A recent study of the question (1898)[50] by the same physiologist showed that these "reënforced pulsations" which he had at first ascribed to reflex action, were in reality due to the fact that the nerves which evoke these phenomena were distributed to the vessels of the thyroid gland and that it was the secretion of this organ which had produced the cardiac "augmentation." The manner in which the thyroid secretion could produce this effect is readily explained by the fact that, as I have shown, this secretion serves to sustain the functional efficiency of the adrenal center. Briefly, it is also through the adrenals—though indirectly—that Cyon produced "reënforced pulsations" of the heart.

The following conclusions seem to me, in the light of the foregoing facts, to summarize the functional mechanism of the heart:—

1. The nervous supply of the heart is derived from the sympathetic system and is composed of two sets of nerves: the accelerator and the moderator (or inhibitory) nerves.

2. The accelerator nerves increase the rapidity of the contractions of the heart, by causing dilation of its arterioles and thus increasing the volume of blood admitted to its muscular elements.

3. The moderator (or inhibitory) nerves diminish the rapidity of the heart's contractions, by causing constriction of its arterioles and thus reducing the volume of blood admitted to its muscular elements.

4. "Augmentation," i.e., *increased power of the heart's contractions is due to increased activity of the adrenals, whose secretion traverses the heart on its way to the lungs.*

As to the physico-chemical process involved—bearing in mind that the muscular elements are inherently contractile—they are, pending additional data, as follows:—

5. The mechanical energy upon which the right heart depends is of two kinds: (1) the contractile action of the adrenal secretion brought to it by the inferior vena cava; (2) the continuous action of the oxidizing substance of the coronary arterial blood upon myosinogen formed from granules β, the latter being granulations derived from leucocytes.

[50] Cyon: Arch. de physiol. norm. et path., vol. x, No. 5, p. 618, 1898.

6. The adrenal secretion and the granulations β enter the right auricle and the right ventricle with the blood of the vena cava.

7. The adrenal secretion, owing to its direct action on muscular tissue, causes the walls of these cavities to contract alternately upon their venous contents and to force a small quantity of the latter into the Thebesian foramen and channels.

8. This blood then penetrates the interfibrillary spaces of Henle,—i.e., *around the bare muscle-cells,—and its granules β are used by the latter to build up their myosinogen.*

9. As the plasma of the coronary arteries and their terminals, the pericellular capillaries of the muscle-elements, contains oxidizing substance (adrenoxidase) contraction of the muscle-cells is induced as it is elsewhere in the organism.

10. The adrenal secretion and the granules β, which do not enter the Thebesian channeds, are carried to the lungs with the venous blood of the right ventricle.

11. The mechanical energy of the left heart is supplied (1) by the oxidizing substance of the arterial blood, which penetrates its muscular structures and its cavities by the coronaries and the pulmonary veins, and (2) by an additional supply of granulations β, and perhaps of adrenal secretion, which find their way to its myocardium through the Thebesian channels that connect it with the right heart.

12. The manner in which the contractile process is carried on in the walls of the left heart is similar to that which prevails in the right heart.

THE ADRENAL SECRETION IN ITS RELATIONS TO RESPIRATORY FUNCTIONS.

The rôle of the adrenal secretion in respiration, and particularly the process through which oxygen is taken up by the blood, was reviewed in the second chapter. I believe that the succeeding chapters, by affirming the importance of the oxidizing substance in every part of the organism, have but confirmed the conclusions reached concerning the process in question. The fact that the interchange of oxygen and carbonic acid between the alveolar air and the blood by mere diffusion was inadequate to account for the experimental results

of various investigators, particularly Bohr and Haldane and Smith, has therefore been correspondingly emphasized. I must also refer to the fact, however, that the belief of Ludwig, Bohr, and others, that the alveolar tissues might be the seat of functions capable of fulfilling the missing requirements of the process, has not been sustained by my inquiry. On the other hand, the rôle of the adrenal secretion in the lungs as I have defined it has adequately met these requirements, notwithstanding the severe tests to which it has been submitted in previous chapters.

We have seen that the adrenal secretion, conveyed to the lungs with the venous blood, is not only able to take up oxygen, but to form an oxidizing substance, *i.e.*, adrenoxidase, with which hæmoglobin can, in the lungs, become replenished with oxygen. The entire set of analyses submitted in this work so far, however, has served further to emphasize another fact: *i.e.*, that *the plasma, and not the corpuscle, is the dispenser of oxygen,* the corpuscle being a mere carrier from which the plasma itself becomes replenished as needed. As already stated, this precisely coincides with the conclusion to which Jaquet was led by chemical methods after Salkowski (1881) had obtained oxidations from blood alone, which he attributed, however, to the blood-corpuscles. Abelous and Biarnés having obtained oxidation of salicylic aldehyde by means of blood-*serum*, Salkowski modified his former view and experimentally confirmed the results of the other investigators.

Finally, we have seen how closely connected the adrenal secretion is with the integrity of the blood, and how readily the hæmoglobin molecule becomes dissociated in proportion as the efficiency of the adrenals becomes weakened.

The next important question to analyze is one fraught with considerable confusion, viz., the manner in which the respiratory process is governed, and the identity of the respiratory center.

THE NERVO-VASCULAR MECHANISM OF THE LUNGS.

According to prevailing teachings the respiratory center is located in the medulla oblongata, *i.e.*, the bulb. But there is considerable evidence on record indicating that the bulbar

center is not supreme in the control of respiration, although the fact that it forms part of the controlling mechanism cannot be denied. Thus, division of the cord below the seventh cervical nerve arrests costal respiration; section below the medulla causes all thoracic movements to cease; removal of the brain *above* the medulla, the seat of the supposed center, does not stop respiration, while cessation of this function occurs when the medulla is removed or extensively injured, save in exceptional cases. After reviewing this evidence Professor Foster adds: "Nay, more; if only a small portion of the medulla—a tract whose limits have *not been clearly defined*,[51] but which may be described as lying below the vasomotor center in the immediate neighborhood of the nuclei of the vagus nerves—be removed or injured, respiration ceases, and death at once ensues. Hence this portion of the nervous system was called by Flourens the vital knot, or ganglion of life: *nœud vital*. We shall speak of it as the *respiratory center*."

Yet, how account for the facts recited in the following quotation from Noel Paton's text[52]: "Both parts of the respiratory center are under the control of higher nerve centers, and through these they may be thrown into action at any time, or even prevented from acting for the space of a minute or so. But, after the lapse of this period, the respiratory mechanism proceeds to act in spite of the most powerful attempts to prevent it.

"To determine its mode of action the influence of afferent nerves upon the center must be considered.

"*Vagus.*—Since the vagus is the nerve of the respiratory tract we should expect it to have an important influence on the center.

"*Section of one vagus* causes the respiration to become slower and deeper; but, after a time, the effect wears off, and the previous rate and depth of respiration is regained.

"*Section of both vagi* causes a very marked slowing and deepening of the respiration, which persists for some time, and passes off slowly and incompletely. Now, if after the vagi have been cut, the connection of the center with the *upper brain*

[51] The italics are mine.
[52] Noel Paton: *Loc. cit.*, p. 291.

tracts is severed, the mode of action of the center totally changes. Instead of discharging rhythmically it remains for a long period at rest, then the inspiratory center discharges violently, causing a strong and prolonged contraction of the muscles of inspiration. This passes off, and again a period of rest of variable duration sets in, to be again interrupted by another more or less long and strong discharge.

"Separation of the respiratory center from the vagi and upper brain tracts brings about a loss of its rhythmic action, *but does not stop its activity.* The center owes the rhythmic nature of its action to afferent impulses. These afferent impulses reach it normally through the vagi, but when these are cut the upper brain takes upon itself the function of maintaining the rhythm."

Howell[53] also says, referring to the "midbrain, at the level of the posterior colliculi" (the corpora quadrigemina) a region above the medulla oblongata: "Martin and Booker[54] found that stimulations in this region caused a marked increase in the rate of inspiratory movements and finally a standstill in inspiration—that is, a complete tetanic contraction of the inspiratory muscles lasting during the stimulation. Lewandowsky[55] has shown that section of the brain stem at or below the inferior colliculi causes an alteration in the respiratory rhythm similar to that following section of both vagi. After cutting through the inferior colliculi further sections more posteriorly do not add to the effect. He considers that there is an automatic inhibitory center in the midbrain which influences continually the automatic activity of the medullary center." Again, Ott[56] writes: "I have made numerous experiments to determine the exact seat of the polypnœic center. To establish a center three things are necessary: (1) that its abolition causes the phenomena to disappear; (2) that irritation—mechanical, chemical or electrical—causes the phenomena to be present, and (3) that the part of the nervous system exhibiting these peculiarities be circumscribed in extent. After numerous observations and

[53] Howell: "T. B. of Physiol.," second edition, p. 640, 1907.
[54] Martin and Booker: Jour. of Physiol., 1, 370, 1878.
[55] Lewandowsky: Archiv f. Physiol., 489, 1896.
[56] Ott: "T. B. of Physiol.," second edition, p. 451, 1907.

experiments it was found that pressure upon the tuber cinereum with a pledget of cotton, or even slight puncture, increased the normal respirations to the point of polypnœa. Complete puncture in a normal animal was followed by a rise to 106° F. within two hours, even though the animal was bound down and had been subjected to considerable shock.

"If now the animal whose tuber is punctured be heated, there will result *no* polypnœa, even though a temperature of 107° F. be reached. I am convinced that the *tuber cinereum is a center of polypnœa and thermotaxis.*"

A suggestive feature asserts itself in this connection: As I have pointed out, and as will be further shown in the second volume the tuber cinereum is precisely the region through which the nerve path from the pituitary body to the adrenals passes to the medulla oblongata, and thence, via the spinal cord and the sympathetic nerves and ganglia, to the adrenals, whose secretion, we have seen, serves to take up the oxygen of the air and to distribute it to the tissues, *i.e.,* to sustain oxygenation. Moreover, as emphasized by considerable evidence submitted in the second volume, the walls and floor (of which the tuber cinereum forms part) of the third ventricle, are the pathways of a vast array of sympathetic fibers which likewise pass from the posterior or neural lobe of the pituitary (via the nucleus magnus grisei) to the medulla and cord and thence to be distributed through the sympathetic chain and its offshoots to all parts of the body including the lungs. We have here the explanation of the presence of so-called heat and respiratory centers in this region, *i.e.,* irritation phenomena following the experimental lesions in the course of these nerve-paths,—a fact further sustained by the observation of many experimenters that removal of the pituitary body—the seat of the heat and main respiratory centers in the light of my views—is followed by marked lowering of the temperature and dyspnœa.

How does the respiratory center—or centers, for as stated, the bulbar center is endowed with important functions—influence the respiratory mechanism? Before this feature of the subject can be analyzed, a brief review of the circulation and innervation of the lungs may prove advantageous.

The pulmonary circulation as regards vascular distribu-

tion is succinctly portrayed in the following description by Miller,[57] as given by Böhm and von Davidoff[58]: "The *pulmonary artery* follows closely the bronchi through their entire length. An arterial branch enters each lobule of the lung at its apex, in close proximity to the bronchus. After entering the lobule the artery divides quite abruptly, a branch going to each infundibulum; from these branches the small *arterioles* arise which supply the alveoli of the lung. 'On reaching the air-sac the artery breaks up into small radicles, which pass to the central side of the sac in the sulci *between* the air-cells, and are finally lost in the rich system of capillaries to which they give rise. This net-work surrounds the whole air-sac and communicates freely with that of the surrounding sacs.' This capillary net-work is exceedingly fine, and is shrunken *into* the epithelium of the air-sacs; so that between the epithelium and the capillary there is only the *extremely delicate* basement membrane. The infundibula, the alveolar ducts and their alveoli, and the alveoli of the respiratory bronchioles are supplied with similar *capillary net-works*. The veins collecting the blood from the lobules lie at the periphery of the lobules in the interlobular connective tissue, and are as far distant from the intralobular arteries as possible. These veins unite to form the larger pulmonary veins. The bronchi, both large and small, as well as the bronchioles, derive their blood-supply from the *bronchial arteries*, which also partly supply the lung itself. Capillaries derived from these arteries surround the bronchial system, their caliber varying according to the structure they supply: finer and more closely arranged in the mucous membrane, and coarser in the connective-tissue walls. In the neighborhood of the terminal bronchial tubes the capillary nets anastomose freely with those of the *respiratory* capillary system." To avoid confusion I may recall the fact that, while the *pulmonary* artery and its branches contain *venous* blood, and the *bronchial arteries* and their branches carry *arterial* blood, the pulmonary *veins*, on the contrary, contain *arterial* blood. When, therefore, bronchial capillaries are said to empty

[57] Miller: Journal of Morphology, vol. viii, p. 165, 1893.
[58] Böhm and von Davidoff: *Loc. cit.*

into the pulmonary veins, it is not used, or venous, blood that is transferred to the latter, but arterial blood originally derived from the thoracic aorta or its primary branches.

The lungs, as is well known, are innervated by the vagus and the sympathetic system. These unite to form plexuses, the anterior and posterior, which enter the organs with the bronchial tubes and accompany them along their ramifications. The anterior pulmonary plexus, made up of vagal and sympathetic filaments, overlies the pulmonary artery, while the richer posterior pulmonary plexus, composed also of vagal filaments, intermixed with sympathetic fibers from the second, third, and fourth thoracic ganglia, follows the bronchi to their ultimate subdivisions.

According to prevailing views, the vagus—both its sensory and motor fibers—is alone regarded as the intermediary between the respiratory center and the organs of respiration, but as shown in the second volume, the neural lobe of the pituitary also contains the sympathetic center. This proximity to the respiratory center and the important rôle the sympathetic plays in respiration pointedly suggest that both centers are functionally united.

Indeed, there is good ground for the belief that the experimental phenomena now ascribed to the vagus are partly of sympathetic origin—sympathetic in the sense that they are essentially vasoconstrictor as in other organs previously reviewed. Sappey, for instance, writes[59]: "Section of both pneumogastrics in the median portion of the neck not only abolishes the sensibility of the respiratory mucous membrane and paralyzes the internal respiratory muscles; it also involves as consequence a mucous *effusion* into the bronchi, *engorgement* of the lungs, emphysema of these organs, and a very sensible diminution in the number of inspirations." We have in the pulmonary engorgement an evident result of variation of vascular caliber, and inasmuch as we are dealing with a *division* of the nerve, the effect on the vessel must have been one of relaxation. On the other hand, we have in the paralysis of the internal respiratory muscles evidence that a motor nerve—

[59] Sappey: "Traité d'Anatomie Descriptive," vol. iii, p. 397.

a vasodilator, or stricto-dilator, in our sense—was also severed. These dual phenomena indicate that the vagus, as we have seen in the case of the heart, must have contained vasoconstrictor, *i.e.*, sympathetic fibers.

The presence of vasoconstrictor fibers is, in fact, generally recognized. François-Franck, in 1881, showed that the sympathetic nerves distributed to the lungs, caused vasoconstriction, these fibers being stimulated at the entrance into the lungs. Bradford and Dean[60] also demonstrated the presence of vasomotor nerves in these organs after a series of exhaustive experiments. In a subsequent study of the subject François-Franck[61] noted the paradoxical fact that vasoconstriction of the pulmonary vessels caused the lungs to swell, instead of being reduced in volume. This is readily accounted for when it is recalled that the vasoconstriction applies only, in the light of my views, to the arterioles. These small pre-capillary vessels being constricted, the arterial blood was dammed up behind the seat of obstruction in François-Franck's experiment, thus causing the larger portions of the vessel, which are not governed by the sympathetic, to dilate.

A source of confusion asserts itself in this connection, however, which we have also encountered while studying the heart. The experiments of Rose Bradford and Dean[62] are thus referred to by François-Franck: "They carefully sought the points of emergence, from the cord, of the filaments which cause elevation of pulmonary pressure and lowering of aortic pressure: that is to say, pulmonary vasoconstriction. These were located from the second to sixth dorsal, and, in respect to maximum effects, on a level with the third, fourth, and fifth nerves. The pulmonary vasoconstrictors ascend the chain up to the first thoracic ganglion, where they become detached, to reach the pulmonary plexuses." The salient feature of the topography of these nerves is that the lower limit of the ganglionic chain through which they pass happens to be the upper limit of the ganglia from which the splanchnic nerves that ultimately carry impulses to the adrenals are given off. While the pulmonary

[60] Bradford and Dean: Jour. of Physiol., vol. xvi, p. 34, 1894.
[61] François-Franck: Arch. de Physiol., T. viii, p. 184, 1896.
[62] Rose, Bradford and Dean: Journal of Physiol., p. 57, 1894.

vasoconstrictors which pass directly to the lungs from the first thoracic to the pulmonary plexuses are, as generally taught, true vasoconstrictors, the presence in the second, third, and fourth ganglia of the sympathetic chain, of the nerves to the adrenals suggests that many vasoconstrictor phenomena attributed to the direct action of nerves, should be ascribed to an increase of adrenal secretion in the blood. Indeed Jacobi[63] found that intense vasoconstriction of the intestinal vessels (inhibition) produced by excitation of the splanchnic was replaced by ordinary vasoconstriction after the suprarenal nerves had been cut.

The fact, moreover, that the introduction of adrenal extract into the circulation produces general vasoconstriction is well known. Mankowsky,[64] for example, noted "a great increase in blood-pressure and stimulation of the cardiac and respiratory centers." This occurred "even when the animals (dogs) were under the influence of chloroform, morphine, or chloral hydrate." "In cats, says Swale Vincent,[65] "by far the most noticeable feature was an enormous rapidity of the respiratory movements in the early stage." The two—now familiar—stages that occur under the influence of toxic doses of suprarenal extract, as well as under that of other poisons, are well illustrated in the following observation by the same investigator: "In the early stage of poisoning respiration is quick and shallow and the heart is excited. Subsequently the breathing and heart-beats become feeble, and finally the respiration is deep and infrequent." Finally, the fact that all these phenomena are independent of the cord has been shown by Biedl,[66] who, as we have seen, obtained marked increase of blood-pressure after injections of suprarenal extract, notwithstanding the fact that all the spinal structures had been removed.

This does not mean that the adrenal secretion fulfills any particular function in the lungs other than that of taking up oxygen therein; it is only intended to show that excitation of the splanchnic nerve may suggest the presence of pulmonary

[63] Jacobi: Archiv f. exper. Path. u. Pharm., vol. xxix, p. 171, 1892.
[64] Mankowsky: Russian Archives of Pathology, etc., Mar, 1898.
[65] Swale Vincent: Jour. of Physiol., Feb. 17, 1898.
[66] Biedl: Wiener klin. Wochen., ix, 1896.

vasoconstrictor nerves in this great nerve-path, when the vasoconstrictor effects witnessed in the lungs are in reality due to the presence in the blood, as a result of splanchnic stimulation, of an excess of adrenal secretion.

As to the rôle of the vagus in the respiratory organs, our views differ from those at present taught only in that they explain, as was the case with other organs, *how* the physiological phenomena are produced.

I have briefly referred to the manner in which the vagal fibers are distributed in the lungs. Sappey[67] also studied the distribution of vagal nerves in the lungs of mammals, including particularly those of man, the ox, and horse, and reached the following conclusions: "1. They follow the subdivisions of the air-tree to their terminal extremities; they do not leave these subdivisions and follow them to the lobules. 2. All those that leave the anterior pulmonary plexus and the much greater number given off by the posterior pulmonary plexus preserve their plexiform arrangement throughout their entire distribution; their meshes are elongated only in the line of their axis, each thus constituting an elongated ellipse. 3. Their ramifications, essentially destined for the muscular coat of the bronchi and respiratory mucous membrane, have no connection with the blood-vessels." Berdal, on the other hand, confirms this, and indicates the rôle of the sympathetic terminals in the following lines: "The branches of the penumogastric are destined for the bronchi; the branches of the great sympathetic are lost in the walls of the arteries."

The statement of Sappey that the vagal ramifications of the vagus have no connection with the blood-vessels, introduces a feature of importance which applies to all other organs reviewed, viz.: that besides the vasodilator and vasoconstrictor nerves which govern the function of any organ, there are sensory terminals which, as such, transmit afferent impulses to the centers (primary or subsidiary) which govern the local blood supply. Indeed, we have seen that section of the vagi in the neck caused loss of sensation in the respiratory mucous membrane, paralyzed the bronchial muscles, and gave rise to effusion of

[67] Sappey: *Loc. cit.*, p. 391.

mucus into the bronchi and engorgement of the lungs. How can all these phenomena be accounted for without granting sensory as well as motor and vasomotor functions to the vagal supply? Loss of sensation points to inhibited function, and not to engorgement of the bronchial mucous membrane. And yet we may have engorgement without functional erethism, if it is due, not to the presence of blood fully charged with oxygen, but to blood which, through the very fact of being dammed up in the vascular channels, is reduced therein to practically the condition of venous blood. The effusion of mucus into the bronchi and pulmonary engorgement would occur as normal consequences of such a state of things. But how account for this vascular dilation without granting such attributes to the vagal plexuses?

Again, the fact that cutting of both nerves in the neck gave rise to paralysis of these muscles points to another suggestive feature, namely: that the vagus must *incite* and *govern* the motor impulses to these muscles, besides presiding over the functional variations of caliber of their vessels. If we now add to these manifestations of *efferent* nervous activity those of *afferent* activity suggested by the loss of sensation over the bronchial mucous membrane, it seems clear that *we have in the vagal nerves referred to an autonomous supply especially devoted to the function of the bronchial tubes and their ramifications down to* — but not including — *the pulmonary lobule.* The importance of this fact asserts itself when we realize that it accounts for the complete isolation of bronchial affections from those of the parenchyma, and gives us a clue to their original cause.

My opinion that the vagus—as motor nerve—acts in the lungs as elsewhere, *i.e.*, as stricto-dilator nerve, is sustained by experimental evidence. As Noel Paton writes[68]: "Strong stimulation of the pulmonary branches of one vagus (below the origin of the superior laryngeal) causes the respiration to become more and more rapid, the inspiratory phase being chiefly accentuated. If the stimulus is very strong respirations are

[68] Noel Paton: *Loc. cit.*, p. 292.