observed in a large number of cases of thyroid intoxication that the blood-serum produced dilatation of the pupil, while thyroidectomy caused this power markedly to decline. The same mydriatic activity was conferred on the serum of animals by giving thyroid extract by the mouth, the mydriatic power corresponding with the dose administered. Hoskins,[17] who refers to the above observations, obtained similar results in guinea-pigs. In both exophthalmic goiter and myxœdema, as we shall see, the participation of the adrenals in the processes shows itself in various ways. Physiology and clinical medicine thus unite in showing that the secretion of the thyroid apparatus enhances the functions of the adrenals. I might, however, express this in a different term. Starling[18] has named "hormone" (from ὅρμαω, arouse or excite) a substance which, originating in one organ, is capable of stimulating another. Internal secretions being included among the hormones, we can state that the hormones produced by the parathyroid apparatus are capable of stimulating the adrenals. That the thyroid secretion does not serve only for this purpose, however, is suggested by the fact that it is component of the blood at large. We can only, therefore, look upon its exciting effect upon the adrenals as an incidental feature of a general function.

What is the nature of this function? We have seen that the prevailing views afford no answer to this question. We are, therefore, brought back to the answer I submitted at the beginning of this section, viz., that "iodine in organic combination which the thyroparathyroid secretions contain renders the phosphorus that all tissue-cells and particularly their nuclei contain more prone to undergo chemical change, *i.e.*, oxidation in this connection, with the adrenal product adrenoxidase as its source of oxygen," and to analyze the evidence which led me to it. The plan adopted for the same purpose in the case of the adrenals will be carried out, viz., to submit the main evidence in detail, though in as terse a form as possible. Starting with the nature of the thyroparathyroid secretions, I shall then trace their itineraries throughout the organism as an organic compound, and finally its function.

[17] Hoskins: Amer. Jour. of Physiol., vol. xxvi, p. 426, 1910.
[18] Starling: "Recent Advances in the Physiology of Digestion," 1906.

The thyroid product is an "iodized globulin" (as Oswald maintains), the globulin being the albuminous constituent of hæmoglobin, i.e., *adrenoxidase.*

As Notkin[19] and also White and Davies[20] hold, the action of the thyroid secretion resembles that of an organized ferment. The identity of this ferment suggests itself, *i.e.*, the adrenal active principle, when we consider Baumann's analyses of his thyroidin. Among other tests, for example, he found that it was practically insoluble in ether and chloroform; that it was not destroyed by digestive ferments, and that it stood a temperature of 100° C.[21] These are the specific tests of adrenalin. That this active principle, in turn, occurs as a constituent of what I have termed "adrenoxidase," is shown by the fact that it also gives the tests of the plasmatic oxidase; Lépinois, for example, found that the thyroid secretion contained an oxidase which gave the blue reaction with tincture of guaiac. Again, we have seen that adrenoxidase is a globulin: Oswald termed his product "thyroglobulin" and described it as an "iodized globulin." Again, adrenoxidase being the oxidizing constituent of the blood, and circulating as it does in all tissues and organs, as the albuminous portion of the hæmoglobin, it must necessarily circulate also in the thyroid and parathyroids as a blood constituent, and out of which the secretions of these organs obtain it.

The actual presence of an oxidizing ferment was further confirmed recently by Youchctchenko.[22] Under the heading of "oxidizing ferments" of the thyroid gland, he states that this organ is "rich in catalases." As I have shown in the preceding chapter, catalysis is a property of the adrenal active principle. He found, moreover, that "the catalase, as well as the oxidizing ferment, is contained in the red blood-corpuscles." This corresponds precisely with the fact I pointed out several years ago in the first edition of the present work. In keeping also with what I had held concerning the influence of the thyroid on oxidation (partly through its influence over the adrenals), Youchctchenko found that in dogs "thyroidectomy was invariably followed by a manifest, at times considerable, lowering of the

[19] Notkin: Wiener med. Woch., Bd. xlv, S. 824 u. 872, 1895.
[20] White and Davies: Cited by Halliburton: Practitioner, Jan., 1897.
[21] Cited by Morat and Doyon: Traité de physiologie, vol. i, p. 467, 1904.
[22] Youchctchenko: Archives des Sciences Biologiques de l'Institut Impérial de Médecine Expérimentale à St. Petersburg, Tome xv, Nos. 3 and 4, p. 173, 1910.

temperature"; "in two dogs," he adds, "this oxidizing power fell almost to one-half of the normal."

Yet in the light of the functions I have ascribed to the adrenals, and the functional stimulation these organs receive from the thyroid product, these effects upon the temperature should correspond with a reduction of the oxyhæmoglobin, the active agent of which is adrenoxidase. That such is the case is shown by the experiments of Albertoni and Tizzoni,[23] who found that removal of the thyroid caused the blood to show *decreased power to fix oxygen;* while Masoin[24] found that the relative quantity of *oxyhæmoglobin* in the blood was diminished gradually as the postoperative phenomena of thyroidectomy progressed.

Another constituent of thyroiodin may be regarded much in the same light, viz., nucleoproteid. Sherrington, Milroy and Malcolm,[25] and others have found that the granulations of the most numerous leucocytes in the blood, the neutrophiles, are composed of nucleoproteid, while the observations of Bail, Stokes, and Wegefarth,[26] Sangree,[27] and others have as clearly shown that these granulations leave the periphery of the cell. We shall see in the next volume that it is through these cells that nucleoproteid reaches the thyroid apparatus. As stated by Beebe,[28] "chemical studies of the gland have demonstrated the presence of three forms of proteid: nucleoproteid, globulin, and albumin, in addition to a number of simpler cleavage products of proteid, the latter being bodies of no especial significance. The normal thyroid contains relatively little of the nucleoproteid, much globulin, and a smaller amount of albumin; the parathyroid, on the other hand, contains a large amount of nucleoproteid, a very small proportion of globulin, and still smaller amounts of albumin." Here, again, we find in the secretion a supposed intrinsic component, nucleoproteid, which, in reality, is but a commonplace, though important, constituent of the blood.

That iodine is the active agent of the thyroparathyroid secretions is now absolutely established. Some observers have

[23] Albertoni and Tizzoni: Cited by Maragliano: Gaz. degli Ospedali, Oct. 20, 1894.
[24] Masoin: Bulletin de l'Académie de Médecine de Belgique, No. 1, p. 88, 1895.
[25] Milroy and Malcolm: Jour. of Phys., vol. xxv, p. 106, 1899.
[26] Bail, Stokes, and Wegefarth: Bull. Johns Hopkins Hosp., Dec., 1897.
[27] Sangree: Phila. Med. Jour., Mar. 12, 1898.
[28] Beebe: Jour. Amer. Med. Assoc., Mar. 4, 1911.

held that the thyroid and parathyroids contain no iodine, in opposition to the findings of many authorities, but this must be ascribed to defective analytic work. Beebe, while stating that "the physiologically active portion of the gland secretion is a protein substance containing iodine in a specific organic combination," also remarks: "I have never been able to obtain a definite protein or proteose from the thyroid absolutely free of iodine." Quantities of iodine varying from 2.05 to 13.04 mg. per gland have been found by Baumann, Weis, Oswald, Rosetzki, Iolen, Gley, and others, in Europe, and Wells (10.79 mg.), in this country. Moreover, "if potassium iodide be given to an animal, there is an increase in the content of the physiologically combined iodine in the gland." As Oswald holds, therefore, the thyroid product is an "iodized globulin."

Again, as stated by Parhon and Golstein[29] in their recent work (1909) referring to the identity of the thyroid product, "Fortunately we are today better informed concerning the functions of the thyroid body, and if we cannot exclude the production of certain enzymes by the thyroid cells we can, on the other hand, affirm that their principal action is due to a more clearly defined substance, which is an iodized globulin."

The foregoing analysis has shown that in keeping with the prevailing view the active principle of the thyroparathyroid secretions is iodine; but inasmuch as its activity in this organic combination exceeds greatly that of iodine or its salts, a property which its combination with a ferment (adrenoxidase) explains, its true identity is more accurately expressed by the term *"thyroiodase,"* which I suggested some years ago.

Why should this combination occur? We will see presently that its purpose is primarily to insure the absorption of the iodine by the red corpuscles, hæmoglobin being the normal host of these cells. Analysis of this question showed that

The thyroid and parathyroid secretions ultimately reach the superior vena cava and are carried to the pulmonary alveoli, where they combine and are taken up by the red corpuscles, along with the adrenal secretion.

King, over a century ago, traced the thyroid secretion to the lymphatics, and Hürthle showed that fluids as well as their

[29] Parhon and Golstein: "Sécrétions Internes," p. 16, Paris, 1909.

colloid passed from the thyroid vesicles to these vessels, a fact confirmed by Horsley and others. Baber found colloid similar to that in the thyroid within the lymphatic vessels. The more recent investigations of Biondi,[30] Zielinska,[31] Vassale and de Brazza[32] on the thyroid, and those of Welsh,[33] and Capobianco and Mazziato,[34] and others on the parathyroids, have shown that the product of these organs passes into the perivascular lymph-spaces. Being then transferred to the larger cervical lymphatics, they are discharged by the right and left lymphatic ducts—the thoracic duct, according to Pembrey[35]—into the subclavian veins, and by way of the superior vena cava to the heart. Here they become merged with the venous blood of the entire organism, *forming a single secretion,* which is then inevitably carried to the heart, and thence to the lungs. As the venous blood carrying the adrenal secretion passes from below to these organs to be oxygenized, so is the thyroparathyroid secretion carried from above to the air-cells.

All these facts tend to controvert the current view that the thyroid and parathyroids are not functionally related. The fact is that the prevailing opinion, referred to on p. 147, is not based on a broad view of the evidence in the case. My own conception sustains and completes that of Gley, which admits a functional association in the sense that one set of organs serves to complete the work of the other. This intimate connection is shown by the observation of Edmunds that, while extirpation of the parathyroids causes histological changes in the thyroid, removal of the latter also causes degeneration of the parathyroids. Moreover, Vassale and Generali[36] found that after death from removal of the latter the thyroid contained no colloid. Lusena[37] noted the same fact, thus showing that the formation of the thyroid secretion depends in some way upon the functions of the parathyroids. Edmunds emphasized this fact by showing that hypertrophy of the thyroid followed parathyroidectomy, both embryonic tissue and vessels showing development. This survival

[30] Biondi: Berl. klin. Woch., Bd. xxv, S. 954, 1888.
[31] Zielinska: Virchow's Archiv, Bd. cxxxvi, S. 170, 1894.
[32] Vassale and de Brazza: Arch. ital. di biol., vol. xxiii, p. 292, 1895.
[33] Welsh: Jour. of Anat. and Physiol., Apr., 1898.
[34] Capobianco and Mazziato: Giorn. Int. de Sci., Nos. 8, 9. and 10, 1899.
[35] Pembrey: Hill's "Recent Advances in Physiology," p. 579.
[36] Vassale and Generali: Riv. di Patol. Nerv. et Ment., vol. i, pp. 95 and 249, 1896.
[37] Lusena: Fisio-patologia dell'Appar. Tiro-parat.. Florence, 1899.

suggests that removal of the parathyroids is not as fatal as generally believed. Indeed, Gley[38] had two dogs survive removal of all the parathyroids leaving only one lobe of the thyroid; the same operation in two other dogs and in a cat was followed by disturbances which became fatal on removing the remaining thyroid lobe. In another dog parathyroidectomy caused only trophic disturbances and death in one month. The same thing was observed in rabbits when two parathyroids only were left. Edmunds[39] also had two survivals in dogs after parathyroidectomy and deems this operation less grave than thyroidectomy, an opinion which is also Gley's.

Again, Halpenny,[40] after a comprehensive series of experiments in the same direction, writes: "I have been unable to confirm the statement that complete parathyroidectomy invariably proves fatal, and that in a short time. In dogs 3 and 7, where serial sections of the thyroid removed post-mortem showed no parathyroid, the animals lived 30 and 27 days, respectively, without symptoms and were killed. In dog 1, symptoms did not occur, and at the post-mortem no parathyroids were found, although serial sections were not cut. In cats 1, 6, and 8, in which at the operation the thyroid lobe with the parathyroids on one side, and the parathyroids alone on the other side, were removed, the animals lived, without symptoms, 23 days, 25 days, and 30 days, respectively, and were then killed. In all three cases a careful post-mortem search was made, and the remaining lobe of the thyroid was cut in serial sections, and no traces of parathyroid was found. There is a tendency to disregard these exceptions—MacCallum and Davidson,[41] Berkeley and Beebe[42]—and explain them by supposing that parathyroids have remained behind unobserved." This explanation is hardly tenable in view of the numerous examples presented. As to accessory glands, as Vincent[43] states, "If accessory glands be so usually present, the question as to the importance to life of these glands ceases to have the value hitherto attached to it." Although I believe Halpenny killed his animals too soon after the operation, Parhon

[38] Gley: Brit. Med. Jour., Sept. 21, 1901.
[39] Edmunds: Jour. of Pathol. and Bacteriol., Jan., 1896.
[40] Halpenny: Surgery, Gynecology, and Obstetrics, May, 1910.
[41] MacCallum and Davidson: Medical News, Apr. 8, 1905.
[42] Berkeley and Beebe: Journal of Medical Research, Feb., 1909.
[43] Vincent: London Lancet, Aug. 11 and 18, 1906.

and Golstein[44] having observed postoperative death (though without tetanic phenomena) as much as 30 and 66 days after thyroparathyroidectomy in the cat, the fact remains that added to the data recorded by Gley his evidence tends to weaken the view that the parathyroids are endowed with independent functions. Swale Vincent, in his recent book (1913), adduces convincing data indicating "an intimate relationship between the two structures," anatomical, physiological, and pathological.

Finally, and pointedly suggesting a combined function, we have seen that a transplanted or grafted piece of thyroid tissue, free of all parathyroid tissue, assumes the functions of both sets of organs, arrests the convulsive disorders due to extirpation of the parathyroids alone, and prevents death.

All this clearly points to a functional connection (probably a nervous one to co-ordinate the relative proportions of their secretions) between these two sets of organs, and thus insures the ultimate formation in the lungs of a perfect, *i.e.*, physiological, thyroparathyroidal product.

The purpose of this itinerary suggests itself when we recall that, as stated by Nothnagel and Rossbach,[45] hæmoglobin can fix large quantities of iodine. It accounts also for the fact that Gley[46] and Bourcet found iodine in the red corpuscles. Being a component of the albuminous hæmoglobin of these cells with adrenoxidase, however, iodine should be found in all tissues. While Bourcet[47] ascertained that such was the case, Justus[48] found it in all cellular nuclei, so rich as is well known in phosphorus. This simultaneous presence of iodine and phosphorus in the nuclei, and also of iodine in the red corpuscles, suggests the nature of process carried on in the cells: viz.,

The thyroparathyroid constituent of the hæmoglobin enhances oxidation by increasing, as a ferment, the vulnerability of the phosphorus, which all cells, particularly their nuclei, contain, to oxidation by the adrenoxidase in the blood.

This action is strikingly shown by the fact that iodine, the active constituent of the thyroid secretion, and its salts, as shown by Henrijean and Corin,[49] Handfield Jones,[50] and others, cause

[44] Parhon and Golstein: "Sécrétions Internes," pp. 607 and 609, Paris, 1899.
[45] Nothnagel and Rossbach: "Therapeutique," p. 261, 1889.
[46] Gley: La Semaine médicale, May 25, 1898.
[47] Bourcet: Cited by Morat and Doyon: Traité de physiologie, i, p. 470, 1904.
[48] Justus: Virchow's Archiv, Bd. clxxvi, S. 1, 1904.
[49] Henrijean and Corin: Arch. de pharmacodyn., ii, 1896.
[50] Handfield Jones: Cited by Wood: "Therapeutics," 13th ed., p. 499, 1906.

excessive elimination of phosphates and phosphoric acid, and that thyroid preparations, according to Roos, Scholtz,[51] Pouchet,[52] and others, act in the same way. "Emphasis must be laid," writes Chittenden,[53] "upon the apparent connection between the thyroid gland and phosphoric acid metabolism," giving as example "the increased excretion of P_2O_5 after feeding thyroids to normal animals, and the great decrease in the case of animals with the thyroids removed."

The untoward effects of large doses of thyroid preparations on the nervous system, owing to its wealth in phosphorus and fats, as manifested by tremor, tachycardia, optic neuritis (Coppez[54]), etc., also bespeak a marked influence on this element; Cyon,[55] in fact, found that injections of iodothyrin excited the depressor nerve directly to such a degree that the vascular pressure often declined to two-thirds of the normal.

A familiar action of the thyroid preparations is a rapid reduction of fat in obese subjects when full doses are administered. The presence in the fat-cell of a nucleus rich in phosphorus whose purpose is promptly to promote oxidation of the fat when the organism requires additional carbohydrates explains this action. Schöndorff[56] found that the reserve fats could be exhausted before the nitrogenous tissues were affected.

The mode of action of the thyroid active principle, iodine, is suggested by the presence of this halogen in all nuclei, as shown by Justus[57] and others. This means that iodine is found wherever phosphorus is present, while, as shown above, it is most active where phosphorus is known to be most plentiful. Now, chemistry furnishes, as previously stated, a clue to the manner in which the phenomena I have enumerated occur: "If a fragment of phosphorus lying on a plate is sprinkled with iodine," writes Wilson,[58] "the substances unite, and heat enough is produced to kindle the phosphorus." Nitrogen, hydrogen, and chlorine are ubiquitous constituents of our tissues, and the vigorous explosives they form with phosphorus and the intense

[51] Scholtz: Centralbl. f. inn. Med., Bd. xvi, S. 1041, 1069; 1895.
[52] Pouchet: Bull. gén. de thérap., Sept. 15, 1905.
[53] Chittenden: Trans. Cong. Amer. Phys. and Surgs., iv, p. 93, 1897.
[54] Coppez: Arch. d'Ophthal., Dec., 1900.
[55] Cyon: Arch. de physiol., x, p. 618, 1898.
[56] Schöndorff: Arch. f. d. ges. Physiol., lxiii, S. 423, 1896; lxxii, p. 395, 1897.
[57] Justus: *Loc. cit.*
[58] Wilson: "Inorganic Chemistry," p. 284, 1897.

liberation of heat the reactions entail are familiar features of the laboratory. Roos[59] found that in a dog in nitrogenous equilibrium iodothyrin "caused at once a marked increase in the output of sodium, sodium chloride, and phosphoric oxide."[60]

Finally, as stated in the italicized postulate, "the thyroparathyroid constituent of the hæmoglobin enhances oxidation by increasing, as a ferment, the vulnerability of all cells" to the action of adrenoxidase. That is shown by many facts.

Chantemesse and Marie, Ballet and Enriquez,[61] Bourneville,[62] Shattuck,[63] Lorand,[64] and many other clinicians, including myself, have noted that thyroid preparations caused a rise of temperature of several degrees. These observations are controlled by those of Stüve and Thiele and Nehring,[65] that thyroid extract increases over 20 per cent. the oxygen intake and to nearly as great a degree the carbonic acid output. This is evidently produced by the active agent of the thyroid secretion, iodine, for this halogen itself increases oxidation as well. Thus, Rabuteau, Milanese, and Bouchard,[66] Henrijean and Corin[67] have all noted an increase of nitrogen excretion. Wood[68] and Cushny[69] state, in fact, that iodine can produce fever. Heinrich Stern[69a] noted a rise of temperature at times of 3° F. in cases of hyperthyroidia.

Removal of the thyroid, on the other hand, lowers oxidation. Albertoni and Tizzoni, and Magnus-Levy[70] found, for example, that this procedure decreased markedly the output of carbon dioxide, and that it caused hypothermia. The fall of temperature is gradual, according to Lorrain-Smith,[71] and most marked, according to Rouxeau,[72] at the end of the operation. The proportion of red corpuscles is reduced, according to Moussu.[73] Reverdin observed in man that the hæmoglobin was also diminished, while Horsley noted increased sensitiveness to cold.

[59] Roos: Münch. med. Woch., No. 47, S. 1157, 1896.
[60] Cited by Chittenden: *Loc. cit.*, p. 98.
[61] Ballet and Enriquez: Cited by Popoff: Arch. gén. de méd., Oct., 1899.
[62] Bourneville: Arch. de neurol., Sept., 1896.
[63] Shattuck: Boston Med. and Surg. Jour., June 30, 1904.
[64] Lorand: Lancet, Nov. 9, 1907.
[65] Thiele and Nehring: Zeit. f. klin. Med., xxx, S. 41, 1896.
[66] Bouchard: C.-r. de la Soc. de Biol., pp. 227, 237, 1873.
[67] Henrijean and Corin: Arch. de pharmacodyn., ii, 1896.
[68] Wood: "Therapeutics," 13th ed., p. 499, 1906.
[69] Cushny: "Pharmacology and Therapeutics," 4th ed., p. 514, 1906.
[69a] Stern: Archives of Diagnosis, July, 1911.
[70] Magnus-Levy: Zeit. f. klin. Med., Bd. xxxiii, S. 269, 1897.
[71] Lorrain-Smith: Jour. of Physiol., vol. xvi, p. 378, 1894.
[72] Rouxeau: Arch. de physiol., vol. xxix. p. 136, 1897.
[73] Moussu: C.-r. de la Soc. de Biol., p. 772, 1903.

Albertoni and Tizzoni and Masoin found that the blood contained less oxygen than normally.

This applies as well to removal of the parathyroids, which was found by Jeandelize[74] also to lower the temperature. That the thyroid apparatus can itself raise the temperature, is shown by the febrile process and sense of heat with flushing observed in the sthenic stage of exophthalmic goiter, *i.e.*, when the thyroid apparatus is still overactive. When thyroid extract is given to such cases, the exchanges may be increased to a surprising degree —77 per cent. in a case observed by Hirschlaff.[75] The disease may in fact be brought on by thyroid preparations, as noted by Notthaft[76] and other clinicians.

Still, as Chittenden states,[77] "according to Baumann, doses of 1 milligramme of iodothyrin, which contain only 0.1 milligramme of iodine, will produce a decided effect upon a goiter after three or four applications, thus clearly indicating that it is not the iodine *per se* that is effective, but rather the iodine compound." This will recall the observations of Notkin and White and Davies that the action of the adrenal secretion resembles that of an organized ferment, and my own that the adrenal principle with which the iodine is combined endows it with the properties of a ferment, the purpose being probably to increase the activity of the iodine on the cellular phosphorus.

THE THYROPARATHYROID SECRETION AS WRIGHT'S OPSONIN.

Fraenkel isolated from the thyroid what he termed a "thyroantitoxin," which he thought served to neutralize in the gland itself toxic substances brought to it by the blood. Notkin also separated a substance he called "thyroproteid," a product of tissue exchanges which he believed reached the organ, to be destroyed therein by a ferment, thyroidin, formed locally. These and all other theories, including Blum's, which restrict the antitoxic process to the gland itself have not stood the test of time. These conceptions are now only of historical interest, many investigators having shown that whatever function the thyroparathyroid apparatus may carry on should be attributed

[74] Jeandelize: "Insuffisance thyroidienne et parathyroidienne," p. 45, 1903.
[75] Hirschlaff: Zeit. f. klin. Med., Bd. xxxvi, Nu. 3-4, S. 200, 1898-99.
[76] Notthaft: Centralbl. f. inn. Med., Apr. 9, 1898.
[77] Chittenden: *Loc. cit.*, p. 99.

to the passage of its secretion into the blood, in which its active principle, in organic combination, has been found by Gley, Bourget, and others, both in man and the lower animals. The evidence submitted in the foregoing pages fully sustains this position.

What the prevailing views are concerning the rôle of the thyroid secretion, and what my own researches represent in respect to them, may be graphically illustrated by quoting the recently published words of Youchctchenko, of the Institute of Experimental Medicine of St. Petersburg.[78] "Some suppose that it [the secretion of the thyroid] is necessary for the development of the bones, the digestion, the nervous system, etc.; others express the opinion that it fills the rôle of antitoxin, which renders non-toxic the toxic products of nutritional exchanges; others, finally, affirm that the toxic substances elaborated in the economy are transformed, under the influence of the ferment in the thyroid, into substances necessary and even indispensable to the life of the organism."

If the function I ascribe to the thyroid apparatus was clearly defined in the foregoing pages, it will be seen that they harmonize all those outlined by Youchctchenko. The labilizing or sensitizing action I attribute to the iodine (in organic combination) on tissue phosphorus explains the action of the thyroid product upon "the development of bones, the digestion, the nervous system," etc., since it is an essential feature of their metabolism —that which renders all tissues susceptible to adequate oxidation, the underlying factor of normal development and function. The "transformation under the influence of the ferment in the thyroid" is naught else than the above process carried out, we have seen, under the influence of a ferment and the organic iodine, *i.e.*, by what I have termed "thyroiodase." As to its rôle as "antitoxin," we shall now see that it is also a feature of the same process.

Youchctchenko credits Marbé, Malvoz, Fassin, and Stépanoff (the first- and last- named investigators being of the Pasteur Institute) with the credit of having first connected the thyroparathyroid secretion with the modern conception of immunity, which takes into account the presence of alexins, opsonin, etc.,

[78] Youchctchenko: *Loc. cit.*, Tome xv, Nos. 3 and 4, 1910.

in the blood; but this is an oversight which Léopold-Lévi and H. de Rothschild, of Paris, corrected in their recent work[79] when they wrote: "Sajous has attributed to the secretion of the thyroid gland an action which he deems similar to that of the opsonins and to autoantitoxins. More recently, Miss Fassin, M. Stépanoff, M. Marbé have confirmed on their side the influence of the thyroid on the blood's asset in alexins and opsonins. All these researches explain the mechanism of everyday infections."

That I am entitled to the priority of this discovery will be shown presently in the course of the evidence in support of my contention, advanced several years ago,[80] that

The thyroparathyroid secretion increases the germicidal and antitoxic power of the blood by endowing the albuminous portion of the hæmoglobin with sensitizing properties. As such, it is the blood constituent Sir A. E. Wright has termed "opsonin."

Bordet's sensitizing substance, or "sensibilisatrice," was thought by this investigator and also by von Dugern to appear in the blood under the influence of the red corpuscles. Nolf[81] showed, however, that it is owing to an action of the alexins or complement upon these cells that "the contents of the latter" are caused *to leave* them; he found also that "the injection of the corpuscular *contents* incites hæmolysis." Now, Savtchenko[82] has pointed out that the "sensibilisatrice" is endowed with specific opsonic properties, acting both on bacteria and leucocytes—the identical sensitizing action discovered by Denys and Leclef[83] in 1895, and which Sir A. E. Wright has since studied with such promising results. Suggestive in this connection is Nolf's statement in reference to the production of antibodies that "it is solely to the injected red corpuscles that the power to bring forth these new substances must be attributed." When this is coupled with Barratt's[84] observation that opsonins "are also produced by injecting red blood-cells in the peritoneal cavity" of experimental animals, and also Briscoe's[85] to the effect that opsonin is present

[79] Léopold-Lévi and Rothschild: "Physio-pathology of the Thyroid Body," etc., 1911.
[80] Sajous: See vol. i, 1st ed., p. 762, 1903, and vol. ii, p. 1093, 1907.
[81] Nolf: Annales de l'Institut Pasteur, xiv, pp. 297 and 492, 1900.
[82] Savtchenko: *Ibid.*, xvi, p. 106, 1902.
[83] Denys and Leclef: "La Cellule," xi, p. 198, 1895.
[84] Barratt: Proc. Royal Soc. of London, lxxvi, p. 534, 1905.
[85] Briscoe: London Lancet, Sept. 7, 1907.