in the fluid of the peritoneal cavity, which normally contains no phagocytes, it becomes evident that opsonin is a product of the red corpuscles.

Under these conditions, however, the administration of thyroid preparations should increase the immunizing properties of the blood, and particularly its opsonic activity. As to the former, I was led to conclude, in 1903,[86] by an analysis of the whole question, that the injection of various bacterial toxins in man and in the lower animals excited more or less actively according to their virulence the pituitary, adrenals, and thyroid (constituting what, as we shall see in another chapter, I termed the "adrenal system"), and that "the various antitoxic sera are more or less active in proportion as to the quantity of thyro-iodine in them is great." Four years later, Miss Fassin[87] found not only that removal of the thyroid decreased the germicidal and hæmolytic alexins in the blood, but that the administration of thyroid by any method increased materially these same alexins. That this actually increases the defensive power of the body was also noted by Reid Hunt,[88] who found that when mice were fed on small amounts of thyroid they showed marked resistance to poisoning by acetonitrile. Ever since the gland has been used as a therapeutic agent, in fact, it has been found useful, though empirically, in intoxications of various kinds. Léopold-Lévi and de Rothschild,[89] for example, observed clinically that thyroid treatment rapidly influenced favorably autointoxications and exogenous infections, including erysipelas. Turró[90] found that the juices of swine and sheep thyroids dissolved almost entirely the comma, typhoid, and anthrax bacilli, the bacillus coli communis, and the streptococcus. Conversely, dogs were found by Charrin[91] to succumb readily to infections, after removal of the thyroid. That toxic intermediate wastes or other toxics are not destroyed adequately in thyroidectomized animals is shown by the observation of Gley[92] that the blood-serum of thyroidectomized dogs is more toxic than normal serum, and gives rise to convulsions when injected into animals. Jeandelize and

[86] Sajous: See vol. i, 1st ed., p. 762, 1903.
[87] Fassin: C. r. de la Soc. de biol., Mar. 9 and 26 and Apr. 20, 1907.
[88] Hunt: Jour. Amer. Med. Assoc., July 20, 1907.
[89] Léopold-Lévi and de Rothschild: *Loc. cit.*
[90] Turró: C. r. de la Soc. de biol., lx, p. 464, 1906.
[91] Charrin: Les Défenses Naturelles de l'Organisme, Paris, 1898.
[92] Gley: Archives de Physiologie, No. 4, p. 770, 1895.

Perrin[93] also found that thyroidectomized rabbits presented less resistance to poisoning by sodium arsenas than normal animals. Lorand observed the same fact in connection with chloroform narcosis. De Luca and d'Angerio[94] and others have found, moreover, that the urine in thyroidectomized animals contains a greater percentage of toxic substances than normal, and that the therapeutic use of thyroid in these animals counteracted this toxicity. It is thus apparent that the evidence from every phase of the question points to the thyroid secretion as an important factor in the immunizing processes of the body.

The process through which the thyroparathyroid secretion carries on this important function differs in no way from that which enables it to sustain metabolism and nutrition. As stated by Jordan:[95] "The bodies of bacteria contain from about 80 to 88 per cent. of water, the amount showing considerable variation and depending partly on the nature of the organism, partly of the culture-medium. The ash is *largely phosphoric acid,* the P_2O_5 often reaching as high as half the total ash weight (tubercle bacillus, 55.23 per cent.; de Schweinitz and Dorsett[96])." Bacteria, therefore, in keeping with many of our tissue-cells, are relatively rich in phosphorus and correspondingly vulnerable to the action of the thyroiodase. As the latter, in turn, renders the phosphorus prone to oxidation by the plasmatic adrenoxidase, the whole pathogenic micro-organism is rendered unstable chemically and vulnerable to the digestive influence of the blood's germicidal agents—which in the above sense include both the thyroparathyroid and adrenal products acting conjointly.

On the whole, the evidence and the confirmatory testimony submitted under the last two headings have shown:—

1. *The thyroparathyroid secretion and the thyroid preparations used therapeutically act by increasing the sensitiveness of the phosphorus of all cells, particularly their nuclei, to the oxidizing action of the adrenoxidase, and thus enhance metabolism and nutrition.*

2. *They also, in virtue of this action, augment the autoprotective, or immunizing, power of the blood, by increasing the*

[93] Jeandelize and Perrin: Réunion biol. de Nancy; cited by Parhon and Golstein, *loc. cit.*, p. 554. 1909.
[94] De Luca and d'Angerio: Revista medica e terapeutica, No. 9, 1896.
[95] Jordan: "General Biology," 2d ed., p. 67, 1910.
[96] De Schweinitz and Dorsett: Centralbl. f. Bakt., Bd. 22, S. 209, 1897.

sensitiveness (as opsonin) of all bacteria, their toxins, endotoxins, toxic wastes, etc., that contain phosphorus to oxidation, and thereby to the digestive or destructive action of the complement, both in the blood and in its phagocytes.

As will be shown elsewhere in this work, this represents the foundation (with the adrenal and pancreatic secretions as additional factors) of the autoprotective process, including the germicidal cytase of phagocytic cells. It traces them to their origin and furnishes their identity, features which Ehrlich's labors have not, so far, determined.

THE PITUITARY BODY AS THE SEAT OF THYROPARATHYROID CENTER.

So important are the functions of the thyroparathyroid apparatus that we cannot but surmise that, in keeping with many other and far less prominent functions, they are regulated by a center. The evidence available, a part of which is given below, and in the second volume, indicates that such is the case.

That it should be the same center which we have seen governs the functions of the adrenals is not only sustained by what evidence there is on the subject, but also by logical reasoning, since the two centers which regulate oxygenation, metabolism, and nutrition, thus conjoined, are placed in the most advantageous position to co-ordinate these all-important functions.

The first clue to such a functional relationship was afforded by the fact that

The active and passive phenomena evoked by the pituitary body and the thyroid apparatus show considerable parallelism.

We have seen that removal of either the pituitary or the thyroid causes a steady decline of the temperature with decreased oxygen intake and carbon dioxide output, and also weakness, tetany, and even epileptic convulsions, while, conversely, overactivity of either organ provokes excessive metabolism with increase of oxygen intake and carbon dioxide output, and glycosuria. We arrest nutrition by removing either the pituitary or the thyroid, just as degenerative changes in either organ entails denutrition lapsing into fatal cachexia. The sthenic stage of acromegaly and gigantism strikingly illustrates the power of the pituitary to incite excessive nutrition and over-

growth; the rapid growth of the cretin under the influence of thyroid preparations exemplifies what the thyroid apparatus can do in the same direction.

The simultaneous presence of degeneration of the pituitary and myxœdema in cases reported by Ponfick,[97] J. Stewart, Codd,[98] Sainton and Rathery,[99] and others; and of acromegaly with exophthalmic goiter by Murray,[100] Lancereaux,[101] and others (two diseases which, as emphasized by Lorand, not only present many characteristics in common, but which, as observed by Magnus-Levy,[102] are attended by excessive oxidation) clearly suggest functional parallelism. This is further emphasized by the enlargement of both organs during pregnancy indicated by the labors of Comte,[103] Launois and Mulon,[104] and Lang[105] and its subsidence when, after parturition, the blood no longer receives the excess of wastes that the presence of the fœtus involved. On the whole, we can certainly say with Thaon[106] that "between the pituitary and the thyroid there is so much analogy that the one cannot be studied without a knowledge of the other."

Zoölogy affords various landmarks in the same direction.

The pituitary body governs oxygenation, metabolism, and nutrition in all animals supplied with a thyroid gland and adrenals.

In tunicata, the homologue of the thyroid, according to zoölogists, is the endostyle, a long gland at the base of the pharynx closely related to the branchial or respiratory chambers. The adrenals in these invertebrates are represented, as personal researches have suggested, by the dorsal tubercle, which is so related to the respiratory chamber that its product, which corresponds with the adrenal secretion, can be secreted into the blood near the oral aperture, the inlet for the water which supplies the animal with oxygen. Suggestive in the light of the views I have submitted is that the dorsal tubercle—the primitive organ of the adrenals from my viewpoint—is connected by a

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[97] Ponfick: Zeit. f. klin. Med., xxxviii, Nos. 1, 2, u. 3, 1900.
[98] Codd: British Medical Journal, May 5, 1895.
[99] Sainton and Rathery: C. r. de la Soc. méd. des hôpitaux, May, 1908.
[100] Murray: Edinburgh Medical Journal, February, 1897.
[101] Lancereaux: La Semaine médicale, June 24, 1896.
[102] Magnus-Levy: British Medical Journal, April 3, 1903.
[103] Comte: Thèse de Lausanne, 1898.
[104] Launois and Mulon: Ann. de gynéc. et d'obstét., 2d series, i, p. 2, 1904.
[105] Lang: Zeit. f. Geburts. u. Gynäk., xl, p. 34, 1889.
[106] Thaon: *Loc. cit.*, p. 116.

delicate duct with an organ, the subneural gland, which Julin, as we shall see presently, has identified as the hypophysis, while the endostyle, the primitive thyroid, along with all other organs, receives nerve-fibers from a nerve-ganglion attached to this ancestral pituitary.

Two important facts impose themselves in this connection: The first is that, as stated by Jacques Loeb[107] in reference to a group of these invertebrates, "the central nervous system is reduced to a single ganglion"; the second is that this single ganglion corresponds with the neural or posterior lobe of the pituitary. Just as the nerve-ganglion governs the functions of the primitive thyroid and adrenals, that is to say, the respiratory processes in these lowly animals, so can it be shown to do at every step of the phylogenetic scale up to man, since it preserves its functional importance throughout. The snail, for example, is supplied with both a cerebral and an œsophageal ganglion; galvanic excitation of the cerebral ganglion, as shown by Vulpian, produces no appreciable effect; but similar excitation of the lower or pharyngeal ganglion, the future neural lobe of the pituitary, provokes violent muscular movements. Again, removal of the cerebral ganglion will not kill the animal, but it will remain motionless. Extirpation of the œsophageal ganglion, on the other hand, causes its death in less than twenty-four hours. All this applies as well to other invertebrates.

We can assimilate all the vertebrates to these primitive forms by removing the brain. That the respiratory mechanism or the processes it influences are not in the least impaired by this operation was shown when we traced the governing centers of this mechanism—to which the thyroid belongs—to the pituitary. The well-known Cornell frog lived several years after its brain had been removed. The decerebrated pigeon is a familiar example of this kind. Another is Goltz's dog which lived eighteen months after both its hemispheres had been removed. Conversely, we have seen how rapidly extirpation of the pituitary proves fatal in the higher mammals, just as it does in the low invertebrates when the œsophageal ganglion is extirpated. We found that all the lethal phenomena are due to arrest of respiration and oxidation, both of which processes are carried on through the adrenals and the thyroids. Again,

[107] Jacques Loeb: "Studies in General Physiology," part i, p. 363, 1905.

In vertebrates the pituitary body is connected with the thyroparathyroid apparatus, as it is with the adrenals, by direct nerve-paths.

The thyroid apparatus, as all textbooks teach, receives its nerves from the sympathetic through the middle and inferior cervical ganglia. That they originate in the pituitary is shown not only by the presence of typical sympathetic fibers between the pituitary and the upper connections of the spinal system with the cervical sympathetic, but also by the effects of electrical excitation of the exposed, but normal pituitary.

As to the origin of the nerves, Cajal,[108] Joris,[109] and others, we have seen, traced in various animals fibers from the pituitary to a nucleus of large gray cells immediately above the infundibulum in the anterior portion of the third ventricle, which nucleus was found by them to project nerves over the ventricular walls. These nerves are also described by Edinger[110] in fishes, reptiles, and birds as "numerous fine, medullated fibers"—the characteristics of sympathetic nerves, as shown by Bidder and Volkmann. In illustrations of sections in various animals, Edinger shows, moreover, that several bundles of these fibers project posteriorly as far as the level of the bulb, whence, as is well known, the fibers which pass over to the sympathetic ganglia begin to leave the spinal system. As the ganglia are the starting points of sympathetic nerves to the various organs, we thus have, through these ganglia, a continuous path from the pituitary to these organs. This is sustained by physiology, since Cyon and also Masay[111] caused an instantaneous rise of pressure of over 100 mm. Hg. by exciting electrically the exposed pituitary. As the vagi were cut during the experiment, and the vasomotor center is independent and located in the bulb, the rise of pressure could only be due to general sympathetic vasoconstriction. I will show in the second volume that the pituitary has a controlling power over the sympathetic system.

When the influence of the pituitary over the adrenals was analyzed, it was possible to trace step by step along the path

[108] Cajal: *Loc. cit.*
[109] Joris: *Loc. cit.*
[110] Edinger: "Anatomy of the Central Nervous System," American edition, p. 260, 1899.
[111] Masay: Ann. de la Soc. roy. des sci. méd. et nat. de Bruxelles, xii, part iii, 1903.

between the two organs all the main phenomena which both were able to provoke. In the case of the thyroid we are deprived of this valuable testimony. As Morat,[112] in his review of the sympathetic system, says, "the thyroid gland receives its vasomotor fibers from the superior portion of the thoracic chain by the cervical cord. Stimulation of the thoracic chain causes either vasoconstriction or vasodilatation on account of the mixture of the two orders of fibers." In other words, the antagonistic nerves which control the functions of the thyroid are so conjoined that transection or excitation would afford no reliable testimony.

The participation of the thyroid in the phenomena awakened by the pituitary and the nerves it projects posteriorly is shown, however, by the intensity of these phenomena. The adrenal secretion alone, as represented by its extracts, causes a rise of temperature of 1° or 2° F. How account for the rise of 10° F. and over caused by puncture of the tuber cinereum (just above the pituitary) by Sakowitsch[113]; of the 6° F. and over noted by Brück and Günther[114] on puncturing between the pons and medulla, and of the 12.4° F. noted by Brodie[115] after an injury of the cervical portion of the spinal cord, with impulses to the adrenals alone to account for these heat phenomena? They obviously fail to do so. On the other hand, they are readily explained by *simultaneous* impulses to the thyroid apparatus, since the action of its secretion upon cellular phosphorus, we have seen, provides an active source of heat energy. This dual action not only accounts for the high temperatures obtained by irritation applied all along the path from the pituitary down to where the nerves to the adrenals and thyroid leave the spinal cord, but it indicates that the two sets of thermogenic nerves follow the same path, down to this region.

Finally, that the pituitary is so related with the nervous system as to be capable of governing these organs, is further shown by the fact that, as stated by Prof. Laulanié,[116] a physiologist who has given considerable attention to the functions of the ductless glands, in reference to the pituitary body, "this gland

[112] Morat: "Physiology of the Nervous System," Syers's ed., p. 334, 1906.
[113] Sakowitsch: *Loc. cit.*
[114] Brück and Günther: *Loc. cit.*
[115] Brodie, Morat, and Doyon: *Loc. cit.*, Article Calorification, p. 413, 1899.
[116] Laulanié: "Eléments de Physiologie," 2d ed., p. 488, 1905.

is, in fact, in relation with the sympathetic, the vagus, and the depressor nerve."

Of course, I am familiar with the prevailing view that the pituitary is a secreting gland. But the data which tend to sustain this opinion are far from convincing, for reasons that I will submit in the tenth chapter. Suggestive in this connection is the fact that its removal for tumors or other lesions which destroy its functions does not in the least compromise life, as is the case after removal of the adrenals or of the thyroparathyroid, which are known to be secreting glands. Were the pituitary the source of any such secretion, its extirpation would obviously provoke serious disturbances. With this organ interpreted in accord with my views, *i.e.*, as a co-ordinating center acting through subsidiary centers in the bulb capable of assuming its functions increasingly as these are being annulled by the pituitary lesion, absence of postoperative complications is explained.

Again, the main evidence of those who believe in the existence of an internal secretion is based on the rise of the blood-pressure observed after injections of pituitary extract. "According to Kohn,"[173] writes Swale Vincent in his recent work,[174] "there is nothing to suggest that the posterior lobe has an internal secretion, in spite of all the results of experiments involving the injection of extracts." . . . "We have seen that the extracts having powerful effect upon the blood-pressure and the flow of urine are obtained from the posterior lobe and not from the epithelial layer which covers it. This view seems to be borne out by the experiments of Franchini. Now, the posterior lobe proper (excluding the epithelial layer) consists of neuroglia, pigment, and occasional nerve-cells." Swale Vincent then aptly remarks: "It is extremely difficult to imagine how such a structure can be regarded as a secreting gland."

Pending additional evidence to this effect, and referring the reader to preceding chapter for testimony concerning the connection between the pituitary and the adrenals, the conclusion is submitted that

The pituitary body contains the governing center of the parathyroid apparatus and adrenals, and co-ordinates the secretory activity of these organs.

[173] Kohn: Münch. med. Woch., Nu. 28, 1910.
[174] Swale Vincent: "Internal Secretion and the Ductless Glands," p. 401, 1913.