tion would be available to account for them. On the other hand, when the three sets of organs are considered as related functionally, *i.e.*, as the adrenal system, the phenomena awakened by each organ occur as normal results of its action upon the organ with which it is linked. Thus, the thyro-parathyroid secretion enhances metabolism by exciting the anterior pituitary body, owing to the presence in the latter of its sensitive test-organ; the anterior pituitary in turn produces the same effect by stimulating the adrenals through the nerve-path which unites it with these glands; finally, the adrenals also sustain metabolic activity through their secretion, the precursor of adrenoxidase. Of the latter substance I have had occasion to say:[172] "It is able not only to endow nonliving though viable proteids with vitality by bringing into play and governing the activity of various other physico-chemical bodies, but it can also sustain the vital process it has initiated in all the cells of an organism." Recalling now that it is through the intermediary of leucocytes laden with exogenous products that the secretions elaborated in the thyroid and the parathyroids can produce such effects, and that toxic wastes are destroyed when excess of adrenoxidase appears in the blood, we obtain an insight into the means through which the body protects itself against disease, *i.e.*, of the *vis medicatrix naturæ*.

On the whole, the evidence submitted in the first volume and in the present section warrants the following conclusions: (1) *the thyroid apparatus (the thyroid and parathyroids), the anterior pituitary body and the adrenals are functionally interdependent and thus constitute the adrenal system;* (2) *the function of the thyroid apparatus is to supply a secretion to the blood which enables the latter, while circulating through the anterior pituitary body, to excite its test-organ;* (3) *the function of the test-organ is to react sufficiently under the influence of the thyro-parathyroid secretion, to stimulate the adrenals and thus to sustain their secretory efficiency;* (4) *the function of the adrenals is to sustain oxygenation and therefore general metabolism—the vital process—by means of its oxygen-laden secretion, adrenoxidase;* (5) *if from any cause the functional activity of either one of the organs composing the adrenal system becomes inadequate or excessive, general metabolism, and therefore the vital process, is influenced accordingly.* Hence, (6) *the functions of the adrenal system are (a) to sustain general metabolism and the vital process, (b) to protect the organism, when toxic wastes accumulate in the blood, by augmenting the proportion of adrenoxidase supplied to the blood and therefore the antitoxic activity of the latter;* (7) *the adrenal system, therefore, is the body's auto-protective or auto-immunizing mechanism.*

[172] *Cf.* this vol., p. 933 *et seq.*

THE THYRO-PARATHYROID SECRETION AS THE SENSITIZING SUBSTANCE OF ALL CELLS AND AS THE PHYSIOLOGICAL EXCITANT OF THE TEST-ORGAN.

As stated in the preceding section, the experiments of Gley, Moussu, and Vassale and Generali showed that the thyroid fulfilled trophic functions, while extirpation of the parathyroids was followed by convulsive phenomena. This is sustained by a large number of experiments in animals and many clinical observations. In young dogs, for instance, extirpation of the thyroid alone provokes all the phenomena of cretinism; as stated by Jeandelize[173] "the animals remain small, become apathetic; the face becomes wrinkled, the trunk broad, the belly rounded, the skin thickened and lobulated owing to myxœdematous infiltration, and the fur rough." Briefly, thyroidectomy pure and simple provokes trophic disorders. Although Kishi[174] found recently that dogs and cats may die after this procedure even though the parathyroids are left intact, the fact remains that even in carnivorous animals, including man, extirpation of the thyroid proper is not usually followed by death, but by the cachexia strumipriva of Reverdin and Kocher, *i.e.*, myxœdema.

Removal of both the thyroid and parathyroids, on the other hand, is generally fatal. Jeandelize collected 427 experiments of this kind on record, all in dogs. The mortality was 91.6 per cent. Edmunds[175] states that this procedure causes "almost invariably the following symptoms: tremors, convulsive attacks with rapidity of breathing and rigidity of limbs passing into paralysis. Death comes on within a few days, usually in

[173] Jeandelize: *Loc. cit.*, p. 41.
[174] Kishi: Virchow's Archiv, Bd. clxxvi, S. 260, 1904.
[175] Edmunds: Practitioner, Apr., 1901.

less than a week." The same writer says also, however: "The excision of the four parathyroids only, leaving the thyroid proper, generally causes the *same symptoms* with the *same termination*. Indeed, Vassale and Generali[176] lost all their nine dogs in eight days; Moussu,[177] all of his eighteen dogs in from two to forty-six days; Lusena,[178] all of his nineteen dogs in three days. Edmunds,[179] however, lost only four out of nine. Vincent and Jolly[180] found also that parathyroidectomy was not necessarily fatal. Be this as it may, the seriousness of the procedure is self-evident; the mortality approximates at least that which follows removal of the thyroid and parathyroids.

This confirms the opinion first advanced by Gley[181] over fifteen years ago that the parathyroids are decidedly the most active organs of what he has termed the "thyroid apparatus." The reason for this became apparent when he found, as we have seen, that the secretion of the parathyroids differed from that of the thyroid in that it contained six times more iodine in the dog, and twenty-five times more in the rabbit. Although these relative proportions are doubtless subject to great variations, they nevertheless suggest that the parathyroids are the source of the principle which endows the secretion of the thyroid with the greater part of its activating or rather energizing property—probably, owing to the comparatively large proportion of iodine it contains.

A striking feature concerning iodine is its uniform presence in organic matter in combination with sodium, potassium, calcium, and magnesium. In the seas it is found in abundance in marine plants, especially the algæ. Spring water was also found by Chatin[182] to contain iodine, but not at the spring itself, and only in water that had followed a course strewn with fragments of organic matter, animal and vegetable. It is also present in the soil. Daubrée[183] found it in the thermal waters

[176] Vassale and Generali: Arch. ital. de Biol., T. xxv, p. 459, 1896.
[177] Moussu: C. r. de la Soc. de biol., Jan. 16, 1897.
[178] Lusena: "Fisio-patologia dell 'apparecchio tiro-parateroideo," Florence, 1899.
[179] Edmunds: Jour. of Pathol. and Bact., May, 1899.
[180] Vincent and Jolly: Jour. of Physiol., vol. xxxii, p. 65, 1904.
[181] Gley: C. r. de la Soc. de biol., p. 843, 1891.
[182] Chatin: Cited by Trousseau and Pidoux: "Traité de Thérap," vol. i, p. 327, 1875.
[183] Daubrée: Cited by Dana: "Manual of Geology," pp. 331 and 335, fourth edition, 1895.

of Bourboule-les-Bains, and many mineral waters are known to contain it. While all waters in which iodine is present tend to eliminate it (hence the greater quantity of iodine at the sea-shore than elsewhere, and in rain-water) all living cells, animal or vegetable, have a marked affinity for it. That it is an important constituent of the living organism is shown by the fact that all marine animals contain more or less of it, the European oyster and the cod probably the largest proportion. Fresh-water fishes, crustaceans and batrachians also show distinct evidence of its presence. We have seen that our blood is after all but a bit of the ocean circulating in our vessels and that, as stated by Claude Bernard, our cells live therein as fishes do in water.

Chittenden,[184] however, justly urges that "the iodine in iodothyrin is certainly not active as iodine; the amount is too small." How then does it act?

Suggestive in this connection is the fact that the thyro-parathyroid secretion embodies not only the compounds that we found in the digestive leucocytes, but also nucleo-proteid and adrenoxidase.

Ten years ago, Halliburton[185] in the course of a paper on the internal secretions, remarked: "Among the earliest to investigate the proteids of the thyroid was Bubnow,[186] and to one of these, thyreo-proteid, Notkin[187] attributes the activity of the organ. He considers that its action resembles that of an enzyme or *unorganized ferment.*" In a foot-note the author states that "the ferment-theory is also urged by White and Davies." Again: "An investigation of the thyroid-proteids was later made by Gourlay[188] under my supervision, and his conclusions are as follows: The only proteid that can be obtained in any quantity from the thyroid is a *nucleo-proteid;* this is derived, at any rate in part, from the *colloid* material in the acini." Halliburton says in this connection, that nucleo-proteid "is proteid in combination with nuclein, the phosphorus-rich constituent of nuclei, but which is also found in

[184] Chittenden: Trans. Congr. of Amer. Phys. and Surgs., vol. iv, p. 101, 1897.
[185] Halliburton: Practitioner, Jan., 1897.
[186] Bubnow: Zeit. f. physiol. Chemie, Bd. viii, S. 1, 1894.
[187] Notkin: Wien. med. Woch., Bd. xlv, S. 824 u. 872, 1895.
[188] Gourlay: Jour. of Physiol., vol. xvi, p. 23, 1894.

the protoplasm of cells"—thus proving that we are dealing with the compound we found elsewhere. Finally, he states that "Hutchison[189] confirms Baumann's theory that the activity of the organ is accounted for by its proteid iodine-containing constituents; after removal of the proteids, thyroid extracts are of no use."

The last sentence shows clearly that iodine is not the only factor in the action of the secretion and that its influence partly depends upon the presence of the proteid—with which, as we have seen in the fourteenth chapter, all ferments are intimately combined. Notkin's observation that the action of the secretion resembled that of a ferment, and the fact, shown by myself, that *all* the ferments of the organism owe their activity to the "ferment of ferments," the active principle of the adrenal secretion—that embodied in adrenoxidase—all point to the presence of the latter in the thyro-parathyroid secretion. Indeed, we have seen that adrenoxidase, corpuscular and plasmatic, is a globulin. Now, R. Hutchison[190] states that the colloid consists of two proteids: "One of these, which makes up *by far the larger part of the secretion,* resembles closely in its behavior the class of proteids spoken of as *globulins;* the other is a nucleo-proteid." He also[191] found that besides containing phosphorus and being rich in iodine, the colloid contained sulphur, an element which, as stated by Gamgee[192] in reference to hæmoglobin, "belongs to the albuminous part of the molecule," *i.e.,* to adrenoxidase. The iodine is evidently bound up with the latter, for Baumann[193] found his iodothyrin in the albumins of the gland as "thyro-*iodoglobulin* or thyro-*iodoalbumin.*" Oswald[194] also isolated a body he termed *thyreoglobulin,* which constituted about 10 per cent. of the gland and contained 14.3 per cent. of iodine and which was found to increase metabolism, and nitrogen excretion, etc.

Briefly, the thyro-parathyroid secretion differs only from the proteolytic triad distributed by leucocytes to all the cells in the organism, in that it contains iodine—9.3 per cent. in Baumann's thyroidin, 14.3 in Oswald's thyreoglobulin—closely bound up with adrenoxidase. As Chittenden says, iodine is certainly not active as such. In fact, Toepfer[195] has shown that one ounce of sheep's thyroid contains but 0.009 ($^1/_7$ grain) of this halogen. The foregoing facts point to its mode of action, viz., that of a "ferment" as stated by Notkin—a triad, from my point of view, in which iodine plays the part of preferment.

[189] Hutchison: Brit. Med. Jour., Mar. 21, 1896; Jour. of Physiol., vol. xx, p. 474, 1896.
[190] R. Hutchison: Practitioner, April, 1901.
[191] Hutchison: Jour. of Physiol., vol. xx, p. 474, 1896.
[192] Gamgee: Schäfer's "T. B. of Physiol." vol. i, p. 202, 1898.
[193] Baumann: *Loc. cit.*
[194] Oswald: Münch. med. Woch., Bd. xlvi, S. 1073, 1899.

What is the physiological action of this iodine triad or "ferment"?

Levene,[196] Justus,[197] and others found iodine in practically all tissues. Gley[198] held that the iodine found in the thyroid is derived from the blood, his researches having shown that the red corpuscles stored it. We have seen, however, that iodine is not taken up by these cells, but, as observed by Labbé and Lortat-Jacob, by leucocytes. The phenomena of iodophilia also show that these cells are prone to absorb this halogen. Its presence in the red corpuscles, however, when considered in the light of my views, is subject to an interpretation other than that advanced by Gley:—

In the preceding chapter, we followed the secretions of the thyroid and parathyroids to the heart, where they entered the general venous circulation jointly, and thence to the pulmonary alveoli. In the first three editions[199] I submitted data which had led me to suggest that the eosinophile leucocytes (which are often found in the sputum in asthma, tuberculosis, etc., and are thought by various authors to take part in the formation of the alveolar epithelium[200]) built up hæmoglobin—its iron-containing portion, hæmatin—with iron derived from the intestine, and carried it to the pulmonary alveoli. Here, I held, the cells secreted their product into the adjacent plasma, where it was "absorbed by the underlying red corpuscles along with the oxygenized secretion" of the adrenals, *i.e.,* adrenoxidase. I was not aware at the time that the eosinophiles had already been associated with this function by Hayem, who described them as the "hæmoglobinic cells."[201] Under these conditions, the pro-

[195] Toepfer: Lancet, Mar. 7, 1896.
[196] Levene: Arch. of Neurol. and Psychopath., vol. ii, p. 571, 1899.
[197] Justus: Virchow's Archiv, Bd. clxxvi, S. 1, 1904.
[198] Gley: Semaine méd., May 25, 1898.
[199] *Cf.* vol. i, p. 716, in the first three editions.
[200] Lenhartz: "Clinical Micros. and Chem.," transl. by Brooks, 1904.
[201] Hayem: Cited by Levaditi: *Loc. cit.,* p. 36.

cess through which the thyro-parathyroid secretion enters the red corpuscles is self-evident: being likewise present in the plasma underlying the aveoli, it is absorbed with the hæmoglobin and its albuminous moiety, adrenoxidase, and distributed with the latter throughout the body. Hence the secretion is distributed by the red corpuscles to all cells and to the plasma itself.

The marked influence of the thyro-parathyroid secretion on metabolism suggests that it is more potent in the vital process than adrenoxidase itself. That such is not the case, however, is shown by the fact that removal of the thyroid and parathyroids does not always cause death. We have seen that Edmunds lost but four out of his nine dogs. Vincent and Jolly[202] were also led experimentally to conclude that "it cannot be truly said that either thyroids or parathyroids are essential for life, since it is frequently possible to remove either or both without causing death," although they fully recognize "as others have done, that fatal results, when they occur, are not due to injuries to surrounding structures accompanying the surgical interference, but must be referred to absence of the glands in question." Again, if the thyro-parathyroid secretion were the chief factor in sustaining the cellular interchanges, removal of the pituitary body or of the adrenals would only give rise to trophic disorders and seldom if ever prove fatal; whereas, in the great majority of instances, death occurs within a few days. This fact in itself, however, affords a clue to the rôle of the secretion. As a large number of experiments have shown, carnivorous animals are readily killed by thyro-parathyroidectomy while many herbivorous animals survive. Moreover, if carnivorous animals are fed on milk only, after the operation, the post-operative life is greatly prolonged. It is plain, therefore, that the influence of the thyro-parathyroid secretion is connected in some way with toxic wastes (which are proportionally much greater under a meat diet than under a vegetable diet) and that this influence is exercised not only, as we have seen, upon the cellular elements of the anterior pituitary, but upon all cells.

The close association of the thyro-parathyroid secretion

[202] Vincent and Jolly: Jour. of Physiol., vol. xxxii, p. 65, 1904.

with adrenoxidase, which led Oswald to term the thyroid secretion "thyroglobulin," corresponds with a constituent of the blood to which I have referred to in the preceding volume, viz., Sir A. E. Wright's *"opsonin,"* a substance which renders microorganisms vulnerable to phagocytes.

Denys and Leclef,[203] in 1895, showed experimentally that leucocytes were able to ingest bacteria only after the latter had been prepared, so to say, by the action of some substance in the blood-plasma. Thus, while the blood of a normal rabbit failed to destroy the streptococcus pyogenes, that of a vaccinated rabbit delayed the multiplication of these germs and sometimes destroyed them. Such a rabbit could stand with impunity a dose of streptococcus sufficient to cause erysipelas in a normal animal. Now, leucocytes from the latter, though unable to destroy streptococci, destroyed actively these germs in the blood of the vaccinated animal, while blood from the latter, when added to that of a normal animal, also caused the leucocytes of this animal to become energetically bactericidal. This shows plainly that the plasma of a vaccinated animal contains a substance which either increases the vulnerability of the germs to phagocytosis or the activity of the phagocytes. Two years later, Mennes[204] noted that the immunity conferred on guinea-pigs with toxins or pneumococcus cultures was due to a change in their serum which increased markedly the activity of phagocytosis, though the phagocytes themselves were not directly influenced. Wright and Douglas[205] termed this substance "opsonin" and showed that it was a constituent of the serum or plasma. They likewise concluded that it prepared the bacteria for phagocytosis without acting on the leucocytes. Neufeld and Rimpau[206] also found in the plasma a substance which "sensitized" bacteria without influencing the leucocytes. Virulent streptococci and pneumococci which failed to be ingested by the latter when they had been previously treated to antistreptococcic serum, were immediately taken up by these cells when the germs had themselves been treated to this serum, though the leucocytes had not. Many other experimenters have

[203] Denys and Leclef: "La Cellule," T. xi, p. 198, 1895.
[204] Mennes: Zeit. f. Hyg., Bd. xxv, S. 413, 1897.
[205] Wright and Douglas: Proc. Royal Society, vol. lxxii, p. 357, 1903.
[206] Neufeld and Rimpau: Deutsche med. Woch., Bd. xxx, S. 1458, 1904.

confirmed these observations without, however, throwing light upon the nature of the process. Moreover, as recently stated by Potter, Ditman and Bradley:[207] "Up to the present time very little has been determined concerning the source of the opsonins," and, referring to the above-named investigators, they state that they have all shown that "the opsonins exist in the blood serum and not in the leucocytes."

This affords a first point in which opsonin corresponds with the thyro-parathyroid secretion: being stored in the red corpuscles it is secreted with the adrenoxidase to which it is linked, and thus becomes a constituent of the plasma.

Again, Bordet, as is well known, termed *substance sensibilisatrice* or "sensitizing substance" and Gruber *preparator* or "preparing substance" (Ehrlich's amboceptor) a body which rendered bacteria, red corpuscles, or any kind of cell in fact, vulnerable to the destructive action of Buchner's alexins (Ehrlich's complement). Now, in the first volume I emphasized repeatedly the fact that Ehrlich's complement—the identity and source of which he has so far failed to show—was the intra-leucocytic trypsin, *i.e.*, the proteolytic triad.

This affords three more facts which harmonize with my interpretation, and with experimentally established data concerning opsonins, since the "sensitizing" substance is shown to affect the bacteria; to do so without influencing the leucocytes; and finally, to prepare the bacteria for the phagocytic leucocytes.

A fifth confirmatory point is available in that, precisely as is the case with the *substance sensibilisatrice*, which, as I state on page 735 of the first volume, "stands, without undergoing alteration, heating up to 60° to 65° C.," Kinghorn and Twichell,[208] referring to the observations of Wright and Douglas, state that opsonins "lose their power when heated up to 60° to 65° C. for ten to fifteen minutes."

Again, Bordet, Buchner and Gruber do not refer to the fact that the "sensitizing substance" is a compound body; in my own allusions to its homologue, the oxidizing substance (now adrenoxidase) in the first volume, its heat limit is always given

[207] Potter, Ditman and Bradley: Jour. Amer. Med. Assoc., Nov. 24, 1906.
[208] Kinghorn and Twichell: Amer. Jour. Med. Sci., Aug., 1906.

as 65° C. Now, opsonins have led to the same error: Potter, Ditman and Bradley[209] state that "Savtchenko[210] and Dean[211] regard certain opsonins and amboceptors as identical"—a seventh point in support of my interpretation.

The same authors also write, however, "Hektoen[212] regards opsonins as distinct from amboceptors, and in proof of his opinion states that under certain circumstances normal serum may possess lytic, but not opsonic powers, and *vice versa;* again, that immunization may give rise to opsonic, but not to lytic substances; and further that heat may destroy the *opsonic* power without affecting the lytic amboceptors, and *vice versa.* Thus, while opsonin for anthrax bacilli, present in the serum of normal dogs, is destroyed by heating at 60° C. for thirty minutes, the amboceptor for anthrax bacilli present in the serum of normal dogs is not affected by heating at 65° for thirty minutes. Moreover, while the serum of white rats is normally anthracidal owing to the presence of a thermostabile substance that is inactivated by neutralization of the serum with oxalic acid, the same serum contains a thermostabile opsonin for anthrax bacilli which, however, is not inactivated by oxalic acid." The presence of two distinct substances is clearly shown in this quotation: (1) the substance destroyed at 60° and (2) the thermostabile substance. Now, as stated by Lazarus Barlow,[213] Metchnikoff holds that while the thermolabile body is confined in the phagocytes (his trypsic cytase), the plasma contains another, which is "thermostable, resisting a temperature of 100° C." We have seen repeatedly that the only substance in the plasma which is able to stand this temperature is adrenoxidase. On the whole, opsonin is not the amboceptor any more than it is adrenoxidase; it is a sensitizing ferment, destroyed at 60-65° C., *combined with adrenoxidase,* which is only destroyed at 100° or may even resist that temperature.

Under these conditions, however, adrenoxidase should contain the various components of the thyro-parathyroid secretion: we have seen that Gley found iodine in the red corpuscles; and the fact that this halogen is also found in practically all tissues

[209] Potter, Ditman and Bradley: *Loc. cit.*
[210] Savtchenko: Ann. de l'Inst. Pasteur, T. xvi, p. 106, 1902.
[211] Dean: Proc. Royal Society, vol. lxxvi, p. 506, 1905.
[212] Hektoen: Jour. Amer. Med. Assoc., May 12, 1906.
[213] Lazarus Barlow: "Manual of Gen. Pathol.," p. 369, second edition, 1904.

shows that it must leave these cells with their adrenoxidase. The blood-platelets, as I have pointed out, are droplets of adrenoxidase: Schäfer[214] states that according to Löwit[215] they consist chiefly of a *"globulin,"* and that "as the result of microchemical work, Lilienfeld[216] considers that they consist of *nucleo-proteid."* The two bodies being combined, the conclusions of both observers are justified. As we have seen that the main constituents of the thyroid secretion are iodine, nucleoproteid and a globulin (the others, xanthin, paraxanthin, etc., being wastes), the correspondence between the secreted products of the red corpuscles and the thyroid secretion are not only evident, but in the light of the facts submitted above, *these supposedly different bodies—originally derived from the thyroparathyroids—and opsonin are one and the same substance.*

This conclusion, which I reached in 1907, has been sustained by the experiments of Marbé[216a] which showed that thyroid extract increased the opsonins in animals.

Finally, Wright showed that vaccines increased the proportion of opsonin in the blood. Metchnikoff,[217] alluding to the experiment of Bordet in animals injected at various times with the blood of foreign species, remarks: "It is the sensitizing substance which appears in very great quantity as a result of these injections. von Dungern[218] has confirmed this observation, and has added the interesting fact that the *sensitizing substance* is found in great excess *in the serum* of the injected animals."

The influence of the thyro-parathyroid secretion or ferment on the anterior pituitary body now suggests itself; it is that produced on all cells. Referring to the pituitary, Böhm, Davidoff and Huber[219] state that "now and then alveoli containing a colloid substance, similar to that found in the alveoli of the thyroid gland, may be observed." Indeed, Schnitzler and Ewald[220] found in the pituitary body, "evidence of considerable iodine." This means, in the light of the evidence submitted, that the colloid substance is a combination of the secretory products of leucocytes (including any noxious substance they may contain) and the secretion of the red corpuscles, *i.e.,* adrenoxidase, including the thyro-parathyroid ferment with which it is combined. The surface of the test-organ is thus not only swept by the current of colloid which contains any noxious substance of which it must take cognizance, but it is simultaneously sensitized by the thyro-parathyroid secretion the colloid contains. Moreover, it is kept sensitive from another direction, viz., through the blood circulating in its sensory elements proper, since, as I have shown, adrenoxidase circulates in all nervous elements as well as in the perineural capillaries. As the thyro-parathyroid secretion is bound up with adrenoxidase, all nervous structures are kept sensitized by it, including the test-organ. The latter, unlike any other organ, is thus sensitized from two directions by a substance provided by the thyroid apparatus. Hence the morbid results observed when the latter's functions are impaired or annuled.

This involves the conclusion that the tissue and other living elements are also sensitized. Bordet's "substance sensibilisatrice" was found by him to sensitize all cells besides bacteria, even the red corpuscles themselves—as is shown indeed by their proneness to hæmolysis.

The test-organ destined by Nature to protect the whole organism against disease is thus kept attuned to the highest pitch to carry on its all-important mission. As the morphological homologue of the olfactory organ, it would, in keeping with the latter, fail to transmit impressions to the posterior pituitary and to awaken therein the secretory-motor stimuli to the adrenals through which cellular metabolism is sustained, were it not constantly stimulated. Cretinism and myxœdema occur when the test-organ is inadequately activated by the thyroparathyroid secretion; the organism lives, but much as does the plant; hence the term *"l'homme-plante"* attributed to cretins.

Yet, we have seen that even plants and ancestral animals utilize iodine. Here again, however, the accumulation of cell-colonies gradually as the higher forms were evolved, imposed the need of a greater supply of the iodine—or iodine-ferment, the compound of which the haloid is a component in all living structures: the delicate endostyle of the Tunicata and lower

[214] Schäfer: "T. B. of Physiol., vol. i, p. 156, 1898.
[215] Löwit: Arch. f. exper. Pathol. u. Pharmak., Bd. xxiv, S. 188, 1888.
[216] Lilienfeld: Arch. f. Physiol., S. 115, 1892.
[216a] Marbé: C. r. de la Société de Biologie, June 13 and 20, 1908.
[217] Metchnikoff: "L'Immunité dans les Maladies Infectieuses," 1903.
[218] von Dungern: Münch. med. Woch., Bd. xlvii, S. 677, 1900.
[219] Böhm, Davidoff and Huber: *Loc. cit.*, p. 423.
[220] Schnitzler and Ewald: Wiener klin. Woch., July 16, 1896.

Chordata (see *end* in the illustration on page 963) gradually developed therefore into the thyro-parathyroid apparatus, remaining throughout the entire phylogenetic scale closely related with the respiratory apparatus—the gill-bars in ancestral vertebrates—the lungs, as I have shown, in the higher vertebrates, including man.

Sensitiveness of the cellular elements thus assumes a cardinal rôle in the vital functions of all organisms. The reason for this imposes itself when the part that *irritability* plays in Nature is recalled: "Every process of stimulation requires two factors," writes Verworn,[221] "a stimulus and a body that is irritable. If the two factors come into correlation there results a phenomenon of stimulation, a reaction." The muscular contractility which will cause detached fragments of the heart muscle to continue beating is but a manifestation of this kind. This applies as well to the skeletal muscles in function. Here, "the irritability depends upon the fact that great quantities of potential energy are accumulated in the living substance of the muscle so that the introduction of only a small quantity is needed to transform it into actual energy." The potential energy is the true source of contraction in the muscular mass; but the relatively diminutive proportion of energy that the nerve impulse adds thereto suffices to provoke contraction. Nourished by leucocytic granules (endowed with life by the adrenal active principle) and kept free of wastes by the hydrolytic triads, the tissue-cell is eminently prepared to *assume* the sensitized state; but pending this event it is latent as a living entity; it lives but cannot work. Throughout Nature, bound up with the albumins and colloids of animals and plants, iodine (as I interpret its rôle) endows it with the capacity to react, *i.e.*, with the power to functionate under appropriate stimuli.

On the whole, the following conclusions appear warranted: (1) *the parathyroids supply a secretion which differs from that of the thyroid only that it is richer in iodine and far more active;* (2) *the secretions of the thyroid and the parathyroids being mixed before reaching the lungs, they constitute, physiologically, but one substance;*. (3) *the thyro-parathyroid secretion is a ferment-like compound of iodine, nucleo-proteid adren-*

[221] Verworn: "General Physiology," Trans. by Lee, p. 353, 1899.

oxidase; (4) *on reaching the pulmonary alveoli, it is absorbed by the red corpuscles along with adrenoxidase, becomes part of the latter, and is distributed with it to all parts of the organism, including the blood;* (5) *its physiological function is to sensitize all cells and cellular elements, physiological or pathogenic, whether in the tissues (including the nervous system) or in the blood (including its digestive leucocytes or phagocytes), and thus to render them vulnerable to the action of the hydrolytic triads or "ferments" they—the tissues, plasma and leucocytes—contain;* (6) *the nervous elements of the pituitary body, including those constituting the test-organ, being, like all other cellular elements, the seat of metabolic exchanges, they are likewise sensitized by the thyro-parathyroid secretion and their functional efficiency, i.e., the vigor with which they react to sensory impressions and initiate motor stimuli, is commensurate with the degree of sensibility thus conferred upon them;* (7) *when the test-organ is adequately sensitized, the intrinsic metabolism of its elements is sufficiently active to sustain the secretory activity of the adrenals, and therefore the vital process itself up to the normal physiological standard;* (8) *when, conversely, it is inadequately sensitized through deficiency or qualitative impairment of the thyro-parathyroid secretion, the adrenals are insufficiently stimulated to insure normal oxygenation, the vital process and therefore all functions are rendered correspondingly torpid—a condition which entails cretinism in the child and myxœdema in the adult.*

Hereafter I will refer to the thyro-parathyroid secretion as *thyroiodase.*

THE INTERNAL SECRETIONS AS THE BODY'S AUTO-PROTECTIVE SUBSTANCES AND AS THE FOUNDATION OF RATIONAL THERAPEUTICS.

In his Herter Lecture at Johns Hopkins (1906), Sir A. E. Wright gave a résumé of his valuable researches and of those of his associates, Drs. Ross and Douglass, upon the rôle of the "opsonins." These were referred to as newly found substances which rendered various bacteria susceptible to the phagocytic action of the leucocytes. After dividing the immunizing constituents of the blood into opsonins, bactericidal (bacteria-kill-