Therapeutics.—All the disorders—*diphtheria, tetanus* and others—in which antitoxins are indicated being infections, it is perhaps needless to state that the physiological action I describe in the foregoing pages accounts clearly for the beneficial effects obtained.

Another feature upon which some stress must be laid is that the physiological action of the antitoxins, as I interpret it, is identical with that provoked by the various drugs described in the present chapter—each of which likewise introduces its own array of evidence. *If,* therefore, *we grant life-saving properties to antitoxin*—which is undoubtedly the case in so far as diphtheria antitoxin is concerned—*we must concede the same value to drugs which are capable of evoking in the blood the formation of the same substance, i.e., auto-antitoxin.*

CHAPTER XIX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*).

THE SYMPATHETIC CONSTRICTORS AND THE CRANIAL STRICTO-DILATORS IN ORGANIC FUNCTION.

We have seen in the sixteenth chapter that the sympathetic system is autonomous as a functional entity, and that its governing center is located in the posterior pituitary, with the centers of motor nerves.

According to prevailing teachings, the sympathetic carries on several different functions. In a succinct review of the subject, W. S. Hall[1] states, for example, that the "more important functions" of the sympathetic system are the following: "(*a*) cardio*acceleration* and cardio*augmentation* through the branches from the cervical ganglia. (*b*) *Secretory* impulses to the salivary glands, the stomach, the pancreas, the liver, the small intestine, the large intestine, the kidneys. (*c*) *Vasomotor* impulses, *both constrictor and dilator,* to all arteries and arterioles. (*d*) *Motor* impulses to the *muscular coats* of the stomach and intestines, causing peristalsis and controlling the pylorus and the cardia of the stomach. (*e*) *Motor* impulses to the *muscularis mucosa* of the alimentary canal, causing movements of the mucosa."

Another function ascribed by physiologists to the sympathetic, is that of *inhibition.* In the heart, as is well known, this is believed to be the physiological function which counteracts cardiac acceleration; in the intestine it is thought by some to oppose peristalsis; it is also believed by many to inhibit the contraction of certain vessels, etc. As this inhibition is produced by stimulating the sympathetic nerves distributed to these various organs, we are brought to the conclusion, in view of the fact that a sympathetic nerve can awaken function by causing vasodilation, that it can also inhibit that

[1] Hall: *Loc. cit.,* p. 106, 1905.

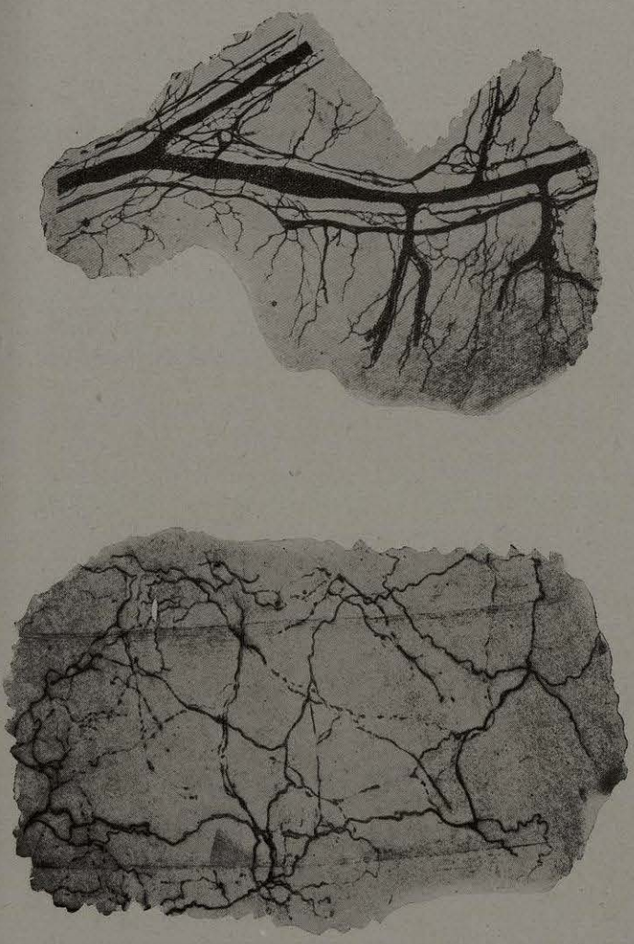
function by causing vasocontriction, or, in other words, that a sympathetic nerve can inhibit its own functions.

That the whole scheme of sympathetic function, as now interpreted, is defective, appears to me very evident. Howell[2] rightly states that "few subjects in physiology are of more practical importance to the physician than that of vasomotor regulation; it plays such a large and constant part in the normal activity of the various organs." So great is this importance, in fact, that it is mainly because the whole question of vasomotor function has been obscured by the problematic rôles ascribed to it by physiologists, that the physiological action of drugs, and what Virchow has termed "physiologic pathology" have remained so obscure.

In the sixteenth chapter, I pointed out that the bulbar vasoconstrictor center was independent of sympathetic vasoconstrictor functions, and that it acted only as intermediary for the transmission of sympathetic impulses down the cord. The source of these impulses was shown to be the pituitary body, stimulation of which, as then shown, caused typical sympathetic vasoconstriction in the periphery and a marked general rise of the blood-pressure, owing to the resistance of the constricted arterioles to the general circulation. These and other facts led me to the conclusion that the neural or posterior lobe of the pituitary body was the seat of the *sympathetic center*. Returning to the confusing functions referred to above, it will now become evident that they are all experimental myths, and that the one function which the sympathetic fulfills—the only one fully sustained by experimental evidence—is that of a *vasoconstrictor of all the small arteries or arterioles.*

Inhibition, in the accepted sense, *i.e.*, a restraint of functional activity, has already imposed itself upon us in the preceding chapter, where we saw certain toxins and drugs cause excessive constriction of the vessels of the pituitary body and heart. That such vasoconstriction, whether produced by the latter or by too strong a current, must correspondingly reduce the caliber of a vessel and reduce the volume of blood passing through it is obvious. We have seen that, as shown by Brown-Séquard and Porter, the caliber of the coronaries can be

[2] Howell: *Loc. cit.*, p. 531, 1905.



VASOMOTOR NERVES OF THE CARDIAC CORONARIES. *[Heymans and Demoor.]*

actively reduced by stimulating the vagal vasomotor nerves, the origin of which I[3] traced to the vasomotor center. Physiological text-books, notwithstanding the evidence submitted by the above-named investigators and myself, still teach that the coronaries are deprived of vasomotor nerves; the plate reproduced herewith must convince them of their error, since it is a microphotograph of coronaries showing unmistakably the presence of these nerves, published over twelve years ago by Heymans and Demoor.[4]

The manner in which the heart is influenced plainly shows that inhibition is due merely to deficiency of blood in the myocardium. Hill[5] states that moderate stimulation of the vagus (which contains the vasomotor fibers) may reduce the output of blood from the heart 30 to 50 per cent. E. Weber[6] observed that during partial inhibition the cardiac contractions were weakened. Schiff[7] found that the muscular elements of the entire organ responded less or not at all to stimuli. François-Franck, Fischel[8] and others observed that the cardiac walls were softer than usual. Gaskell[9] characterizes as "most striking" the attending depression of activity.

Can we regard as a physiological or normal function a process which entails paralysis of the heart? In the preceding chapter we found that toxic doses of certain drugs could produce a similar effect—drugs which, in excessive doses, were capable of so violently stimulating the *vasomotor* center, that the caliber of the coronaries became sufficiently narrowed to reduce the quantity of blood in the cardiac muscle below the physiological limit, which means enough contractile power to project the blood into the lungs. That inhibition here is a process brought on *artificially* in the laboratory, or morbidly by a poison, seems plain.

This shows that excessive constriction of even large arteries (for the coronaries are large vessels, when compared to those supplied by sympathetic nerves) can arrest function.

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[3] Sajous: N. Y. Med. Jour., May 14 and 21, 1904.
[4] Heymans and Demoor: Mem. couron. de l'Acad. roy. de med. de Belgique, T. xiii, p. 1, 1894.
[5] Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 1, 1900.
[6] E. Weber: "Handw. d. Physiol.," Bd. ii, S. 42, 1846.
[7] Schiff: Archiv f. physiol. Heilk., 9 ter Jahrg., S. 22, 1850-51.
[8] Fischel: Archiv f. exp. Path. u. Pharm., Bd. xxxviii, S. 228, 1897.
[9] Gaskell: Schäfer's "T. B. of Physiol.," vol. ii, p. 169, 1900.

May we not expect that the "small arteries and arterioles of the body," in view of their diminutive caliber, will be constricted even more readily—sufficiently, in fact, to obliterate their lumen and arrest function?

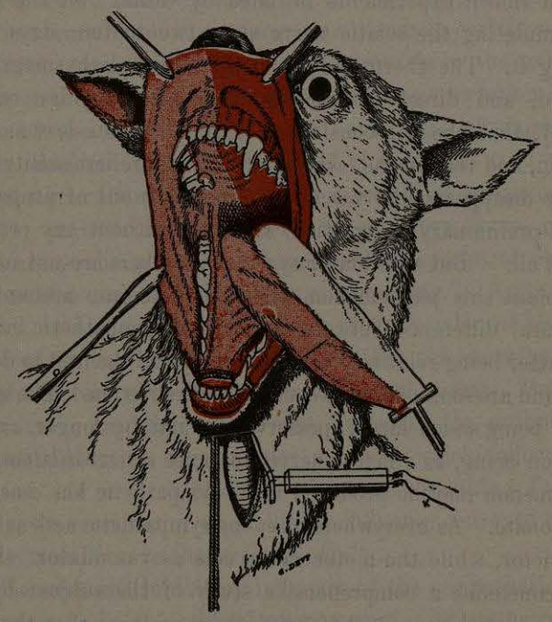
That such is the case may be shown by the following evidence, which has been thought to prove the existence of "inhibitory" sympathetic fibers:—

"Section of the sympathetic paralyzes the *muscles of the vessels* which are located in the field of distribution of the great sympathetic," writes Morat,[10] "and its stimulation causes them to *contract.*" This conclusion is based on another classical experiment by Claude Bernard, outlined by the same author, as follows: "Having cut the sympathetic in the neck of a rabbit, he observed that the temperature of the whole of the corresponding side of the head, especially of the ear, was remarkably raised. On making the counter-experiment by stimulating the superior end, he observed that the temperature fell below the original temperature, as Brown-Séquard had observed almost contemporaneously." The rise of temperature was, of course, due to the entrance of additional blood in the capillaries supplied by vessels innervated by the cut sympathetic, while conversely, stimulation of the upper end of the latter caused constriction of the same vessels, exsanguination of the same area and hypothermia. In other words, this illustrates the one function which the sympathetic carries on, but in the small vessels and arterioles *only*.

How "inhibition" can be provoked in these vessels will now appear. Morat[11] writes: "Dastre and Morat showed, in 1881, that stimulation of the great cervical sympathetic causes, in addition to the oculo-pupillary effects [described below], and of the constriction of the vessels of localities which are habitually obvious, like the ear, dilatation of those *of neighboring regions*, the upper and lower lip, the palatine arch, and this very clearly in the dog. Hence the sympathetic contains inhibitory vascular nerves." Interpreted from my standpoint, however, this does not indicate the presence of such nerves. Thus, Morat publishes the colored engraving reproduced below,

[10] Morat: "Physiol. of the Nerv. Sys.," transl. by Syers, p. 317, 1906.
[11] Morat: *Loc. cit.*, p. 318.

in which the effects of stimulation of the sympathetic are clearly illustrated. Dilation of the pupil and exophthalmos are plainly shown, but the salient features are the *pallor* of one side of the tongue and ear, as contrasted with the *congestion* of the lips, gums and palatine arch of the corresponding side. Now, Morat ascribes the localized pallor to vasoconstriction—which is undoubtedly true; the congestion, however, he attributes to inhibition of this vascular constriction, the sympathetic



EFFECTS OF STIMULATION OF THE CERVICAL SYMPATHETIC. (*Morat*).

being supposed to send vasodilator fibers to the vessels of the corresponding area. The nerve is thus regarded as acting simultaneously as constrictor and dilator, though in different areas. From my standpoint, a simpler and more logical explanation asserts itself, *viz.*, the *arterioles* of the pale area being *alone* supplied by the cervical sympathetic, they contract when the latter is stimulated; these small vessels being markedly constricted as shown by the pallor, the circulation through them is blocked and the blood accumulates in the other vessels—those of the congested area. That the vessels of one side

only should be affected is obviously due to the fact that each side has its own arterial supply derived from the corresponding carotid.

As to the supposed vasodilator properties of sympathetic nerves, Langley,[12] who, by the way, referring to the presence of such vasodilators, thinks it "premature to regard the question as settled," writes: "The strongest evidence for the presence of vasodilator fibers in the sciatic is that afforded by the series of well-known experiments initiated by Goltz,[13] on the effect of stimulating the sciatic nerve some two to four days after cutting it. The thermometric method, the plethysmographic method, and direct observation have given similar results, namely, that the vasoconstrictor action becomes less as time goes on, and that in the last day or two, before irritability completely disappears, the vascular dilatation is out of proportion to the preliminary contraction, or occurs without any contraction at all." But vasodilator sympathetic fibers are not needed to explain this phenomenon when we take into account the structural difference between motor and sympathetic nerves. The latter being relatively very thin, they are the first to degenerate and are soon unable to cause vasoconstriction. The motor nerve, being much larger, preserves its activity longer, and its function being, as a motor nerve, to cause stricto-*dilation*, this phenomenon may be produced after sympathetic has ceased to functionate. As everywhere else, the sympathetic acts as vasoconstrictor, while the motor nerve acts as vasodilator. Langley[14] concludes a comprehensive study of the subject by the statement that there is "no satisfactory evidence that the sympathetic sends vasodilator fibers to the skeletal muscles"—nor anywhere else, I would add.

Another supposed proof that the sympathetic can act as inhibitory nerve (of a function in this connection) is that of producing intense secretion of the sebaceous, lachrymal and Meibomian glands by dividing the nerve in the neck. But relaxation of the arterioles, and the consequent engorgement of the glandular elements, will produce this identical effect—

[12] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 626, 1900.
[13] Goltz: Archiv f. d. ges. Physiol., Bd. ix, S. 174, 1874.
[14] Langley: *Loc. cit.*, p. 641.

without in the least pointing to the presence of sympathetic "inhibitory" or "vasodilator" nerves.

This indicates that "inhibition" is not a function at all, and that what has been regarded as such is but an experimental phenomenon, and that the sympathetic has no "dilator" functions.

The "secretory" function of the sympathetic is poised on an equally weak foundation. Morat[15] writes: "In 1880, Luchsinger observed that stimulation of the cervical cord causes an abundant secretion of the sudoriparous glands in certain regions of the face (groin [snout] in the pig, muzzle in the ox), just as that of the dorso-lumbar sympathetic causes secretion of the glands of the hindlimb in the cat and dog. Czermak had already observed that stimulation of the cervical cord reacts on the submaxillary gland, causing a *very thick saliva* to flow from it; in both cases the motor or secretory nerves of the glands are put in action, this being another species of nervous action which may be added to the preceding." Again, "Cl. Bernard, in investigating the effects of the section of the cervical cord in the horse, had observed that the corresponding side of the face and neck was covered with sweat. But this phenomenon was then interpreted," remarks the author, "as being dependent on the vascular paralysis which follows this secretion. It is probable that it means something further, namely, the cessation of an inhibitory influence conveyed by the great sympathetic to the sweat-glands."

The supposed inhibitory influence of the sympathetic having proven to be an artificial phenomenon, as just shown, the opinion of Claude Bernard, that the sweating following division of the sympathetic was due to paralysis of the vessels, *i.e.*, to their passive relaxation, stands. Bernard's conclusion is not only sustained by my views, but it affords, moreover, the clue to secretory phenomena observed when the central end of the cut nerve is stimulated. Indeed, the fluid secreted differs from true saliva both in physical properties and quantity secreted. It is far more viscid, and, as shown by Heidenhain, the quantity secreted, both in dogs and rabbits, is very limited. "Unless the gland has been secreting under the influence of the cranial

[15] Morat: *Loc. cit.*, p. 319.

nerve [the chorda tympani], before stimulation of the sympathetic," writes Langley,[16] "this stimulation causes secretion of a few drops only, or it may be much less. Thus, in the dog, stimulation of the sympathetic for a minute will ordinarily produce two or three drops from the submaxillary gland, and perhaps half a drop from the sublingual." To call this a "secretion" requires, to say the least, considerable good-will, especially in view of the fact that if the sympathetic fibers are regarded as the vasoconstrictors of the glandular vessels, constriction of the latter by stimulating the cervical sympathetic suffices to cause the forcible projection, into the gland, of an excess of blood sufficient to account for the "saliva" secreted—a few drops of a serum-like fluid. In fact, if the vessels are allowed to relax and to fill again, the secreting process may be renewed at corresponding intervals. Thus, Langley writes: "The maximum total amount of saliva is obtained by stimulating the sympathetic for short periods, with short intervals of rest. Stimulated in this way—say, during every half-minute—the sympathetic will give from the submaxillary gland of the dog one-thirtieth to one-sixtieth of the quantity of saliva that would be obtained by similar stimulation of the chorda tympani."

Here, again, we are certainly not dealing with a secretory function, but with an artificial process. And this applies as well to Luchsinger's observation upon the snout of swine and the muzzle of oxen. By stimulating the cervical sympathetic, he caused excessive constriction of the smaller arteries and arterioles supplied by this nerve, and caused them to increase momentarily the work of the sudoriferous glands of the regions mentioned.

A brief review of the three main organs, the stomach, intestine and heart, in which the sympathetic is supposed to produce "inhibition" or carry on "secretory" or "motor" functions, will also show their true identity.

Secretory functions are ascribed to the sympathetic supply of the *stomach* by some investigators, in addition to those so conclusively shown by Pawlow to belong to the vagus. But Fremont[17] found that when the stomach was solely supplied

[16] Langley: Schäfer's "T. B. of Physiol.," vol. i, p. 495, 1898.
[17] Fremont: C. r. de l'Acad. de méd., Séance du 19 Nov., 1895.

by this nerve, *i.e.*, when both vagi had been divided, the secretion obtained was neutral and mucoid, and that it differed totally from the active gastric juice obtained when the vagi were whole, a fact which coincides with the experimental phenomena witnessed in the submaxillary gland. Pawlow[18] showed that division of the splanchnic nerve did not influence the character of the gastric secretion, thus indirectly sustaining Fremont's conclusion. Contejean[19] ascertained that in frogs, the sympathetic had but little influence upon the secretion. A similar conclusion was reached by Onuf and Collins[20] after experiments in cats. Nor are the movements of the stomach even governed by this nerve. Schiff taught that motor fibers were supplied by the sympathetic, and Morat "observed one case in which the rhythmical contractions of the stomach (and intestines) were augmented on stimulation of the splanchnics."[21] As a rule, however, he found that "excitation of these nerves caused diminution of the tonus as well as of the rhythmic contractions of the stomach." Starling[22] points to the trend of modern thought in this connection, when he says: "All observers, however, agree in describing the vagus as a motor nerve for the stomach."

It is clear, therefore, that the sympathetic is not the *secretory* nerve of the stomach, nor the *motor* nerve of its walls, and that the only nerve concerned with these functions is the vagus. On the other hand, the diminution of the tonus points clearly to excessive vasoconstriction—*i.e.*, to the vasoconstrictor rôle of the sympathetic.

Concerning the vasomotor innervation of the *intestine*, Langley[23] states that "nothing is yet known as to the nerve-cell connection of the cranial nerve-fibers to the gut," and, referring specifically to the sympathetic, the cranial and the sacral autonomic systems, says: "The relation of the enteric nervous system to those just mentioned is at present only a matter of guesswork." This state of things is plainly due to the misleading influence of excessive experimental vasoconstriction.

[18] Pawlow: Archiv f. Physiol., S. 53, 1895.
[19] Contejean: Arch. de physiol. norm. et path., Oct., 1892.
[20] Onuf and Collins: Arch. of Neurol. and Psycho-Path., vol. iii, p. 3, 1900.
[21] Cited by Starling: Schäfer's "T. B. of Physiol.," vol. ii, p. 324, 1900.
[22] Starling: *Ibid.*, p. 323.
[23] Langley: *Ibid.*, p. 694.

The innervation of the intestine may be said to correspond with that of the stomach. Kaiser,[24] Ludwig, Ogata[25] and others have shown that the digestive process may proceed in the absence of the stomach. Now, Howell,[26] voicing the prevailing opinion, states that the fibers received from the sympathetic "give mainly an inhibitory effect when stimulated, although some motor fibers may apparently take this path." As "inhibition" means, in the light of foregoing facts, hyperconstriction of the arterioles, Howell's statement proves that the sympathetic supplies vasoconstrictor fibers to the intestine. Indeed, several investigators, including Betz, van Braam-Houckgeest,[27] Mall[28] and Starling,[29] found that anæmia "inhibited" all the movements of the intestines. Experimental diminution of blood in the intestinal vessels produces a corresponding effect. Thus, Starling states that if the aorta in the chest be obstructed, "there is a gradual diminution of intestinal tonus." . . . . . "If now," adds this physiologist, "the blood be let in, the intestines contract immediately once or twice, then pause, and then recommence their rhythmic movements." This clearly shows that inhibition is due here, as elsewhere, to a deficiency of blood, whether the supply be reduced by excessive constriction of the intrinsic vessels or by obstruction of the afferent blood-stream at a remote spot.

While the sympathetic thus clearly asserts itself as the vasomotor nerve of the intestine, the true motor nerve of the intestine is as evidently the vagus: "The small intestine and the greater part of the large intestine," writes Howell,[30] "receive visceromotor nerve fibers from the vagi and the sympathetic chain. The *former*, according to most observers, when artificially stimulated, cause movements of the intestine, and are therefore regarded as the *motor* fibers."

All this does not mean that either the stomach or intestine are totally dependent upon their connections with the central nervous system either for their secretory or motor functions. Considerable testimony is available to show that they

[24] Kaiser: Czerny's "Beiträgen zur operat. Chirurgie," Stuttgart, 1873.
[25] Ogata: DuBois-Reymond's Archiv, p. 89, 1883.
[26] Howell: "Amer. T. B. of Physiol.," p. 384, 1900.
[27] van Braam-Houckgeest: Archiv f. d. ges. physiol., Bd. vi, S. 266, 1872.
[28] Mall: Johns Hopkins Hosp. Rep., vol. i, p. 37, 1896.
[29] Starling: *Loc. cit.*, vol. ii, p. 331.
[30] Howell: "T. B. of Physiol.," p. 648, 1905.

can autonomously secrete and undergo peristaltic movements, in virtue solely of their inherent irritability. Adrenoxidase is an important factor in this connection, since, as we have seen, the irritability of all cellular elements is governed by the activity of the interchanges of which they are the seat.

As to the *heart*, we have already seen that its coronaries are supplied with true vasomotor nerves, and I referred at the time to the fact that the large vessels differed from the smaller as to the source of the vasoconstrictor fibers, the sympathetic being an autonomous system. Indeed, the sympathetic gives rise to its own characteristic phenomena when, from any cause, it produces vasoconstriction of the terminal arterioles which it supplies. "It has long been known," write Brodie and Russell,[31] "that slowing of the heart or arrest of the heart can be brought about reflexly by excitation of almost any afferent nerve of the body if the stimulus be sufficiently great." Particularly sensitive in this connection are the abdominal viscera, especially, according to Tarchanoff[32] and François-Franck,[33] when these organs are inflamed. Goltz[34] found that tapping of a frog's intestines or stomach readily inhibited the heart. We have in the pugilistic "solar plexus" blow a familiar cause of reflex inhibition—not any more a physiological process than the supposed controlling influence of the vagus on the heart. The manner in which the sympathetic vasomotor terminals produce this reflex inhibition is suggested by the fact that Newell Martin[35] "found that stimulation of the vagus causes *dilatation* of the small arteries on the surface of the heart as seen through the hand lens." "Moreover," writes Howell[36] in this connection, "when the heart is exposed and artificial respiration is stopped, the arteries may be seen to dilate before the asphyxia causes any general rise of arterial pressure." These results are readily accounted for when it is borne in mind that the sympathetic fibers are distributed only to the terminal arterioles. The two exciting agents (toxic wastes due to hypocatabolism when artificial respiration ceased, as to the second

[31] Brodie and Russell: Jour. of Physiol., vol. xxvi, p. 92, 1900.
[32] Tarchanoff: Arch. de physiol. norm. et path., T. ii, 2 série, p. 498, 1875.
[33] François-Franck: Trav. du Lab. de Marey, ii, p. 221, 1876.
[34] Goltz: Virchow's Archiv, Bd. xxvi. S. 1, 1863.
[35] Newell Martin: Trans. Med. and Chir. Faculty of Maryland, p. 291, 1891.
[36] Howell: "T. B. of Physiol.," p. 550, 1905.