What is the identity of these leucocytes? The cells to which Welsh refers as varying greatly in number, and even as absent at times—thus emphasizing their migratory nature—are granular oxyphiles which "readily take up eosin." This happens to coincide with the leucocytes, which take up iodine physiologically.

Iodine is now generally recognized as the main active principle of the parathyroid secretion. Gley found[55] that the relative proportion of iodine was six times greater in the parathyroids than in the thyroid in dogs, and twenty-five times greater in the parathyroids than in the thyroid in rabbits. Pagel[56] also found iodine in the parathyroids. Now iodine is not only taken by eosinophile leucocytes, but these particular cells are found in the alimentary canal and tend to accumulate in certain organs—thus accounting for their accumulation in the parathyroids.

That leucocytes absorb iodine under normal conditions was recently demonstrated by M. Labbé and Lortat-Jacob.[57] Labbé,[58] alluding to this paper, writes: "Immediately after injecting either Gram's solution or iodine dissolved in vaseline into the peritoneum [of various animals], certain leucocytes may be seen to have taken it up, the drug forming a yellow crescent in the periphery of their protoplasm. Soon, this coloration disappears and the yellow crescent is replaced by a 'rocky' (*sic*) formation indicating the modification undergone by the iodine in the interior of the leucocyte. Its presence may be discerned by chemical reagents: a saturated solution of sublimate gives a brown precipitate if the cell contains iodine only, and a mixture of brilliant red and reddish-brown precipitate if an iodo-iodine solution has been absorbed by it. These reactions are no longer obtainable after a certain time, a fact which appears to me to indicate a more complete transformation and assimilation of the iodine by the protoplasm of the cell. With starch the reaction is still more temporary and disappears much more rapidly." The author states, moreover, that when iodine is assimilated and incorporated into the

[55] Gley: See also Archives de physiol., vol. xxiv, p. 146, 1892; C. r. de la Soc. de biol., p. 843, 1891.
[56] Pagel: Cited by Jeandelize: *Loc. cit.*
[57] M. Labbé and Lortat-Jacob: *Loc. cit.*
[58] Labbé: Presse médicale, Aug. 10, 1904.

organic molecule, it is no longer possible to detect it, at least by ordinary methods, and that "it is thus found combined as thyroidine in the thyroid." This applies as well to the parathyroids, since we have seen that they also contain iodine.

The fact that eosinophiles, Welsh's "oxyphiles," are not phagocytes suggests that these cells do not take up iodine. Not only do they absorb it in eosinophilia—though less actively than neutrophiles—but the fact that, in normal animals, the absorption occurs through the surface or periphery of this cell—a process which differs from the "englobing" peculiar to phagocytes—suggests that the eosinophiles must carry on the physiological rôle of taking up this halogen—owing, I may add, to its identity as a specific tissue constituent. Drawn chemotactically to any region in which iodine appears, the alimentary canal, the subcutaneous tissues, the blood, etc., the cells then travel to the organ in which it is either stored or used physiologically. Indeed, while Opie,[59] in a recent comprehensive study of this leucocyte, states that "large *accumulations*" of them "are not infrequently noted in various organs" . . . . "notably in the mucosa of the *gastro-intestinal* tract, in the mucosa of the air passages, in the lymphatic tissues and in the spleen," Levaditi[60] quotes the observations of Seifert and Leredde that the use of potassium iodide is accompanied by an increase of eosinophiles in the blood. The "digestion leucocytosis" affords a clear example of the process, though in the present connection the oxyphile-eosinophiles play the active rôle when iodine or the iodides are ingested or injected subcutaneously, and transfer them to special tissues, including the parathyroids.

What is the relationship of these cells to the elaboration of the iodine-laden secretion of the parathyroids?

This is met, to a certain extent, by the observation of Labbé that the iodine is transformed chemically *in* the leucocytes—to such a degree, in fact, that after a given time, it forms part of a new molecule and can no longer be detected by tests which do not break down the latter. "These transformations," says this investigator, "occur under the influence of the active *ferments* contained in the body of the leucocytes; the

[59] Opie: Amer. Jour. Med. Sci., Feb., 1904.
[60] Levaditi: "Le leucocyte et ses granulations," p. 116, 1902.

oxidases, the presence of which was demonstrated by Portier, doubtless play an important rôle in these chemical reactions." This recalls a salient feature emphasized in a preceding chapter: that leucocytes are minute laboratories in which compound substances required by tissue-elements are built up ready for use. That we are dealing in the present connection with a physiological function carried on by certain leucocytes as elsewhere is evident; the specific function here being to elaborate a secretory product now supposed to be formed by glandular elements.

This conclusion would appear to be weakened by the fact that iodine in relatively large quantities may be obtained readily from the parathyroids and, therefore, before it is bound up in the organic molecule. This does not hold, however, in view of the fact that the leucocytes studied by Labbé and Lortat-Jacob were observed *in vitro*. The intracellular transformations noted, therefore, exemplified those which occur *after* the specific leucocytes enter the parathyroids, even though on reaching the organ the iodine is still in a sufficiently free state to be isolated.

It now becomes a question as to the manner in which the eosinophiles dispose of their secretion in the parathyroid.

The anatomical characteristics of a parathyroid correspond very closely with those of the anterior pituitary. It is also divided into tubules by a reticulum. Welsh, for instance, states that "from the deep surface of the capsule fibrous septa may be given off which penetrate the gland and produce an irregular lobule formation." The "lobules" are evidently tubular and contain leucocytes, for Carnot and Delion[61] refer to the presence in tuberculous parathyroids studied by them of a *leucocytosis* "in their epithelial gut-like tubes"—a fitting description of the anastomosing tubules. Their mode of penetration into these cavities—by migrating therein—is evidently the same as in the anterior pituitary, for, according to Minot,[62] "the capillaries between the cell masses . . . . may be regarded as sinusoids" —the typical arterial channels found in the anterior pituitary.

The blood (and its leucocytes) penetrates into the organ

[61] Carnot and Delion: C. r. de la Soc. de biol., Oct. 21, p. 321, 1905.
[62] Minot: Böhm, Davidoff and Huber: "Text-book of Histology," p. 321, 1905.

also by way of its pedicle and is distributed by a fan-like system of irrigating channels, as is the case in the anterior pituitary. MacCallum describes its supply as made up of a "stalk of minute blood-vessels which spring, in the case of the upper gland (unless it is greatly displaced), from the superior thyroid, while those supplying the lower gland arise from a branch of the inferior thyroid artery." Welsh[63] states, however, that "only one artery, as a rule, enters each parathyroid, usually at its more tapering extremity. It then runs parallel to the long axis of the gland, and, on transverse section, is found to occupy a more or less central position. From the *central artery* lateral branches are given off at frequent intervals along its course. They do not pass off at right angles to it, *but radiate obliquely*, being directed towards the broader extremity of the gland."

A parathyroid differs from the anterior pituitary, however, in that its blood is returned, at least in great part, after permeating the organ, by venous sinuses underlying the capsule. Thus Welsh writes: "The venous return is effected in two ways: (1) By venous branches accompanying the arteries and opening into a central channel which runs alongside the central artery and emerges with it. The veins into which these vessels discharge vary according to the position of the parathyroid. Thus they may join the venous branches on the surface of the thyroid. (2) Numerous venous channels lie *immediately underneath the capsule* of the parathyroid, and form the delicate reticulum, which is a character of the naked eye appearance of the gland. Microscopically, they may appear as *dilated, thin-walled sinuses*. They do not seem to have any constant course, but empty into œsophageal, tracheal, or thyroidal veins indifferently."

Interpreted from my standpoint, Welsh's description indicates the itinerary of the eosinophiles in a parathyroid: they enter with the blood of the central artery and are distributed through the intermediary of its radiating branches. They migrate through the walls of these capillaries and into the tubules where we found them.

The nature of the functions of these endogenous cells may be surmised from their behavior in the anterior pituitary:

[63] Welsh: *Loc. cit.*

they secrete granulations in the tubules and these, dissolved in the plasma (including adrenoxidase, as will be shown) derived from the capillaries, form the secretion of the organ. We will see presently that "a homogeneous granular substance" which gives the reactions of the colloid is present around the vessels.

What is the nature of the second type of cells, those to which Welsh refers as the "principal" cells?

The fact that this author states that "no matter how deeply the cell protoplasm may stain, there is almost never any distinct granularity, and that in the exceptional instances in which it is present, the granules are exceedingly fine and take on only *basic* dyes," suggests, in accord with the prevailing interpretation, that they are simply epithelial cells. Several features lead me, however, to consider them as basophile leucocytes.

The absence of granulations does not militate against this view, since, as we have seen, in the fifteenth chapter, these cells readily secrete these products. The "principal" cells, considered in this light, are merely basophiles which have shed their granulations. Levaditi states, in fact, that "basophile granulations resist but slightly dissolving agents."' Like these leucocytes, the "principal" cells, as stated by Welsh, and also by Kölliker,[64] are supplied with a chromatic network. They vary in size, thus showing transitional phases of development, which does not apply to true epithelium. In the pituitary, "basophile cells" which presented all the stain affinities peculiar to basophile leucocytes, were found by Launois to occur in groups and form a lining for the tubules. Welsh refers to a similar disposal of his principal cells. Another feature which militates against the presence of a true epithelium is that "the granular cells [eosinophiles, which vary greatly in number and may even be absent] occur irregularly scattered *among* the principal cells, either singly or in groups of three or four without definite arrangement."

In the parathyroids, basophiles likewise penetrate into the tubules, for, as stated by Welsh, they form in certain areas "isolated masses" surrounded by a fine "fibrillar stroma" in which course "delicate capillaries" or "processes of dense fibrous tissues carrying large vessels." They are evidently the

[64] Kölliker: "Handb. d. Gewebelehre d. Mensch.," Bd. iii, H. i, S. 325, 1899.

source of a secretion, for here and there they are clearly "grouped in a single layer around a small circular lumen" containing a "colloid substance." The eosinophile cells are also stated by Welsh to form "definite acini, the lumen being occupied by a mass of colloid material." These are not true acini, however. As Petersen[65] says, the colloid "presses the cells into duct-shaped structures."

On the whole, it becomes apparent that, judging even from the meager histological work available, the parathyroids owe their secretory activity to the presence of two varieties of leucocytes which are known to secrete their products. That iodine-laden eosinophilic granulations should combine, when dissolved in the plasma, with the phosphorus-laden nucleo-proteid granulations secreted by the phosphorus-laden basophiles, and with the adrenoxidase of the plasma found in the parathyroidal tubules, is not only suggested by the facts submitted, but also, as I will show in another section, by the actual presence of these substances in the parathyroid secretion.

How is this secretion eliminated?

The oxyphiles and basophiles are mixed in certain parts of the organ, but on the whole those of the one variety tend to form closely packed groups, large areas appearing to be composed of only one kind of cell. This is apt to be the case near the capsule, *i.e.*, in close proximity to the sinuses the latter contains. As these sinuses are channels for venous blood, they can hardly serve for the elimination of the secretion. It appears more likely that the colloid substance passes into perivascular lymphatics and through these to what Benjamins has termed the "parathyroid ducts." In the ox, Welsh found "a duct-like structure" containing apparently several channels. Benjamins,[66] as had Kohn in 1885, also found passages to which he gave the above name. "The only histological indication of a duct in man" observed by Welsh "was met in sections of a large parathyroid, in which a few large *spaces* were found lying just outside the gland tissue. These spaces were lined by cubical epithelium, and were filled with colloid matter of different degrees of density." As this refers to the pedicle of the organ,

[65] Petersen: Virchow's Archiv, Bd. 174, Nu. 3, S. 413, 1903.
[66] Benjamins: Ziegler's Beiträge z. path. Anat., Bd. xxxi, S. 143, 1902.

the duct or ducts accompanied the vessels. Welsh's observation harmonizes with that of Capobianco and Mazziotto,[67] who found that the blood-vessels were surrounded by spaces that contained a homogeneous granular substance which gave the reactions of the colloid substance—the secretion. This fact [also urged by Biedl,[67a]] suggests the identity of the channels which the secretions ultimately reach, for the description of the Italian investigators corresponds with that of perivascular lymphatics.

The close functional relationship between the parathyroids and the thyroid, and the fact that the former or their pedicle are sometimes embedded in the parenchyma of the latter—as I have observed in the ox, and as is often the case in the rat (Christiani) and common enough in the dog (MacCallum)—suggest that the secretion of the smaller organs is voided into the larger. In truth, as stated by MacCallum,[68] "it is rare to find them [the parathyroids] very intimately connected with the thyroid." As shown in the annexed diagrams, they are connected with vessels posterior to the latter. "Various irregular combinations of these relations occur," says MacCallum, "and sometimes one or other of the glands is found quite widely separated from the thyroid." In the illustrations annexed to Welsh's paper, some instances are shown in which they lie on the trachea considerably below the thyroid. Rogers and Ferguson[69] refer to an instance in which "a parathyroid gland was found on the middle of the posterior surface of the pharynx at the level of the lower border of the cricoid cartilage, being far distant from the nearest margin of the thyroid gland." In Fig. 6 of the annexed illustration, although complete atrophy of one lobe of the thyroid had occurred, the parathyroid of the corresponding side is nevertheless present. The perivascular lymphatic networks afford a ready means for the transfer of the parathyroid secretion to larger lymphatics of the neck and through these to the subclavian veins, and finally by the superior vena cava to the heart, where it becomes mixed with the venous blood from the entire organism.

The *thyroid* is in many respects a counterpart of the parathyroids, as may be shown by a few salient facts. The struc-

[67] Capobianco and Mazziotto: Giorn. Int. de Scienze, Nos. 8, 9, 10, 1899.
[67a] Biedl: "Internal Secretory Organs," p. 28, 1913.
[68] MacCallum: Brit. Med. Jour., Nov. 10, 1906.
[69] Rogers and Ferguson: *Loc. cit.*

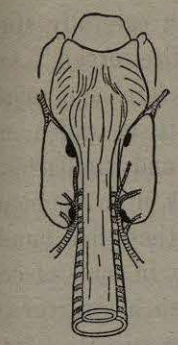


Fig. 1.—Organs of neck from behind. Four parathyroids in their most usual position.

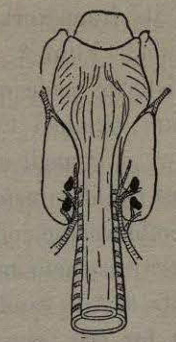


Fig. 2.—The two upper parathyroid glands lie close to the lower pair, which are in their usual position.

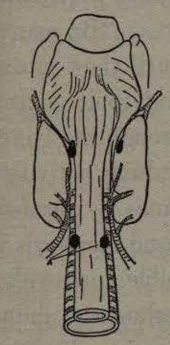


Fig. 3.—The left upper and right lower glands are in their most typical position. The right upper gland lies in the region of the inferior thyroid artery, the left lower gland, supplied by a long arterial branch, is embedded in the posterior surface of the thyroid near its outer margin.

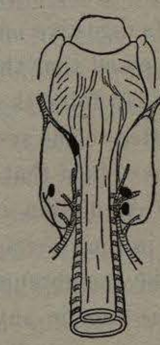


Fig. 4.—The two upper parathyroids are in the common position. The two lower glands lie on the anterior surface of the trachea.

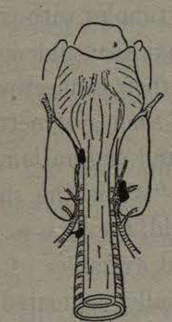


Fig. 5.—Two parathyroids exist on the left side. On the right only one large gland is to be found.

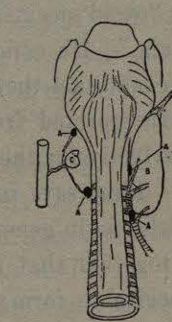


Fig. 6.—On the right side the condition is practically normal; on the left the thyroid lobe is almost completely atrophied, but the parathyroids are found in about the usual situation.

ANATOMICAL RELATIONS OF THE PARATHYROIDS. (*MacCallum.*)

ture of its framework has recently been carefully studied by J. Marshall Flint.[70] "Almost the entire organ," says this anatomist, "is made up of follicles, the form and relations of which are retained by the connective tissue which embraces them" . . . . "small arterioles, venules and capillaries can be made out in the interfollicular framework or on the membranes which embrace the follicles" . . . . "at times fine bundles run across the basement membranes. These, in some places, form the walls of the capillaries." That such a structure is well adapted for the transmigration of leucocytes, as I have suggested, is well shown in Fig. 1 of the annexed plate, which represents the framework after its contents have been eliminated by Flint's digestive method. He also writes: "By many it has been supposed that the follicles enlarge until they rupture like the Graafian follicles of the ovary, and that their contents are then carried to the systemic circulation through the lymphatics. Others have held that the products of glandular activity passed into the circulation through the membranes by osmosis. At any rate in the specimens of human, dog's and monkey's thyroid where the membranes are distinctly visible, no evidence of rupture is seen in any of them. The meshes are unquestionably large enough for the nourishment and end-products of glandular activity to pass to and from the cells through the reticulated membranes."

The shape of the follicles is likewise that of the tubules in the parathyroids and anterior pituitary. Streiff[71] described them as "ovoid saccules or short-branched tubules with frequent diverticula." He concluded, however, that they did not communicate, and that they were separated by their connective tissue walls. Interpreted from my standpoint, such a structure answers perfectly for the free immigration and emigration of leucocytes. Flint says in this connection: "While the shape of the follicles is, in general, ovoid or spheroid, they are so closely packed together that it is possible to find examples of almost any conceivable form; some are occasionally elongated, some polygonal, others prismatic, and still others almost cylindrical, but the predominating type is distinctly ovoidal or spheroidal."

[70] J. Marshall Flint: Johns Hopkins Hosp. Bull., Feb., 1903.
[71] Streiff: Cited by Ferguson: "Normal Histology and Microscopical Anatomy," p. 451, 1905.

This is well shown in the annexed plate, also from Flint's paper, the walls being those upon which—according to my views—the leucocytes adjust themselves in more or less orderly fashion, to form the so-called "glandular epithelium."

That leucocytes—and other blood constituents—traverse the meshes of the framework is illustrated by the fact that Baber[72] found that the viscid fluid in the follicles—the colloid —often contains blood (and therefore adrenoxidase); and furthermore, that large round cells "migrate into the interior of the gland-vesicles." There are no round cells other than leucocytes in the blood that "migrate;" hence, in accord with what I have shown in the case of the anterior pituitary and the parathyroids, leucocytes evidently enter the follicles. Again, I have pointed out that the walls of the follicles in the organs were formed of rows of leucocytes. Baber terms the migrating cells referred to "parenchymatous cells," owing to their tendency to form part of the glandular parenchyma.

That leucocytes, derived from intestinal canal or the blood, can reach the thyroid as they do the parathyroids, *i.e.*, with the circulating blood, is self-evident. Now, the characteristic stains of eosinophile and basophile granulations are also reproduced in the thyroid: "All follicles which possess any considerable lumen contain a peculiar *acidophile* substance, known as colloid," writes Ferguson,[73] "which is apparently formed by the secretory activity of the glandular epithelium lining the follicles. Colloid is a homogeneous or very finely *granular* substance which stains readily with *eosin*." Again: "Occasionally a single large vacuole, often containing *basophile granules* or crystalloid particles, occupies the centre of the colloid mass in the large follicles."

In the microphotograph from Ferguson's "Histology"[74] reproduced opposite page 1070 (Fig. 2), the leucocytes—the supposed granular epithelium—are not arranged in the beautiful, orderly manner usually depicted by artists in the textbooks: they merely spread out in close proximity to each other promiscuously around the follicles (*a*) and may even accumulate indiscriminately (*b*). This differs widely from the true secreting

[72] Baber: Philosoph. Transactions, Pt. iii, 1881.
[73] Ferguson: *Loc. cit.*, p. 452.
[74] Ferguson: *Ibid.*

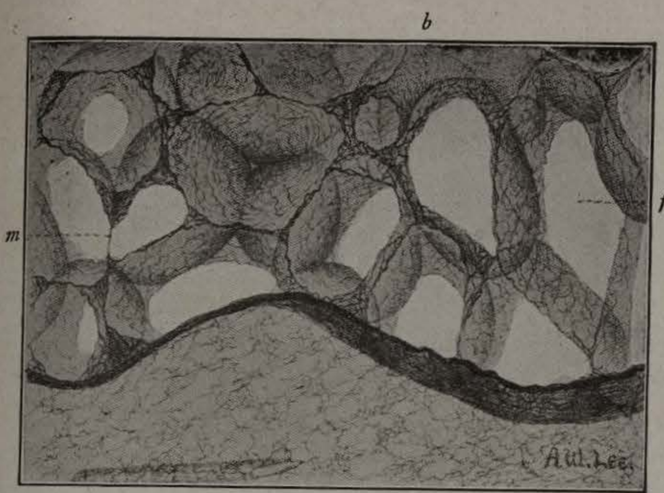
epithelium, that of the salivary glands, the minute epithelium of the renal convoluted tubules, the intestinal epithelium, etc.

The granules evidently originate from the cells, for Ferguson states that "the cytoplasm of the epithelium is finely granular and decidedly acidophile" and that "minute spheroidal granules which give the color reactions of the colloid are also found in the cytoplasm of the epithelial cells." Finally, he refers to the fact that Hürthle, "by staining with the Biondi-Ehrlich mixture, succeeded in differentiating two types of cells, one lightly staining, the 'chief cells,' the other, a darker colloid-containing type which he designated as 'colloid cells.'" The correspondence with Welsh's parathyroid "principal cells" and the eosinophiles which form acini "occupied by a mass of colloid material" is obvious.

The manner in which the secretion reaches the circulation coincides also with the corresponding process in the pituitary and parathyroids. King long ago traced it to the lymph-vessels. Biondi[75] found that the special secretion of the thyroid in reptiles, apes and other mammalia was produced by the cells lining the follicles and is poured out into the neighboring lymph-spaces. Zielinska[76] showed that although the colloid varied in amount in the thyroids of dogs, the lymph-spaces under the capsule and the parenchymatous lymphatics always contained some. Vassale and de Brazza[77] discovered, around the follicles of the thyroid, a rich network of lymphatics filled with colloid substance from the follicles; and also a similar network in the capsule of the gland. Finally, Zielinska[78] found a colloid substance identical with that in the lymphatics of the gland, in the lymphatic vessels in the neighborhood of the organ. It is evident, therefore, that, as is the case with the parathyroid secretion, it passes to the larger cervical lymphatics; through these to the subclavian veins, and finally by way of the superior vena cava to the heart.

The nerves of the thyroid have alone been carefully studied. Parameschko found that both the arterioles and the parenchyma were supplied with fibers, while Crisafelli showed

[75] Biondi: Berl. klin. Woch., Bd. xxv, S. 954, 1888.
[76] Zielinska: Virchow's Archiv, Bd. cxxxvi, S. 170, 1894.
[77] Vassale and de Brazza: Arch. ital. de Biologie, T. xxiii, p. 292, 1895.
[78] Zielinska: *Loc. cit.*



SECTION OF DOG'S THYROID 160μ THICK, SHOWING FRAMEWORK OF FOLLICLES, x180. *[J. Marshall Flint.]*

f, follicles; b, blood-vessels; m, reticulated basement membrane.

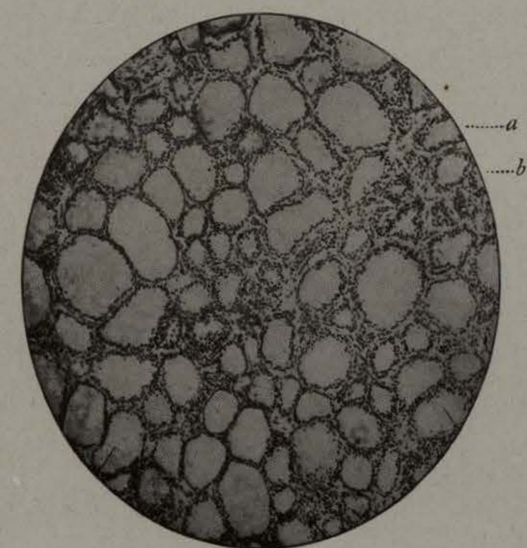


Fig. 2. MICROPHOTOGRAPH OF A SECTION OF THE HUMAN THYROID. *[Ferguson.]*

a, follicles; b, tangential section of follicular wall.

that the vessels were surrounded by plexuses which also involved the parenchyma. Using the Golgi method, Andersson[79] had also noted that they followed the vessels to the latter, but Berkley[80] was first to show their true distribution by the Golgi method, viz., "a meshwork of fibers situated almost immediately *upon the basal surfaces* of the epithelial cells of the follicles." Interpreted from my standpoint, the meaning of this is obvious: the basal membrane facing the interior of the tubules is lined with a meshwork of fibers and it is upon these that the leucocytes lie.

That the thyroid and the parathyroids are morphologically very similar as to the nature of their cellular elements is evident. Another feature asserts itself in the light of the evidence submitted above: the secretions of both sets of organs—the thyroid apparatus as Gley calls them—meet in the superior cava and passing to the heart, must inevitably become thoroughly mixed therein; and then proceed with the venous blood from the organism at large to the pulmonary alveoli, where, as I will show in another section, they are taken up by the *red corpuscles* to be distributed to the body at large—including the anterior pituitary body.

This evidence has served mainly to suggest that both the thyroid and the parathyroids, as well as the anterior pituitary, owe their functional activity to leucocytes and that these cells are their only secretory elements. This means much when the functional relationship between the parathyroids and the thyroid is taken into account, since, as will be shown in the next section, these organs jointly influence the functional activity of the test-organ and through it the secretory activity of the adrenals. The secretion of the latter becoming, when converted into adrenoxidase, the active agent in the vital process, the thyroid and parathyroids supply a link with the vital mechanism on the one hand, and on the other, through the leucocytes, another link with external agencies whether these be introduced through the alimentary canal, the subcutaneous tissues or the veins. From the standpoint of therapeutics and immunity, this fact is of commanding importance, since it places

[79] Andersson: Biol. Förening Förhand., Bd. iv, Hft. 5-6, 1891.
[80] Berkley: Johns Hopkins Hosp. Reports, Nos. 4 and 5, p. 112, 1894.