tion or any other form of toxæmia. Indeed, so intense is this action in the case of some of these agents that the blood-cells themselves are digested (hæmolysis) along with the bacteria. The practical experience accumulated by clinicians during the many years—centuries in some instances—that these agents have been employed, and the researches of therapeutists into their physiological action, have given us a working field which it will take decades of steady labor upon all questions relating to the use of tuberculin or other bacterial products by inoculation even to approach. We need not, therefore, deprive the present generation of the advantages that the magnificent lore of our profession affords. Within our reach are weapons whose every part is known to all and which, in power to destroy the greatest enemies of mankind, are second to none—provided their present empirical use give way to their scientific use, viz., with the test-organ of the pituitary and the organs which it controls as the foundation of the body's auto-protective resources. This binds indissolubly pharmacotherapeutics to the general principle of immunity—precisely the field I opened in the first volume of this work. We must learn to bow to Nature's powers; had her mode of work—the doctrine of Hippocrates—inspired all researches since his time, Medicine would not only rank as a Science to-day, but it would exceed all other sciences in perfection.

As a final conclusion of this chapter, I would submit, therefore, that *immunizing medication is the foundation of rational therapeutics.*

CHAPTER XVIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS.

THE PRESENT STATUS OF THERAPEUTICS.

In a Presidential Address[1] A. H. Bampton said recently (1907): "Scepticism is in the air. Even in this society, if any daring member has introduced a subject bearing on medical treatment, it has been with an apologetic air and humble mien, well knowing that if his remarks had any reference to the utility of drugs in the treatment of disease they would be subjected to good-humored banter, and received by those sitting in the seat of the scornful with amused incredulity." That the same spirit reigns on this side of the ocean hardly needs to be emphasized. But few years had elapsed since Frank Billings, also in a Presidential Address,[2] declared that "drugs, with the exception of quinine in malaria and mercury in syphilis, are valueless as cures," and what has been termed Osler's "black, hopeless, helpless, therapeutic pessimism," is quite as applicable to a large proportion of the medical men of our country. The present work, in fact, was begun under the influence of a very similar state of mind. It would be unfair, however, to incriminate only pharmacological knowledge on this score; pathology is quite as invalid when the relations of cause to effect are scrutinized. Indeed, Lewellys F. Barker's previously quoted estimate that "drugs of *unknown physiological action* cannot conscientiously be set to act upon bodily tissue *in disease in which we are ignorant of deviations from the normal,*" exemplifies succinctly the dual cause of the rather ignominious position in which practical medicine finds itself. The contents of the foregoing chapters account for this: they show that functions of the first order have been overlooked: functions which, in pathogenesis and therapeutics, play the leading part, and without which these fundamental branches must remain inscrutable.

[1] A. H. Bampton: Leeds and West Riding Medico-Chirurgical Soc., Lancet, Jan. 19, 1907.
[2] Billings: 54th Annual Session of the Amer. Med. Assoc., 1903.

Referring only for the time-being to therapeutics, no apology is needed, therefore, if the interpretations of the physiological action of drugs I present herein differ totally from any yet advanced. The introduction of a series of functions besides, even, those of the adrenal system, viz., the various processes carried on by the anterior and posterior pituitary bodies and by the different leucocytes, the additional rôle attributed to the red corpuscles, the several blood constituents which play so important a part in the life process itself and the defence of the organism, etc., normally entails a complete transformation of the prevailing conceptions.

Our fund of experimental and clinical facts has not in the least been set aside. Indeed, experimental therapeutists have contributed a vast array of positive data which, utilized individually, *i.e.*, irrespective of any interpretation formulated by the investigators themselves, and suitably grouped, afford a rich source of material for the elaboration of doctrines based only on established facts, and, therefore, poised on a sound foundation. It is to Horatio C. Wood that we owe mainly this mode of investigation, and if it has not as yet borne substantial fruit, it is not owing to the fact that the principle is unsound, but because the building materials were incomplete. Besides the various organs enumerated above, are others, the functions of which have also been overlooked, Ludwig and Cyon's depressor nerve, for instance, discovered by these physiologists in 1866. As I will show below, this nerve plays an important part in the self-defence of the organism against disease. Again, the fact that the majority of the body-functions have remained unexplained by physiologists has rendered it impossible to understand many phenomena provoked by drugs. The manner in which a motor nerve produces its effects, for instance, is as obscure to-day as it was fifty years ago. Vasodilation is a prominent feature of the action of drugs, and yet the manner in which it is brought about is absolutely unknown. As pointed out under the next heading, this problem is readily solved when the presence of adrenoxidase in the blood-stream is taken into account.

Again, the accumulated evidence of all the practitioners of christendom for centuries is certainly of some value. As

Bampton states: "Although our treatment then, as now in part, may be stigmatized *empirical*, it was none the less founded upon careful clinical experience." Here also we have a vast array of solid data for the elucidation of the relations between cause and effect, *i.e.*, of the manner in which the organism responds to exogenous influences. Unfortunately, the laboratory experimenter is too prone to ignore the teachings of clinical experience, forgetting that, judged as an experiment, the use of a remedy in a given case is at least as elucidative, with the refined methods of investigation now at the disposal of the clinician, as his own. Were he to add this fund of information to his own resources, and scrutinize as closely as the protocol of his experiments the recorded results of the administration of the corresponding remedy in disease, he would soon withdraw therapeutics from the position into which it has undeservedly fallen, and raise it to the dignity of a science.

In the various familiar drugs studied in the following chapters, I have availed myself—as far as space would permit—of these two great sources of information; besides the functions of the organs I have introduced into the various problems. That this plan must be fruitful, is suggested by an important result reached, viz., that *in the case of each drug* the physiological action I submit, though differing totally from that now taught, *explains clearly how the disease or morbid symptom for which it is used is antagonized and overcome.* This, in itself, affords strong testimony to the effect that the new conception of pharmacodynamics I submit is, in its general lines, poised on a solid foundation.

Before study of the various agents considered in this chapter can be undertaken, however, the manner in which the vasodilator and depressor nerves produce their effects requires attention.

THE MECHANISM OF VASODILATION AND ITS RELATIONS TO ORGANIC FUNCTION.

The existence of vasoconstrictor nerves discovered by Claude Bernard in 1851, confirmed by Brown-Séquard the following year, has become one of the keystones of modern physi-

ology, and its solidity has never been shaken. The mode of action of vasoconstrictors is also established. We cannot say the same, however, of the vasodilators; the actual existence of a dilator center, or even of true vasodilator nerves, in fact, is still undetermined.

In his summary of vasomotor actions, Foster,[3] for instance, says that "there is no adequate evidence that these vasodilator fibers serve as channels for tonic dilating impulses or influences." Landois and Stirling,[4] referring to the "vasodilator center" in the medulla, state that "its existence there has been surmised," and furthermore, that "the existence of vasodilator nerves is assumed." In the last edition of the same text-book[5] published eighteen years later (1905), this is modified to the statement that, "although a center for vasodilator or vessel-relaxing nerves has not yet been demonstrated, the existence of such a center in the medulla may nevertheless be suspected." J. G. Curtis[6] states that "it is not known whether a vasodilator center is present in the bulb." The actual state of the question is aptly summarized by H. C. Chapman,[7] when he says: "Though numerous explanations have been offered of the manner in which the vasodilator nerves act, it must be admitted that none of them are satisfactory, and that it is not yet understood how their stimulation causes dilatation of the blood-vessels."

Even the stronger lines of testimony, those based on cutaneous hyperæmia, blushing, etc., in favor of the presence of vasodilator nerves in the spinal cord, including that afforded by excitation of the upper segment of the cervical sympathetic, after section, cannot stand close scrutiny. "Flushing of the skin, or a rise of temperature in it," writes Langley,[8] "are at times and in certain circumstances, produced by stimulation of the sympthetic; and it is generally believed that the changes are due to the presence of vasodilators. The evidence, on the whole, is in favor of the presence of such nerve-fibers, but it is I think, premature to regard the question as settled." The

[3] Foster: "T. B. of Physiol.," sixth American edition, p. 229, 1895.
[4] Landois and Stirling: "T. B. of Physiol.," vol. ii, p. 959, 1886.
[5] Landois: "T. B. of Human Physiology," tenth edition, p. 771, 1905.
[6] J. G. Curtis: "Amer. T. B. of Physiol.," vol. i, p. 199, 1900.
[7] H. C. Chapman: "Treatise on Human Physiology," second edition, p. 692, 1899.
[8] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 626.

weakness of the whole scheme hardly needs to be further emphasized. When we consider that vasodilation is *the all-important factor of function in all organs,* the need of ascertaining the nature of this process imposes itself.

No one, of course, denies that dilator *effects* are witnessed in various organs; the obscure feature of the question is the *manner* in which these effects are brought about. Even Claude Bernard's memorable experiment, which conclusively demonstrated the existence of nerves capable of causing vasodilation, has remained unexplained, as far as the mode of action of the chorda tympani is concerned. The fact that division of the sympathetic (constrictor) fibers distributed to the submaxillary gland's vessels is followed by dilation of the latter and an increased outflow of blood led Bernard to suggest that the chorda tympani inhibited the sympathetic fibers. Granting that it does represent a physiological function, this interpretation fails to harmonize with several established facts. Among these is the observation of Schiff (1856) and confirmed by several investigators since, that "the vessels of any organ are dilated to a greater degree by excitation of the vasodilators than they are by paralysis of the vasoconstrictors."[9] It is evident that "inhibition" or "paralysis" should simply counteract the constrictor effects, the vessels retaining their normal diameter. In reality, the dilation is much more marked under excitation, and the submaxillary gland is no exception to the rule. Langley,[10] in discussing the mode of action of inhibitory fibers, refers to this view as untenable, and, alluding to "the bucco-facial region of the dog, the inhibitory fibers of the heart and the inhibitory fibers of the stomach and intestine," remarks: "We may conclude for all cases that the inhibition which we are considering is not produced by a lowering of the activity of sympathetic or similar nerve cells." Foster's[11] estimate in this connection is conclusive: "We may, if we please, speak of an 'inhibitory mechanism' placed in the heart itself," says this investigator, "but we have no exact knowledge of the nature of such a mechanism."

In the vasodilator phenomenon discovered by Claude Ber-

[9] Schiff: Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 135.
[10] Langley: *Ibid.*, vol. ii, p. 673.
[11] Foster: *Loc. cit.*, p. 207.

nard we have an illustration of the *active* functions of all organs. But *how* does the chorda tympani cause vasodilation? The solution of this problem furnishes that of a multitude of questions in the domains of physiology, pathology, and therapeutics.

If the foregoing estimates are reduced to their simplest expression, our knowledge of the source and nature of vasodilator impulses is about as follows: we have a *problematic* center, grafted upon another center known to transmit impulses of an *opposite* kind; this problematic center is *supposed* to be the source of dilator impulses through nerves which have *not* been shown to act as channels for them, and which serve to dilate vessels which do so *automatically*, when all nerves distributed to them are severed. In other words, the conception is illogical from start to finish. It may be objected that the cord itself is the source of dilator impulses, and that nervi erigentes, for instance, may be made to produce dilator phenomena reflexly when the cord is severed above the lumbar region. But this in no way modifies the situation, for the spinal centers are thus merely brought into line with others credited with similar functions: the pontine nucleus of the facial nerve, the source of the chorda tympani's stimuli, for example. The manner in which these spinal centers cause vasodilation is no less obscure.

A key to the situation is within reach if all prevailing theories are set aside and *facts* only are accepted as guides. We *know* that constrictor impulses originate from a vasomotor center or subsidiary centers; we *know* that vasodilator effects are produced. Why should *constrictor* impulses not give rise to *dilator effects?*

Claude Bernard's experiment is outlined by Leonard Hill[12] in the following words: "Exposing the submaxillary gland, he opened one of the efferent veins and observed the outflow of blood. On dividing the cervical sympathetic nerve, the blood flowed in increased volume and became more arterial in color. On exciting the same nerve the outflow entirely ceased and the gland became pale in color. He next excited the chorda tympani nerve; the gland blushed red, and almost immediately

[12] Leonard Hill: *Loc. cit.*, p. 132.

bright arterial blood gushed out from the vein. The vascular dilatation was, in this case, so great that the blood, with each pulsation of the artery, flowed from the veins in jets."

The chorda tympani fulfills a dual rôle. "When the chorda is stimulated," says Foster,[13] "there pass down the nerve, *in addition* to impulses affecting the blood-supply, impulses affecting directly the protoplasm of the secreting cells, and calling it into action." These fibers were traced to the secretory elements by Pflüger, and his observation was confirmed by Paladino in 1876, and subsequently by Navalichin and Kytmanoff, Fusari and Panasci, and Ramon y Cajal.[14] When, however, the fibers to the secretory cells are paralyzed, the vascular phenomena are not modified. "If a small quantity of atropine be injected into the veins," says Foster,[15] "stimulation of the chorda produces no secretion of saliva at all, though the *dilatation* of the blood-vessels takes place *as usual;* in spite of the greatly increased blood-supply."* This is a familiar physiological fact, first observed by Ludwig many years ago, which shows that however produced, the vasodilator effects must be ascribed to the chorda tympani only.

The salient features of Bernard's experiment, besides the vascular dilation, are an increased volume of blood, the presence of arterial blood, and the expulsion of the latter in jets coinciding with arterial pulsations. To meet the needs of the first of these phenomena, it is, of course, necessary (1) that an increased volume of blood be *admitted* to the organ, and (2) that the blood-pressure be increased behind the column of blood so admitted. Obvious as these two conditions are, however, they embody, it seems to me, a solution of the question in point, for: given an adequate pressure *behind* an increased *volume* of blood, we have a column which exerts centrifugal pressure upon the walls of the vessels through which it passes and capable, therefore, of *dilating* them. To account for the arterial character of this column of blood and its expulsion in jets, we require larger vessels than the arteriole in the gland proper. The three or four submaxillary branches which sup-

* The italics are my own.—S.

[13] Foster: *Loc. cit.*, p. 265.

[14] Ramon y Cajal: Testut: "Traité d'Anatomie Humaine;" third edition, vol. iii, p. 175, 1895.

[15] Foster: *Loc. cit.*, p. 264.

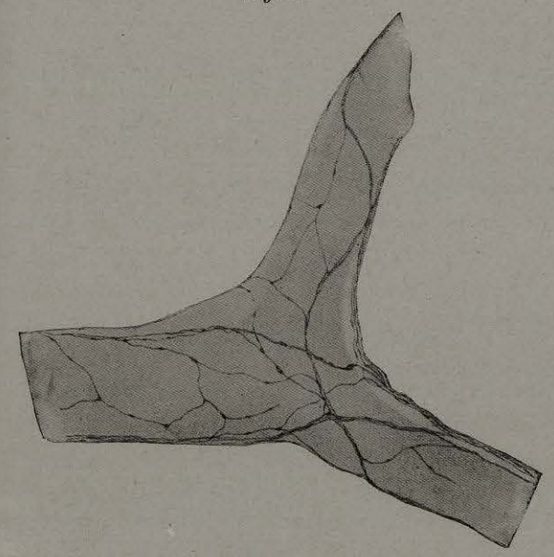
ply the gland furnish enough blood when the organ is inactive to form "a thin slow stream" and supply the needs of the mechanism. Derived as they are from the facial artery, any increase of their caliber would normally give free sway to the marked back pressure which this vessel affords. The close proximity of the facial artery to the external carotid, of which it is a branch, its anatomical relations with the submaxillary gland, and the fact that it pulsates actively, clearly point to this vessel as a prominent factor of the process. But how is it made suddenly to shift, as it were, an additional volume of blood into its submaxillary branches—which requires widening of the lumens through which the blood enters the latter—and simultaneously increase its own propulsive power? This increase must be very marked, for "during stimulation," says Foster, "the blood rushes out in rapid, full stream." A very simple mechanism, the various parts of which are familiar anatomical landmarks, seems to me to satisfy all the needs of the function.

We have seen that the chorda tympani alone increases the functional activity of the gland. This nerve has two sets of fibers: secretory and vasodilator. Both of these are given off (anatomically) from a small ganglion, the submaxillary, found above the hilum of the organ. A feature of the distribution of this ganglion's fibers, however, is that some of them penetrate the gland proper, while others pass directly to the walls of the submaxillary branches of the facial artery, and to the latter likewise. Now, all these vessels are within the limits of those supplied with vasa vasorum, at least that first given by Henle, 1.1 millimeter. Their walls thus receive blood as do other structures, and are also oxygenated directly from the general circulation. These nutrient arteries, the largest of which, according to Gimbert,[16] have a diameter of 0.017 millimeter, form an anastomosing network in the tunica adventitia, composed chiefly of fibrous connective tissue intermixed with a network of elastic fibers, but Kölliker, Eberth,[17] Aeby[18] and others since found that the outer third of the middle coat, which contains a large proportion of muscular cells disposed mainly in

[16] Gimbert: Jour. de l'anat. et de physiol., T. ii, p. 630, 1865.
[17] Eberth: Stricker's "Handbuch," S. 192, 1869.
[18] Aeby: "Der Bau d. menschl. Körpers," S. 782, 1871.

Fig. 1.

Fig. 2.



VASO-CONSTRICTOR NETWORKS AROUND ARTERIOLES. *[Joris.]*

Fig. 1, Arteriole of 280 microns x 55.
Fig. 2, Arteriole of 45 microns x 520.

a circular manner, was also provided with them. As shown by Ranvier,[19] vascularization of this coat, however, is an accompaniment of local pathological processes, and it is now generally thought that nutrient vessels do not penetrate this coat, except in the largest vessels. Shakespeare[20] says in this connection: "In the large vessels the middle and outer coats are supplied with blood-vessels—the vasa vasorum. In a few instances capillaries enter the tunica intima." While, therefore, vasa vasorum form an irregular but close meshwork in the fibro-elastic layer, they can only be said to reach in man the *surface* of the deeper or muscular layer.

That this network of nutrient capillaries is not itself supplied with vasomotor nerves is self-evident. These are doubtless distributed to the arterioles from which the capillaries are given off. That very minute arterioles are supplied with a vasomotor network is well shown in the annexed plate by Joris,[21] the upper vessel being about one-quarter of a millimeter, while the lower is but forty-five thousandths of a millimeter in diameter.

Important in this connection is the structure of the small vessels which, though referred to generally as "arteries," are, in reality, *arterioles* as regards histological structure and size. In this class of vessels, the internal coat is composed of endothelial plates only. Overlying this coat is one composed of what Ranvier termed the "internal elastic lamina," and of a layer of nonstriated muscular cells. Both this layer and the elastic layer are thus blended functionally, as it were. Now, if a cross section of such a vessel is examined, the elastic coat will be seen to have a wavy or festooned circular outline. "The internal elastic layer," says Ranvier,[22] "as are all structures composed of elastic material, are elastic only to a limited extent, and when it is compressed by the annular muscular layer, it often happens that the lower limit of elasticity is surpassed, and that in order to accommodate itself within the restricted space reserved for it, it must fall into longitudinal

[19] Ranvier: "Traité technique d'histologie," 1875.
[20] Shakespeare: Allen's "Anatomy," p. 72, 1884.
[21] Joris: Bull. de l'Acad. Roy. de Méd. de Belg., T. xx, p. 502, 1906.
[22] Ranvier: *Ibid.*

folds. Hence the festoon seen in cross sections, whereas in longitudinal sections of small arteries the folds formed under the influence of the muscular contraction cause it to appear as longitudinal striæ."

The manner in which the muscular coat of arterioles (meaning thereby the smallest of arteries, those which join the capillaries or the so-called pre-capillary vessels) is disposed around them is also of considerable importance. Thus, referring to these particular vessels, Berdal[23] writes: "The muscular cells form a single and continuous layer around the small arterial vessel. They are rolled spirally around the arteriole." As I will show in the next chapter, this enables these vessels (under the influence of sympathetic impulses) to propel their blood into the capillary system and to cause the arterioles to resume their normal diameter after they have been caused to dilate through the mechanism now in question.

The mechanical process of vasodilation will now appear. As nutrient arteries, the vasa vasorum supply the walls of the vessels to which they are distributed with blood obtained from a neighboring artery. This blood, as elsewhere, enhances the functional activity of these tissues by increasing metabolism in the cellular elements of which they are composed. Again, Roy[24] showed that the thermo-elastic properties of animal tissues differed from that of most other substances, and that they contracted when the temperature was raised and expanded when the temperature was lowered. We thus have two interdependent factors, one chemical and the other physical, dependent upon *the blood of the vasa vasorum*, capable of influencing the caliber of the vessels to which they are distributed. It is now evident that constriction of the vasa vasorum, by arresting or reducing the flow of blood to the walls of the vessels they nourish, will lower both metabolism and heat in these vessels, thus causing relaxation of their spiral muscular elements, and as a normal consequence, dilation. We thus have *vasodilation* of arteries and veins produced by *vasoconstriction* of their nutrient vessels—as illustrated in the next chapter.

This interpretation meets the—so far unexplained—fact

[23] Berdal: "Histologie Normale," fourth edition, p. 307, 1894.
[24] Roy: Jour. of Physiol., vol. iii, p. 125, 1880.

that, as observed by Schiff, vessels dilated by their vasodilators expand to a greater degree than when their constrictors are severed. In the latter case, nerve impulses are alone arrested, and the vessel continuing to receive its nutrient blood, it soon resumes its normal caliber. When the nutrient blood of the vasa vasorum, on the other hand, cannot reach the vascular walls, *both* causes of constriction fail, since the walls are no longer able to respond to nervous stimulation. Again, it accounts for all the phenomena observed by Claude Bernard. The dilation of the gland's vessels is left, to a certain extent, under the influence of the volume of blood forced through them from behind. Here the source of general supply being the facial, a branch of the external carotid, we have not only—after vasodilation of the submaxillary arteries induced by constriction of their nutrient vessels—a marked increase of the volume of blood in transit through the organ, but it is propelled with such rapidity through the latter that the change to venous blood cannot occur. Finally, the streams, under the influence of the greater artery's periodical contractions, leave the gland in jets.

Again, it does away with the need of a dilator center which no one has ever located, and of dilator nerves which no one has ever seen. Inasmuch, however, as Langley[25] found that extirpation of the superior cervical ganglion, which causes degeneration of the sympathetic fibers distributed to the vessels of the gland, did not prevent vasodilation when the chorda was stimulated, the constrictor fibers of the vasa vasorum are not sympathetic fibers. They are evidently the fibers in *cranial* nerves which *incite* functional activity in all organs by increasing the volume of their blood supply. In view of the fact that they provoke *dilator* effects by transmitting *constrictor* impulses, I will henceforth refer to them as *"stricto-dilator"* nerves—a distinction of paramount importance in therapeutics, as will be shown.

Finally, it meets all the conditions which, according to modern physiologists, an explanation of the mechanism of vasodilation should embody. Thus Howell[26] (1905) writes: "There

[25] Langley: *Ibid.*, vol. vi, p. 87, 1885.
[26] Howell: "T. B. of Physiol.," p. 545, 1905.