THE PITUITARY BODY AS THE GOVERNING CENTER OF THE ADRENALS, AND AS THE THERMOGENIC AND RESPIRATORY CENTER.

In the first volume, I pointed out that the pituitary body contained the adrenal center. The importance of this conclusion is apparent in view of the fact that the adrenals are the source of the secretion which, in the lungs, becomes adrenoxidase. This is further emphasized by the relationship of the pituitary body, as heat center, with the function of oxygenation. We saw in the preceding section, that the supposed heat "centers" found by Ott and others in the floor of the third ventricle were in reality not centers, and that the effects produced were due to irritation of the nerve-paths from the pituitary body which reached the spinal cord by way of the basal tissues.

In the preceding section, it was shown also that the sensory and motor nerves to and from the pituitary body were connected with the mass of gray matter overlying the infundibular opening in the floor of the third ventricle, the giant-celled supra-infundibular nucleus, and that the sympathetic nerve-paths took this route. A suggestive feature asserts itself in this connection: While these motor paths (which, as shown by the researches of comparative anatomists, especially Edinger, are probably present in all vertebrates) correspond clearly with those observed histologically by Ramon y Cajal, the fibers which Gentès traced from the neural or posterior lobe of the pituitary to the tuber cinereum in the floor of the third ventricle, and which Andriezen traced directly from the pituitary to the neighborhood of the pons, were not involved in these functions, and have remained, as it were, without occupation. Now, the fibers traced by Gentès are precisely those derived indirectly from the sensitive cells (similar to those of the olfactory area) which this investigator found in the partition between the two lobes of the pituitary, and which area I assimilate to the test-organ of mollusks, the lower chordata, etc.

That the fibers from the test-organ form part of the nerve-chain which terminates in the adrenals, is suggested also by the fact that it is also among its fibers in the tuber cinereum that

punctures—from below by way of the mouth as well as from above—were found by Ott, and others after him, to cause a marked rise of temperature. With the adrenals as the source of the secretion which, converted into adrenoxidase, supplies the entire organism with oxygen, and a direct nerve-path from the "test-organ" of the pituitary, by way of the floor of the third ventricle and the cord, to the adrenals, we have a self-evident mechanism to explain an obscure function, *i.e.*, the manner in which the temperature is raised.

Another important function is linked intimately with this mechanism, viz., that of *respiratory* center. Soury,[143] quoting Ott, states that "the gray substance of the anterior portion of the floor of the third ventricle" (immediately above the pituitary body) is "identical with the thermo-polypnœic center" and that "removal of this center diminishes the number of respiratory movements." Ott therefore regards the tuber cinereum as a "center of polypnœa and *thermo*taxis." In view of the foregoing facts, this points not only to the "test-organs" as the thermogenic or "heat" center, but also as the *polypnœic* or *respiratory* center, and, moreover, to the tuber cinereum as the bed for the nerve-paths from these centers to the pons and medulla. This adds testimony as to the functional connection between the pituitary body and the adrenals, since it is the secretion of the latter which, as adrenoxidase, supplies oxygen to the entire organism.

The rôle of the respiratory center involves, however, a concomitant influence upon the large array of inspiratory and expiratory muscles (chest, diaphragm, abdomen, etc.) which carry on their functions rhythmically without voluntary control. We have seen in the preceding section that the posterior lobe of the pituitary, in which the thermogenic fibers arise, is also the origin of the nerve-chains that govern muscular activity. In most text-books the respiratory center is said to be located in the medulla near the vasomotor center. As Howell[144] says, however, "the region has been delimited by vivisection experiments only" and "no especial group of cells can be found in this region sufficiently separated anatomically to make it probable

[143] Soury: *Loc. cit.*, vol. ii, p. 1256.
[144] Howell: "T. B. of Physiol., p. 611, 1905.

that they constitute the center in question." This cannot be said of the posterior pituitary body. Not only does it present all the attributes of a highly differentiated co-ordinating organ, such as the presence of various centers closely connected functionally requires, but its removal (with the anterior lobe) is followed, as we have seen, by marked muscular relaxation, dyspnœa and hypothermia.

The adrenals thus represent the normal terminal of a nerve-chain which begins in the "test-organ," passes thence by way of the neural lobe of the pituitary to the tuber cinereum and then to the ponto-medullar region. Here, a continuation of this path is evidently present, for Reichert[145] refers to a "pontobulbar *thermo*augmentor center," the presence of which in this location he determined experimentally. What is the course of the adrenal nerve-path from this region to the adrenals?

Goltz and Ewald[146] have shown that an animal from which the entire spinal cord below the bulb had been removed—thus leaving intact all the cranial nerves and the basal structures, including the pituitary body—could live several years. Soon after the operation the vessels recover their tonicity and the circulation becomes practically normal. Yet there occurs a curious phenomenon which continues several weeks: the animal is in constant danger of death from *cold* unless it be kept in a superheated medium. Goltz emphasized another striking feature, *i.e.*, the occurrence of marked trophic bilateral lesions of the skin when, in gradually shortening the cord from below, in successive operations, he reached the upper *dorsal* vertebra. These two features suggest that the upper part of the cord is of great functional importance in thermogenesis and nutrition. Claude Bernard[147] had shown many years before that transection of the cord in the upper dorsal region could bring the rectal temperature down 16° C. (28.8° F.) in five hours. Indeed, Pochoy[148] found that a section in this region brought the rectal temperature down over 22° C. (41.6° F.) in twenty-four hours in guinea-pigs and that it continued to decline until

[145] Reichert: Jour. Amer. Med. Assoc., Jan. 18, 1902.
[146] Goltz and Ewald: Archiv f. d. ges. Physiol., Bd. lxiii, pp. 362, 400, 1896.
[147] Claude Bernard: "Leçons sur la chaleur animale," p. 161, 1876.
[148] Pochoy: Thèse de Paris, 1870.

death ensued. It is evident, therefore, that division of the upper dorsal cord seriously invalidates the thermogenic apparatus.

The truth of this is emphasized by the fact that transection of the cord lower down causes only temporary torpor of the automatic functions. "If we wait for a time," says Stewart,[149] "we shall find that this torpor of the *lower dorsal* and lumbar cord is far from giving a true picture of its normal state; that, cut off as it is from the influence of the brain, it is still endowed with marvelous powers. If we wait long enough, we shall see that, although voluntary motion never returns, reflex movements of the hind-limbs, complex and co-ordinated to a high degree, are readily induced. Vasomotor tone comes back. The functions of defecation and micturition are normally performed." As I will show below, this is due to the fact that the nerves to the adrenals are not included in the portion of the cord separated from the centers. The subsidiary vasomotor centers in the lower or separated segment of the cord being nourished and oxygenized as usual after the shock of the operation has passed and when a collateral circulation is reëstablished, the vasomotor functions are resumed. This explains also why the process of repair proceeds unfailingly, whereas section in the upper portion of the cord, unless great precautions are taken, follows a lethal course.

Ott[150] states that "destruction of the spinal cord from the *fifth dorsal* vertebra down permits the animal to generate *as much heat as before* the operation." This harmonizes with my own conception of the process: below this level, the only morbid phenomenon connected with the circulation which can be caused is vasodilatation; hence the comparatively benign results. Above it, however, the transection involves not only the vasomotor supply, but, also, the "thermogenic" nerves, *i.e.*, those to the adrenals. It follows that these nerves constitute an autonomous path, one totally independent of the vasomotor path. Now this has repeatedly misled physiologists. Overlooking the presence of this independent thermogenic nerve, they have ascribed to vasomotor influence, vasoconstrictor phenomena that were due

[149] Stewart: *Loc. cit.*, p. 694.
[150] Ott: *Loc. cit.*, p. 348.

to stimulation of the adrenals, the secretion of which, as is well known, causes a rise of the blood-pressure. "Hardly any other agent will produce such an enormous increase of pressure," writes Schäfer,[151] referring to injections of adrenal extract after division of the vagi, "except direct stimulation of the vasomotor center."

Moreover a *dual effect* is produced when this part of the path or its branches are stimulated which does not occur when the influence of the adrenals is removed. Thus, François-Franck and Hallion[152] have shown that the vasomotor nerves of the liver leave the spinal cord by the rami *below* the fifth, *i.e.*, the sixth down to the second lumbar. These limits have been confirmed by Langley.[153] The former physiologists remark, however, that "centrifugal excitation of the *vertebral* nerve (composed of four or five of the lower cervical nerves) after section of the upper rami communicantes (from the *first* to the *fifth*) *no longer* produces hepatic vasoconstriction"—a statement which implies that stimulation of the vertebral nerve *does* produce hepatic vasoconstriction. The manner in which this effect is brought about, François-Franck and Hallion were unable to explain, however; they ascribed them therefore, to "reflex action" or to some *unexplained "indirect influence."* This influence, interpreted from my standpoint, is that of the adrenals.

The mode of action of the adrenal secretion, in the light of the facts submitted in the first chapter, is, of course, indirect, in the sense that it is first of all converted into adrenoxidase. This latter substance being the activating agent in all metabolic processes, an excess in the blood enhances its oxygenizing power in proportion. When such blood is supplied to the arteries and veins by their vasa vasorum, their muscular elements are abnormally stimulated and contract, reducing the caliber of the vessels.

The thermogenic fibers proceeding no further down the cord, as shown by Ott's experiment, than the fifth dorsal vertebra, this "unexplained indirect influence," *i.e.*, overactivity of the adrenals, should occur when the upper five dorsal nerves (which pass to the sympathetic cord of ganglia) are stimulated.

[151] Schäfer: "T. B. of Physiol.," vol. i, p. 955, 1898.
[152] François-Franck and Hallion: Arch. de physiol., T. viii, No. 5, p. 936, 1896.
[153] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 644, 1900.

François-Franck and Hallion found that stimulation of the sympathetic chain where, they state, *"it has not as yet received from the spinal cord the hepatic vasoconstrictor rami"* caused "a marked rise of aortic pressure." Even more striking is the effect produced when the sympathetic cord had been *isolated* by dividing the rami containing the *hepatic vasomotor nerves.* This caused, as stated by these physiologists and as shown by their tracings, "the *maximum vasomotor effect.*" Obviously, the upper portion of the sympathetic chain was capable of causing, irrespective of any vasomotor influence, a very marked increase of vascular tension in the liver—an effect due to the general rise of blood-pressure caused by the excessive adrenal secretion, *i.e.*, adrenoxidase, produced.

What is the identity of the nerves which, out of the five upper dorsal nerves, produce this effect by transmitting centric impulses to the adrenals?

These impulses doubtless pass to the sympathetic chain through more than one ramus. Thus, François-Franck and Hallion state: "Division of the upper root was followed by marked reduction of the vasoconstrictor effect," but they do not refer to the specific influence of the four remaining rami. Fortunately, however, this gap is filled by the experiments of Biedl to which reference was made in a previous chapter.[154]

We have seen that it was on stimulating the peripheral end of the cut splanchnic that he increased the secretory activity of the adrenals, a result confirmed by Dreyer. Biedl thus showed that the splanchnic contained the secretory nerves of the adrenals. In order to ascertain, if possible, whether these organs contained vasomotor nerves also, he exposed and divided all the spinal roots from the *third* thoracic to the third lumbar, and stimulated both their anterior and posterior segments "with a strong induction current." Not only did he not observe vasoconstrictor effects, in the adrenals, but he failed to obtain any evidence of overactivity of these organs, *i.e.*, an increased blood-flow through them. This experiment—which Biedl repeated three times, always with the same result—indicates that the secretory nerves to the adrenals do not originate in the spinal cord up to the third thoracic.

[154] *Cf.* this vol., p. 810.

This gives us the identity of the path to the adrenals. Inasmuch as François-Franck and Hallion markedly reduced the "maximum vasomotor effects" (so-called) observed by them, by dividing the first thoracic ramus, a part of these effects remains unaccounted for. This is supplied by Biedl's experiment since it left, as the only ramus to supply this want, the second. This points to the *first* and *second dorsal rami* as the paths of the thermogenic fibers to the sympathetic chain and thence to the greater splanchnic.

Additional experiments suggest, however, that the third thoracic ramus likewise contains fibers to the adrenals and that Biedl did not detect them because impulses through a single bundle were inadequate to satisfy the needs of a process carried on normally through three sets. Thus precisely as François-Franck and Hallion obtained hepatic (so-called) "vasomotor" effects by stimulating the sympathetic chain *above* the course of the liver's true vasomotor nerves, so have Bulgak, Schäfer and Moore and Bunch obtained "vasomotor" effects in various organs from the third thoracic nerve, among others, though their normal vasomotor paths are lower down. Bunch,[155] for example, had established the limits of the innervation of the small intestine from the sixth thoracic and fifth lumbar, inclusive. Later, however,[156] he likewise obtained "vasomotor" effects in the small intestine by stimulating the upper thoracic nerves from the second down. Langley,[157] referring to these results, expresses his belief that the origin of these nerves is less extensive and that the uppermost nerve to send fibers to the solar ganglia is the *fourth* or fifth thoracic. Yet, we cannot doubt that the above-named physiologists, including Bunch, obtained "vasomotor" effects by stimulating nerves above the fourth thoracic: but only through the intermediary of the adrenals.

Indeed, a nerve-path is present in the sympathetic chain which is *distinct* from the true vasomotor, and which extends to the upper thoracic limit of the sympathetic chain. Quain,[158] for instance, states that some fibers of the splanchnic's higher roots "may be traced upward in the sympathetic cord as far as

[155] Bunch: Jour. of Physiol., vol. xxii, p. 357, 1898.
[156] Bunch: *Ibid.*, vol. xxiv, p. 72, 1899.
[157] Langley: Schäfer's "T. B. of Physiol.," vol. ii. pp. 644 and 695, 1900.
[158] Quain: "Anatomy," seventh edition, vol. ii, 1867.

the *first* and *second* thoracic ganglia. Gray[159] gives the same limits. Cruveilhier[160] says that these filaments "are merely *in contact* with the sympathetic."

Proof that the adrenal secretion can produce vasomotor effects may also be furnished by showing that in the parts influenced, the small intestine, for instance, there are, as in the case of the liver, two distinct forms of vasoconstriction, one due to vasomotor nerves and the other to the local action of adrenoxidase, and that when one is removed the other persists. Intestinal inhibition affords evidence of this dual action. We have seen that "inhibition" is merely excessive vasoconstriction. Now, Schiff, Ludwig and Kupffer, Bechterew and Mislawsky (Starling[161]) have observed both a motor effect (increased peristalis) sometimes, and inhibition at others. Bunch has also shown that stimulation of the splanchnic could cause increased intestinal activity and at other times inhibition. "Jacobi," says Starling, in a review of the subject, "states that the intestinal inhibitory fibers of the splanchnics take a different course from the vasomotor fibers, and that section of the nerves running from the *suprarenals* to the solar plexus *annuls* the inhibitory action of the splanchnics *without affecting their vasoconstrictor effect*." Suppression of the adrenal influence in this experiment obviously prevented excessive vasoconstriction.

It is evident, therefore, that the *first, second* and *third* thoracic nerves—the three *above* the uppermost limit set by Langley for sympathetic vasomotor fibers which run to the solar plexus—constitute a separate path, the secretory nerves to the adrenals.

Having attributed to the pituitary the rôle of "heat" center, owing to a nervous connection with the adrenals, and the presence of such a connection having now been shown to exist, the adrenal secretion should be capable of raising the temperature when in excess (as adrenoxidase) in the blood. This is a recognized effect of adrenal extractives. Thus Oliver and Schäfer[162] observed under its effects "slight *transitory* disturbance of the rate of the heart beats, of the respiration, and of the

[159] Gray: "Anatomy," fifteenth edition, 1901.
[160] Cruveilhier: "Anatomy," Amer. edition, 1844.
[161] Starling: Schäfer's "T. B. of Physiol.," vol. ii, p. 313, 1900.
[162] Oliver and Schäfer: Jour. of Physiol., vol. xviii, p. 230, 1895.

body temperature." Pellacani,[163] Foà[164] and other physiologists have likewise observed, besides the characteristic effects, a rise of temperature. E. T. Reichert[165] noted that among other effects an intravenous injection of 0.0005 gramme adrenalin caused "an increase of general metabolism and body temperature." His experiments showed that "the pulse and arterial pressure are the first to be affected, then the respiratory movements, and then general metabolism and body temperature." This is a suggestive sequence when we consider that the adrenal secretion, after absorbing oxygen in the lungs, becomes, as I have shown, the body's oxygenizing principle. Conversely, we have seen that removal of the adrenals, precisely as is the case when the pituitary body is destroyed, is followed by a steady decline of the temperature until death occurs.

Finally, blocking of the vessels which carry the adrenal secretion to the inferior vena cava not only causes a marked decline of the blood-pressure by decreasing the activity of the metabolic exchanges in the vascular walls, but it arrests also all oxidation processes, *i.e.*, life itself. Thus Strehl and Weiss[166] found that after removing one adrenal, the blood-pressure could be lowered by clamping the suprarenal vein of the remaining organ, thus depriving the blood of any adrenal secretion, and that by releasing this vein the blood-pressure was soon restored to its previous level. When the second adrenal was also removed, the blood-pressure at once fell 20 to 30 mm. Hg., and continued to fall slowly until death ensued.

This explains why Gray,[167] alluding to the suprarenal plexus, remarks: "The branches of this plexus are remarkable for their large size in comparison with the size of the organ they supply." The function they govern through the adrenals, as I have now shown, is one of the most important of the organism.

That there exists a functional relationship between the pituitary and the adrenals is shown also by the pathology and symptomatology of various disorders in which the pituitary is either implicated or the seat of primary lesions.

[163] Pellacani: Archiv per le scienze med., vol. iii, No. 24, 1879..
[164] Foà: *Ibid.*, vol. iv, p. 451, 1880.
[165] E. T. Reichert: Univ. of Penna. Med. Bull., Apr., 1901.
[166] Strehl and Weiss: Pflüger's Archiv, Bd. lxxxvi, S. 107, 1901.
[167] Gray: "Anatomy," fifteenth edition, p. 808, 1901.

In *Addison's disease*, the lesions are usually situated in the adrenals or in the nervous connections of these organs; and yet the phenomena witnessed are the counterpart, so to say, of those that attend destructive disorders of the pituitary. Thus Schäfer[168] states that the symptoms that follow removal of the pituitary body are "(1) diminution of the body temperature; (2) anorexia and lassitude; (3) muscular twitchings and tremors, developing later into spasms; (4) dyspnœa"—the list, we have seen, of phenomena that follow removal of the adrenals. Again, Harlow Brooks,[169] referring to the cachectic stage of acromegaly, states that "a general brownish pigmentation is present in the average case which at times strongly resembles that found in Addison's disease." E. Wasdin,[170] in a case of fracture of the maxillary and sphenoid implicating destruction and gangrene of the pituitary body, verified after death, observed among other symptoms, bronzing of the skin.

The extreme muscular weakness following removal of the pituitary to which Schäfer refers was also witnessed, as we have seen, by many other physiologists, the "ataxia being complete" in Masay's dogs. A similar condition follows the removal of the adrenals. Thus, Brown-Séquard called attention to the "progressive paralysis" which followed this procedure. Abelous and Langlois[171] observed the same effects in frogs, the paralysis beginning in the lower limbs and spreading anteriorly. Boinet[172] noted the same symptom in fifty-nine rats; the movements became slow, then impossible. Several other investigators have also referred to this symptom.

Tracing the pathological changes found in this disease outside of the adrenals, the semilunar ganglia are the first to appear. These structures, as is well known, are often found congested, caseous, sclerosed, etc. Now, removal of these ganglia, as stated by Rolleston,[173] is followed by "rapid emaciation, asthenia, low temperature, diminution of the amount of urea in the urine." These are all subjective symptoms of Addison's disease; while the reduced urea output points to reduced

[168] Schäfer: *Loc. cit.*, vol. i, p. 946.
[169] Harlow Brooks: Archives of Neurol. and Psychol., vol. i, p. 485, 1898.
[170] E. Wasdin: Monthly Cyclop. of Pract. Med., Mar., 1903.
[171] Abelous and Langlois: Archives de physiol. norm. et path., 5 Série, vol. iv, p. 269, 1892.
[172] Boinet: Marseille méd., Sept. 1, 1899.
[173] Rolleston: Allbutt's "Practice of Medicine," vol. v, p. 540 ,1897.

metabolism, *i.e.*, lowered oxygenation. The path thence to the cord, the splanchnic nerves, may be found to contain degenerated fibers. Jürgens[174] even goes so far as to state that gray degeneration is always present in the splanchnic in true cases of Addison's disease. What he found was doubtless broken-down chromaffin cells, first described by Henle in 1865, as constituents of the adrenals, but which subsequent observers found also in the ganglia adjoining the adrenals in birds (Rabl),[175] in the splanchnic nerves of amphibia and reptiles (Zellnester),[176] in the ganglia of the sympathetic chain (Kose),[177] and which, as shown recently by Wiesel,[178] are destroyed in Addison's disease. Tizzoni,[179] Kalendero and Babès,[180] and many others have found spinal lesions, a fact confirmed experimentally by Alezais and Arnaud,[181] who found ascending degeneration of the lateral columns of the cord in animals that had survived sufficiently long removal of the adrenals. Even the pituitary body may show lesions. Thus Pansini and Benenati,[182] in a typical case of Addison's disease in which the whole cutaneous surface was a deep bronze color, found both adrenals in a state of caseous degeneration and the pituitary body markedly enlarged. This hypertrophy, verified microscopically, is readily accounted for when the organ is considered as the governing center of the adrenals: it was the result of overactivity, having for its purpose to enhance the secretory activity of what remained of the diseased adrenals, in order to sustain as long as possible the oxidation processes of the organism at large.

Briefly, removal of the pituitary body not only produces symptoms similar to those that attend Addison's disease or follow removal of the adrenals, but when ascending degeneration occurs in Addison's disease, it proceeds along the nerve-paths that unite the adrenals to the pituitary body.

Acromegaly is another disease which emphasizes the functional relationship between the pituitary body and the adrenals. It is especially interesting in this connection because its initial lesion occurs in the anterior lobe, that to which the test-organ (though forming part of the partition) really belongs. Thus, while Massolongo[183] ascribed acromegaly to hyperactivity of this organ, Tamburini[184] identified as cases of true acromegaly only those characterized by hypertrophy and over-activity of the anterior lobe. This was confirmed by Harlow Brooks[185] in a study limited to cases in which the pituitary had been examined microscopically, who found in every instance reported, save one, that the enlargement of the organ had been confined to the anterior lobe.

[174] Jürgens: Deut. med. Woch., Bd. xi, S. 153, 1885; Berl. klin. Woch., Bd. xxi, S. 824, 1884.
[175] Rabl: Archiv f. mikrosk. Anat., Bd. xxxviii, S. 492, 1891.
[176] Zellnester: Sitzungsb. d. Kais. Akad. v. Wien, Bd. lxvi, Abth. i, S. 121, 1872.
[177] Kose: Anat. Anzeiger, Bd. xxii, S. 162, 1902.
[178] Wiesel: Zeit. f. Heilkunde, Bd. xxiv, S. 257, 1903.
[179] Tizzoni: Mem. della R. Acc. dell Scienze, Bologna, ser iv, T. ix, p. 27; London Med. Recorder, Feb. 20, 1890.
[180] Kalendero and Babès: La Semaine médicale, Feb. 22, 1889.
[181] Alezais and Arnaud: Revue de méd., vol. ii, p. 283, 1891.
[182] Pansini and Benenati: Il Policlinico, Apr. and May, 1902.

With the test-organ of this lobe directly connected by nerve-paths with the adrenals, and the latter as the source of the secretion which becomes adrenoxidase and sustains tissue metabolism, and therefore nutrition, we have a normal explanation of the underlying cause of the disease, *i.e.*, hypernutrition. This feature—though unexplained so far—has in fact formed the basis of most theories as to the pathogenesis of the disease. Dallemagne,[186] for instance, ascribes it to the presence of trophic centers in various parts of the nervous system. Von Recklinghausen[187] considered acromegaly as a trophic neurosis dependent upon auto-intoxication. Mossé looked upon the disease as a trophic neurosis of vasomotor origin. Klebs[189] ascribed it to over-development of the vascular system combined with thymic hyperactivity, etc. The effects of overnutrition are shown with especial clearness in the acromegalic giants, in which the overgrowth is widespread instead of being restricted to the bones.

The familiar vascular lesions of the disease also indicate that overactivity of the adrenals—due to morbid stimulation by the test-organ—is a prominent feature of the disease. In a case reported by Harlow Brooks,[190] the posterior pituitary was found normal on microscopical examination. Its connection

[183] Massolongo: Riforma Med.,. vol. viii, p. 10, 1892, and Centralbl. f. Nervenh., Bd. xviii, S. 281, 1895.
[184] Tamburini: Rivista sper. di fren., p. 559, 1894, and 414, 1895.
[185] Harlow Brooks: *Loc. cit.*
[186] Dallemagne: Arch. de méd. exp., T. vii, p. 589, 1895.
[187] Von Recklinghausen: Arch. f. path. Anat., Bd. cxix, S. 36, 1890.
[188] Mossé: Mercredi médical, Sept. 11, 1895.
[189] Klebs: "Allgemeine Pathologie," Bd. ii, 1889.
[190] Harlow Brooks: *Loc. cit.*