stopped in the phase of inspiration. Weak stimuli, on the other hand, may cause inhibition of inspiration.

"Such experiments prove that impulses are constantly traveling from the lungs to the center whereby the rhythmic activity of the center is maintained.

"How do these impulses originate in the lungs? Apparently from their alternate expansion and contraction.

"If the lungs be forcibly inflated—*e.g.*, with a bellows—the inspiration becomes feebler and feebler and finally stops. The nature of the gas, if non-irritant, with which this inflation is carried out is of no consequence. If, on the other hand, the lungs be collapsed by sucking air out of them, the inspiration becomes more and more powerful, and may end in a spasm of the inspiratory muscles.

"This shows that with each expiration a stimulus passes up the vagus which acts upon the inspiratory center to make it discharge. The vagus is thus *a true excito-motor nerve*, making the center act in a reflex manner. With each collapse of the lung the vagus is thrown into action, as the lungs expand it ceases to act, and, as a result, the inspiratory center stops acting, the muscles of inspiration cease to contract, and expiration occurs.

"While ordinary respiration may thus be considered as a rhythmic reflex act, it must not be forgotten that the respiratory center can and does act rhythmically under the influence of the higher center, or a-rhythmically and spasmodically when these as well as the vagi are severed from it."

The mode of action of the vagus as a "true excito-motor nerve" is thus subject in a great measure to the respiratory centers—the main one of which, in the light of my views is located in the neural lobe of the pituitary body. The vagal sensory terminals of the bronchi transmit sensory impulses to this center and excito-motor impulses are transmitted by it to the entire respiratory apparatus, including the thoracic respiratory muscles. The manner in which all these muscles are excited to increased activity by the efferent or excito-motor vagal fibers does not differ from that of all organs reviewed: an excess of blood is admitted into the contractile elements, through dilation of its arterioles. An excess of blood-plasma laden with



oxidizing substance is admitted, as previously shown, to the myosinogen of the muscular elements, where inspiration is in order; hence the fact that strong excitation of the vagus "causes the respiration to become," as Paton says, "more and more rapid, the inspiratory phase being chiefly accentuated." When—physiologically—excessive inspiration is to cease, the sympathetic vasoconstrictors come into play: they restore the muscular arterioles to their normal caliber; less blood is admitted to the muscular elements and the inspirations resume their normal rhythm.

But a third factor must now be taken into account: that represented by the functions of the adrenals. And from the standpoint of the clinician, this factor is by far the most important of all the physiological phenomena of the function of respiration. Indeed as will be shown in the second volume, dyspnœa is often the result of adrenal insufficiency, the adrenal secretion produced being inadequate to sustain the oxygenation of the body at large. Again, Miller, we have seen, refers to the subdivision of the pulmonary artery "which divides quite abruptly, a branch going to each infundibulum"; from the latter "small *arterioles* arise which supply the alveoli," while these on reaching the air-sac are said to culminate in "the rich system of capillaries to which they give rise." If the "small arterioles which supply the alveoli" are abnormally dilated through some general dyscrasia and the stream of venous blood of oxygenation of the adrenal secretion it contains is thus imperfectly exposed to the air, we have a logical explanation of the well known beneficial action of belladonna—a sympathetic stimulant which, as we will see, causes constriction of the arterioles, and of potassium iodide, a powerful adrenal stimulant.

That fluctuations in the secretory activity of the adrenals may provoke dyspnœa is well illustrated by the effects of all drugs that are sufficiently active to markedly affect adrenal functions. The action of venoms even more strikingly shows the morbid connection that exists between variations of suprarenal activity and pulmonary functions, even the stage of blood-disintegration being sometimes reached. Noé,[69] for instance,

[69] Noé: *Loc. cit.*

refers to the many observers who have reported intense respiratory phenomena after cobra-bites. Viper-venom was also found by Phisalix to produce at first "accelerated respiration," then "somnolence, with slowing of respiration." Bee-venom in sufficient quantity gives rise to dyspnœa, according to Paul Bert, *black blood* being found in the vessels. Toad-, salamander-, scorpion-, and eel- venoms were found to affect respiration in a similar manner. Mosso noted that the process of death varied with the dose: medium doses first arrest respiration, then the heart; stronger doses arrest both simultaneously. Paralysis of the motor end-plates had evidently nothing to do with this process, since Mosso found the thoracic nerves responsive to the induced current.

Removal of the adrenals under these conditions should give rise to phenomena similar to a violent dose of venom. Cybulski not only observed,[70] under such conditions, marked dyspnœa, a fall of the vascular pressure to zero, and hæmoglobinuria, but also found that the injection into the veins of an aqueous 10-per-cent. solution of suprarenal extract "immediately caused these phenomena to disappear." Boinet[71] states that after removal of both organs in a large number of rats the respiration became "slow, painful, and difficult." Briefly, the functions of the adrenals are as important features of the respiratory function as any of those generally recognized. It is now possible to understand why the nerve paths of the heat and respiratory centers are so intimately related in the third ventricle. Originating from a common center, the pituitary body, the vagal, sympathetic and adrenal nerves, jointly project from their common source, the pituitary body, to reach, by way of the tuber cinereum, the walls of the third ventricle and the midbrain, the medulla oblongata, where they form subsidiary (and probably coördinating) centers whence the impulses to the respiratory organs are transmitted.

The newer features of the nervo-vascular mechanism of (ordinary tranquil) respiration which I submit in the foregoing pages, pending additional evidence and detail, may be summarized as follows:—

[70] Cybulski: Gazeta Lekarska, March 23, 1895.
[71] Boinet: *Loc. cit.*



*1. The bulbar respiratory center is not, as now believed, the sole, or even the most important, center of this class; it is a subsidiary and, probably, a co-ordinating center.*

*2. The primary and chief respiratory center is located in the pituitary body and consists of three functionally related centers, the adrenal, vagal, and sympathetic centers, which, in turn, are connected by nerve-chains with the corresponding subsidiary centers in the bulb, and govern, through the intermediary of the latter, the respiratory mechanism.*

*The chief respiratory center carries on its functions as follows:—*

*Its adrenal center, by governing the production of the adrenal secretion, which takes up the oxygen of the air and forms the albuminous constituent (96 per cent.) of hæmoglobin, regulates the proportion of this oxidizing substance (the adrenoxidase) supplied to the blood.*

*Its vagal center, acting through the vagus (the intercostals and phrenic) as excito-motor (stricto-dilator) nerves of inspiration, provokes contraction of the muscles which dilate the larynx, the bronchi, and the thorax and depress the diaphragm, and thus increase the intake of air by the lungs,* i.e., *the supply of oxygen from which the adrenal secretion and the hæmoglobin absorb oxygen to distribute it to the tissues.*

*Its sympathetic center, acting, through the sympathetic nervous system, as antagonist of the vagal center to provoke expiration, causes all the above-mentioned respiratory muscles to relax passively (by constricting their arterioles), thus enabling the larynx and bronchi to resume their normal caliber, the thorax to contract, and the diaphragm to rise, in order to insure the expulsion of the expiratory air laden with carbonic acid.*

## THE ADRENAL SYSTEM AND THE KIDNEYS.

The belief that the kidneys are the source of an internal secretion dates back to 1869, when Brown-Séquard showed that injections of renal extract postponed the development of uremia in nephrectomized animals, and prolonged life. Lépine found in addition that a filtrate of a watery extract of kidney caused a rise of temperature and dyspnea. Moreover, Oliver and Schäfer showed in 1898 that a cold-water extract of fresh kidney, when injected intravenously in rabbits, soon produced a more or less marked rise of the blood-pressure. This observation has been sustained by Bingel and Strauss,[72] who isolated the pressor substance and called it "rennin." Conversely, Pearce[73] found that extracts of the kidneys of dogs with experimental uranium and chromium nephritis, prepared at a time when the urine is free of the normally present depressor substance, have no pressor effect. Pearce holds that it is thereby conclusively shown that the dog's kidney does not contain a pressor substance. Yet, so many observers have confirmed the results of Oliver and Schäfer that for the time being, at least, the presence of a pressor substance in the kidney must be regarded as at least probable.

In the light of the data I have adduced, however, none of the above phenomena can be attributed to a renal internal secretion: They represent merely the effects of extracts of adrenal rests contained in renal tissue. Evidence to this effect is submitted in the section on the organotherapy of kidney substance on page 703 of the present volume. The existence of adrenal rests is the recognized source of hypernephromata (see page 129); indeed, Lewandowsky found that the effects obtained from renal venous blood differed in no way from corresponding quantities of venous blood obtained elsewhere in the body. As to the rise of temperature, the elevated blood-pressure, and the dyspnea, they are all typical effects of adrenal extracts. Fuchs and Roth[74] found that adrenalin increased markedly the intake of oxygen and the output of carbon dioxide, while Reichert, Lépine, and Morel noted that adrenal extracts increased the temperature along with the blood-pressure. Oliver and Schäfer not only demonstrated the latter phenomenon, but also the fact that adrenal extracts produced dyspnea and could even arrest respiration. This observation, which was recently confirmed by Langlois and Garrelon, is obviously due to toxic spasm of the respiratory muscles, the precursor of the convulsions witnessed. As to the benefit obtained with renal extracts, they were simply due to the detoxicatory action of the adrenal principle first

[72] Bingel and Strauss: Deut. Archiv für klin. Med., B. xcvi, S. 476, 1909.
[73] Pearce: Archives of Intern. Med., March, 1912.
[74] Fuchs and Roth: Zeitsch. f. Pathol. u. Ther., B. x, p. 187, 1912.



pointed out by Langlois and now generally recognized. On the whole, the following conclusion seems to me warranted.

*No internal secretion of the kidneys exists; all effects of renal extracts witnessed are due to the adrenal principle the kidney normally contains.*

What evidence is available tends to show that the kidneys are closely related functionally with the ductless glands and with the adrenals in particular.

As stated by Howell,[75] "the kidneys receive a rich supply of nerve-fibers," although "most histologists have been unable to trace any connection between these fibers and the epithelial cells of the kidney tubules." Interpreted from my viewpoint such a connection is not in the least necessary, since, as shown by Claude Bernard, the function of an organ is dependent upon the volume of arterial blood circulating through it. My view is fully sustained by the prevailing doctrine, since, as Howell says, the marked effects obtained during purely physiological experiments are "all explicable by the changes produced in the blood-flow through the organ." It becomes a question, therefore, as to how and by what nerves this blood-flow is regulated, for, as stated by Stewart,[76] "increased blood-flow entails increased secretion."

That the vasodilation necessary to the inception of an exacerbation of function—as it is in the submaxillary gland—occurs in the kidney as well as in the organs previously reviewed, is shown by the experiments of Bradford,[77] who found that vasodilator nerves entered the kidney with the vasoconstrictor fibers, and that when the anterior roots of the eleventh, twelfth, and thirteenth dorsal nerve roots were stimulated with induction shocks one second apart, the organ swelled though no sufficiently marked rise of blood-pressure occurred to account for it.

Stewart[78] also states that the presence of dilator fibers for the kidney has been "demonstrated in the splanchnic nerves." That it is these vasodilators which enhance the flow of urine is sustained by the prevailing opinion that true secretory nerves,

[75] Howell: T. B. of Physiol., second edition, p. 763, 1907.
[76] Stewart: *Loc. cit.*, p. 419.
[77] Bradford: Jour. of Physiol., vol. x, p. 358, 1889.
[78] Stewart: *Loc. cit.*, p. 152.

*i.e.*, nerves influencing directly the epithelial elements, are not present in the kidney.

The source of these renal vasodilator nerves is disclosed by the fact that it is only by stimulating the splanchnic that the caliber of the renal arteries is increased. Indeed, Eckhard[79] found that stimulation of the vagi below the diaphragm does not influence the flow of urine. This imposed the conclusion that even the vasodilators of the kidney belong to the sympathetic system. This is confirmed by the researches of Berkley[80] which showed that "the innervation of the kidney is dependent directly upon the great sympathetic; and histologically speaking, it is found that all the nerves of the glands belong to the non-medullated type." Briefly, the vasodilator nerves of the kidney which promote the flow of urine belong to the sympathetic system.

How are the arteries restored to their normal caliber—that compatible with the normal excretion of urine?

In the light of the conclusions submitted in the foregoing pages the kidneys should receive filaments capable of causing constriction of the renal arteries when the excretory activity of the organs is to be decreased. That such is the case has been shown experimentally by many observers. In the dog, the vasoconstrictor nerves leave the cord, according to Stewart, "by the anterior roots of the sixth thoracic to the second lumbar nerves and especially the last three thoracic." Langley[81] observed prompt and great pallor of the kidney and upper part of the ureter on stimulating the first lumbar nerve, and slower, though still great, pallor on stimulating the second lumbar in the cat. As stated by Starling[82] a rise of the general blood-pressure coincides with marked shrinkage of the kidney, so that the effects observed by Langley must be of vasomotor origin. Moreover various toxics known to raise the vascular pressure produce effects similar to stimulation of the renal vasomotor nerves. Thus Sakussow[83] recently found that digitalin in 1 to 1,000,000 solution caused contraction of the renal vessels.

[79] Eckhard: Cited by Starling, Schäfer's "T. B. of Physiol.," vol. i, p. 645.
[80] Berkley: Jour. of Path. and Bact., vol. i, p. 406, 1893.
[81] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 643.
[82] Starling: *Ibid.*, vol. i, p. 645.
[83] Sakussow: Vratch, April 10, 1904.



The same effect was obtained from a 1 to 1,000,000 solution of adrenalin. The latter result accounts for the fact that Bradford[84] obtained renal vasoconstriction by stimulating, besides the nerves included within the above limits, the fourth and fifth thoracic, thus including among those stimulated the fibers which pass to the splanchnic and thence to the kidneys. He found, however, that the most active vasomotor nerves were those of eleventh, twelfth, and thirteenth thoracic. That all these filaments are distributed to the arterioles in the organs has not only been established histologically, but, as stated by Böhm, Davidoff, and Huber,[85] "from the plexuses surrounding the vessels small branches are given off which end on the muscle-cells of the media.

As to the source of the vasoconstrictor fibers, it corresponds with that of the vasoconstrictors supplied to other abdominal organs, the splanchnic. Thus Nollner[86] and others have traced these nerves from the sympathetic chain through the great and small splanchnics to the solar plexus, and thence to a network of fibers lying in the fat between the adrenal and the kidney. Several of the filaments were found by Nollner to enter the latter with the renal artery.

We thus find ourselves in the presence of the surprising fact that both the vasodilator and vasoconstrictor nerves of the kidneys, those which preside over the functions of these organs, are of sympathetic origin. Indeed, as will be shown later, this is a characteristic of the adrenals, these organs and the kidneys working in harmony: the adrenals by supplying, as we have seen, the oxidizing substance of the blood, which takes part, among other functions, in the disintegration or proteolysis of waste-products in order to convert them into eliminable end-products; the kidneys, by insuring the excretion of these end-products from the system.

This accounts for various observations that present knowledge fails to explain. Thus Aubertin and Ambert[87] found concomitant lesions, both on naked eye and microscopical examination, in the adrenals and kidneys in all cases of nephritis

[84] Bradford: Jour. of Physiol., vol. x, p. 358, 1896.
[85] Böhm, Davidoff, and Huber: *Loc. cit.*, p. 335, 1905.
[86] Nollner: Beiträge z. Anat. u. Physiol. v. Eckhard. B. iv, S. 139, 1869.
[87] Aubertin and Ambert: Tribune médicale, p. 119, 1904.

studied by them characterized by high-pulse tension. The latter phenomenon suggests that while an excess of adrenal secretion was being produced—this product and adrenalin causing, as is well known, a marked rise of the vascular tension—the kidneys had also been overworked in these cases, *i.e.*, excessive excretory activity had brought on the nephritis. In other words, marked increased functional activity of the kidneys, as represented by renal vasodilation, should coincide—since the adrenals are simultaneously stimulated—with increased vascular tension. This has been actually observed experimentally by Cavazzani,[88] though unexplained by him. He found that urea caused simultaneously expansion of the kidney—and therefore an increased production of urine—and general vasoconstriction. Puncture of the floor of the fourth ventricle (Bernard's *piqûre*) produces glycosuria through the intermediary of the adrenals, as will be shown elsewhere; a similar puncture also produces, as stated by Stewart, "a copious flow of urine." We need not go beyond common experience to find ample proof of the fact that polyuria is a prominent symptom of diabetes, *i.e.*, that the adrenals and the kidneys work in harmony. The importance of this relationship asserts itself when the obscurity surrounding the question is recalled. Thus referring to polyuria, Hensell, Well, and Jelliffe[89] mention their observation that "it is common to two diseases—diabetes mellitus and chronic interstitial nephritis—but in either case a clear explanation of this symptom does not exist."

Pending additional evidence to this effect the following conclusions as to the functions of the kidney appear to us warranted:—

*1. When the flow of urine is to be increased, the renal arterioles are dilated by vasodilator terminals of the sympathetic which reach the organ by way of the splanchnic nerves and the semilunar ganglia. The glomerular tufts being thus traversed by a greater volume of blood the components of urine are thus filtered out into Bowman's capsule.*

*2. When the flow of urine is to be decreased the same arterioles are reduced to their normal caliber by the vasoconstrictor*

[88] Cavazzani: Arch. ital. de biol., vol. xviii, p. 158.

[89] Hensel, Well, and Jelliffe: "The Urine and Fæces," 1905.



*filaments of the sympathetic which reach the kidneys also by way of the splanchnic nerves.*

*3. The adrenals and the kidneys are functionally united, the adrenals contributing by their secretion to the conversion of waste-products into end-products which the kidneys excrete with the urine.*

With the functions of the kidneys as complemental to those of the adrenals, what we have termed the "adrenal system" acquires greater importance in the vital functions of the organism as a whole: it supplies the body the substances which sustain oxygenation and metabolism, but provides also for the elimination of end-products of catabolism and other wastes. By "substances" here are meant both the adrenal and thyroid secretions. The former of these, by becoming oxygenized in the lungs, constitutes the oxidizing substance of the blood, *i.e.*, the albuminous portion of its hæmoglobin; the thyroid secretion as previously stated, and as will be shown, enhances the vulnerability of all tissues to oxidation, including the adrenal center in the pituitary body.

As to the functional relationship between all these organs, they may be briefly summarized as follows, pending additional evidence:—

*The pituitary body contains a center which governs the functional activity of the adrenal system and of the kidneys. Any excitation of this center by certain toxics that may occur in the blood increases the functional activity of the organs of this system; the adrenals and thyroid apparatus, and also the kidneys, and, therefore, general metabolism and renal excretion.*

The importance of this functional combination is self-evident. *While the adrenal system sustains metabolism, the kidneys, governed by the same center, can eliminate the waste products formed in the course of this process uninterruptedly as they appear in the blood.*

## THE ADRENAL SYSTEM AND THE GENERATIVE GLANDS.

TESTICLES.—Leydig showed in 1850 that the interlobular connective tissue of the testicle contained epithelial cells. All evidence available tends to show that, in accord with the conclusions of Regaud and Policard,[90] confirmed repeatedly by other observers, these cells, which are situated between the seminiferous tubules, are the source of the internal secretion which endows the body with the male characteristics. The Leydig cells are functionally united with the sperm-cells, and, as shown by Regaud and others, undergo considerable development prior to spermatogenesis. Besides this functional connection with the latter process, their secretion is supplied to the organism at large, through the intermediary of the lymph- or blood- vessels.

The influence of the internal secretion of the cells of Leydig on the body at large is well shown by the influence of early removal of the testes, *i.e.*, castration. A tendency to obesity of a feminine type, due to slowed catabolism of fats, scantiness of hair, deficient development of the thorax, pelvis, and larynx, the voice remaining high pitched as in the child. The muscles lose their tone and the prostate and vesiculæ seminales fail to develop, the bones of the extremities, however, growing abnormally long. The mental attributes of the male sex are also lacking; while the intelligence may be normal, there is absence of aggressiveness and initiative and intellection is slow. As stated by Schaefer,[91] "the effects are mainly upon metabolism, although the limit of assimilation of carbohydrates is lowered."

While the effects of castration on man and the lower animals are well known, the manner in which they are produced has remained obscure. Analysis of the question has led me[92] to suggest that the testicles did not produce a true internal secretion, but that the adrenal rests (interrenal tissue) which they contain contribute to the elaboration of the sperm; and, moreover, that when *through sexual abstention the secretion is unused, it is taken up by the circulation and distributed throughout the body, producing the effects of the adrenal secretion (in organic combination) upon the tissues at large.*

The presence of interrenal tissue or adrenal rests in the testicle is well known. Wiesel[93] found it imbedded in both the testicular tissue and in the paradidymis. These correspond with the cortical portion of the adrenals, the cytoplasm of the inter-

[90] Regaud and Policard: C.-r. de la Soc. de Biologie, April, 1901.
[91] Schaefer: "Lane Medical Lectures," p. 988, 1913.
[92] Sajous: New York Med. Jour., Sept. 4, 1909.
[93] Wiesel: Sitzamgsberichte d. k. Akad. z. Wien, S. 108, 1899.



stitial cells containing also the lipoid granules, blackened by osmic acid (Schaefer[94]), and also, according to Reinke,[95] crystals the nature of which is unknown. The medullary portion of the adrenals is also represented as a constituent evidently of the seminiferous tubules or sperm-cells, since spermin (isolated by Poehl) gives the reaction, chemical and physiological, of adrenalin. Thus spermin was identified by Poehl as an oxidizing body, acting catalytically, a property I had attributed to the adrenal principle. As is the case with the latter also, spermin resists heat 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. It likewise raises the blood-pressure, slows the heart, and produces all other physiological effects peculiar to the adrenal principle. 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. As does adrenalin, it produces quickening of the respiration, while large quantities inhibit it, as shown by Dixon, Langlois, and others.

Its independence of any connection with sex characteristics is shown by the fact that it has been found in the blood of females as well as in that of males.

Additional testimony is afforded by the fact that while, as stated by Hansemann,[96] "the cells of Leydig are concerned in the production of testicular tumor," the characteristic effects of such tumors on the organism at large are precisely those produced by a tumor of the adrenal cortex, or of adrenal rests in the kidney, which represent 17 per cent. of the tumors of this organ. These tumors, as we have seen under a previous heading, cause in children abnormal sexual and physical development, with marked increase of strength, abnormal growth of hair over the pubis, axillæ, legs, and trunk, lowering of the voice,—an aggregate of anomalies which cause a child of 5 years, for instance, to be transformed into a young adult in weight, strength, sexual development, etc. (See the illustration on next page.) Now, as to the testicular growths Schaefer[97] writes: "Remarkable cases

[94] Schaefer: *Loc. cit.*, p. 88.
[95] Reinke: Archiv f. mik. Anat., B. 42, 1896.
[96] Hansemann: Cited by Biedl, "Internal Secretory Organs," p. 398, 1913.
[97] Schaefer: *Loc. cit.*, p. 90.