cause), by causing constriction of these terminal vessels, obstruct their blood-stream, and cause the latter to expand the vessels *behind* the seat of obstruction.

This brings us to the specific functions of the sympathetic terminals. Howell,[37] in his review of the tonic activity of vasomotor nerves, says: "Normally, the arteries—*that is, the arterioles*—are kept in a condition of tone by impulses received through the vasoconstrictor fibers." He evidently means sympathetic fibers, for all the examples he cites refer to stimulation of sympathetic nerves. Moreover, Hall, in accord with all other physiologists, states that the smaller arteries and *arterioles* are supplied with sympathetic vasoconstrictor fibers. Now, Howell writes: "When *vasoconstrictor fibers* are stimulated there is a *rise* of blood-pressure in the *artery* supplying the organ and a *fall* of pressure in the *veins* emerging from the organ. This result is what we should expect if the constriction takes place in the region of the arterioles." This clearly identifies the sympathetic with the function of the organ, and suggests that it influences in some way the *volume* of blood admitted into it.

The need of such a regulative factor almost imposes itself in view of the following additional statements by Howell: "The capillary region, including the smallest arterioles and veins, offers a great resistance to the flow of blood, and this resistance is spoken of as the *peripheral resistance*. Its effect is to raise the pressure on the arterial side and lower it on the venous side. When other conditions in the circulation remain constant it is found that an increase in peripheral resistance, caused usually by a constriction of the arterioles, is followed by a rise of arterial pressures and a fall of venous pressures. On the contrary, a *dilatation of the arterioles* in any organ is followed by a fall of pressure in its artery or arteries and a rise of pressure in its veins." This quotation repeats, in a measure, the contents of the foregoing paragraph. If, however, the two are carefully compared, a salient feature will assert itself, namely, *it is the sympathetic fibers supplied to the arterioles which govern peripheral resistance and that, therefore, peripheral resistance is governed by the sympathetic center.*

[37] Howell: *Ibid.*, p. 538.

The far-reaching importance of this function will now assert itself. Osler[38] remarks: "Tissue irrigation is primarily from the heart, but in all extensive systems of this sort, provision is made at the local territories for variations in the supply, according to the needs of a part. The sluices are arranged by means of the *stop-cock action of the arteries*, which contract or expand under the influence of the vasomotor ganglia, central and peripheral. If the sluices of one large district are too widely open, so much blood may enter that other important regions have not enough to keep them at work." Now, this "stop-cock action of the arteries" cannot be accounted for when the vasomotor system *per se* is considered as the mechanical factor in the process, since constriction of the larger vessels would overcome that of the smaller into which they drive their blood. The body is, therefore, as I have shown in the sixteenth chapter, provided with an autonomous vasomotor system, the sympathetic, which presides solely over this "stop-cock action." The ganglia to which Osler refers are, in fact, as every one knows, the sympathetic ganglia.

This "stop-cock action" has a specific purpose in this connection, however, namely, that of *enforcing the resumption of their normal caliber to the small vessels and arterioles after dilation by the stricto-dilators.* Through this rôle, sympathetic fibers take an active part in all organic functions, as will now be shown.

In the eighteenth chapter I submitted the evidence which had led me to conclude (1) that an exacerbation of activity in any organ was the result of the admission into it of an excess of blood over and above that circulating through it during repose; (2) that this was brought about by dilation of the arteries which admitted the blood into this organ; (3) that this dilation was due to diminution of adrenoxidase in the walls of these arteries and the resulting hypocatabolism therein; and finally (4) that this was accomplished by cranial motor-nerve terminals distributed to the vasa vasorum or capillaries which nourished these vessels.

Now, this "stricto-dilation" of the supply arteries may well be compared to turning on of the blood-stream by opening the

[38] Osler: "Pract. of Medicine," p. 718, 1905.

stop-cock. It is obvious, however, that so important a function as the resumption by the dilated arterioles of their normal caliber, *i.e.*, to a degree of contraction exactly adapted to nutrition and just short of functional activity, cannot be left to so uncertain a process as passive dilation. Nor can it be left to the fibers of the vasomotor system, for this would entail constriction of the larger arteries of the body also, and, by forcibly dilating the small arteries of the organ, defeat the object in view. But this object is fulfilled by terminal fibers of the sympathetic which provoke vasoconstriction of the arterioles. They reduce the volume of blood admitted into the organ during active function—partly turn off the stop-cock, as it were (not entirely, since this would cause arrest of function, *i.e.*, inhibition), and cause the organ to resume the passive state—a condition in which it is ever ready to become active when the stream of blood passing through it is again enlarged through the vasodilator impulses of the stricto-dilators.

The schematic illustration shown herewith represents in Figs. 1 and 2 the mechanism through which an arteriole is dilated by the stricto-dilators, which are fibers of a *cranial* motor or secretory nerve (the vagus, facial, etc.), during function; and then restored to the passive state by the sympathetic vasoconstrictor fibers. This accounts for the fact that the sympathetic center is located, as I pointed out in the sixteenth chapter, in the same organ to which I had traced the cranial nerves, *viz.*, the posterior or neural lobe of the pituitary body. The purpose of this intimate relationship is self-evident, now that we have seen that the functions of all organs are carried on by the joint action of the terminals of a cranial and sympathetic nerve.

Briefly, it appears to me: (1) *That the sympathetic system does not, as now believed, carry on motor, dilator, secretory, or inhibitory functions;* (2) *that its function is purely vasoconstrictor, its field being limited to the small arteries or arterioles;* (3) *that it is entirely independent of the vasomotor system (whose action is general), being capable, unlike the latter, of influencing each organ individually;* (4) *that its terminals form part of the mechanism of all organs;* (5) *that the specific rôle of its terminal fibers is to oppose the stricto-*

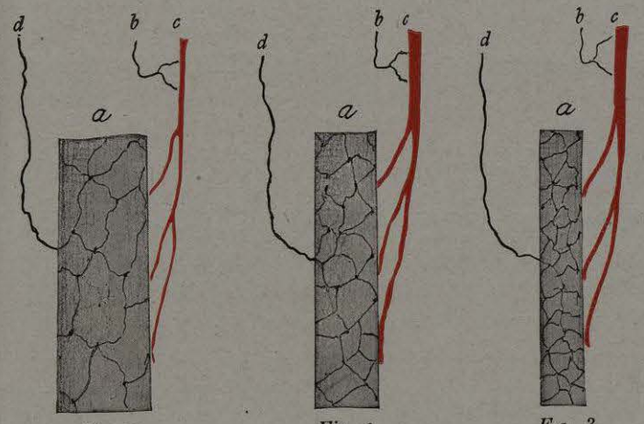

Fig. 1. *Fig. 2.* *Fig. 3.*

SCHEMA OF THE STRICTO-DILATOR (CRANIAL-MOTOR) AND SYMPATHETIC NERVES IN THEIR RELATIONS TO ORGANIC FUNCTION.

[Sajous.]

Fig. 1. DURING FUNCTION: Arteriole a dilated; stricto-dilator b active and vasa vasorum c constricted; sympathetic d passive.

Fig. 2. DURING REST, organ being kept nourished: Arteriole a semi-contracted; stricto-dilator b passive and vasa vasorum c dilated; sympathetic d active.

Fig. 3. DURING INHIBITION (excessive and therefore morbid constriction), the organ being deprived of blood: Arteriole a, lumen obliterated; stricto-dilator b passive and vasa vasorum c dilated; sympathetic d over-active.

dilators and restore the arterioles of an organ to their normal caliber when the functional activity of that organ is to cease; (6) *that the volume of blood which circulates through any organ, whether the latter be in the passive state or functionally active, is regulated by the joint action of the motor and sympathetic centers in the posterior pituitary;* (7) *when the organ is to become functionally active, the stricto-dilators cause its vessels to relax and to augment the volume of blood coursing through it; when its activity is to cease, the sympathetic constrictors cause the vessels to contract sufficiently to reduce the blood in transit to the volume required for adequate local nutrition.*

The conjoined action of the sympathetic and cranial terminals subserves another rôle of special importance in pathology and therapeutics.

That the sympathetic fibers distributed to the arterioles serve to maintain their tone is a recognized fact. It becomes a question, however, whether so simple a mechanism meets the needs of the functions these small vessels must perform. The blood they transfer into the capillaries meets therein very great resistance, not only in the skin, the familiar "peripheral resistance," but in all organs. The diffusion of the blood-plasma through the endothelial walls of the capillaries is so closely interwoven with the vital process itself that the need of a mechanism to regulate the pressure in the capillaries almost imposes itself. The regulation of the surface temperature, so important to the well-being of the entire organism, also seems to require the presence of a local mechanism capable of adjusting the cutaneous circulation to the needs of the moment. Blushing, which under the influence of emotion may occur suddenly and last as long as the emotion lasts, betokens the presence of something more than a system of fibers calculated to sustain vascular tonicity, especially when peripheral resistance is taken into account. The flushings of menopause, the "heat-waves" of various disorders, localized inflammation, etc., all of which occur irrespective of any general febrile state and fever itself, are but examples of many patho-physiological phenomena which point in the same direction.

All the evidence submitted in the foregoing pages not only

affords additional testimony to the effect that a more important mechanism is present at the threshold of the capillary system than has as yet been discerned, but it indicates a close parallelism between the physiological rôle of the heart and that of the arterioles. The heart's innervation consists likewise of cranial and sympathetic filaments by which the organ's contractile power and rhythm are regulated. Like the arterioles, it has great resistance to overcome, and does it by periodical muscular contractions—dilation to admit the blood it is to distribute through the arteries, constriction to project it into these vessels. Briefly, the arterioles, considered in this light, are, like the heart, contractile muscular organs which, owing to their contractility (governed by cranial and sympathetic nerves through impulses received from their respective centers in the posterior pituitary), are able to project and actually *propel* the blood with sufficient vigor to overcome resistance. While the heart impels its blood into the arteries, the arterioles project theirs into the capillaries—pumping each wave in, as it were.

We have striking examples of such a function in many lower forms, *i.e.*, animals in which a vessel may even fulfill the functions of a heart. "In the various groups of worms there are many which possess a very elaborate vascular system," writes Willey, "while not one of them possesses a heart. In fact, in the last mentioned forms, the place of a heart is taken, functionally, by *contractile blood-vessels*. And this is the case with Amphioxus"—a lively little animal, as any one knows who has handled it.

The manner in which the blood streaming through the arterioles is further propelled by the contractions of these vessels at each pulsation, suggests itself when a peculiarity in the structure of the muscular coat of these small arteries is taken into account. Berdal[38a] states that "muscle-cells form a single and continuous layer around the small vessel" and that "they are wrapped *spirally* around the arteriole." This is shown in the annexed plate. That they receive nerve-fibers, *i.e.*, sympathetic filaments, we have seen. Now, nerve-impulses to muscle-cells so disposed around a vessel, cause not only constriction, but also

[38a] Berdal: "Histologie Normale," p. 307, 1894.

—the contraction starting from the inner end of the spiral muscle and proceeding toward the capillary—centrifugal propulsion of the blood. This mechanism, which may be likened to that of a tight ring slid along a flexible tube, is a counterpart of that to which the propulsion of food-stuffs in the intestinal canal is due. Indeed, this parallelism appears to me very suggestive, since the intestines and arterioles represent in reality the extremities of the alimentary system: the intestines for the admission of food materials, and the arterioles for their distribution to the tissues.

As a corollary to the foregoing conclusions, I would suggest, therefore: (1) *that the cranial and sympathetic filaments distributed to the arterioles carry on an additional and more important function than that of maintaining their tonus;* (2) *that these nerves, owing to the presence in the walls of the arterioles of spirally disposed muscles, endow these vessels with a special property: that of increasing the vis a tergo motion of the blood in order to overcome the resistance of the capillaries.*

DRUGS WHICH PROMOTE THE FORMATION OF AUTO-ANTITOXIN AND INCITE AN ARTIFICIAL FEVER BY EXCITING THE VASOMOTOR AND SYMPATHETIC CENTERS.

"Since the researches of Claude Bernard, of Vulpian, of Kölliker," writes Richet,[39] "the term 'curarizing poisons' is given to many substances which, like curare, abolish the action of motor nerves upon muscles. The action of these substances," adds this eminent physiologist, however, "is hardly better known than that of curare itself. It is generally admitted that it is upon the intramuscular terminals that these poisons elect to attack; but we are far from being informed as to the modifications of which they are the seat." The list of the poisons referred to includes the alkaloids of drugs in general use, atropine, aconitine and brucine, for instance.

As interpreted from my standpoint, the prevailing belief that these drugs act directly upon the nerve-endings is erroneous and misleading.

That a motor nerve augments the volume of blood supplied to an organ, and thereby incites functional activity, was shown

[39] Richet: *Loc. cit.*, p. 622.

by Claude Bernard. Indeed, as emphasized by Arnold, Brown-Séquard, Budge, and recently by Jacques Loeb,[40] ganglia and nerves serve only to increase the inherent sensitiveness of a given structure by enhancing, through a greater blood supply, its intrinsic metabolism. I have just pointed out how this is accomplished, viz., by stricto-dilation of the arterioles of an organ. We have seen, moreover, that when the functions of this organ are to cease, the sympathetic fibers distributed to the muscular layer of its arterioles cause the latter to contract.

The effects of curare—and of the many poisons it exemplifies—are no longer obscure when this mechanism is taken into account.

It is now claimed that the classical experiments of Claude Bernard and Kölliker, in which ligation of the arteries of one leg protects it from the effects of the poison, prove that curare acts directly upon the peripheral tissues and not primarily on the central nervous system. This claim is unfounded, however, in the light of my views, since the immunity of the leg referred to can be explained in another way. Thus, if the injected curare, by acting directly upon the *sympathetic center*, were to cause sufficient constriction of the arterioles of the leg-muscles, ligation of the artery of that leg would also annul the effects of the poison in that leg, since the resulting ischæmia of the walls of the arterioles below the ligature would prevent the marked constriction of the sympathetic terminals, which causes paralysis by blocking the circulation to the nerve terminals, the muscles, etc. The poison, by irritating the central origin of the nerves to the arterioles, would thus paralyze all the muscles of the body with the exception of those of the limb, as observed experimentally.

As we will see, this general principle is applicable to many drugs, including anæsthetics and analgesics. In the case, at least, of some of the latter, the action on the sympathetic center is of such importance that the peripheral effects are arrested experimentally by section of the basal or spinal paths through which sympathetic impulses are transmitted.

Richet also says, however: "Nerve-cells are exceedingly varied, and the various poisons do not exert the same action

[40] Jacques Loeb: *Loc. cit.*, p. 36.

upon them. There are special affinities by this or that nervous element, for this or that poison. Atropine will fix itself upon the nerve-terminals of the motor cells of the third or tenth pair; curare, upon the motor nerves of vegetative life; muscarine, upon the cardiac ganglia; digitaline, upon the bulbar cardiac centers; cocaine, upon the sensory terminals of nerves." While the fact that the *local* application of the drugs referred to produces these effects, such is not the case (in the light of my views) when they are administered orally, subcutaneously or intravenously; all the "curarizing" drugs act in the manner specified above, viz., by exciting the sympathetic center, either alone or as one of the *centers* of a group for which the drug may have special affinity—precisely as it has for peripheral nerve-cells when applied topically.

The action of a drug upon the *vasomotor center*—affecting through it the larger vessels—is shown in the following experiment related by Leonard Hill:[41] "By the injection of essential oil of absinthe in a curarized animal, the vasomotor center can be excited to the discharge of a succession of powerful spasms, by each of which the *arterial pressure* is driven up *to a great height*. This phenomenon suggests a clonic fit of the center, the clonus of involuntary muscle naturally taking place at a far slower rate than that of skeletal muscles." It is evidently the action of the vasomotor center alone which caused the great rise of pressure, since—interpreted from my viewpoint—the curare had already excited the sympathetic center, producing excessive constriction of the arterioles and (what is now believed to be paralysis of the nerve terminals directly by the poison) ischæmia of the nerve-endings and arrest of their functions. The great rise of blood-pressure itself thus becomes a normal result of the obstruction presented by the constricted arterioles to the blood projected towards the periphery by the deeper and greater vessels which are themselves constricted, but through impulses from the vasomotor center. An important feature is emphasized by these facts, viz., that the vasomotor center can be stimulated independently of the sympathetic center, and *vice versa*.

These two centers may even be caused to antagonize each

[41] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 139, 1900.

other. Thus, as stated by Stewart,[42] a small dose of atropia, given hypodermically, "abolishes the secretory action of the chorda tympani." He also says, however, that "pilocarpine is the physiological antagonist of atropia, and restores the secretion which atropia has abolished," as first shown by Langley. Now, after atropia, by stimulating the sympathetic center, has caused hyperconstriction of the arterioles, the chorda tympani can no longer increase the flow of saliva when excited, because the arterioles are *kept* constricted by the sympathetic constrictors. This is overcome by pilocarpine, however, because it causes (1) "after a few moments," as stated by Wood,[43] "the characteristic phenomena of a slow pulse with increased arterial pressure"—which means that it excites powerfully the vasomotor center, the slowing of the heart being due to the increased resistance of the blood-column. This provides a mechanical agent capable of enforcing relaxation of the constricted arterioles: the centrifugal pressure of the blood projected into it by the deeper contracting arteries.

We thus have two centers acting individually, *sympathetic* and *vasomotor*, and peripheral effects which require no local action of the drugs to account for them. If we now add the *adrenal center*, influenced through the test-organ, and the reaction of which to toxics has already been shown, we have three centers which (simply because of their identity as the most highly organized sensitive structures of the body) are stimulated—or better, irritated—by certain agents, several of which are among our time-honored remedies.

The remedies studied in the present chapter will include those which, besides calling forth a reaction of the test-organ and through it increased functional activity of the adrenal center, excite (as a foreign constituent of the blood) either the sympathetic center or the vasomotor center. It will be shown that in each case the specific action of the drug is accounted for through the *combination of centers* affected, and the degree of irritation to which the drug submits each of them. Although the latter are always placed in evidence, and the data submitted, in accord with recorded experimental evidence, point

[42] Stewart: "Manual of Physiol.," p. 347, 1900.
[43] Wood: *Loc. cit.*, thirteenth edition, p. 724, 1906.

to them as the nervous elements (owing to their greater inherent sensitiveness) most actively excited by the drug, it is possible that in the case of some agents, strychnine for example, the subsidiary centers of the cord, bulbar and spinal, may be likewise excited as they are in the lower vertebrates, the frog, for instance. This applies mainly, however, to those drugs which affect the vasomotor (bulbar) center. In drugs of the coal-tar series, such as antipyrin and other antipyretics, for example, all effects cease when the base of the brain is transected far above the bulb and immediately in front of the pituitary body—the organ which contains the adrenal and sympathetic centers.

A salient fact asserts itself in this connection, however, *viz.*, that drugs administered internally invariably affect nerve-cells of the spinal system only. There is no tangible proof in support of the prevailing belief that drugs, belladonna and cocaine, for instance, produce delirium by acting directly on the cerebral nerve-cells; while, conversely, there is ample evidence to the effect that hyperæmia of these cells—especially in view of the fact pointed out by myself that adrenoxidase-laden plasma circulates in nervous elements as it does in all other cellular elements—can provoke this symptom. Hyperæmia is purely a motor phenomenon, *i.e.*, an excess of blood driven into the brain by excessive vasomotor activity. We have in the cutaneous hyperæsthesia produced by corresponding drugs, not only evidence to this effect, but proof that the sensory elements—such as those of which the *entire* cerebrum is composed—(though capable of transmitting impulses to the cord which therein awaken motor stimuli) can be rendered overactive by a supranormal supply of blood.

On the whole, in the light of my views, (1) *drugs administered by the mouth or hypodermically produce none of their effects by acting directly on peripheral structures, including the cerebrum, heart and cutaneous sensory nerve organs;* (2) *they invariably do so by stimulating or depressing one or more centers in the spinal system, and particularly, and in many instances solely, those located in its chief center, the posterior pituitary body.*

The drugs reviewed in the present chapter are those which

—as I interpret their physiological action—stimulate the three centers referred to—all of which influence the body at large. When stimulated by either of these drugs, the *sympathetic center* reacts in its own specific way. In other words, it is the function of the sympathetic terminals to regulate the tonus of the arterioles, *i.e.*, their mean caliber during their dilation and contraction at each pulsation, and it is this function that they exaggerate when their center is excited: they reduce this mean caliber. At first, however, or when small therapeutic doses are given, this serves only to *increase the propulsive activity of the arterioles*, for the abnormal narrowing of these vessels is followed by their *reflex* dilation (stricto-dilation from my viewpoint)—a generally recognized function, the increase of the propulsive power being due to the fact that both dilation and contraction of the vessels are exaggerated. Gradually as the dose is increased, however, the sympathetic stimuli become so energetic that the arterioles are kept constricted, the vasodilator reflex action being increasingly overpowered. Finally, their constriction becomes such that their lumen is obliterated, a condition which entails death by arrest of the circulation in the heart muscle.

The drugs which excite the *vasomotor center*, by provoking constriction of the larger and deeper vessels, force an increased volume of blood towards the periphery. The arterioles may not only remain passive under these conditions, but they may be forcibly dilated by the centrifugal streams, and the blood invade the tissues. The symptoms of excessive hyperæmia witnessed, cerebral, muscular, etc., are but normal results of such a process.

The drugs reviewed in the present section are all able more or less actively to excite the test-organ, and thus to increase, through the *adreno-thyroid center*, the volume of adrenoxidase and thyroidase produced. This means that they can enhance the protective properties of the blood by augmenting its proportion of auto-antitoxin. The main subjective phenomenon awakened is a rise of temperature, the adrenal center being, as I have shown, the heat or thermogenic center. Although the adrenal center is alone mentioned in this connection, it is because the only phenomena in evidence are traceable only to this

center. That its "thyroid" moiety is also active is probable, however, since an increase of adrenoxidase involves a corresponding increase of all its constituents, including thyroidase.

The effect produced by the simultaneous excitation of various combinations of these three centers can be best illustrated by an outline of the mode of action of the various drugs treated in this chapter. It will serve to show, moreover, that notwithstanding the simpler explanation of their action which I submit, the specific action of each drug remains clearly defined.

The physiological action of *belladonna* and *atropine* illustrates the joint action of the adrenal and sympathetic centers. A protective reaction of the test-organ being provoked, the blood is rendered richer in adrenoxidase and therefore in auto-antitoxin. The sympathetic center being simultaneously excited, the propulsive activity of the arterioles is enhanced and an unusual quantity of blood rich in adrenoxidase and auto-antitoxin is thus projected into the capillaries of all organs. Hence the cutaneous hyperæmia and other symptoms observed. The beneficial effects thus become plain: it initiates an artificial fever, and enhances circulatory activity in exposed organs. Its toxic effects become manifest through the sympathetic center, the result being excessive constriction of the arterioles of the heart and anterior pituitary, the circulation in these organs becoming inadequate to sustain life.

Digitalis likewise stimulates the two centers affected by belladonna. Indeed, like atropine, digitaline in large doses causes dryness of the throat, dilation of the pupil, hallucinations, etc. Digitalis differs from belladonna, however, in that it excites much more actively the adrenal center, and with less vigor the sympathetic center. The blood is thus not only made richer in adrenoxidase and other substances which sustain metabolism and nutrition, but, the center which governs the propelling power of the arterioles being activated, the nutritional elements are driven into the tissues, including the vascular and cardiac muscle, with unusual vigor. The energy with which digitalis excites the test-organ, and through it the adrenals, manifests itself in another way: the direct action of the excess of secretion on the right ventricle. So marked is this action that large doses disturb the synchronism of the two