CHAPTER II.

THE FUNCTIONS AND DISEASES OF THE ADRENALS.

UNEXPLAINED PROPERTIES OF THE ADRENAL SECRETION.

As we have seen, adrenal preparations—extracts, the powdered gland, the active principles, epinephrin, supracapsulin, adrenalin, etc.—cause a rise of the blood-pressure with slowing of the heart-beat, a minute dose sufficing to produce a marked effect. But, as Howell[1] states, "the effects produced by such extracts are quite temporary in character. In the course of a few minutes the blood-pressure returns to normal, as also the heart-beat, showing that the substance has been destroyed in some way in the body, although *where and how this destruction occurs is not known.*" All that is established is that, as stated by Swale Vincent,[2] the secretion is formed in the adrenal medulla, and that "it passes by way of the adrenal veins into the general circulation, in order to assist the activity, or maintain the tone of sympathetically innervated muscle and other tissue," the latter including, as shown by Cardone,[2a] the skeletal muscles. The fate of the secretion in the blood has not been determined. From my viewpoint, *it forms part of the respiratory mechanism, as a constituent of the hemoglobin, besides acting as stated above.*

Adrenal preparations are all endowed, as first observed by Vulpian many years ago, with marked reducing activity, *i.e.*, with a marked tendency to take up oxygen. Abel, who isolated the adrenal active principle he termed "epinephrin," for instance, found this tendency so marked that it proved a source of inconvenience. Takamine noted that the colorless aqueous solution of his "adrenalin" was easily oxidized by contact with the air, its color changing from pink to red, and eventually to brown. Cybulski also observed that the addition of potassium permanganate, a powerful oxidizing agent, destroyed the activity of

[1] Howell: *Loc. cit.*, p. 842.

[2] Swale Vincent: "Internal Secretions and the Ductless Glands," London, 1913.

[2a] Cardone: Il Policlinico, fasc. 11, 12, 1910.

adrenal extract. What is the relationship between this reducing property and the blood-pressure raising power?

Various experimenters and clinicians, including Reichert,[3] Morel,[4] and Lépine,[5] have observed that even non-toxic doses of adrenal preparations caused a rise of temperature. Others, Courmont,[6] for example, found that adrenal grafts could produce such a rise as to warrant the phrase "formidable hyperthermia." Conversely we know that destructive disorders of the adrenals, Addison's disease, for example, or removal of the adrenals, cause a rapid decline of the temperature. This suggests that the adrenal secretion must be endowed with oxidizing power, and yet we have seen that it is a reducing agent. How account for this anomaly and for the power of adrenal products to raise the temperature?

When the adrenal tissue is excessive, as in the hypernephroma of children, there is excessive oxidation and overnutrition of the subject. The process of growth and development are such in some cases as to cause a child to appear several times its age—a child of 4 years, for example, being as large as one of 16. How account for this phenomenon as a result of an excessive production of adrenal secretion, which presumably occurs when the secreting elements are also in excess?

Not all vessels are influenced by the adrenal secretion or extractives. A striking fact in this connection is the apparent exemption of the pulmonary tissues to the effects of the secretion. Wallace and Mogk[7] found that, while adrenal extract caused a rise of the systemic blood-pressure due to the contraction of *the arterioles*, the pressure in the pulmonary arteries is not raised, these vessels, in their opinion, not being acted upon as are the others. This observation was confirmed by Brodie and Dixon.[8] Velich,[9] on the other hand, found, by a series of experiments instituted to ascertain whether vasoconstrictor fibers existed for the pulmonary vessels, that adrenal extract gave rise to but a slight rise of pressure. Warm adrenal extract, which,

[3] Reichert: Univ. of Penna. Med. Bull., April, 1901.

[4] Morel: Le Progrès Médical, Aug. 3, 1903.

[5] Lépine: La Semaine médicale, Feb. 18, 1903.

[6] Courmont: Congrès de Médecine Interne, Montpellier, 1898.

[7] Wallace and Mogk: Transactions of the Physiological Society, Dec. 28-30, 1898.

[8] Brodie and Dixon: Journal of Physiol., vol. xxx, p. 416, 1903.

[9] Velich: Wiener med. Wochenschrift, No. 26, 1898.

when applied even to the skin, causes pallor, was found by him to exercise no such effect upon the surface of the lungs. This accounts for the familiar fact upon which Parhon and Golstein[10] lay stress, that intravenous injections of adrenalin can produce acute pulmonary œdema, owing doubtless to the marked rise of blood-pressure in the rest of the organism. Why this exception?

Such were the questions which I attempted to answer in the first edition of this work, which appeared in 1903. The only experiments on the connection between the adrenal secretion and respiration had been those of Oliver and Schäfer and Langley—the injection of adrenal extracts into animals, with temporary arrest of respiratory movements—due doubtless to spasm of the respiratory muscles—as result. But obviously they taught nothing as to the respiratory process *per se.* When, however, the avidity of the adrenal product for oxygen, its influence over general oxidation and nutrition, and the invulnerability of the lungs to its action, on the one hand, and the fact that both pulmonary and tissue respiration still belonged to the domain of conjecture, on the other, are taken into account, there was good ground for the belief that a connection between the adrenals and the respiratory process actually existed.

THE ADRENAL SECRETION AS THE OXIDIZING AGENT OF THE HÆMOGLOBIN.

That the prevailing view on the physiology of respiration, based on the diffusion of gases, has not been, and is not now, endorsed by all physiologists is now well known. "When," writes Professor Mathias Duval,[11] of Paris, "an animal is caused to breathe in the smallest possible space—the air imprisoned in its lungs—it uses up all the oxygen in the air. This is because hæmoglobin, in virtue of its chemical affinity, *takes up the oxygen as fast as this gas is dissolved in the serum*,[12] so that the latter, always despoiled, is never able to satisfy its absorption coefficient for oxygen, however low be this coefficient, and however slight be the tension of the oxygen in the surrounding air. As to the exhalation of carbonic acid, it is not produced so simply as would *a priori* seem, by mere gaseous diffusion or by

[10] Parhon and Golstein: *Loc. cit.*, p. 725.
[11] Mathias Duval: Cours de physiologie, 1892.
[12] All italics are my own.

the mere giving off of a gas in solution, because of the scarcity of the gas in the surrounding atmosphere. Indeed, the air in the pulmonary vesicles contains 8 per cent. of carbonic acid, hardly a favorable condition for the escape of carbonic acid from the blood, especially since a portion of this gas is not dissolved, but combined with the serum salts. It is therefore probable that the pulmonary tissues are the seat of an action having for its object to rapidly dislodge the carbonic acid. *This action is probably of a chemical nature.* . . . Whenever oxygen is mixed with venous blood, even *in vitro* during experiments, the carbonic acid is immediately given off. One is led to admit, therefore, that the combination of oxygen with the blood-corpuscles (oxyhæmoglobulin) plays a rôle analogous to that of an acid, and involving the elimination of carbonic acid from venous blood." He refers to Robin and Verdeil's view in respect to the existence of a hypothetic "pneumonic acid" and to the experiments of Garnier,[13] who observed that ultramarine blue, sprayed into the lungs of living guinea-pigs, lost its color: a phenomenon which could only occur through the presence of a strong acid, neither taurin nor carbonic acid being capable of producing it. "Chemical analysis of the lung has not disclosed a specific acid, however."

"It is, perhaps, wrong," adds Professor Duval, himself a prominent physiologist, "for physiologists to continue to only see in these phenomena mere results of endosmosis of liquids and of diffusion of gases through an inert membrane." As a clinician, I would urge that this theory is harmful in its far-reaching consequences. I have pointed out that the aërotonometer, upon which it is mainly founded, is a defective instrument, and that it is because of this that the results recorded by various physiologists have been divergent to such a degree that, in some instances, the diffusion of oxygen should occur, to correspond with its indication in the wrong direction, *i.e.*, from the hæmoglobin to the alveolar air, the tension of oxygen in the arterial blood being actually higher than the pressure of oxygen in the air-cells.

I characterize the prevailing theory as "harmful" because the physiologist, engrossed in his own field, does not realize that

[13] Garnier: Comptes-Rendus de l'Académie des Sciences, July 26, 1886.

he is dealing with the foundation of probably the most important problem of our day in its influence over human life, viz., immunity not only in the tissues at large, but at the very threshold of infection—the pulmonary alveolar surface, and the alimentary canal, as will be shown later.

THE ADRENAL SECRETION IN PULMONARY RESPIRATION.—In the first edition of the present work (1903) I advanced the view, sustained by considerable evidence, that the adrenals took a leading part in the respiratory process by supplying a secretion which absorbed the oxygen of the air in the pulmonary alveoli, then became a part of the hæmoglobin and of the blood-plasma, which in turn carried it, as oxidizing principle, to all tissues.

Three years after this opinion was formulated, a noted English physiologist, Pembrey, wrote[14] in an impartial review of the recent advances in physiology and bio-chemistry: "It is impossible to give a satisfactory account of the gaseous exchange between the blood and the alveolar air." . . . "The body of evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen." This theory is that of Bohr, advanced in 1891, which attributes the oxygen-absorbing power and the excretion of carbon dioxide to active secretory processes carried on by the lining membrane of the air-cells. While the need of a secretion capable of absorbing the oxygen has been steadily growing in favor, however, the secreting membrane has not been found.

This is explained when the respiratory process is considered from my viewpoint: *It is not by a local membrane that the reducing secretion is produced, but by the adrenals.* As shown below, its properties and itinerary are precisely those required for the process, while its presence can be traced at every step to the hæmoglobin itself, of which it forms part.

A succinct review of the experimental evidence which has invalidated the diffusion doctrine, and of that upon which my conception of the respiratory process is based, will perhaps serve better than a prolonged analysis of the question (for which the reader is referred to previous editions) to convey the actual status of the question.

[14] Pembrey: Hill's "Recent Advances in Physiology and Bio-Chemistry," p. 549, 1906.

Paul Bert,[15] thirty years ago, showed experimentally that the absorption of oxygen by the pulmonary blood persisted, even when the pressure of this gas was almost *nil*. Müller also observed that a strangulated animal exhausted the air in its lungs of *all* its oxygen, while Setschenow and Holmgren,[16] Zuntz,[17] and others found but traces of oxygen in the arterial blood of asphyxiated animals. This suggested that the diffusion doctrine was defective, and that the absorption of oxygen from the air was due to the presence, in the blood circulating through the lungs, of some substance capable of taking up this gas. This conclusion was sustained by the researches of Bohr,[18] Haldane and Lorrain Smith,[19] Vaughan Harley,[20] and Bohr and Henriques,[21] the last-named investigators referring to it as a substance "having greater avidity for oxygen than the blood itself" and presumably "a kind of internal secretion."

This view has been antagonized by some of the advocates of the diffusion theory (whose aërotonometric figures are suggestively discordant), but as we have seen the "evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen."

Having repeatedly noted the powerful reducing properties of adrenal extractives, it occurred to me that the secretion of the adrenals might fulfill this rôle. Anatomical studies in various lower animals and in man, and a systematic research in the literature of the subject, demonstrated that it met all the conditions required to satisfy so important a function.

The first deduction imposed by these researches was that

The secretion of the adrenals has a marked affinity for oxygen, and inevitably reaches the pulmonary air-cells.

Vulpian,[22] over fifty years ago, found that adrenal juice reduced iron perchloride and iodine. Cybulski[23] recorded a similar action on potassium permanganate; Langlois[24] noted, however, that adrenal extract lost its reducing properties *in vitro*

[15] Paul Bert: C. r. de l'Acad. des sci., Oct. 28, 1878.
[16] Setschenow and Holmgren, cited by Ludwig: Wiener med. Jahrb., 21st year. i, p. 145, 1865.
[17] Zuntz: Hermann's "Handbuch," iv, part 2, p. 43, 1882.
[18] Bohr: Skand'n. Archiv für Physiologie, p. 236, 1891.
[19] Haldane and Lorrain Smith: Jour. of Physiol., xxii, No. 3, p. 231, 1897.
[20] Vaughan Harley: *Ibid.*, xxv, No. 1, p. 33, 1899.
[21] Bohr and Henriques: Arch. de physiol., ix, pp. 459 and 819, 1897.
[22] Vulpian: C. r. de l'Acad. des sci., p. 663, Sept. 29, 1856.
[23] Cybulski: Gazeta Lekarska, 2d series, xv, pp. 299-308, 1895.
[24] Langlois: Arch. de physiol. norm. et pathol., x, p. 124, 1898.

when oxidizing compounds were added. As to the action of the atmospheric oxygen, Battelli[25] found that adrenalin did not lose its properties when contact with air was prevented, while Abel,[26] Takamine,[27] and others refer to this property as a source of trouble in laboratories, the latter chemist specifying, in fact, that adrenalin becomes oxidized by contact *with the air.*

That the adrenal secretion inevitably reaches the air-cells was made clear by a study of the anatomical relations between the adrenals and the lungs. The blood of the efferent vessels of the adrenals, their veins, passes to the inferior vena cava, directly on the right side, and by way of the renal vein on the left. The actual presence of the adrenal secretion in the blood of the adrenal veins is shown by many experimental facts. Gottschau,[28] for example, traced hyaline granules (found subsequently to be their secretion) from the interior of the adrenals to their veins. This observation was confirmed and amplified by Manasse,[29] Aulde,[30] and Stilling.[31] Pfaundler[32] traced the same granules from the interior of the organ along the adrenal veins to the vena cava itself. It is doubtless the adrenal secretion and no other which is carried by the blood of the vena cava, for, when blood originating from the adrenals on its way to this great trunk was injected into animals by Cybulski and Scymonowicz,[33] it produced the characteristic effects of adrenal extract. These results were confirmed by Biedl,[34] Langlois,[35] and Dreyer.[36] Scymonowicz, Biedl, Dreyer, Salvioli, and Pizzolini[37] found, moreover, that such effects could not be obtained with venous blood obtained from other parts of the body.

The next fact to assert itself was that

On reaching the air-cells, the adrenal secretion absorbs oxygen and becomes a constituent of hæmoglobin and of the red corpuscles.

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25 Battelli: C. r. de la Soc. de biol., liv, p. 1435, 1902.
26 Abel: Bull. Johns Hopkins Hosp., p. 215, Sept.-Oct., 1898.
27 Takamine: Therapeutic Gazette, p. 221, April 15, 1901.
28 Gottschau: Arch. f. Anat. u. Physiol., Anat. Abth., p. 412, 1883.
29 Manasse: Arch. f. Path. u. Physiol., cxxxv, p. 263, 1894.
30 Aulde: Brit. Med. Jour., May 4, 1894.
31 Stilling: Arch. f. path. Anat., cix, p. 324, 1897.
32 Pfaundler: Sitzungsber. d. k. Akad. d. Wissensch. Mathem., cl, p. 3, 1892.
33 Cybulski and Scymonowicz: Gazeta Lekarska, 2d series, xv, pp. 299-308, 1895; Archiv f. d. ges. Physiol., lxiv, Nos. 3 and 4, p. 97, 1896.
34 Biedl: Archiv f. d. ges. Physiol., lxvii, part 9-10, 1897.
35 Langlois: Arch. de physiol. norm. et pathol., ix, p. 152. 1897.
36 Dreyer: American Journal of Physiology, ii, p. 203, 1899.
37 Salvioli and Pizzolini: Gazetta degli osped., Mar. 23, 1902.

While a reducing substance has been found necessary, we have seen, to account for the absorption of oxygen from the alveolar air, it happened that the greater part of the hæmoglobin molecule was composed almost entirely of an albuminous substance which had remained unidentified. Gamgee,[38] for instance, states that "hæmoglobin exists in the blood-corpuscles in the form of a compound with a yet unknown constituent of the corpuscles." This body he defines as the "albuminous moiety of the hæmoglobin molecule" and,[39] as representing 96 per cent. of this molecule, the remaining 4 per cent. being the iron-laden hæmatin. Now, I found that this "unknown constituent" of hæmoglobin corresponded in its physicochemical properties with the adrenal secretion. Gamgee,[40] for example, states that hæmoglobin is insoluble in absolute alcohol, chloroform, benzol, ether, and all organic solvents: Vulpian[41] had already noted that, of all glandular products, that of the adrenals alone showed this peculiarity. Gautier,[42] Moore,[43] and Takamine also refer to it. Again, according to Moore and Purinton,[44] adrenal extracts are rapidly destroyed by alkalies; this is also a characteristic of hæmoglobin. This pigment likewise resists heat up to the boiling point; this applies also, according to Cybulski,[45] Moore,[46] and others to adrenal extract. Finally, Mulon[47] found that the red corpuscles gave the histochemical reactions of the active principle of the adrenals, thus showing that these blood-cells actually contain this principle. Since then the adrenal reaction has been obtained from blood-elements wherever sought, including that of the placenta.

In confirmation of this conclusion is the fact that

The oxygen-laden adrenal secretion is a constituent of the albuminous hæmoglobin in the blood-plasma.

Battelli[48] and Kraus[48a] found adrenalin in the blood, the latter author in Graves's disease. That this principle is a constituent of the albuminous portion of hæmoglobin voided

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38 Gamgee: Schäfer's "Text-book of Physiology," i, p. 189, 1898.
39 Gamgee: *Ibid.*, p. 207, 1898.
40 Gamgee: *Ibid.*, p. 206, 1898.
41 Vulpian: C.-r. de l'Acad. des Sci. de Paris, Sept. 29, 1856.
42 Gautier: Chimie biologique, p. 355, 1892.
43 Moore: Journal of Physiology, xvii, p. xiv, 1894-95.
44 Moore and Purinton: American Journal of Physiology, iii, p. 15, 1900.
45 Cybulski: Gazeta Lekarska, Mar. 23, 1895.
46 Moore: *Loc. cit.*
47 Mulon: Personal Communication.
48 Battelli: C.-r. de la Soc. de Biol., liv, p. 1179, 1902.
48a Kraus: Cited by Brugsch, Folia Therapeutica, Jan., 1909.

by red corpuscles in the plasma suggested itself when Schmiedeberg,[49] Jaquet,[50] Abelous and Biarnès,[51] and other chemists showed that blood-plasma contains an oxidizing substance, subsequently known as oxidase. Not only was it found to resist heat at least up to the boiling point and to possess other chemical characteristics of the adrenal principle, but the actual presence of the latter is confirmed by other facts. Thus, in 1853, Traube had concluded that hæmoglobin could not fulfill the physicochemical functions ascribed to it without the aid of a catalyzer. Poehl[52] showed that the adrenal principle was a catalyzer, while Jolles[53] pointed out that the activity of a given volume of blood as a catalyzer corresponded with the number of red corpuscles it contained. It is because of this that Oliver and Schäfer found that oxidation of the adrenal principle does not occur in the blood; acting as a catalyzer it simply transfers oxygen from the pulmonary air to the tissues without being itself modified by the contact. Finally, Bernstein and Falta[54] recently found that "injections of adrenalin in healthy persons produced an increase of the consumption of oxygen and of the production of carbonic acid together with an increase of the respiratory quotient."

Additional evidence to this effect and an explanation of the rôle of the red corpuscles were afforded by the next conclusion reached: That

The red corpuscles, after absorbing the oxygenized adrenal secretion (the albuminous constituent of their hæmoglobin) yield it to the blood-plasma in the form of droplets, the so-called "blood-platelets."

As Gamgee[55] teaches, hæmoglobin, under the influence of various chemical agents, "undergoes a decomposition of which the chief products are, an *albuminous* substance or substances, and a *coloring matter* which contains the whole of the iron"; but, as he also says, "the coloring matter of the red corpuscles is not extracted from them by the plasma." This does not, however, apply to their albuminous substance. That they discharge the

[49] Schmiedeberg: Archiv f. exper. Path. u. Pharm., vi, p. 233, 1876.
[50] Jaquet, cited by Salkowski: Archiv f. path. Anat., Jan. 4, 1897.
[51] Abelous and Biarnès: Arch. de physiol. norm. et pathol., 5th series, vii, pp. 195, 239, 1895.
[52] Poehl: Indian Lancet, May 22, 1904.
[53] Jolles: Münch. med. Woch., p. 2083, Nov. 22, 1904.
[54] Bernstein and Falta: Abst. in London Lancet, June 29, 1912.
[55] Gamgee: *Loc. cit.*, i, p. 189, 1898.

latter in the plasma is rendered evident by various facts. Louis Elsberg,[56] thirty years ago, observed "a projection of a pediculated granule or knob" from the periphery of red corpuscles. Hirschfeld[57] traced these granules from the interior of these cells, through one or more minute apertures which closed up again, to the surrounding plasma. Brockbank[58] gave recently a beautiful microphotograph of "platelets in, or being extruded from, red cells." Again, Detemann[59] noted that the buds on the surface of the red cells "at first are attached to the cell by protoplasmic processes and contain hæmoglobin"; but that, "later, the buds become separated from the cell, losing their hæmoglobin." This does not militate against Gamgee's statement that the coloring matter remains in the corpuscles, but it indicates that the albuminous constituent is voided into the plasma.

These albuminous droplets (which, in 1903,[60] I identified as the familiar *blood-platelets*), having absorbed oxygen in the lungs, should, in the light of preceding deductions and owing to the catalyzing property of their adrenal principle, be able to surrender their oxygen to any agent in the blood or tissues possessed of sufficient reducing power to appropriate it. That this applies to the droplets is shown by the reaction to certain stains. Litten[61] and others found, for example, that blood-platelets derived from the red corpuscles are best stained with methylene-blue; Stengel, White, and Pepper[62] state, in fact, that "methylene-blue gave the only positive results." This indicates that the droplets are certainly rich in oxygen—as their identity as the oxygenized adrenal secretion would suggest—for, as Ehrlich teaches, one of the conditions "essential to the methylene-blue reaction" is "oxygen saturation."[63]

A study of the melanins then showed that

The albuminous constituent of the hæmoglobin, or oxygen-laden adrenal secretion, is distributed by the red corpuscles to all parts of the body as an oxidizing agent.

[56] Louis Elsberg: Annals of the N. Y. Acad. of Sci., i, 1879.
[57] Hirschfeld: Virchow's Archiv, clxvi, part 2, p. 195, 1901.
[58] Brockbank: Med. Chronicle, Mar., 1908.
[59] Determann: Deut. Archiv f. klin. Med., lxi, part 4, p. 365, 1898.
[60] Sajous: The present work, 1st ed., vol. i, p. 715, 1903.
[61] Litten: Deut. med. Woch., No. 44, Nov. 2, 1899.
[62] Stengel, White, and Pepper: Amer. Jour. Med. Sci., May 9, 1902.
[63] Quoted by L. F. Barker: New York Medical Journal, May 15 *et seq.*, 1897 to 1898.

Leonard Hill,[64] Hirschfeld, Chittenden and Albro,[65] and most classic writers look upon melanins, the brown and black pigments found in certain forms of sarcoma, in the tissues, the blood, the urine, etc., in various morbid states, as hæmoglobin derivatives. While Mörner, Brandl, and L. Pfeiffer[66] found that it contained iron, and accept this origin, Nencki and Berdez[67] do not, because they failed to find this metal in the pigment isolated from a melanotic sarcoma. These discordant opinions are harmonized, however, by the newer conception I submit: The first-named authors dealt with whole hæmoglobin, containing, therefore, its iron; while Nencki and Berdez dealt quite as surely with hæmoglobin, but only with its albuminous constituent.

Having traced to the adrenals the origin of the active agent of this albuminous hæmoglobin and this substance being melanin, the presence of the adrenal principle in melanins should be shown. In the first place these pigments were found by Walter Jones[68] insoluble in alcohol, ether, benzol, chloroform, etc., *i.e.*, precisely as Vulpian, Moore, and others had found to be the case with the adrenal principle. This applies as well to the action of alkalies, to which Jones, Abel and Davis[69] found melanins very sensitive, and to other tests. In the second place direct evidence was afforded by Boinet,[70] who found chemically that the bronze pigment of Addison's disease was identical to melanin, and also by Mühlmann,[71] who discovered independently that the Addisonian pigment was a product of the adrenals.

Finally, as the connection of the adrenal product with respiration and oxygenation I urge, suggests:—

An excess of adrenal secretion causes a rise of temperature.

This action was first observed by Oliver and Schäfer.[72] Reichert[73] recorded a rise of 1° C. in the dog, having reached this temperature "in less than forty minutes." In three experimental animals it "continued hypernormal for over two hours."

[64] Leonard Hill: "Text-book of Chemistry," p. 374, 1903.
[65] Chittenden and Albro: Amer. Jour. of Physiol., ii, p. 291, 1899.
[66] Mörner, Brandl, and L. Pfeiffer, cited by Hammarsten: "Text-book of Physiological Chemistry," 5th American Ed., p. 688, 1908.
[67] Nencki and Berdez: *Ibid.*
[68] Walter Jones: Amer. Jour. of Physiol., ii, p. 380, 1899.
[69] Abel and Davis: Jour. of Exper. Med., i, p. 381, 1879.
[70] Boinet: Marseille méd., April 15, 1896.
[71] Mühlmann: Deut. med. Woch., No. 26, p. 409, 1896.
[72] Oliver and Schäfer: Jour. of Physiol., xviii, p. 230, 1895.
[73] Reichert: Univ. of Penna. Med. Bull., April, 1901.

Morel[74] noted a rise of 0.5° to 1° C. (0.9° to 1.8° F.) in guinea-pigs. Lépine[75] states that the increase of blood-pressure caused by adrenal extract is always followed by a rise of temperature. This is controlled by the familiar fact, first observed by Brown-Séquard, that removal of the adrenals is followed by a steady decline of temperature and by the hypothermia which attends Addison's disease.

Additional evidence on this particular feature of the general problem will be found in Volume II. I studied, for example, the evolution of the red corpuscles throughout the animal scale[76] and learned that they were tardy additions to the blood as storage cells when the hæmoglobin diffused in the plasma, as it is in many invertebrates and in certain low vertebrates, failed to satisfy the needs of the vital process. Having been brought to the conclusion that, contrary to what is now taught, it is the plasmatic hæmoglobin which carries oxygen to the tissues and not the red cells (though these act as storage cells for it as a constituent of their albuminous hæmoglobin), I traced this substance in various tissues and organs, including the nervous system, the guaiac and methylene-blue tests being those most frequently employed. Again, I found that the oxidases gave the reactions of the oxygen-laden adrenal secretion. Hence the term I applied to the latter: *adrenoxidase.*[77]

On the whole, this evidence, considered collectively, seems to me to afford a solid foundation for the conclusion that

It is the adrenal secretion which, after absorbing oxygen from the pulmonary air and being taken up by the red corpuscles, supplies the whole organism, including the blood, with its oxygen. It is, as such, the oxidizing constituent of the hæmoglobin, which, in turn, sustains tissue oxidation and metabolism.

This latter function is treated in detail in the second volume. "That the suprarenals are related *in some way* to metabolic changes in the tissues and organs," says Schäfer,[78] "there can be but little doubt. This is indicated by the symptoms of Addison's disease."

Additional evidence in favor of this conception of the rôle

[74] Morel: Le Progrès médical, Aug. 3, 1903.
[75] Lépine: La Semaine médicale, Feb. 18, 1903.
[76] Sajous: The present work, p. 828.
[77] Sajous: *Ibid.*, p. 822.
[78] Schäfer: British Med. Jour., June 6, 1908.