with the infundibulum was normal, "though the remainder of the pituitary body," says the author, was "made of the enlarged anterior lobe." It proved to be gliomatous, and made up entirely of chromophilous cells, the typical structure of the anterior lobe, and was the seat of the changes "found early in the development of acromegaly and which are most essential in its production." We thus have a typical case in which the test-organ lobe is alone diseased. Now, the vascular lesions were also typical of acromegaly. Examined histologically, the small arteries showed hyperplasia, proliferation of the endothelial cells of the intima, etc.,—all signs of active engorgement—and the large ones fibrous thickening. With overactivity of the test-organ as the source of correspondingly energetic stimuli to the adrenals, this morbid process is clearly explained: an excessive amount of adrenal secretion, *i.e.*, adrenoxidase, is continuously present in the blood, and the vascular walls, receiving such blood through their vasa vasorum, are the seat of hyperplasia, proliferation, etc. In the larger vessels this morbid process, owing to the greater blood-supply, is pushed beyond this stage, *i.e.*, to that of fibrosis. The enlargement of the extremities, bones and soft tissues, including the proliferation of capillaries, and the hypertrophy of the muscles during the erethic stage, are normal sequences of such a process, the capillary system being not only constantly gorged with blood, owing to the state of contraction to which both the arteries and veins are submitted, but with blood whose oxygenizing properties exceed the normal. The general symptoms of Brooks's case plainly indicate excessive peripheral hyperæmia, viz., hyperæsthesia, "hot-flesh," as expressed by the patient, polyuria, etc. Glycosuria was likewise present, a symptom clearly traceable, as shown below, to overactivity of the adrenal center—the test-organ of the anterior pituitary.

The strength of this conception of the pathogenesis of acromegaly is sustained indirectly by the fact that this phase of the problem has remained obscure. Beyond the facts that it is essentially a trophic neurosis, and that this is due "to remarkable changes in the pituitary," *i.e.*, Marie's "pituitary hypothesis," nothing is known of the manner in which general nutrition is influenced by this organ.

In brief, with the anterior lobe as the adrenal center and as the seat of the primary lesions in acromegaly, we have a normal explanation of the hypertrophic processes which characterize this disease, since overactivity of the pituitary by producing a corresponding overactivity of the adrenals, causes the presence in the blood of an excess of adrenoxidase, the dynamic principle in tissue metabolism and nutrition.

Glycosuria, we have just seen, was present in Brooks's case, in which the anterior lobe, the seat of the test-organ, was alone diseased. M. Loeb[191] pointed out in 1884 that glycosuria was a frequent accompaniment of tumors of the pituitary body. A more recent study of the literature of acromegaly led him to conclude that the association of this disease with glycosuria could not be accidental. He found, moreover, that glycosuria did not occur during the post-operative life of animals from which the pituitary body had been removed, a fact which indicates that it is due to over-activity of the organ and not to insufficiency. Marie observed it in one-half of the cases he examined. Guy Hinsdale[192] states that the urine often contains sugar and refers to fourteen authors who had observed the symptom. In sixteen cases of diabetic acromegaly the records of which were studied by Launois and Roy[193] a tumor of the pituitary was always found. In every instance the presence of the pituitary neoplasm had been confirmed post-mortem. Schlesinger[194] also emphasized the frequent coincidence of acromegaly and diabetes, having observed the latter in three consecutive cases of his own.

As a result of these observations, investigators have been driven to the conclusion that a "diabetic center" must exist in the neighborhood of the pituitary. "The theory of Loeb," write Launois and Roy,[195] in this connection, that of "compression by the pituitary tumor upon adjoining parts, seems in accord with clinical observations (Finzi, Strumpell), and with an experimental fact recorded by Caselli.[196] A glycogenic center is supposed to exist, apparently in the region of the *tuber cin-*

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[191] M. Loeb: Centralbl. f. inn. Med., Sept. 3, 1898.
[192] Guy Hinsdale: "Acromegaly," Detroit, 1898.
[193] Launois and Roy: C. r. de la Soc. de biol., vol. lv, p. 382, 1903.
[194] Schlesinger: Wiener klin. Rundschau, Apr. 15, 1900.
[195] Launois and Roy: *Loc. cit.*
[196] Caselli: *Loc. cit.*

ereum, which is abundantly supplied with highly organized nervous elements (Caselli)." The cause of the glycosuria is self-evident in view of the fact that the path from the test-organ to the adrenals lies in the tuber cinereum: Caselli's experimental excitation of this structure, therefore, provoked glycosuria because it stimulated the adrenals.

A similar procedure in the course of the pituitero-adrenal path in the medulla likewise causes glycosuria. Claude Bernard's puncture is a familiar proof of the fact. "Bernard," says Schäfer,[197] discovered "that certain lesions of the central nervous system, and especially a puncture in the region of the floor of the fourth ventricle, which corresponds, as we now know, *very nearly* to the position of the vasomotor center, produces a condition of glycosuria." The glycogenic impulses evidently pass downward, for as shown by Chauveau and Kaufmann,[198] division of the spinal cord in the cervical and upper dorsal regions prevents the diabetes caused by removal of the pancreas. The same procedure had already been found by Bernard to cause hypoglycæmia. These are all normal results in view of the fact that, as I pointed out in the preceding chapter, the nerves to the adrenals pass down the cord, leave the latter in the three upper dorsal nerves to enter the sympathetic chain, and then the splanchnic. (See Frontispiece, Vol. I.) Such being the case, however, division of the splanchnic should likewise arrest glycosuria. Landois[199] says in this connection: "It is a remarkable fact that glycosuria, when present, can be removed by division of the splanchnic nerves." Even the glycosuria caused by Claude Bernard's puncture can be arrested by this procedure, an observation confirmed by Eckhard, Kaufmann[200] and others.

Finally, as is now well known, the adrenal extract, as shown by Blum,[201] Croftan,[202] Metzger,[203] Herter,[204] and others, causes glycosuria when injected subcutaneously, endovenously, or into the peritoneal cavity. Herter[205] found also that intravenous injections of adrenalin were followed by a large excre-

[197] Schäfer: *Loc. cit.*, vol. i, pp. 926, 927.
[198] Chauveau and Kaufmann: C. r. de la Soc. de biol., p. 29, 1893.
[199] Landois: *Loc. cit.*, p. 315.
[200] Kaufmann: C. r. de la Soc. de biol., p. 284, 1894.
[201] Blum: Deutsch. Archiv f. Med., Bd. lxxi, Nu. 2 u. 3, S. 146, 1901.
[202] Croftan: Amer. Med. Jan. 18, 1902.
[203] Metzger: Münch. Med. Woch., Bd. xlix, S. 478, 1902.
[204] Herter: Med. News, Oct. 25, 1902.
[205] Herter: Amer. Med., May 10, 1902.

tion of sugar and that "a rise of blood-pressure is an accompaniment of glycosuria"—the former phenomenon being, as is well known, a characteristic effect of adrenal extract. The adrenal secretion proper is doubtless able to produce a similar effect, for Herter and Wakeman[206] ascertained experimentally that compression of the adrenal glands [thus increasing the secretion] is followed by glycosuria; while their exclusion, by extirpation or ligation of their vessels, is followed by a considerable fall of the sugar-content of the blood." Kaufman[207] found, moreover, that ligation of the inferior vena cava caused a rapid diminution of sugar both in normal glycæmia and in glycosuria. We have seen that it is in the blood of this great vessel that the adrenals secrete their product.

This evidence, in the light of the facts previously submitted, speaks for itself: Acromegaly gives rise to glycosuria because the diseased organ, the anterior pituitary, stimulates excessively the adrenals, the secretion of which has been shown experimentally to cause glycosuria. This affords additional proof to the effect that the adrenals are governed by the anterior lobe of the pituitary body through the intermediary of a direct nerve-path.

On the whole, the evidence presented in the present section appears to me to warrant the following postulates:—

1. *The thermogenic (or heat) center and the respiratory (or polypnœic) center are not, as believed by some observers, located in the tuber cinereum, the bulb, or the spinal cord, the thermogenic areas in these regions being but subsidiary centers—if anything but thermogenic nerve-paths—of which the bulbar are the most important.*

2. *The thermogenic center is located in the partition between the two lobes of the pituitary body, and in mammals is the highly developed homologue of the test-organ or osphradium of lower forms. As such it is the governing center of the adrenals, its nerve-path to these organs being as follows: from the test-organ to the posterior lobe of the pituitary and thence upward to the tuber cinereum; along this structure to the pons and bulb, and down the spinal cord to the first, second and third dorsal*

[206] Herter and Wakeman: Amer. Jour. Med. Sci., Jan., 1903.
[207] Kaufmann: Arch. de physiol., T. viii, p. 150, 1896.

nerves; thence to the sympathetic chain; down this chain to the greater splanchnic nerves in which it reaches the suprarenal plexus and through it the adrenals.

3. *The respiratory center is located in the posterior or neural lobe of the pituitary body and represents therein the aggregate of nuclei which are themselves the chief centers of all the cranial nerves that govern the respiratory muscles.*

4. *The nerve-chains from the respiratory center pass upward to the supra-infundibular nucleus, and thence posteriorly to the bulb, where they become merged with the (subsidiary) centers of the various cranial nerves which govern the functions of the respiratory muscles.*

Jacques Loeb's prediction that "through the oxidases one may in time be able to control life as the artist governs the keys of the piano," and his belief that "not merely the normal course of life, but also that vast gamut of diseases characterized by metabolic derangements, might be controlled if we only knew how to favor or retard the action of the oxidases," are afforded a foundation in the views submitted in the present and foregoing chapters. Selecting only out of the various functions I have pointed out those that bear directly upon this feature of the general problem, this foundation may be said to consist of the following facts:

1. Adrenoxidase is an aggregate of the body's oxidases, and the dynamic principle in metabolism and therefore of the vital process. It follows, therefore, that *adrenoxidase (the oxidases) is the agent through which life may be controlled.*

2. Adrenoxidase is the oxygen-laden secretion of the adrenals, while these organs are, in turn, governed through a nerve-path whose center is located in the pituitary body. Hence, *it is the center of the adrenals in the pituitary body which, through the adrenals and their adrenoxidase-forming secretion, controls life.*

3. The adrenal center is primarily a sensory organ and the homologue of the "test-organ" which in the lower chordata serves to test the "respiratory fluid" and thereby to protect these animals "against the intrusion of noxious substances." As in the higher chordata, including man, the "respiratory fluid" is the blood, it follows that *the adrenal center is an organ having for its purpose to test the blood and protect it against the intrusion of noxious substances.*

4. Adrenoxidase embodying, as it does, the ferment of ferments, it is the dynamic principle of tissue metabolism. The proportion of adrenoxidase in the blood being governed by the adrenal center, it follows that *noxious substances introduced into the blood can, by provoking a reaction of the adrenal center, enhance the activity of metabolic processes.*

5. While the adrenal center is the thermogenic or heat center, adrenoxidase, as the dynamic principle of metabolism, supplies the oxygen which, by combining with the phosphorus of nucleins, liberates the bulk of the body's heat energy. Fever being the expression of an excess of heat energy thus produced, the adrenal center is also the governing center of the febrile process. It follows *that inasmuch as we can therapeutically (all drugs being toxics as far as the test-organ is concerned) increase or abate fever, we can also control tissue metabolism and its derangements.*

The test-organ is thus the key-board through which we can "favor or retard the action of the oxidases," *i.e.*, the vital process itself.

General Remarks.—Landois in the last American edition of his text-book of Physiology (1905) states that "but little is known concerning the function of the pituitary" and devotes *nine lines* to this organ. Few works on physiology published within the last two years give the subject more than one page. Leonard Hill, in his "Recent Advances in Physiology and Bio-Chemistry" (1906), omits the subject altogether. This affords an idea of the scant attention given to the pituitary body at the present time (1907) in works upon which the practitioner must depend for his knowledge of normal functions, when he attempts to elucidate morbid processes, the body's auto-protective resources, and the physiological action of drugs.

Need we wonder at his inability to do so?

"In spite of the extraordinary keenness of diagnostic power which has been developed in internal medicine, the painfully exact studies in pathological histology and in physiological and pathological chemistry, the wide-spread activity in pharmaco-

logical and pharmocodynamical experiment and the indefatigable efforts of the manufacturing chemist to supply new drugs," says Barker,[208] "the view is prevalent and rightly so, that in the treatment of internal diseases we have more to hope for the future than to entrust to the present." Referring to Skoda's dictum "We can diagnose disease, describe it and get a grasp of it, but we dare not expect by any means to cure it," he adds: "In such a temper *drugs of unknown physiological action* cannot conscientiously be set to act upon bodily tissues in disease in which *we are ignorant of the deviation from the normal* of the chemical and physical processes going on in the cells. The death-blow came first to polypharmacy; to-day, with many, pharmacotherapy, as a whole, is almost moribund."

[208] Barker: Johns Hopkins Hosp. Bull., July, Aug., 1900.

CHAPTER XVII.

THE LEUCOCYTES, PITUITARY, THYROID, PARATHYROIDS, AND ADRENALS, AS THE FUNDAMENTAL ORGANS IN PATHOGENESIS, IMMUNITY AND THERAPEUTICS.

THE LEUCOCYTES AS THE DISTRIBUTORS OF REMEDIES AND POISONS.

In the first volume of the present work and elsewhere,[1] I pointed out that the anterior pituitary was the governing center of the body's auto-protective or immunizing mechanism, and that by means of our remedies its functional activity could be enhanced at will, and thus caused to activate the antitoxic properties of the blood. An eminent French clinician, Hayem,[2] wrote recently: "Therapeutic weapons are wanted which will *reinforce the defensive power of the organism* by increasing the functional activity of the leucocytes or by developing chemical antidotes"—the trend of our day being in harmony with Hippocrates's belief in the *vis medicatrix naturæ*. That this is precisely the underlying thought of my own doctrine is self-evident; but it does what no other doctrine has done: it points to the identity of Nature's mechanism and to the means she adopts to attain her object.

We have reviewed the main features of this mechanism. We have seen that the pituitary contains a test-organ related by nerve-paths with the adrenals, which in turn govern, through their secretion, the activity of all metabolic processes in the blood as well as in the tissues. As the thermogenic center, this test-organ also presides over the febrile process—which is but an exacerbation of catabolic activity, raising it when need be—to destroy, not only tissue-wastes, but all toxic substances which adventitiously gain access to the blood-stream. The process through which the protective activity of the test-organ

[1] Sajous: Monthly Cyclo. of Pract. Med., Jan., 1903; Phila. Med. Jour., Mar. 7, 1903.
[2] Hayem: Presse médicale, Aug. 12, 1903.