# CHAPTER XI.

## THE INTERNAL SECRETIONS AND THE LEUCOCYTES IN IMMUNITY AND FEVER.

### THE ADRENAL SYSTEM AS THE FOUNDATION OF IMMUNITY.

To understand the *vis medicatrix naturæ,* i.e., nature's way of antagonizing disease, and learn how to enhance her resources when these fail has increasingly imposed itself as the goal for which we should strive. So concordant is the thought, in fact, with our highest aims as physicians and humanitarians that it may be said to have seen light at the very dawn of medicine, and to have grown apace with time. Indeed, twenty-three centuries ago Hippocrates[1] taught: "It is to the efforts of nature that the attentive and able physician looks for guidance." Galen[2] was no less affirmative when he wrote: "Nature having originally formed the body must, when disease assails it, restore health." Today, the most virile trend of modern thought is a corresponding principle, that conveyed by the term "immunity." Whether we seek to identify the nature of antibodies, the process through which they are caused to appear in the blood, or the manner in which they and the phagocytes oppose infection, we are but following the path opened by the father of medicine 400 years before the Christian era.

We have now learned through the painstaking labors of a host of investigators that our organism is supplied with autoprotective substances; but, so far, the identity of these substances has not been revealed by them. Even Ehrlich's theory has failed in this particular. His side-chain theory, notwithstanding the many collateral facts the labors devoted to it have brought out, has remained but a clever figment of imagination in so far as the side-chain feature itself is concerned—a pure assumption the truth of which he is yet to demonstrate, notwithstanding the many years it has been most carefully studied.

[1] Œuvres médicales d'Hippocrate, ed. Foës, ii, p. 195, 1801.
[2] Galen: "Contra Julianum."





Nor have the sources of the various substances which take part in the immunizing process so far been identified. Ehrlich hypothetically attributes this rôle to the tissue-cell, but, even granting that this be so, we are only driven back—unless we remain with him within the field of conjecture—to the necessity of showing whence these cells obtain their immunizing bodies, his so-called receptors. This he has failed to do, along with all other investigators in the same direction, because, in my opinion, he and they have overlooked the one field which, experimentally and clinically, offers the only solid foundation for a profitable analysis of the question, that of the ductless glands. Brown-Séquard, Langlois, Abelous, Charrin, Albanese, Zucco, and many others, we have seen, have laid stress on the antitoxic functions of the adrenals, while Vassale, Gley, Fano, and Zanda, and many other investigators and clinicians have urged a similar rôle in respect to the thyroid and parathyroids. This applies equally well to the pituitary body, according to Marie, Guerrini, Gemelli, and others. We thus have a series of organs found *experimentally and clinically* to protect in some way the body against intoxication. Is it not logical to conclude that they claim attention as the more likely to furnish the factors for a solution of this all-important problem?

Prompted by these indications, I advanced the view in the first edition of the present work (1903) that the body was supplied with *an immunizing mechanism.* I showed that the adrenals and the thyroid were the sources of two substances regarded by pathologists as prominent agents in the immunizing process, but the source of which they had not identified, and that the secretory functions of these organs were governed by a center located in the pituitary body. I suggested, moreover, that it was probably by exciting this center that various familiar drugs, mercury, for instance, and certain toxins, tuberculin, Coley's toxins, and the like, produced their beneficial effects. The eight years that have elapsed since these views were advanced have served only to strengthen them.

The identity of this mechanism suggests itself in view of the details already submitted in the chapters upon the adrenals, the parathyroid apparatus, the pituitary body, and the

kidneys. But to facilitate the discussion of the subject, I will merely recall that, interpreted from my viewpoint, the functions of these organs, both physiological and defensive, are as follows:—

*Adrenals.*—These organs supply a secretion which, on reaching the lungs, absorbs the oxygen of the air and becomes a constituent of hæmoglobin—its albuminous constituent. It is, as such, taken up by the red corpuscles and secreted by these cells as droplets (the so-called "blood-platelets") in all parts of the body, including the *blood-plasma* itself. The purpose of this albuminous hæmoglobin, which I have termed "adrenoxidase," is to supply oxygen to the tissues and to the blood. Important in this connection, however, is that this adrenoxidase gives the reactions and presents other characteristics of a familiar agent in the classic immunizing process, the *immune body* or *amboceptor*.

The active participation of the adrenal secretion in the defensive function suggests itself when the connection between oxidation and fever is recalled. Adrenoxidase being the active agent in all oxidation processes, and being capable of raising the temperature, we have a clue to the identity of one of the most important of the symptoms we meet on all sides, and the actual nature of which has not, so far, been explained, namely, *fever*. Indeed, as stated by Lazarus Barlow[3]: "Even if we grant that fever is beneficial, we are completely ignorant of the manner in which it acts."

We may speak of neurogenic fever caused by injury to the corpora striata; of aseptic fever due to crushed tissue; of infective fever caused by certain pathogenic organisms or their toxins, or of hyperthermia, and of the nature of the substances that are oxidized, but the identity of the oxidizing agent, the *deus ex machina* in all these types, has remained obscure. This is the feature of the problem which, from my viewpoint, the adrenal secretion, converted in the lungs into adrenoxidase, supplies.

Barlow writes, moreover: "Experiment seems strongly to support the view that hyperthermia has a curative action, and thence it is but a short step to considering fever as beneficial,

[3] Barlow: "General Pathology," 2d ed., p. 435, 1904.



and as evidence of the setting in motion by the organism of one of its defensive mechanisms. And certainly in pneumonia, erysipelas, cerebrospinal meningitis, typhoid fever, the prognosis is better if the patient's temperature is moderately high than if it is definitely low." Now, we have seen by the labors of Albanese, Abelous and Langlois, Charrin, Oppenheim, and others that the adrenals also enhance the defensive power of the body, thus combining the production of fever with the beneficial action—which dates back to Hippocrates and has been defended by many of the most illustrious investigators of modern times—to which Barlow refers.

*Thyroparathyroid Apparatus.*—The thyroid gland and the parathyroid glandules, which constitute this apparatus, produce secretions which, on passing out of the lymphatics (into which they are secreted), enter the left subclavian vein, and become merged into a single substance. Passing then into the blood of the superior vena cava, this secretion is carried to the lungs, and on reaching the air-cells is taken up by the red corpuscles—along with the oxygenized adrenal secretion. A salient feature of the immunizing process appears in this connection, viz., the thyroparathyroid product is also secreted by the red corpuscles into the blood and tissues, and, by acting directly upon the phosphorus which the nuclei of all tissue-cells, pathogenic organisms, etc., contain, increases their inflammability, *i.e.*, their sensitiveness to oxidation. As such, it acts both as *opsonin* and *agglutinin*.

The thyroparathyroid secretion taking part in tissue oxidation with the adrenal product, it becomes also, logically, a normal participant in the production of fever. Now, this is so striking a feature of thyroid functions that the thyroid gland has been associated with the production of fever by Lorand and other authorities on the ductless glands. Lorand[4] urges in this connection the various manifestations of the febrile state, elevation of the temperature and the sensation of heat observed in Graves's disease, due, as is well known, to excessive activity of the thyroid, and many other phenomena peculiar to the febrile state. "Both in Graves's disease and fever," he writes, "there is an augmentation of the processes

[4] Lorand: Lancet, Nov. 9, 1907.

of oxidation." Again, as previously shown, thyroid feeding causes febrile phenomena, *i.e.*, a rise of temperature of several degrees, both in man and animals, as shown by the researches of Chantemesse and Marie, Ballet and Enriques, Bourneville, and others; it increases the intake of oxygen and the output of carbonic acid, the output of sodium chloride, phosphoric acid, etc. Finally, operative or morbid arrest of thyroid functions causes hypothermia.

Once more, and in keeping with Barlow's remarks concerning the beneficial influence of fever, do we find the thermogenic properties of the thyroid associated with marked defensive or immunizing activity. Besides the evidence to this effect I have already offered (see page 163) may be mentioned the protection it affords against toxic products of protein decomposition noted by Breisacher[5]—as far back as 1889, and by Blum,[6] Galeotti, and Lindemann[7]—and others. The increased vulnerability of myxœdematous subjects to infection, the rapidity with which thyroidectomized animals succumb to practically any infection that happens around are now familiar clinical facts. In his recent work, Swale Vincent[7a] states that "it may be supposed that the function of the internal secretion is to prevent poisoning by the products of body metabolism or by infections from without." My opinion that the thyroparathyroid product is what Wright has termed "opsonin" has been sustained, we have seen, by the investigations of Marbé, Malvoz, Stepanoff, and others.

THE PITUITARY BODY AS THE SEAT OF THE IMMUNIZING CENTER.—Considered in connection with immunity only, the pituitary body contains, from my viewpoint, a center—the immunizing center—located in the pars intermedia (between the two lobes) and connected with the adrenals and the thyroparathyroid apparatus by nerves. Through these nerves the immunizing center governs the functional activity of these two sets of organs, and, therefore, the production of adrenoxidase (amboceptor) and of thyroiodase (opsonin and agglutinin), besides general oxidation. As such, the immunizing center is also the heat of *fever* center, the febrile state indicating that one or

[5] Breisacher: Arch. für Anat. u. Physiol. Supp., p. 509, 1889.
[6] Blum: Archiv f. d. Ges. Physiol., p. 617, 1902.
[7] Lindemann: Virchow's Archiv, p. 202, 1897.
[7a] Swale Vincent: "Internal Secretions and the Ductless Glands," p. 352. London, 1913.



more poisons are present in the blood which this dual center is antagonizing through its militant agents, the thyroparathyroid apparatus and the adrenals—and also indirectly, as we shall see later, through the phagocytes.

To interpret this process intelligently, I will submit, as was done in the cases of the adrenals, the thyroparathyroid, and the pituitary, an outline of the main features of the evidence I have to offer, referring the reader to the second volume for a detail study of the whole question.

Of fundamental importance in this connection, is that

*The pituitary body of all animals, from mollusks to man, contains a sensory organ which structurally resembles the nasal olfactory membrane.*

Julin[8] urged, in 1881, that in ascidians the subneural gland (conjoined to the nerve ganglion which I assimilate to the posterior or neural lobe) was the ancestor of the pituitary body of vertebrates. Lloyd Andriezen[9] confirmed this view after a comprehensive study of the organ, from amphioxus to man. Personal work in the same line led to a similar conclusion. Now, at least as low down as mollusks there exists in the corresponding location a patch of epithelium, which Spengel has termed "the olfactory organ," and Ray Lankester[10] the "osphradium." Unaware of the connection between this structure in ancestral forms and the pituitary, Peremeschko,[11] Müller,[12] and also Cadiat[13] described a cleft between the two lobes of the latter organ, the walls of which they found to be lined with epithelium. The structure of this epithelium was only made clear, however, when the Golgi method was available. Gentès[14] then found that it was merged in the partition (the *pars intermedia*) separating the two lobes, and that it contained elongated nerve-cells which sent their neuraxons into the posterior lobe, and thence to the base of the brain. According to Gentès, these cells recall exactly the sensory elements of the nasal olfactory membrane. Caselli

[8] Julin: "Recherches sur l'organis des ascides simples," Arch. de biol., ii, pp. 59, 211, 1881.
[9] Lloyd Andriezen: British Medical Journal, January 13, 1894.
[10] Ray Lankester: Article Mollusca, in Encyclopædia Britannica, 9th ed., xvi, p. 636.
[11] Peremeschko: Virchow's Archiv, xxxviii, p. 329, 1867.
[12] Müller: Jenaische Zeit. f. Naturw., vii, p. 327, 1873.
[13] Cadiat: Anatomie générale, cited by Guépin, Tribune méd., December 10, 1891.
[14] Gentès: C. r. de la Soc. de biol., lv, p. 100, 1903.

also found sensory elements in the pituitary of higher animals, while Boeke[15] and Gemelli[16] discerned them in the pituitary of fishes. A personal distinctive study of this organ from the true olfactory apparatus has shown, moreover, that the former could be traced down to lower forms, gradually receding in importance until the patch of epithelium "supplied with a special nerve and ganglion," as Ray Lankester describes it, in mollusks is reached.

Suggestive in this connection, as a feature of the immunizing process, is that

*In ancestral animals the "test organ" serves to test the purity of the sea water ingested by them.*

Spengel's olfactory organ, Ray Lankester's osphradium, has for its purpose, according to zoölogists, to test the respiratory fluid. In amphioxus, the lowest of vertebrates, similar protection is afforded by what Willey[17] describes as a "vestibule richly provided with sensitive cells," and by Andriezen as a "nervous organ" which "serves to test the quality of the water which passes over the respiratory organ."

That a corresponding autoprotective function exists in the higher animals, including man, is not only sustained by considerable evidence, but a solid foundation for the whole scheme is afforded by the fact that the blood of these higher animals is the physiological and qualitative homologue of sea water. Claude Bernard[18] taught forty years ago that "the blood is an internal medium in which anatomical elements live as do fishes in water." René Quinton[19] showed that our plasma was a fluid which chemically, in so far as the relative proportion of the various elements was concerned, corresponded with sea water. A. B. Macallum[20] also holds that both animal and vegetable protoplasm derive their relations to the elements sodium, potassium, calcium, and magnesium from the composition of sea water which obtained when all forms were unicellular. The labors of Bunge,[21] Jacques Loeb,[22]

[15] Boeke: Anat. Anz., xx, p. 17, 1902.
[16] Gemelli: Jour. de l'anat. et de la physiol., 42d year, No. 1, 1906.
[17] Willey: "Amphioxus and the Ancestry of Vertebrates," p. 19, 1894.
[18] Claude Bernard: "Leçons sur les propriétés des tissus vivants," pp. 55-58, 1866.
[19] René Quinton: Paris Correspondent, Lancet, April 16, 1904.
[20] Macallum: Trans. Canadian Institute, p. 181, 1903-4.
[21] Bunge: "Physiological and Pathological Chemistry," English translation by Starling, pp. 101, 102, 1902.
[22] Loeb: Pflüger's Archiv, cvii, p. 252, 1905.



Matthews, Fisher, Overton,[23] and others have all contributed testimony to the solidity of this view.

Considered in the light of the anatomical connections of the pituitary with the thyroid and adrenals, and the functions I have ascribed to these organs, the conclusion seems warranted that

*In the higher animals, including man, the "test organ" tests the purity of the qualitative homologue of sea water, the blood, for toxic substances and, where possible, causes destruction of these substances.*

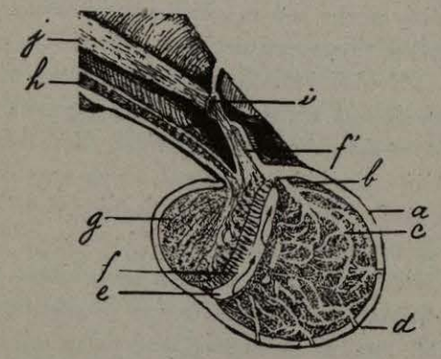


Fig. 1.—Pituitary Body, Containing Immunizing Center (semi-schematic). *a*, anterior lobe; *b*, arteries and, *d*, arterioles; *c*, course of blood diffused through sinusoidal capillaries of epithelium; *e*, cleft into which contents of blood-cells (colloid) and cellular detritus are driven, and whence they pass into lymphatics; *f*, sensory test organ (immunizing center) excited by colloid when the blood (and therefore the colloid) contains certain poisons; *g*, posterior pituitary containing origin of paths to adrenals and thyroid; *h*, tuber cinereum, showing secretory path to adrenals and thyroid; *i*, retro-optic nucleus which transmits, *j*, sympathetic vasoconstrictor nerves to various organs, including the thyroid.

We have only to analyze the pathogenesis of the convulsions that follow removal of the pituitary to realize that the rôle of its test organ is also to prevent general intoxication in the higher animals, including man. This procedure, as observed by Marinesco,[24] Vassale and Sacchi,[25] Masay,[26] and others, produces, as Schäfer[27] expresses it, "muscular twitchings and tremors developing later into spasms." This exemplifies the familiar convulsions caused in children by autointoxication; those ascribed

[23] Overton: *Ibid.*, cv, p. 176, 1904.
[24] Marinesco: C. r. de la Soc. de biol., p. 509, 1892.
[25] Vassale and Sacchi: Arch. ital. di biol., xxii, p. 133, 1895.
[26] Masay: *Loc. cit.*
[27] Schäfer: "Textbook of Physiology," i, p. 946, 1898.

to tetanotoxin; those of puerperal eclampsia which Williamson,[28] Grandin,[29] and others ascribe to poisonous substance circulating in the blood; those provoked in animals by Herter,[30] Krainsky,[31] and in man by Ceni[32] with hypertoxic serum derived from epileptics, a fitting corollary for Pierce Clark's[33] conclusion, based on a study of 150,000 epileptic seizures, that "we must see the pathogenesis in an initial toxin or autointoxication." I have urged in this connection, and others besides myself have found, that in appropriate cases of epilepsy, those in which the thyroid is inadequately active and in which gliosis has not been given time to develop, thyroid extract proves effective in arresting the paroxysms. Need I refer to its corresponding action in the convulsions—of both tetanic and epileptic type—that follow extirpation of the thyroid and parathyroids? Here there is directly introduced into the blood the agent which sensitizes the toxic wastes and renders them vulnerable to the destructive action of the other defensive substances.

THE MODE OF ACTION OF THE IMMUNIZING MECHANISM AND THE GENESIS OF FEVER.—In view of the foregoing facts, physiological, clinical, histological, and zoölogical, the introduction of a toxic into the blood should, by exciting the test organ, awaken the defensive resources of the body to action through the intermediary of the thyroid apparatus and adrenals. Crucial experiments are available to show that such is the case, *i.e.*, that the test organ when excited by a poison stimulates the adrenals and the thyroid apparatus and thus induces destruction of that poison, and, moreover, that when the test organ cannot transmit its impulses to the adrenals and thyroid the autoprotective process does not manifest itself. These experiments were those of Sawadowski[34] and of other investigators referred to below. They indicate, when explained in the light of my views, that

*Fever is the physiological expression of the defensive mechanism when a toxic capable of exciting the test organ is present in the blood.*

[28] Williamson: Obstetrics, p. 703, 1903.
[29] Grandin: Grandin and Jarman's "Practical Obstetrics," p. 94, 3d ed., 1900.
[30] Herter: Jour. of Nerv. and Ment. Dis., February, 1899.
[31] Krainsky: Wiener klin. Woch., February 24, 1898.
[32] Ceni: Riv. Sper. di Fren., xxxi, No. ii, 1905.
[33] Clark: Medical News, July 18, 1903.
[34] Sawadowski: Centralbl. f. d. med. Wissen., 26th year, No. 9, p. 161, 1888.



I have urged that the pituitary contained the heat center, and that it produced a rise of temperature through the intermediary of the adrenals and thyroid. The test organ is evidently closely connected with the heat center, for the protective process it awakens when certain poisons occur in the body is a rise of temperature. Now, Sawadowski noted, after injecting putrid substances into the blood, and in accordance with familiar experience, that it caused fever, even *after the cerebrum had been removed* from the midbrain. He found, moreover, that antipyrin controlled this fever. But his experiments revealed an important fact, viz., that section through the optic thalami or the posterior edges of the corpora striata (which, from my viewpoint, also severed the nerve paths from the test organ or heat center to the adrenals and thyroid) prevented these effects. "After these sections," he writes, "neither the putrid materials nor the antipyrin exerted any influence upon the temperature. The sinking of the temperature was not arrested by the putrid substances." The last statement refers to the fact that, notwithstanding the presence of putrid substances which had caused fever, the temperature steadily went down—after the operation—from 38.1° C. in the colon to 31.4° C. This recalls the steady decline that occurs after removal of the pituitary. Ott and Scott[35] also found that the marked rise of temperature that follows the intravenous injection of betatetrahydronaphthylamin in normal rabbits did not occur after they had transected the base of the brain behind the tuber cinereum.

The heat, or thermogenic, center thus influenced cannot be located in the cerebrum, for we have seen that removal of this organ does not affect the temperature. Nor can it be located in the optic thalamus or the corpus striatum, for Ott and Harris[36] provoked the typical rise of temperature by puncturing with a needle, through the mouth, "only the lower surface of the tuber." Its true location is shown by the fact that Ott found a thermogenic center in the anterior portion of the floor of the third ventricle, *i.e.*, immediately above the pituitary. Moreover, it is precisely traversed by the nerves which Andriezen, Gentès,

[35] Ott and Scott: Jour. of Exper. Med., November, 1907.
[36] Ott and Harris: Therap. Gaz., June 15, 1903.

Joris, and others traced from this organ, and which Andriezen followed to the region of the pons.

Under these conditions, however, transection of the pons should also have prevented the thermogenic action of putrid materials in Sawadowski's experiments. Such proved to be the case. Of this experiment, carried out with the aid of Pawlow, Sawadowski writes: "Following out Ischetschichin's method, a diagonal section was made through the pons Varolii. When the section was complete, free from hæmorrhage or of any condition which might excite the surface of the cut tissues, a gradual diminution of the temperature occurred in the rectum and between the toes. In one experiment, for example, in which the preoperative temperature was 38° C. in the rectum, and 34.5° C. on the skin, nine hours after the operation the first had fallen to 27° and the second to 25° C." This applies as well to the spinal cord; "when the section was made quite high up," he says, "no rise of temperature could be obtained with putrid materials, nor did the antipyrin lower it."

In the portion of the cervical region, however, he found that transection of the spinal cord did not completely prevent the influence of either the putrid materials or the antipyrin. But we have in this paradoxical phenomenon only confirmatory testimony to the presence of a nervous connection between the pituitary and the thyroid apparatus, for in these "low sections," as he terms them, he severed the cord below the origin of the nerves to the thyroid, thus leaving untouched the nerves which connected it with the pituitary and its test organ, though severing the path to the adrenals. What effects were obtained were due to the thyroid apparatus, which remained under the influence of the test organ, and therefore of the thermogenic poison and antipyretic.

These experiments speak for themselves—especially in view of the fact that Sawadowski mentions among the concomitant effects of his sections "disorders of respiration and circulation," and also blueness of the blood—obvious evidences of defective oxygenation. Added to the foregoing evidence, they seem to me to warrant the following general deductions:—

*1. Man, in keeping with many animals lower in the phylogenetic scale, is supplied with an autoprotective mechanism.*



*2. This mechanism includes: 1, the immunizing center, an organ of special sense annexed to the heat center, both centers being located in the pituitary body; 2, the thyroparathyroid glands; 3, the adrenals, and, 4, special nerves which connect the immunizing center (or overactive heat center) with these two sets of organs.*

*3. The immunizing center, which governs the autoprotective mechanism, is the developed "osphradium" or "test organ" described by zoölogists in mollusks and certain ancestral vertebrates.*

*4. While the osphradium of primitive animals tests their respiratory fluid, sea water, its prototype, the immunizing center of higher animals, including man, tests the blood, also a respiratory fluid and a qualitative homologue of sea water.*

*5. When the functional activity of the immunizing center is increased through the presence in the blood of some toxic,* i.e., *wastes, toxins or endotoxins, mineral and vegetable poisons, certain venoms, drugs, etc., capable of exciting this center, it stimulates correspondingly the heat center and thus awakens the immunizing process.*

*6. Fever indicates that the autoprotective mechanism is active. The rise of temperature is due to the increased production of thyroparathyroid and adrenal secretions, and the resultant increment of metabolic activity. The immunizing process is a consequence of this hypermetabolism, all the immunizing agents, plasmatic and cellular, being produced in greater quantities.*

But Lazarus Barlow states we have seen—and he is amply sustained, I may add, by the teachings of clinical experience—that "in pneumonia, erysipelas, cerebrospinal meningitis, typhoid fever, the prognosis is better if the patient's temperature is moderately high than if it is definitely low." This is met by the interpretation of the febrile process I submit in the next conclusion:—

*7. Absence of fever in a toxæmia of any kind is due to inability of the immunizing center to react under the influence of the toxic, owing to deficient sensitiveness (inherited or acquired) of this center, or to the fact that the toxic is itself a paralyzant or anæsthetic of its sensory elements.*