

1, That the pituitary is connected with the adrenals by direct nerve-paths; 2, that it thus governs, through the adrenals, general oxidation, metabolism, and nutrition.

HYPOADRENIA.

This designation is submitted as a more exact one than the term "hypoadrenalism" now increasingly used. The latter suggesting to the uninitiated that the condition it describes is one of habitual insufficiency of the adrenals is misleading, since the secretory activity of these organs is subject at all times, even where advanced lesions exist, to fluctuations. The phrases "insufficiency of the adrenal" and "adrenal insufficiency" portray, more acceptably the true condition present, but they are obviously cumbersome and as ill calculated to designate this condition from a scientific standpoint as would "deficiency of red corpuscles" for anemia.

While we owe to Addison, a clinician, the first observations (1855) which indicated that the adrenals were of signal importance to the welfare of the organism, it was Brown-Séquard, a physiologist, who (1856), we have seen, first demonstrated their true importance to life. The symptoms caused by a deficient production of adrenal secretion were not, however, erected to the rank of a special syndrome quite independent of, and capable of occurring without the presence of, Addison's disease, and as a manifestation of other diseases, until Sergent and Bernard¹⁵¹ did so in 1899.

Viewed from my standpoint, however, the symptom-complex of this condition is subject to quite a different interpretation than the prevailing one, all the labors anterior to my own having taken as foundation only two functions: that of sustaining the cardio-vascular tone (Oliver and Schäfer), and that of producing an antitoxic substance capable of neutralizing toxic products of muscular activity, and other undetermined poisons (Abelous and Langlois). The processes through which these effects are brought about having remained obscure, however, more or less empirical conceptions have had to be employed to fill the gaps. Thus, the muscular asthenia in Addison's disease is attributed to the toxic effects of the muscular poisons that the adrenals

¹⁵¹ Sergent and Bernard: Archives gén. de méd., July, 1899.

in their normal state should have destroyed, while, to explain bronzing, irritation of the sympathetic plexuses around the adrenals has to be invoked. The hypothermia, dyspnoea, and other symptoms are indifferently attributed to the low blood-pressure or to the intoxication. If we ask, however, *how* irritation of the sympathetic plexus produces bronzing, or *why* after adrenalectomy the temperature, both rectal and peripheral, steadily declines, or fathom to any depth the explanations that are furnished, it soon becomes apparent that some important factor is missing.

It is this factor which my labors seem to me to have supplied. They afford an explanation of all the symptoms brought on by inadequate functional activity of the adrenals. Being based primarily upon the array of experimental data submitted in the earlier portion of this chapter, they also constitute a foundation for a more exact conception of the various disorders of the adrenals than the prevailing teachings afford.

Another feature which my interpretation of the functions of the adrenals seems to me to elucidate, as will be shown in a special chapter, is the process through which these organs carry on antitoxic functions other than those concerned with toxic wastes of muscular origin. This property, observed by Albanese,¹⁵² who noted a decreased resistance of decapsulated frogs to neurine as compared to normal frogs, was first placed on a solid footing by the researches of Abelous¹⁵³ and Langlois, which showed similar results with atropine in the frog, and strychnine and curare in the rabbit, though less marked. Charrin and Langlois¹⁵⁴ then found that the addition of adrenal extract to nicotine *in vitro* reduced the toxic activity of the latter, and that injected nicotine was also less poisonous when adrenal extract was added to it. Oppenheim¹⁵⁵ then obtained uncertain results with potassium arsenate and atropine, but marked results with phosphorus, guinea-pigs in which the injection of this toxic was followed by that of adrenal extract surviving from two to four times longer in some in-

¹⁵² Albanese: Arch. Italiennes de Biol., pp. 49 and 338, 1892.

¹⁵³ Abelous: Rev. Générale des Sciences, May 15, p. 273, 1893, and Bull. de la Soc. de Biol., April 2, 1898.

¹⁵⁴ Charrin and Langlois: Bull. de la Soc. de Biol., p. 708, 1896.

¹⁵⁵ Oppenheim: Bull. de la Soc. de Biol., March 22, 1901; also "Les Capsules Surrénales. Leur fonction antitoxique," Paris, 1902.

stances, and altogether in others. Strychnine, $\frac{1}{60}$ grain, which killed guinea-pigs in three and four minutes, produced but few spasms and proved harmless as to life when its injection was followed a minute later by one of 2 c.c. of adrenal extract. A larger dose of strychnine ($\frac{1}{48}$ grain) proved fatal, however. These and other experiments with various toxins led Oppenheim to conclude that "the adrenals, which normally destroy poisons elaborated during muscular work, assume great importance during pathological states and must be classed among the most useful of protective organs."

On the whole, in the light of the personal views submitted, hypoadrenia or insufficiency of the adrenals means far more than the effects of lowered blood-pressure and the adequate destruction of muscular wastes; it means besides: *inadequate oxidation and therefore imperfect tissue metabolism and nutrition, and also impairment of the auto-protective functions of the body at large.*

The bearing of this conclusion will be gradually developed while analyzing the three clinical forms into which I have divided hypoadrenia,—a classification which appears to me necessary to enable us to apply prophylactic and remedial measures judiciously. These three forms are the following:—

1. *Functional hypoadrenia*, a form in which the adrenals, though not the seat of organic lesions, are functionally deficient because of tardy development, debilitating influences such as fatigue, starvation, etc., and old age;

2. *Progressive hypoadrenia, or Addison's disease*, a form in which the functions of the adrenals or of their secretory nerves are progressively impaired by organic lesions, tuberculosis, cancer, fibrosis, etc.;

3. *Terminal hypoadrenia*, a form which occurs as a more or less tardy complication of infectious diseases and toxæmias, owing to exhaustion of the secretory activity of the adrenals during the earlier and febrile stage of the causative disease.

FUNCTIONAL HYPOADRENIA.

The adrenals playing so important a rôle in the maintenance of the life process itself, it is obvious that, apart from any organic lesion in these organs, any marked depression of

their functional activity should manifest itself by symptoms corresponding with this depression. To the symptom-complex of this condition I have given the name of "functional hypoadrenia" to distinguish it from the forms due to destructive disorders of the adrenals, which constitute Addison's disease, and offer, of course, a far graver prognosis. As a definition of this condition, I would submit that

Functional hypoadrenia is the symptom-complex of deficient activity of the adrenals due to inadequate development, exhaustion by fatigue, senile degeneration, or any other factor which, without provoking organic lesions in the organs or their nerve-paths, is capable of reducing their secretory activity. Asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anæmia, slow metabolism, constipation, and psychasthenia are the main symptoms of this condition.

The field covered by functional hypoadrenia is necessarily a vast one, since it includes the asthenias so often met with in the four main stages of life: infancy, childhood, adult, and old age, usually attributed to "weakness" or "exhaustion," and often "neurasthenia," which have been traced to no tangible cause. All I can submit herein, therefore, is a cursory analysis of the subject.

FUNCTIONAL HYPOADRENIA OF INFANCY AND CHILDHOOD.

—Although the adrenals are relatively large in the infant (one-third the size of the kidney at birth), their functions are limited to the carrying on of the vital process, at least during the first year of life, the mother's milk supplying the antitoxic products capable of protecting it against the destructive action of poisons of endogenous and exogenous origin. This protective influence of maternal milk is clearly defined in the following quotation from Prof. William Welch's Harvey Lecture: "It is an important function of the mother to transfer to the suckling, through her milk, immunizing bodies, and the infant's stomach has the capacity, which is afterward lost, of absorbing these substances in active state. The relative richness of the suckling's blood in protective antibodies as contrasted with the artificially fed infant explains the greater freedom of the former from infectious diseases." Striking proof of this is

afforded by the fact that during the siege of Paris in 1870-71, according to J. E. Winters,¹⁵⁶ "while the general mortality was doubled, that of infants was lowered 40 per cent. owing to mothers being driven to suckle their infants."

The predilection of children to certain infectious diseases obviously indicates that it is not only in infancy that vulnerability to these disorders exists; it exposes life during the first decade, and more, of the child's existence. If, then, in the infant the maternal milk, as Welch says, protects the suckling against such diseases, at least to a considerable extent, we must conclude that the same underlying cause of vulnerability persists several years, *i.e.*, until it has in some way been overcome. How this occurs we have seen. The adrenals acquire, with other organs, we shall see, the power to supplant the mother in contributing antitoxic bodies to the blood; they supply internal secretions which fulfill this rôle.

These facts point to the adrenals as at least prominent organs among those whose inadequate development explain the special vulnerability of children to certain infections, the "children's diseases." It becomes a question now whether there are degrees of this hypoadrenia which render the child more or less liable to infection.

That degrees of hypoadrenia exist in children is in reality a familiar fact to every physician when the signs of this condition are placed before him. The ruddy, warm, hard-muscled, heavy, out-of-door, romping child with keen appetite and normal functions, is one in whom the adrenals are as active as the development commensurate with its age will permit. He is ruddy and warm because oxidation and metabolism are perfect and the blood-pressure sufficiently high to keep the peripheral tissues well filled with blood; his muscles, skeletal, cardiac, and vascular, are strong because, in addition to being well nourished, they are exercised and well supplied with the adrenal secretion, which, as shown by Oliver and Schäfer, sustains muscular tone. As normal outcome of this state, we have constant stimulation of the functional activity of the adrenals. The muscular exercise and maximum food intake involve a demand for increased metabolism and oxidation, and the resulting

¹⁵⁶ Winters: "Practical Infant Feeding," p. 6.

greater output of wastes imposes upon the adrenals, as participants in the oxidation and auto-protective processes, greater work, more active growth and development, *with increase of defensive efficiency* as normal result.

The pale, emaciated, or pasty child with cold hands and feet, flabby muscles, whose appetite is capricious or deficient—the pampered house-plant so often met among the rich—represents the converse of the healthful child described, just as does the ill-fed, perhaps overworked child of the slums. The emaciation, the cold extremities, indicate deficient oxidation, metabolism and nutrition owing to the torpor of the adrenal functions; the pallor is mainly due to a deficiency of the adrenal principle in the blood and to the resulting low blood-pressure, which entails retrocession of the blood from the surface. This child is not ill, but the hypoadrenia which prevails normally, owing to the undeveloped state of its adrenals, is abnormally low, and it is vulnerable to infection.

That all conditions which in the adult tend to produce functional hypoadrenia affect the child at least to the same extent is self-evident.

FUNCTIONAL HYPOADRENIA IN THE ADULT.—As in the child, the adrenals may be inherently weak. Such subjects do not, as in hypothyroidia, show signs of myxœdema; but their circulation and heart action are feeble, they tend to adiposis, and show other signs of hypoadrenia. I have witnessed suggestive bronze spots in such cases. As a rule, however, the development of the adrenals in adults is an accomplished fact—as also that of their coworkers in the immunizing process, the thyroid and pituitary, we shall see. The adrenals, fully capable of sustaining oxidation and metabolism, are able to defend the organism adequately; indeed, they do more: by sustaining oxidation and metabolism up to its highest standard in all organs, they also preserve the efficiency of all other defensive resources, including phagocytosis, with which the body is endowed to their highest level. On the whole, the *normal adult whose adrenals functionate normally is relatively resistant to infection*. The infrequency with which the physician is infected, notwithstanding daily exposure in his professional work, attests to this fact.

Functional hypoadrenia appears, however, when, irrespective

of any disease, and as a result of the vicissitudes of our existence, the adrenals are exhausted by the excessive secretory activity that exaggerated labor or exercise imposes upon them.

Fatigue is a prominent factor in this connection. Mosso's ergograph shows clearly the functional efficiency of the forearm. If by means of this instrument we compare the muscular power of a case of Addison's disease with that of any other kind of sufferer whose muscles are organically normal, a striking difference will be noticed: signs of fatigue appear very soon, and muscular impotence asserts itself where an advanced case of tuberculosis, for example, will be able to show appreciable strength. Intense asthenia is, in fact, a symptom of Addison's disease almost as characteristic as the bronze spots. It is as pre-eminent after experimental removal of both adrenals. This harmonizes with Oliver and Schäfer's demonstration of the influence of the adrenal secretion over muscular tone. Many other proofs could be adduced to show that there is a close relationship between fatigue and the functions of the adrenals. The pale and drawn face of an exhausted man, the readiness with which he suffers from the effects of cold and exposure, especially in the intestines, are familiar features of daily life.

The unusual prevalence of disease among soldiers in the field is of course partly due to the defective sanitation that a campaign entails; but fatigue—particularly that due to heavy marching, carrying heavy accoutrements—is, in my opinion, an important predisposing cause, through its influence upon the adrenals. Not only are these organs called upon to sustain general oxidation and metabolism at a rate exceeding by far that which amply suffices for normal avocations, but the fact that, as shown by Abelous and Langlois,¹⁵⁷ they also serve to destroy the toxic products of muscular activity constitutes another cause of drain upon their secretory resources. "Fatigue," write Morat and Doyon,¹⁵⁸ referring to experimental fatigue in animals deprived of their adrenals, "has an aggravating influence, as first indicated by Abelous and Langlois, and confirmed by Albanese and all authors. Hultgren and Andersson have even

¹⁵⁷ Abelous and Langlois: *Loc. cit.*

¹⁵⁸ Morat and Doyon: "Traité de Physiologie," Art. "Sécrétions Internes," p. 441, 1904.

observed sudden death as a result of powerful movements of the body." Sézary^{158a} has termed "hypoepinephry" a permanent inability of the adrenals to protect the body against infection.

Debility from any source: starvation, loss of blood, etc., as efficiently renders the body vulnerable to disease: "Combine toxin and antitoxin, and inject the mixture," writes Prof. Charrin;¹⁵⁹ "no harm will follow. But weaken the animal by starvation or slight bleeding and administer the same injection; death will follow with all the signs of poisoning by the toxin, with congested adrenals." . . . "That relations exist between the adrenals and infection," urges the same authority, "is today an incontrovertible fact." It follows, therefore, that hypoadrenia from any source should render the body vulnerable to disease. Deficient food, excessive work, that of the sweatshops for example, account for much of the predilection of those subjected to them to disease.

Masturbation and excessive venery are important morbid factors in this connection. The pallor and asthenia witnessed in these cases, so far unexplained, can readily be accounted for if, as I believe, the liquid portion of the semen is rich in adrenal principle. This is suggested by the fact that spermin, the purest of testicular preparations, gives the same tests and acts precisely as does the adrenal principle. The latter is an oxidizing body acting catalytically; it resists all temperatures up to, and even, boiling; it is insoluble in ether and practically insoluble in absolute alcohol, and gives the guaiac, Florence, and other hæmin tests. Now, spermin not only raises the blood-pressure, slows the heart and produces all other physiological effects peculiar to the adrenal principles, but its solubilities are the same; it gives the same tests; it resists boiling. Moreover, it is regarded in Europe as a powerful "oxidizing tonic" and has been found equally useful in disorders in which adrenal preparations had given good results. The inference that spermin consists mainly of the adrenal product suggests that it is not specific to the testes, but, instead, a constituent of the blood at large; not only did this prove to be the case, but it was found in the blood of females as well as in that of males.

^{158a} Sézary: *Paris médical*, Apr. 20, 1912.

¹⁵⁹ Charrin: "Les Défenses Naturelles de l'Organisme," p. 63, Paris, 1898.

FUNCTIONAL HYPOADRENIA OF OLD AGE.—Perpetual life would doubtless be ours were it not that all living organic matter is subjected, after more or less precarious periods of growth and adult existence, to one of decline and final disintegration. This applies particularly to the adrenals, if their functions are, as I hold, to sustain oxidation and metabolism, the fundamental processes of the living state. Indeed, the senile state may be said to be as evident in these organs as it is in the features of the aged.

According to Landau,¹⁶⁰ Ecker, Henie, and von Kolliker found that fat occurred in increasing quantities in the adrenal cortex as age advanced, while Hultgren and Andersson found fibrous tissue between the cortex and medulla in very old animals. Minervini¹⁶¹ found a similar condition in the medulla of aged individuals. Dostojewski, moreover, observed a marked—occasionally very great—reduction in the size of the adrenals in the aged. Rolleston¹⁶² has also called attention to this fact. Landau studied the influence of age on the vessels of the adrenals, adopting for the purpose a process introduced by Rauber and applied by many others, including Bezold, Hyrtl, and Lieberkühn, to the study of other organs, viz., injection of the vessels with some hardening substance, and the subsequent use of a corrosion method to destroy the parenchyma. The adrenals receiving their blood through a number of small arteries, the adrenal vein, which contains no valves, was used for the injection. The annexed plate shows the result. The vessels, and therefore the adrenals, are well developed and in full bloom, as it were, in the adrenals of the three young adults, while those of the aged are shrunken and correspondingly deficient as blood-channels—a certain index of the lowered activity of the adrenal functions, and, through these, of the vital process they sustain.

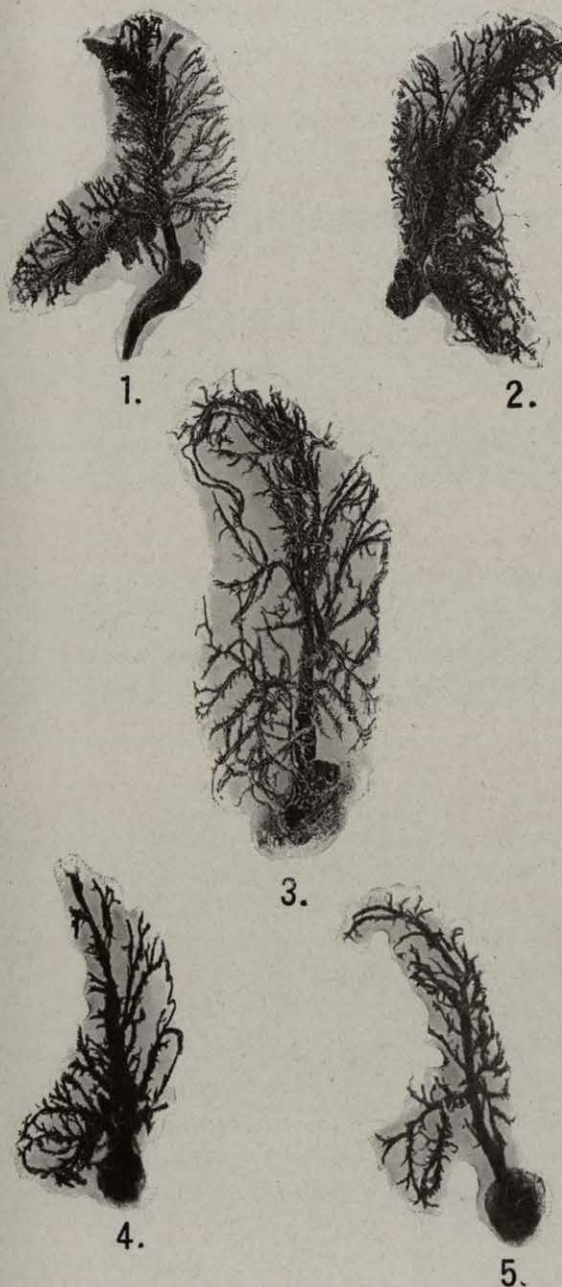
The asthenia of old age thus finds a normal explanation in the defective supply of adrenal secretion—precisely as it does in Addison's disease. In fact, Rolleston states that atrophy of the glands in the young may produce this disease. Lorand,¹⁶³ in

¹⁶⁰ Landau: St. Petersburg. med. Woch., June 14, 1908.

¹⁶¹ Minervini: Jour. d'anat. et de physiol., pp. 449 and 639, 1904.

¹⁶² Rolleston: Lancet, Mar. 23, 1895.

¹⁶³ Lorand: "Old Age Deferred," Am. ed., p. 111, 1910.



THE ADRENAL VESSELS IN THE YOUNG AND OLD

1, Man 22 years old. 2, Woman 30 years old. 3, Pregnant woman 22 years old. 4, Man 80 years old. 5, Woman 82 years old. (Landau.)

his recently published book on old age, urges in fact that "old age is caused by degeneration of the ductless glands, and that there exists a condition of autointoxication in old age" quite in keeping, I may add, with a decline of the antitoxic power shown by the adrenals. Lorand, who has antedated others in showing the influence of the ductless glands upon old age, has found his views confirmed by Campbell,¹⁶⁴ Pineles, Sir Herman Weber and also—though he denies a relationship between old age and myxœdema—Metchnikoff. We shall see in a succeeding chapter, however, that there exists a close connection between the adrenals and the thyroid in the genesis of old age, in the form of a functional relationship.

In his closing remarks on the causation of old age, Lorand remarks: "It is evident from the above considerations that all hygienic errors, be they errors of diet or any kind of excess, will bring about their own punishment, and that premature old age, or a shortened life, will be the result. In fact it is mainly our fault if we become senile at 60 or 70, and die before 90 or 100." Hence the motto of his title page:—

"Man does not die,
He kills himself."

—Seneca.

In the light of the data I have submitted, however, it is clear that the lesions to which the adrenals are subjected during infections and autointoxication, from birth to the last day of life, do greatly to shorten it by limiting the functional area of the organs through the local fibrosis they entail. It is quite probable, in fact, that centenarians owe their prolonged longevity mainly to integrity of their adrenals.

Hygiene, and particularly those of its divisions which bear directly upon the prevention of infectious diseases, thus asserts itself as one of the most useful of our sciences in another direction, viz., that of preserving of organism against those diseases which, seemingly benign because they are recovered from, measles for example, in the end shorten our existence by compromising the integrity of the organs which sustain the vital process itself.

PROPHYLAXIS AND TREATMENT.—Though we are dealing with depraved states of a physiological condition, we cannot

¹⁶⁴ Campbell: *Lancet*, July, 1905.