed during hyperactivity such as that observed in eclampsia (Launois and Mulon), the early stages of acromegaly, etc., and contracts again when the venous and lymphatic channels are widely opened. The "currents and whirlpools," etc., observed by Launois in the para-nervous cavity clearly suggest that some such propulsive mechanism must exist in the organ, the semi-fluid substance being no longer within the capillaries and, therefore, under the influence of the *vis a tergo* motion of the blood. The colloid substance being derived from the tubules, the compression necessary to drive it out through the meshes of their connective tissue (see the homologue of such a network in the plate opposite page

1068) must begin in the periphery of the organ—a function for which the elastic capsule is eminently fitted. On the other hand, the pillow of venous blood which separates the pituitary from its pedestal, the sella turcica, affords ample leeway for its preliminary dilatation.

The para-nervous cavity is probably itself distensible, a fact which would account for the variations in shape, the approximation of its walls or "the widened and somewhat globular" outline observed by Launois. Dilatation owing to the accumulation of leucocytic products swept into it when the anterior pituitary contracts, at one time, and contraction when it is emptied at another, affords a logical explanation of the post-mortem appearances witnessed.

The manner in which the blood deprived of the leucocytes that have migrated into the tubules passes out of the anterior lobe is made clear by the fact that it remains in the sinusoidal capillaries. It is therefore returned to the circulation by the venules which terminate in the large veins in the infundibulum.

As to the detritus, scavenger cells, etc., they have a path of their own—one common, as regards the corresponding process, to all lymphatic structures. Müller,[38] in the course of a comprehensive study of the pituitary body from Myxine to man, found that the partition between the two lobes was supplied with a rich network of lymphatics through which glandular products found their way to the general lymphatic system. Lymphatic vessels seem to be absent elsewhere in the anterior pituitary. The process of elimination during life must be a very active one. The microphotograph facing the next page shows a large number of cells in the act of being ejected from the organ (the effect of periodical contractions such as those of the spleen) in a current of "colloid"—an aggregate of lymph, adrenoxidase, dissolved granules, etc., as previously stated. Here as in several slides studied, the mass occurred in what corresponds with the external orifice of the lymphatic spaces, while in other slides the cells had not as yet reached the outlet when death of the organism of which it formed part took place, arresting the progress of the cells to the external lymphatic vessels.

Summarizing all these facts, it seems evident (1) *that the*

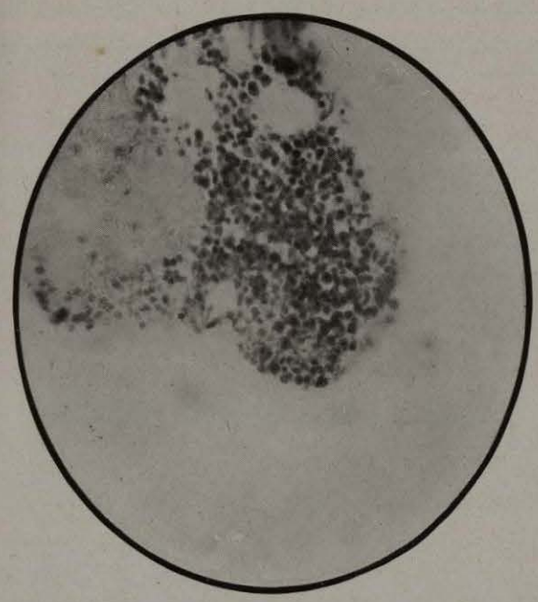
[38] Müller: Jenaische Zeitsch., Bd. vi, 1873; cited by Guépin: Tribune médicale, Dec. 10, 1891.

anterior pituitary is, like all lymphoid glands, intimately connected with the defensive functions of the body, through the presence in it of large mononuclear macrophages; (2) *that these large mononuclears are epithelioid cells in the sense that they form in the organ an irregular epithelium;* (3) *that after the smaller phagocytic leucocytes, especially the neutrophiles, secrete (as they do elsewhere in the body) their granulations and other products of food-materials, waste-products, drugs, poisons, toxins, etc., ingested by them anywhere in the body, those leucocytes which have been killed by microbes, poisons, etc., are removed as detritus from the anterior pituitary by its mononuclear macrophages; and* (4) *that this process of elimination is assisted by periodical contractions of the organ such as those of the spleen, which project all living leucocytes and a current of colloid—an aggregate of lymph, adrenoxidase, dissolved granulations, drugs, wastes, poisons, etc.,—into the lymphatic spaces of the organ and then into the lymphatic system, whence they pass into the blood to be destroyed.*

The cardinal feature of all this evidence, however, is that the contents of the leucocytes which penetrate into the tubules, *i.e.*, their nutrient granules—more or less dissolved—and any noxious substance that may be harmful to the organism at large, are brought—more or less modified probably by the ciliated epithelium of the anterior wall of the para-nervous cavity—*into contact with the sensitive epithelium, i.e., the test-organ.*

The identity of this organ as a sensitive structure asserts itself from various directions. Gentès, who described this structure in the higher animals, does not refer to the possibility of its being the homologue of the test-organ of ancestral forms. This adds value to his description of the developed organ—to which I attribute such important functions. Thus, while he describes its superficial layer in the higher mammals as composed of "stratified cylindrical epithelium which resembles certain sensory epithelia," Ray Lankester defines the corresponding organ in ancestral animals—as to location and anatomical relations—as "a patch of epithelium . . . . peculiarly modified and supplied with a nerve and ganglion." Still more to the point is the remark of Huxley and Martin[39] con-

[39] Huxley and Martin: "Practical Biology," p. 312, 1892.



LEUCOCYTES WHICH HAVE SHED THEIR GRANULES, LYMPHOCYTES, ETC., IN THE ACT OF BEING EJECTED FROM THE ANTERIOR PITUITARY. *[Sajous.]*

cerning the mussel, that "as the parieto-splanchnic ganglia are immediately connected with a patch of *sensiferous epithelium* in the roof of the inhalent siphon, they are sometimes regarded as *olfactory*."

In its fully developed condition, however, *i.e.*, in the adult dog, cat, rabbit, rat, guinea-pig, sheep, porcupine, etc., in which Gentès studied the organ, it is no longer limited to a mere patch of epithelium, but has become a structure occupying a considerable portion of the partition between the two lobes. On the side exposed to the "para-neural" cavity are five or six layers of cylindrical epithelial cells which give the surface a bosselated appearance, and "recall exactly," says Gentès, "the sustentacular element of *the olfactory* mucous membrane." These cells were found to send numerous fibers to the deeper elements and to connect with "foot-shaped" cells which, in turn, were the source of many fibers distributed very freely throughout the structure. Underlying the cell bodies of the epithelial cells, were two or three rows of bipolar cells which sent fibers towards the surface and also to the deepest layers. A third set of fibers was found to arise in the midst of all these elements and to pass posteriorly through the partition and thence into the maze of cells and fibers which form the neural lobe. These fibers, we have seen, were finally traced by Gentès some distance in the organ and thence by way of the infundibulum to the tuber cinereum.

May not these fibers have come into contact in the neural lobe with other cellular elements? In that case, there would be complete correspondence between the olfactory organ of the pituitary with that of the nasal cavities, including its cerebral segment of the olfactory bulb. Indeed, while Gentès emphasizes the striking resemblance of the sensitive epithelium of the structure described by him to the sustentacular cells of the olfactory region—which are superficial sensory elements—Berkley,[40] ten years before, alluding to certain cells in the posterior lobe, wrote: "Very much more strongly do they resemble the endings of the *mitral* cells of the olfactory bulbs." The fibers traced by Gentès would, under these conditions, be the functional homologues of the olfactory nerves.

[40] Berkley: *Loc. cit.*

Whether this connection exists or not, the fact remains that the sensitive organ—the test-organ—sends nerves to the tuber cinereum, where they connect, as I have shown in the previous section, with a nerve-chain which terminates in the adrenals, the secretion of which, as will be shown presently, is the fundamental factor of the body's auto-protective or immunizing functions.

The main function now attributed to the anterior pituitary body by all authors—that of a secreting organ—finds no place in my interpretation of its rôle in the organism. That it has ceased to secrete when fully developed, *i.e.*, in the higher animals, is shown by various facts:—

The thyroid gland and the adrenals, which are positively known to be the source of a secretion, produce extracts which are very active. Such is not the case, however, with extracts obtained from the anterior pituitary. Howell[41] found that such extracts "when injected intravenously have little or no physiological effect." Garnier and Thaon[42] recently confirmed Howell's observation with extracts prepared from the anterior pituitary of oxen. This is accounted for by the fact that, as I interpret the phylogenetic history of the organ, it ceases to secrete when the adrenals appear.

In the diagram of a sea-squirt shown herewith—a longitudinal section of the animal—the pituitary body (*hyp*) may be seen to send a projection to the respiratory apparatus (*stig*) *i.e*, the duct of the pituitary. The purpose of this relationship is not known. In my opinion this secretion penetrates into the cellular elements composing the respiratory organ, and *endows its blood with the property of absorbing oxygen*, while the water is driven through the stigmata by the active movements of their ciliated epithelium. Indeed, we have seen that in the experiments of Piéri and Portier and others, including my own, in the clam, oyster, and sea-mussel, the (colorless) blood of the gills gave the guaiac-test most actively, thus showing that it was rich in oxidase—the substance which in animals supplied with adrenals I have termed "adrenoxidase." As shown by Abelous and Biarnès, this same active reaction was obtained from the

[41] Howell: "Text-book of Physiology," p. 778, 1905.
[42] Garnier and Thaon: Jour. de physiol. et path. génér., Mar., 1906.

corresponding blood in crayfish, by Phisalix in batrachians, and so on until the highest mammals were reached—always with blood derived from the respiratory organs.

This interpretation is further sustained by the evident connection between the "subneural gland"—the primitive anterior pituitary—and the respiratory organs of another ascidian in which the duct is very long, *Phallusia mentula*. Willey,[43] referring to the structure in which the duct terminates, describes it as the "dorsal tubercle, the opening of the hypophysis into the *branchial* sac." Briefly, in the light of my work, in these

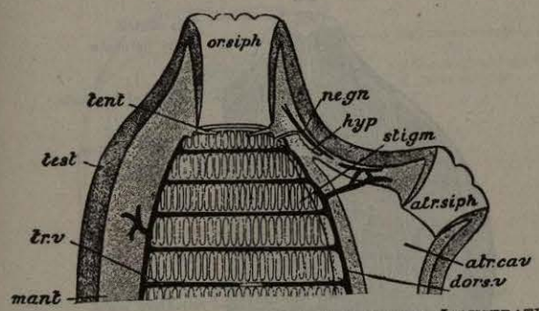


DIAGRAM OF THE UPPER SEGMENT OF A SEA-SQUIRT, ILLUSTRATING THE CONNECTION BETWEEN THE PITUITARY BODY (*hyp*) AND THE ANIMAL'S RESPIRATORY APPARATUS (*stigm*).

ne. gn., nerve-ganglion or general nerve-center; *or. siph.*, oral siphon; *atr. siph.*, atrial siphon; *tent.*, tentacles; *test*, bag; *mant.*, mantle; *tr. v.*, transverse vessel; *dors. v.*, dorsal vessel; *atr. cav.*, atrial cavity. (*Parker and Haswell.*)

invertebrates the ancestral anterior pituitary fulfills the functions which in the higher animals are carried on by the adrenals.

When does the transition take place? This question cannot be answered with any degree of accuracy in the light of available knowledge. The adrenals are now thought to occur in the vertebrates only. A study of the question has led me to believe, however, that they appear much earlier, and that in many invertebrates organs which are now regarded as nephridia—and which as such occupy anomalous positions in their relations to the heart and other organs—are naught else, functionally, than adrenals. This question cannot of course be treated in the present work.

Remaining in this connection within the precincts of ac-

[43] Willey: "Amphioxus and the Ancestry of Vertebrates," p. 190, 1894.

cepted views based on the embryology, phylogeny and comparative morphology of the subject, we may conclude with Launois that "from Tunicata to man, there occurs, in all species of animals, towards the base of the encephalon an organ formed by the intimate contact of a nervous projection with a projection of the stomodæum. In all except Myxine, doomed to retrogression owing to its parasitic life, the stomodæal projection becomes glandular. The gland thus formed is tubular and

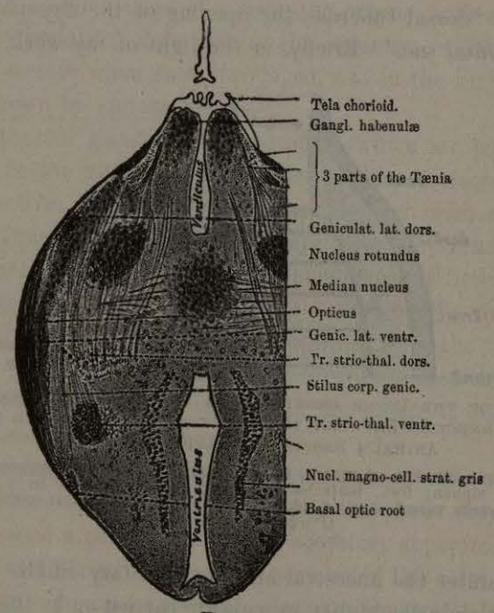


FIG. 1.

VERTICAL SECTION THROUGH THALAMUS OF A YOUNG ALLIGATOR, SHOWING THE GREAT-CELL (NUCL. MAGNO-CELL. STRAT. GRIS.) NUCLEUS OF GRAY MATTER. (*Edinger.*)

rich in blood-vessels. While it opens externally in Tunicata and Amphioxus, it *becomes a closed gland* from the earliest of vertebrates." Hence the prevailing belief that it supplies the blood an internal secretion. Not only, however, has the rôle of this supposed secretion in the organism never been found, but, as we have seen, the organ contains no active substance, while the promiscuous distribution of its cells, the character of the latter, and other facts, indicate that the anterior pituitary is not a secreting gland.

With the evident connection between the anterior pituitary and the respiratory organs of ancestral animals I have indicated, the obliteration of the external opening in the early vertebrates assumes a normal aspect in that it coincides with the appearance of the classical adrenals. Indeed, these organs are not only present in the higher mammals, but also in amphibians and fishes, including those classed among the lowest Chordata, the Elasmobranchii (shark, dog-fish and ray). In these animals, moreover, a suggestive feature asserts itself, viz., the presence in the floor of the third ventricle of the nervous structure

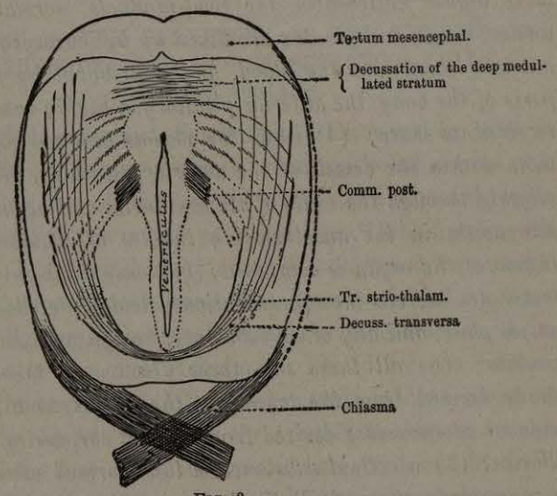


FIG. 2.

HORIZONTAL SECTION THROUGH BASE OF BRAIN OF A SHARK, SHOWING FIBERS FROM GREAT-CELL NUCLEUS. (*Edinger.*)

through which, as I have shown, the pituitary body is united with the upper portion of the spinal system. "One finds in birds and reptiles, probably also in fishes, in the midst of the gray matter that surrounds the median ventricle," writes Edinger,[44] "an elongated nucleus of large cells: *Nuc. magno-cellularis strati grisei.* It is probably fibers from it that pass ventrally to cross just over the infundibulum as the *Decussatio supra-infundibularis.* Besides this, it probably sends bundles off posteriorly." In the annexed illustrations, Fig. 1 indicates the great-cell nucleus, divided vertically, while Fig. 2 shows

[44] Edinger: "Anat. of the Central Nervous System," p. 132, 1899.

fibers derived from it proceeding posteriorly—the path which, as shown in the preceding section, leads to the adrenals.

The evidence submitted in this section appears to me to warrant the following conclusions: (1) *The anterior lobe of the pituitary is not, as now believed, a secreting gland, nor the source of an internal secretion;* (2) *it fulfills in all higher animals, the same function that the osphradium or test-organ does in various invertebrates and lower vertebrates, viz., it tests the purity of the respiratory and nutritional fluids, i.e., the blood in the higher vertebrates, including man;* (3) *inasmuch as, in these higher vertebrates, the food-products, normal and toxic wastes, drugs, and poisons are taken up by leucocytes in the alimentary canal and the blood, and distributed by them to all parts of the body, the anterior pituitary, a highly vascular organ, receives its share;* (4) *while the plasma and red corpuscles remain within the vessels of the anterior pituitary, the leucocytes migrate through the walls of its capillaries and accumulate promiscuously in the anastomosing tubules of which the parenchyma of the organ is composed;* (5) *once in these tubules, the leucocytes secrete their granulations, acidophile, basophile and amphophile, and any other substance, benign or toxic, they may contain;* (6) *all these substances dissolve in the tubules, in fluids derived from the leucocytes themselves, and (as will be shown) adrenoxidase derived from the red corpuscles in the capillaries;* (7) *a colloid substance is thus formed which contains a given proportion of all the benign and toxic substances that are being distributed to the body at large;* (8) *this colloid substance represents, therefore, a specimen of the nutritive materials which the tissue cells are assimilating;* (9) *this specimen enables the test-organ of the anterior pituitary to take cognizance of any noxious substance or drug that may be contaminating these nutritive materials.* (10) *The test-organ of the higher vertebrates, including man, is located in the superficial tissues of the partition separating the anterior from the posterior pituitary, and faces the parenchyma of the former;* (11) *the elastic capsule of the anterior pituitary contracts periodically, each contraction causing compression of its sponge-like parenchyma and propulsion of its colloid substance posteriorly, i.e., towards the test-organ;* (12) *the colloid substance is thus projected into a cavity between the parenchyma and the test-organ and brought into contact with the latter on its way out of the pituitary through lymphatics;* (13) *the test-organ is a sensitive structure the surface of which—that exposed to the colloid substance—is similar to that of the olfactory membrane;* (14) *it sends fibers into the posterior lobe of the pituitary, which fibers* ultimately pass upward to the tuber cinereum, where they merge with the nerve-chain that terminates in the adrenals—the organs which, when stimulated by the test-organ, awaken a protective reaction in the body at large.*

LEUCOCYTES AS THE PURVEYORS OF THE THYROID AND PARATHYROIDS, AND AS THE SECRETING CELLS OF THESE ORGANS.

A Swedish anatomist, Sandström,[45] discovered in 1880, in man and various other mammals, small epithelial organs near to, or forming part of, the thyroid gland, *i.e.*, the parathyroids. Thanks mainly to the investigations of Gley,[46] who first showed their great physiological importance, Moussu,[47] and Vassale and Generali,[48] whose observations have been confirmed by many other investigators, these small organs have been shown to influence greatly the vital functions. The difference between them and the thyroid in this respect is quite evident, however: as stated by Jeandelize,[49] "to the thyroid belongs a trophic function of the first order, its removal being followed by disorders of nutrition, while, conversely, extirpation of the parathyroids is followed by convulsive phenomena."

Notwithstanding the considerable labor bestowed upon the thyroid and parathyroids, the nature of the relationship between them has remained obscure. Thus Howell,[50] in his recently published text-book (1905), states that "the functional connection between these two organs is as yet quite unex-

* Further histological researches will doubtless show that the fibers of the test-organ do not themselves ascend to the tuber cinereum, and that they terminate in the posterior pituitary, but in functional contact with the cell-bodies of motor neurons, whose neuraxons would then become the inital fibers of the pituitero-adrenal nerve-chain.—S.

[45] Sandström: Upsala Läkareförenings Förhandlingar, Bd. xv, S. 441, 1879-1880.
[46] Gley: C. r. de la Soc. de biol., p. 843, 1891.
[47] Moussu: Thèse de Paris, 1896-97.
[48] Vassale and Generali: Arch. ital. de Biol., vol. xxxiii, p. 33, 1900.
[49] Jeandelize: "Insuffisance thyroidienne et parathyroidienne," p. 3, 1903.
[50] Howell: *Loc. cit.*, p. 774.

plained." This applies as well to the physiological purpose of the parathyroids. H. Richardson,[51] for instance, in another work published recently (1905), writes: "Of the function of the parathyroids little is known at present; they appear to be connected with the thyroid and perhaps to have some special relation to the nervous system." The facts submitted in the two preceding sections appear to me to elucidate several features of the problem.

D. A. Welsh,[52] after an elaborate anatomical and experimental research upon the parathyroid glands, concludes: "The anterior lobe of the pituitary body bears a close resemblance in some of its structural features to the parathyroid glands: (1) In both there occur two kinds of cells, the one characterized by a homogeneous diffusely staining protoplasm and a relatively large pale nucleus, the other by a relatively small dark nucleus and an oxyphile granulation of its protoplasm. (2) In both there may occur acini whose lumina may be occupied by small lobules of colloid substance, or, more sparsely, larger spaces containing larger masses of colloid."

The resemblance to the anterior pituitary asserts itself even more strongly when various facts recorded by Welsh are compared with some quoted from Launois's work—that reviewed in the preceding section. Thus, we have seen that the parenchyma of the anterior pituitary was composed of leucocytes distributed promiscuously, and of anastomosing tubules separated by connective tissue partitions in which coursed the capillaries, arterial and venous. Welsh, in describing the parenchyma of the parathyroids, refers to a type in which "the cells tend to be arranged in continuous anastomosing columns, between which connective tissue septa and capillary channels are found." Of another type he says: "The irregular cells occur irregularly scattered among the principal cells, either singly or in groups of three or four, without definite arrangement." These cells, as he also states, have "a very characteristic and constant structure" while their protoplasm "shows a distinct fine granulation. The granules are highly *oxyphile* and readily take up *eosin* and other dyes." He says, moreover, that

[51] Richardson: "The Thyroid and Parathyroid Glands," p. 72, 1905.
[52] D. A. Welsh: Jour. of Anat. and Physiol., Apr., 1898.

"they show a striking resemblance to the granules of the erythrophile cells of the pituitary body, which are also eosinophilic."

Occurring in greater number than the oxyphiles is that type of cell which Welsh designates as the "principal" cells. These also "may show considerable variation both in the details of their structure and, more particularly, in their arrangement within the gland." He also found that their protoplasm "stains very variously, being sometimes exceedingly clear and faint, at other times darker, with very fine *basophile granulations*. Differences of staining may occur in cells lying side by side in the same acinus." These facts suggest pointedly that, as is the case with the anterior pituitary, the cellular elements of the parathyroids include leucocytes.

Such a conclusion is further sustained by the fact that the proportion of cells is a fluctuating one. Indeed, as stated by Welsh, "the granular oxyphile cell may not be present at all." If we were dealing with organized epithelial tissues, the elements themselves would not disappear. Again, as stated by Rogers and Ferguson,[53] referring to human parathyroids, "they are small and they rapidly decompose or rather undergo autolysis; hence the ordinary dissecting-room cadaver cannot be utilized for their study." This is readily accounted for when its cells are regarded as leucocytes, for we have seen that leucocytes contain ferments, adrenoxidase, etc., *i.e.*, various digestive triads. Again, such a structure—a delicate spongy framework in which the parenchyma of a true secreting organ is replaced by blood-fluids, colloid material and flowing, amœboid cells—should be readily compressible and easily influenced by blood tides. In describing the parathyroids, MacCallum[54] writes: "In color they are of a clear light brown, which may be rendered pale by anæmia and the accumulation of fat, or converted into a brownish-red by congestion. It is particularly this light brown color, together with their flabby softness, which makes them easily recognizable."

This evidence only permits of one conclusion, however, viz., that *leucocytes penetrate into the parathyroids, and secrete their granulations therein.*

[53] Rogers and Ferguson: Amer. Jour. Med. Sci., May, 1906.
[54] MacCallum: Brit. Med. Jour., Nov. 10, 1906.