CHAPTER XIII.

THE SECRETION OF THE ADRENALS IN RESPIRATION.

In the first volume a succinct review of the functions of various ductless glands was submitted, along with the recent corroborative evidence. The following chapters will be devoted mainly to a more detailed study of my views as formulated in 1903 and 1907 and a review of the data which led up to them.

THE NEED OF A SECRETION TO ACCOUNT FOR THE RESPIRATORY PROCESS.

While the blood of vertebrates—fishes, reptiles, birds and mammals—contains both white and red corpuscles, that of invertebrates, with very few exceptions, is not supplied with the latter. Even the blood of Amphioxus, an animal classed among vertebrates, contains no red corpuscles. The presence of hæmoglobin or hæmocyanin in the plasma of various lower forms might be said to afford a means for the absorption and distribution of oxygen; but how are these functions fulfilled?

Again, as stated by Griffiths,[1] "the majority of Invertebrata have white blood, *e.g.*, the Insecta, Crustacea, Mollusca, etc."; and yet, the intracellular processes are hardly more sluggish in many of these than in animals far higher in the phylogenetic scale. This clearly betokens a correspondingly active vital process sustained by active oxygenation. Indeed, there exists in these animals, as well as in the colorless blood of any other organism deprived of red corpuscles or of blood-pigment, a substance endowed with quite as marked an affinity for oxygen as that shown by hæmoglobin in higher forms. What is the nature of this substance?

The process of respiration is ascribed by physiologists to diffusion of gases, and to the affinity of the hæmoglobin in the red corpuscles for oxygen, the red cells absorbing the gas from the plasma as it enters this fluid in order to carry it to all parts

[1] Griffiths: "The Physiol. of the Invertebrates," p. 123, 1892.

of the body. This doctrine fails, however, to explain the respiratory process in the largest division of the animal kingdom, the invertebrates just referred to. The absence of red cells and of their hæmoglobin logically entails, in the present conception of respiration, absence of any agent in the blood having affinity for oxygen; and, unless it can be shown that diffusion alone will satisfy the needs of the process, it is evident that we are left with nothing to account for either the oxygen intake or the carbon dioxide output, or for the manner in which the tissues of these lower organisms carry on respiration.

The weakness of the diffusion doctrine as an explanation of the respiratory process becomes apparent when we take into account the fact, emphasized by Paul Bert[2] many years ago, that an animal will exhaust the oxygen in the air of its lungs even though this be reduced to one-half of one per cent. As stated by Mathias Duval,[3] this shows that "absorption of oxygen by the blood occurs even though the pressure of this gas be almost *nil*." Indeed, Müller observed that when strangulated, an animal exhausted *all* the air in its lungs of oxygen, while Setschenow and Holmgren,[4] Zuntz[5] and others[6] found that "in the last stages of asphyxia the arterial blood contains only traces of oxygen," thus showing that the tissues themselves absorbed this gas through a process of active reduction.

Bohr,[7] using an improved aërotonometer, sustained the conclusions of Robin, Müller, Setschenow and Holmgren and other investigators to the effect that the diffusion doctrine did not satisfy the needs of the respiratory process. He found that the carbonic acid tension was often much lower in the arterial blood than in the alveolar air, and also that the oxygen tension was higher, at times, in the arterial blood than in the latter. He concluded, therefore, that the absorption of oxygen and elimination of carbonic acid were not due merely to diffusion, but to *active* processes where the blood meets the air, *i.e.*, in the pulmonary alveoli. Haldane and Lorrain Smith[8]

[2] Paul Bert: C.-r. de l'Acad. des Sci., Oct. 28, 1878.
[3] Mathias Duval: "Cours de physiol.," seventh edition, p. 440, 1892.
[4] Setschenow and Holmgren: Cited by Ludwig: Wiener med. Jahrb., Jahrg. xxi, Bd. i., S. 145, 1865.
[5] Zuntz: Hermann's "Handbuch," Bd. iv, Th. 2, S. 43, 1882.
[6] Pembrey: Schäfer's "T. B. of Physiol.," vol. i, p. 765, 1893.
[7] Bohr: Skandin. Archiv f. Physiol., S. 236, 1891.
[8] Haldane and Lorrain Smith: Jour. of Physiol., vol. xxii, No. 3, p. 231, 1897.

confirmed Bohr's results. They reached the conclusions that "the *normal* oxygen tension in the arterial blood is *always* higher than in the alveolar air; and is in some animals even much higher than in the inspired air," and that "the absorption of oxygen by the lungs thus cannot be explained by diffusion alone." Moreover, they observed that active absorption of oxygen continued when the oxygen in the alveolar air was artificially increased, the oxygen tension in the blood increasing almost proportionally. This obviously shows that the blood contained some substance which actively reduced the air.

Again, therefore, are we brought to the need of some substance in the lungs capable of absorbing oxygen.

Additional evidence to this effect has been contributed by Vaughan Harley.[9] This observer found that when "one pleural space was filled up so that the lung on one side was compressed, the rate of breathing was increased, and more air was breathed per minute by the active lung than was previously breathed by the two lungs together." This was accompanied "by an increase in the quantity of oxygen absorbed and of carbonic acid eliminated by the animal, the two being increased *pari passu*, so that the respiratory quotient, as a rule, was not altered." After showing experimentally that this could not be ascribed either to an increased rate of respiration alone, to an increase in the temperature, or to displacement of the heart, he concluded that "the only explanation which appears to be satisfactory is that we accept the theory of Bohr."

Bohr's views have met with considerable opposition, though strongly sustained by the comprehensive experiments of Haldane and Smith, Vaughan Harley and older investigators, the antagonism being based on the fact that the gasometric experiments of some observers failed to confirm his results. This objection would have weight did the results recorded by Bohr's opponents agree. But such is not the case; Pembrey,[10] for instance, refers to them as being "very discordant."

This is accounted for, it seems to me, by the fact that gasometric methods do not provide for the absorption of oxygen by other constituents of the blood. That the relative volume

[9] Vaughan Harley: Jour. of Physiol., vol. xxv, No. 1, p. 33, 1899.
[10] Pembrey: Schäfer's "T. B. of Physiol.," vol. i, p. 776, 1898.

of this gas must be decreased while the blood is in transit to the aërotonometer is suggested by Pflüger's[11] observation that arterial blood *used up a portion of its own oxygen* on leaving the animal's vessels. "The blood contains," says Schäfer,[12] "a substance or substances ('reducing substances' of Pflüger) which greedily appropriate any free oxygen which may be present in the plasma, and are even capable of abstracting the oxygen which is combined with hæmoglobin, so that arterial blood rapidly becomes converted into venous blood, when it is not exposed to the access of fresh oxygen. It is not known upon what substance or substances these properties depend." Various factors thus come into play which investigators have not taken into account:—the dimensions of the tube between the animal and the instrument, the friction to which the blood is subjected therein, the time elapsed while it is in transit, etc., all of which are quite sufficient to account for the discordant results obtained. Of course, this applies to Bohr's observations as well, but as with his tonometer "a constant and *rapid* stream of arterial blood could be maintained," while his oxygen ratios exceed those of his opponents, the probability that his results are more exact than theirs is apparent.

In fact, Landois, in his well-known text-book,[13] rejects the diffusion doctrine totally. "The absorption of oxygen from the alveolar air for the purpose of oxidation of the venous blood in the pulmonary capillaries," says this physiologist, "is a chemical process, as the gas-free hæmoglobin in the lungs takes up oxygen to form oxyhæmoglobin. That this absorption depends, not on diffusion of the gases, but on the atomic combination pertaining to the chemical process, is shown by the fact that the blood does not take up more oxygen when the pure gas is respired than when atmospheric air is respired; further, that animals that are made to breathe in a small, closed space will absorb into their blood all of the oxygen but traces, to the point of suffocation. If the respiratory absorption of oxygen were a diffusion-process, much more oxygen would have to be taken up in the first case in accordance with the partial

[11] Pflüger: Centralbl. f. d. med. Wissen., Bd. v, S. 321, 1867.
[12] Schäfer: *Loc. cit.*, vol. i, pp. 152 and 153, 1898.
[13] Landois: "T. B. of Physiol.," 10th Amer. Ed., edited by A. P. Brubaker, p. 239, 1905.

pressure of the gas; while in the latter case such an extensive absorption could not take place."

Another series of experiments, performed by Bohr and Henriques,[14] further emphasizes the presence in the alveolar walls of a substance capable of absorbing the atmospheric oxygen. Mechanical obstruction of the aorta, if the process had been one of diffusion, should have soon inhibited greatly the respiratory exchanges. These investigators found not only that the exchanges were not as markedly inhibited as is generally believed, but that when, in addition to the aorta, the main branches given off by this vessel were closed, the respiratory exchanges were sometimes *increased*. They reasoned that the absorption of oxygen was due to the presence in the blood of substances *"having greater avidity for oxygen than the blood itself."* That the increased absorption was due to the fact that obstruction of the efferent blood-paths caused the oxyphile substance to accumulate in the lungs, is self-evident.

On the whole, it seems plain that *the respiratory process is carried on through the intermediary of some substance capable of taking up the oxygen of the pulmonary air.* But it is in this connection that Bohr's views have met their only true obstacle. He finally proved the important facts, which several experimenters had previously emphasized, that simple diffusion did not account for the respiratory process and that a powerful reducing secretion was necessary; but he did not reveal the identity of this secretion nor the manner in which it carried on its functions.

This is precisely the function I have found the secretion of the adrenals to fulfill.

THE ADRENAL SECRETION AS THE BLOOD CONSTITUENT WHICH TAKES UP THE OXYGEN OF THE AIR.

Bohr suggested that the pulmonary cells took an active part in the absorption of oxygen and the elimination of carbonic acid gas, basing his hypothesis on the corresponding phenomena observed in the air-bladder of fishes. In 1897, in a paper written in conjunction with Henriques,[15] he deemed it

[14] Bohr and Henriques: Arch. de physiol., T. ix, pp. 459 and 819, 1897.
[15] Bohr and Henriques: *Ibid.*, T. ix, p. 819, 1897.

demonstrated that the lungs, "presumably by means of *a kind of internal secretion,*" could "modify the blood's holdings in oxygen and subsequently the distribution of oxygen to the corpuscles and plasma."

My own conclusion that the secretion of the adrenals fulfilled this all-important function was suggested by the reducing properties of adrenal extractives. Vulpian nearly fifty years ago[16] observed that the expressed juice of the adrenals gave ferric chloride an emerald-green color—the result of the juice's affinity for oxygen, the brownish ferric salt being converted into the green ferrous salt. When suprarenal extracts came into general use they were found to be endowed with the same property. Moore[17] not only found them to be powerful reducing substances, but Cybulski[18] observed that even weak solutions of potassium permanganate destroyed the activity of suprarenal extract, the salt doubtless yielding its oxygen. Battelli,[19] moreover, found that the activity of adrenalin did not become manifest "in the absence of oxygen." Abel, Takamine and other chemists have laid considerable stress on this property, Takamine emphasizing the fact that an aqueous solution of adrenalin becomes oxidized by *contact with the air.*

Inasmuch as the adrenals secrete their product into the blood of the suprarenal veins which open into the inferior vena cava, their secretion must necessarily find its way (*via* the heart) to the lungs. Again, since the blood of the inferior cava meets that of the superior cava in the right auricle, all the blood of the organism, when about to be exposed to the air, cannot but be supplied with a given proportion of adrenal secretion and be evenly distributed by the venous blood among the seven hundred millions of air-cells that the lungs contain.

Proof that the secretion of the adrenals actually passes upward by the inferior cava and that once in the lungs it takes part in the respiratory process, is strikingly furnished by the experiments of Bohr and Henriques,[20] although these observers in no way refer to the adrenals. They found, as we have seen, that when the aorta and the main vessels given off by this great trunk

[16] Vulpian: C. r. de l'Acad. des sci. de Paris, Sept. 29, 1856.
[17] Moore: Jour. of Physiol., vol. xvii, p. xiv, 1894-95.
[18] Cybulski: Gazeta Lekarska, Mar. 23, 1895.
[19] Battelli: C. r. de la Soc. de biol., T. liv, p. 1435, 1902.
[20] Bohr and Henriques: *Loc. cit.*

were closed, the respiratory exchanges were often increased—evidence that an accumulation of the oxyphile secretion had occurred in the lungs. Now, matters were reversed when they also closed the only channel through which the secretion passes upward, *i.e.*, the inferior vena cava. "It is only when, along with all other arteries (excepting the coronary arteries)," write these investigators, "the vena cava [above the adrenals as shown by the report of their experiments] was also omitted from the circulation, that the exchanges dropped to the minimum."

The well-known action of adrenal extractives on the heart affords tangible proof of the passage of this secretion through the cardiac cavities.

The investigations of recent years tend to sustain the view that the heart's power to contract rhythmically is distinctly a property of the cardiac muscle. Small pieces of the ganglion-free apex of the frog's heart, strips of the ventricle of the tortoise, etc., will beat rhythmically a long time when placed in suitable media, blood serum or artifically prepared fluids, saline solution, etc., especially if these contain calcium and potassium salts, and if they are kept supplied with oxygen under pressure. Yet "it must also be borne in mind," writes Stewart,[21] "that when we have localized the essential mechanism of the rhythmical contraction in the muscle of the heart, we have still to ask whether this mechanism is not put into action by some stimulus external to the muscle." My investigations have led me to ascribe this function to the secretion of the adrenals.

Over sixty years ago, Brown-Séquard[22] emphasized the importance of the venous blood in cardiac dynamism. While admitting that arterial blood tended to promote the contractile power of the cardiac muscle, he contended that the contractions were due to a stimulating action of the venous blood. The erroneous belief that CO_2 was the energizing agent soon caused this view to be antagonized successfully. When the CO_2 is left out of the question, however, it becomes evident that the blood of the inferior vena cava *does* contain a principle capable of

[21] Stewart: "Manual of Physiology," fourth edition, p. 131, 1900.
[22] Brown-Séquard: "Experimental Researches applied to Physiology and Pathology," p. 104, 1853.

contracting the heart-muscle. Oliver and Schäfer[23] and others have demonstrated conclusively that intravenous injections of adrenal extract produce "a powerful physiological action upon the muscular system in general, but especially upon the muscular walls of the blood-vessels, and the muscular wall of the heart." My own researches on the ox heart[24] have led me to conclude that some of the adrenal secretion which enters the heart with the blood of the inferior vena cava—which contains of course only *reduced* oxyhæmoglobin—penetrates into the myocardium by way of the Thebesian foramina and that it plays a leading part in cardiac contraction. Mousset[25] also contends that the adrenal secretion acts directly on the heart muscle. As the adrenal secretion inevitably enters the heart with the blood of the inferior vena cava, it is difficult to conceive how it can fail to influence cardiac dynamism.

This accounts not only for the experimental results recorded by Brown-Séquard, but also for the now well-known powerful action of adrenal extractives in the various forms of cardiac adynamia shown by Reichert,[26] Crile,[27] Martin and Pennington,[28] and others. Moreover, Beaman Douglass[29] found that when the ventricles of a turtle's heart were detached from its auricles and left in the open air, they began to beat at once when immersed in a 0.001 suprarenal solution. This shows that its action on the heart is independent of the nervous supply of this organ, a fact also suggested by the increase in force of the contractions which occurs, as emphasized by Wallace and Mogk,[30] when "the vagus influence is removed."

That the adrenals supply to the blood of the inferior vena cava a substance capable of provoking the phenomena obtained by *intravenous* injections of adrenal extractives is also fully sustained experimentally. Considerable evidence to this effect has already been submitted in the first volume. A summary of this evidence, enriched by facts found in literature since, may prove helpful at this stage.

[23] Oliver and Schäfer: Jour. of Physiol., vol. xvi, p. i, 1894; and vol. xvii, p. ix, 1895.
[24] *Cf.* vol. i, pp. 421-454 of the first three editions.
[25] Mousset: "Les principes actifs des cap. surrénales," 1903.
[26] Reichert: Univ. of Penna. Med. Bull., Apr., 1901.
[27] Crile: Boston Med. & Surg. Jour., Mar. 5, 1913.
[28] Martin and Pennington: Amer. Med., Nov. 21, 1903.
[29] Beaman Douglass: Amer. Jour. Med. Sci., Jan., 1905.
[30] Wallace and Mogk: Amer. Jour. of Physiol., vol. ii, p. v, 1899.

Gottschau[31] observed in histological preparations of the adrenals that protoplasmic masses projected from the medullary cells into the central vein of the organ, and that very slight pressure upon the latter would cause blood containing these masses to issue from it. They then assumed the aspect of bright, intensely refractive and colorless granules, which, singly or in clumps of fifteen or twenty, were contained in the blood issuing from the organ. Manasse[32] also noticed that hyaline masses were secreted by rows of cells in the medullary canal of the adrenals and that they then passed into the vessels of the latter. A similar observation was recorded by Auld,[33] who refers to the secretion as a colloid. Stilling[34] found the granules referred to by Gottschau not only in the cortical and medullary layers, but also in the tissue spaces. Pfaundler[35] discovered similar granules in the lumina of the adrenal vessels and in the *suprarenal* vein where it opens into the vena cava.

Again, Cybulski and Szymonowicz[36] having convinced themselves of the correctness of Brown-Séquard's conclusion that in animals from which both adrenals had been removed, the ensuing symptoms could all be arrested by intravenous injections of extracts of the glands, ascertained experimentally that living adrenals secreted the substance which gave adrenal extracts their characteristic properties, and that blood drawn from the suprarenal veins produced effects similar to those that follow injections of these extracts. Langlois[37] was able to corroborate these results. They were also confirmed by Dreyer in a series of experiments referred to below. Biedl[38] ascertained that while fresh blood from *other* veins produced practically no effect when slowly injected intravenously, blood taken from the adrenal veins injected in the same way caused the characteristic pulse and blood-pressure curves, *i.e.*, a primary slight rise due to the addition of the fluid, followed a few seconds later by an increase of volume and slowing of the pulse, and from one to one

[31] Gottschau: Archiv f. Anat. u. Physiol., Anat. Abth., S. 412, 1883.
[32] Manasse: Archiv f. path. Anat., Bd. cxxxv, S. 263, 1894.
[33] Auld: Brit. Med. Jour., May 12, 1894.
[34] Stilling: Arch. f. Path. Anat., Bd. clx, S. 234, 1887.
[35] Pfaundler: Sitzungs-Bericht d. k. Akad. d. Wissensch. mathem., Bd. cl, S. 3, 1892.
[36] Cybulski and Szymonowicz: Gazeta Lekarska., Mar. 25, 1895.
[37] Langlois: Revue scientifique, p. 303, 1897.
[38] Biedl: Archiv f. d. gesam. Physiol., Bd. lxvii, H. 9 u. 10, S. 443, 1897.

and one-half minutes later by the maximum rise of blood-pressure.

All this is further emphasized by experimental stimulation of the nerves supplied to the organs. To ascertain, if possible, the identity of their secretory nerves, Biedl tied the vena cava above and below the adrenal veins and inserted a cannula into the vena cava, suspending the nozzle of the instrument over a small drum connected with a recorder. The number of blood-drops falling upon the drum in a given time, as the blood-pressure in the vessels was increased by stimulating the nerves distributed to the adrenals, could thus be accurately recorded. Having cut both splanchnics in the thoracic cavity, he stimulated the peripheral ends electrically. "During the first 6 to 9 seconds," says the physiologist, "the number of drops remained the same; at the 7th second—sometimes later, about the 10th—a gradual increase in the number of drops occurred, until 20 to 25 seconds had elapsed, when the number of drops multiplied 3 to 5 times." The increased flow continued from 10 to 20 seconds *after* the current was no longer applied, and also after the increased pressure in the organ's vascular supply, caused by the current, had ceased. The effects could no longer be obtained when the suprarenal nerves, which are remarkable for their size, were severed. Although Biedl was thus able to demonstrate that the splanchnic contained fibers which, when stimulated, increased the flow of blood through the adrenals, he did not succeed in establishing their identity as secretory nerves.

To settle this important feature of the problem, Dreyer,[39] in a series of experiments, placed a ligature around the vein on either side of the gland, the ligature "on the mesial side serving to tie off the central end of the vein, the other, on the lateral side, being used to tie in the cannula," a straight glass tube. In this way, the blood from the tube issued with certainty from the gland. Specimens of the blood were then collected from the femoral vein, from the adrenal vein before stimulation, and from the adrenal vein during stimulation. The comparative effects of these various bloods when injected intravenously into the animals from which they had been ob-

[39] Dreyer: Amer. Jour. of Physiol., vol. ii, p. 203, 1899.

tained or into others, were then carefully recorded. The eight experiments reported demonstrated that excitation of the cut splanchnic not only increased the blood-flow, but also the proportion of secretion in that blood. Both sets of animals—those from which the blood had been taken and the controls—when "stimulation" blood was injected into them, showed a corresponding increase of the characteristic effects of adrenal extract. Briefly, using Dreyer's words: "A given bulk of adrenal blood taken during stimulation [of the cut splanchnic] had a decidedly greater effect than the same bulk of normal blood, meaning by normal blood that which was taken when not stimulating."

It is plain, therefore, that the secretion of the adrenals themselves produces effects similar to those caused by intravenous injections of adrenal extracts. That this applies to human adrenals as well has been shown, we have seen in the first volume (page 10), by Guinard and Martin, the expressed juice of adrenals derived from an executed criminal being used.

Finally, the symptoms of certain diseases or that follow extirpation of the adrenals strikingly emphasize a connection between these organs on the one hand and the heart and respiratory process on the other. In Addison's disease, for example, the *systole* is greatly weakened and the pulse is small, extremely soft and compressible. Lowering of general metabolism—due to lowered general oxygenation—is shown by the facts that the temperature, when no complication is present, is subnormal, and that the extremities are cold. Rolleston in Allbutt's Practice[40] states that a cadaveric odor is sometimes emitted by these cases—a self-evident sign of lowered vitality. As emphasized by Sergent and L. Bernard,[41] the identical symptoms ascribed to Addison's disease are met with in the many distinctive disorders of which the adrenals may be the seat.

The effects of removal of these organs have been reviewed at length in the first volume. Most prominent among these, however, are, as first shown by Brown-Séquard, lowering of the temperature and of the blood-pressure, accompanied by intense weakness, hardly perceptible heart-beat, very weak and rapid

[40] Rolleston: Allbutt's "Practice," vol. v, p. 540, 1897.
[41] Sergent and L. Bernard: Arch. gén. de méd., July, p. 27, 1899.

pulse, etc. That we are dealing with morbid phenomena due to absence of the *secretion* of these glands was also demonstrated by Brown-Séquard, extracts prepared from healthy adrenals and administered subcutaneously having restored the experimental animals as long as the extracts were used.

Pathological and physiological evidence, plus new data submitted in the first volume, unite, therefore, in pointing to the secretion of the adrenals as the *constituent of the blood which absorbs the oxygen of the air, in order to carry on oxygenation of the body at large.*

THE OXIDIZING SUBSTANCE (OXIDASE) AS A RESPIRATORY CONSTITUENT OF ALL ORGANISMS.

In the first volume, I showed that the secretion of the adrenals lost its identity as such when it reached the lungs, and that when the venous blood had been exposed to the air of the alveoli and had become arterial, it contained a new substance, the oxidizing substance. This compound was then traced with the plasma into the minute capillaries of the cellular elements of the various organs and into the axis-cylinders of the nerves, neuro-fibrils, etc., and shown capable, moreover, of subserving therein not only the needs of nutrition, but also those of active function—in so far, at least, as the oxygen can contribute to these processes.

Exception has been taken to my conclusions on this score on the plea that the blood-plasma *per se* did not contain such a substance, this being based on results obtained with the gas-pump. We have seen, however, that shed blood does not give even an approximate idea of the oxygen-content of living blood, its oxygen being rapidly reduced by another constituent. This applies to defibrinated blood as well, since the fibrin itself carries off a large proportion of the oxygen. The gas-pump is as useless an instrument in this connection as the aërotonometers referred to in the preceding section, and like them has contributed much to prevailing misconceptions.

The blood-plasma of animals, including man, not only contains such an oxidizing substance, but its presence may be demonstrated at every stage of organic life, *i.e.*, in the vegetable and animal kingdoms. So important is this feature of the

problem, in fact, that I deem it necessary to review some, at least, of the evidence at our disposal to this effect.

Stress was laid in the earlier editions of this work on the presence in the blood of what Schmiedeberg (1876 and 1881), Salkowski, Jaquet, and Abelous and Biarnès had characterized as an "oxidizing ferment," freely soluble, as shown by Jaquet, in the blood fluids. Claude Bernard, Pavy and Lépine had found that the plasma could oxidize sugar, the process being accompanied by the production of carbon dioxide, according to Kraus. This was also found by Pohl, Spitzer and other observers to apply to intracellular or tissue juices. Importance was attached to the fact that Abelous and Biarnès had, in 1895, "succeeded in causing oxidation of salicylic aldehyde by means of blood-serum, that is to say, *blood absolutely deprived of its corpuscles,*" and furthermore, that these chemists had found, as had Salkowski and Jaquet, that the passage of air through the blood during the experiment was an essential factor of the oxidation process. These experiments thus made it evident that the oxidizing ferment in the blood-serum could *absorb the oxygen of the air and then transfer it* to the salicylic aldehyde, converting the latter into salicylic acid. The importance of this fact, with respect to the general question in point, is very great, since it shows that the oxidizing ferment referred to can fulfill precisely the rôle generally ascribed to the *corpuscular hæmoglobin.* In other words, while it is believed that this hæmoglobin carries the oxygen from the seat of external respiration, the pulmonary alveoli, to the seat of internal respiration, the tissue-cells, the foregoing experiments have shown that the *plasma* contains "oxidizing ferments" or "oxidases" capable of carrying on this identical function.

Now, it happens that physiologists have failed so far to discover the identity of an important constituent of hæmoglobin. Gamgee,[42] for instance, after reviewing our knowledge of hæmoglobin, concludes that "without attempting to speculate beyond the facts which we possess"....."it may be assumed that hæmoglobin exists in the blood-corpuscles in the form of a compound with a yet *unknown constituent* of the corpuscle."

It happens also that the blood contains a group of oxidizing

[42] Gamgee: Schäfer's "T. B. of Physiol.," vol. i, p. 189, 1898.