ventricles. It is through both the arterial and venous blood it receives that the heart's power is increased and sustained by adequate nutrition.

Nux vomica and *strychnine* introduce another combination: stimulation of the adrenal center (through the test-organ) and of the bulbar vasomotor center. Here, the metabolic activity of all organs and their nutrition is likewise enhanced, but instead of activating the sympathetic center which increases the propulsive power of the arterioles, strychnine excites the vasomotor center only, and by thus provoking constriction of the deeper vessels, it causes a greater volume of blood to circulate in the smaller vessels and capillaries. Therapeutic doses, therefore, thus transfer to the arterioles an unusual quantity of blood—and thereby enable these small vessels to nourish the tissues more actively. When large doses are given, however, the stream forcibly dilates the arterioles, and highly oxygenized blood invades the cerebro-spinal system, the muscles, the skin, etc., in such quantities that convulsions occur.

Coca and *cocaine* assert themselves as more powerful stimulants of the test-organ and adrenal center than either belladonna, digitalis, or strychnine. The resulting marked increase of adrenoxidase in the blood not only augments correspondingly the activity of all metabolic processes, but as both coca and cocaine, like strychnine, excite the bulbar vasomotor center, this blood is projected in greater quantity into the arterioles, and, therefore, into the tissues. The characteristic effect of coca on the muscular system is due mainly, therefore, to its very marked action on the adrenal center, sustained by the rise of vascular tension, which floods, so to say, the muscular elements with highly oxygenized blood. The kinship with belladonna is shown by the fact that it causes, in large doses, dilation of the pupil, dryness of the mouth and throat, etc.; with digitalis, by its powerful action on the heart-muscle; and with strychnine, by its marked action on all muscles and its tendency in toxic doses to produce convulsions, the so-called "cocaine epilepsy."

Quinine introduces a different phase of action, *viz.*, irritation of an increasing number of centers as the dose of the drug is increased. Thus, when given in therapeutic doses, it excites

the vasomotor center, causing peripheral hyperæmia; larger doses excite the sympathetic center besides; still larger doses excite the test-organ in addition to the two others, and through it the adrenal center. The effects produced thus begin with slight cutaneous warmth and hyperæsthesia, and gradually, as the dose is raised, increase to headache, flushing, tinnitus, etc., and then, in some cases, to a marked rise of the temperature. The latter effect is shown to be due to the specific property which quinine shows prominently in malaria, *i.e.*, a direct toxic action upon certain parasites, including the plasmodium malariæ—but, unfortunately, the leucocytes also. This action is exercised irrespective of the influence of the drug upon the various centers, but the latter assists materially the curative process by causing a greater volume of blood to circulate in the capillaries—which include those of the liver and skin—thereby bringing about an artificial febrile process in which the quinine acts as the body's immunizing agent.

That these simplified conceptions of the physiological action of these various drugs are sound, is shown by the fact that in every instance the indications they suggest in the many diseases in which they are used harmonize perfectly with the teachings of clinical experience.

Idiosyncrasy.—This term is applied to the marked susceptibility shown by many persons to the action of various drugs. The cause of this phenomenon becomes evident when, in accord with my views, nerve-centers are regarded as the structures directly irritated by drugs. In the first volume I referred to the posterior pituitary body as the *sensorium commune, i.e.*, as the organ through which all violent emotions, shock, surgical shock, etc.—and to which I may add another obscure phenomenon, concussion, react upon the organism at large, all owing to the extreme sensitiveness of its highly organized centers. That blood contaminated by irritating drugs, poisons, toxins, etc., in circulating in the nervous elements of such an organ, should readily excite these elements is self-evident. That such blood should not excite these centers to the same degree in all individuals, however, is as obvious; it is here that, in my opinion, the secret of idiosyncrasy lies, viz., in *an abnormal sensitiveness*

of the nerve-centers upon which drugs act, and particularly the sympathetic center.

This feature of the problem is illustrated by the action of some of the drugs studied in the present and in the next chapters.

BELLADONNA AND ATROPINE.

Physiological Action.—Belladonna and its alkaloid, atropine, owe their therapeutic properties to the fact that they stimulate (1) the test-organ (anterior pituitary), and through it the adrenal center;* and (2) the sympathetic center (posterior pituitary), which governs the tonus and propulsive activity of the arterioles.*

The experiments of Lombard,[44] confirmed by Calmette,[45] have shown that the leucocytes ingest atropine injected in the blood, and that the latter itself contains but a very small proportion of the poison. As these cells ultimately secrete their contents, the drug is doubtless returned to the circulation, as is the case with other drugs. The influence of the drug upon the test-organ and adrenal center (which is also the heat or thermogenic center) is shown by its marked influence upon the temperature. Thus, Meuriot[46] observed, in man, an elevation of temperature ranging from 0.5° to 1.1° C. (0.9° to 2° F.) after the use of therapeutic doses, and refers to Eulenburg as having made a similar observation. He also obtained in dogs, from doses corresponding with the equivalents of therapeutic doses in man, a rise of from 1° to 3° C. (1.8° to 5.4° F.) and alludes to Duméril, Demarquay and Lecointe as having caused a *rise* of 4° C. (7.2° F.) after *small* doses, and a *fall* of 3° C. (5.4° F.) after *toxic* doses. That this rise is due to excitation of the adrenal center, where I located the heat-center, is shown by the experiments of Ott and Collmar,[47] who found that the rise of temperature occurred irrespective of the variations of blood-pressure, and ascribed it, therefore, to a stimulating action of the drug on the thermogenetic centers. Again, we have seen that excitation of the test-organ, and through it the adrenal center, caused glycosuria; now Raphaël[48] not only observed glycosuria when atropine was used experimentally, but also in individuals under the influence of large doses.

The action of atropine upon the vascular mechanism is generally recognized. That it is the arterioles which are mainly influenced (since all vessels are to a certain degree constricted through the presence of an excess of adrenoxidase in the blood) is shown by the fact that toxic doses produce arteriole hyperconstriction, *i.e.*, "inhibition." Thus Bezold and Bloebaum[49] found that when large doses of atropine were injected into the brainward blood-stream, *i.e.*, the carotid, the heart was at once greatly slowed. That this is due to paralysis of the heart through

* *Author's conclusion.*
[44] Lombard: Thèse de Paris, 1901.
[45] Calmette: Cited by Labbé: *Loc. cit.*
[46] Meuriot: Thèse de Paris, 1868.
[47] Ott and Collmar: Therap. Gaz., Aug., 1887.
[48] Raphaël: Deut. med. Woch., Bd. xxv, S. 451, 1899.
[49] Bezold and Bloebaum: Untersuchungen aus der physiol. Lab. zu Würzburg, B. I.

deficient blood supply is shown by Cushny's statement,[50] that large quantities of atropine "weaken and depress the heart muscle, and the contractions consequently become slower and weaker, and the output of the heart is less than normal."

The central origin of all the phenomena produced by belladonna and atropine is demonstrated by the fact that Bezold and Bloebaum[51] found transection of the upper portion of the spinal cord annulled its action on the blood-pressure, a fact confirmed by Wood.

By its action on the test-organ and adrenal center belladonna increases the proportion of adrenoxidase in the blood, while by its action on the sympathetic center, it enhances the blood-propelling power of the arterioles.* As a result, the capillaries of the entire organism are traversed by a supranormal quantity of arterial blood unusually active in oxygenizing properties.* Hence the sensation of warmth in the skin and mucous membranes, and the rise of temperature and transient flushing, observed even when small doses are taken.* This is soon accompanied by dryness of the throat, owing to capillary engorgement of the acini in the latter and of the sudoriferous glands in the skin, and mechanical interference with their functions.

When the dose is large, various symptoms due to hyperæmia and hypermetabolic activity in the organs influenced* are witnessed. Thus, a bright red flush, recalling that of scarlatina, though more diffuse, may appear on the face and gradually involve the entire surface. Slight congestive headache, with giddiness, insomnia, mental confusion, garrulousness with illusions, delirium, which may become violent, visions, etc., are also observed, along with, in some cases, priapism, muscular restlessness and forcible micturition, due to more or less sudden involuntary contraction of the bladder. The pulse-rate is also greatly increased, and the cardiac contractions (unless toxic doses be taken) strong, owing to similar overactivity of the cardiac muscle.*

Cushny[52] states that the cause of the rise of temperature induced by atropine "cannot be said to be definitely known." The presence of an excess of adrenoxidase in the blood, coupled with the capillary engorgement, as previously explained, accounts not only for this phenomenon, but also for the familiar symptoms outlined above. The concurrence of the pyrexia with cutaneous disorders is plainly shown in all cases attended with untoward effects. In a case brought on by the use

* *Author's conclusion.*
[50] Cushny: *Loc. cit.*, fourth edition, p. 286, 1906.
[51] Bezold and Bloebaum: *Loc. cit.*
[52] Cushny: *Loc. cit.*, fourth edition, p. 288, 1906.

of atropine as a mydriatic, observed by Spurgin,[53] for instance, a diffuse rash resembling that of scarlet fever, observable also in the fauces, coincided with a temperature of 102.7° F. and a pulse-rate of 140. In another instance reported by the same observer, the cutaneous lesions were not quite as marked, the temperature was 101.3° F. and the pulse-rate 116. In both cases the morbid symptoms disappeared on discontinuing the use of the drug.

The mydriatic action of atropine is due to a corresponding process when the drug is given internally.* Here, however, there are two sets of muscles: the constrictor fibers, which cause contraction of the pupil, and the dilator fibers, which act in the opposite way. As both muscles are rendered overactive by the excess of arterial blood rich in adrenoxidase propelled into them by the arterioles, the delicate muscular equipoise which enables the pupil to carry on its functions is lost and it becomes a question as to which of the antagonistic muscles will overcome the other.* The radiating fibers being best disposed mechanically (owing to direct traction),* they draw back the edges of the iris, enlarging the pupil.

The local application of atropine produces the same effect, but in a different way.* It paralyzes directly the sympathetic terminals* of the arterioles, thus causing dilation of these vessels. An excess of blood being admitted to the muscular elements of the iris,* the antagonistic action of the muscles is awakened* and the radiating fibers cause dilation of the pupil by drawing back the iridial curtain.

Landois (1905) concludes[54] that "as to the action of poisons on the iris [including atropine] ignorance still prevails." The greater contractile power of the radiating muscles when the functional equipoise between the two sets of muscles is disturbed is well shown by the observations of Bernstein and Dogiel, confirmed by Engelhardt,[55] that when electrodes were applied "to the eyes in such a way as to affect directly the iris, contraction occurred."[56] Again, the dependence of the process upon some difference in the relative power of the antagonistic muscles is suggested by the fact that in birds and reptiles atropine does not cause dilation of the pupil (Wharton Jones, Ivanoff, Wood and others).

The muscular antagonism and the participation of the sympathetic in the process are shown by the following lines by Cushny:[57] "A further question is whether this [paralysis] is the only effect of atropine on the pupil, or whether the terminations of the dilating *sympathetic fibers* are not *stimulated* at the same time, and this cannot as yet be said to be generally agreed upon, although there is very strong evidence against the latter view. Its advocates have generally ignored the fact

* *Author's conclusion.*
[53] Spurgin: Lancet, Sept. 30, 1905.
[54] Landois: *Loc. cit.*, p. 843, 1905.
[55] Engelhardt: Untersuchungen a. d. physiol. Lab. zu Würzburg, ii, S. 321.
[56] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 177, 1906.
[57] Cushny: *Loc. cit.*, fourth edition, p. 284, 1906.

that the constrictor muscle is constantly opposed by dilator fibers, and that when the former is thrown out of activity by the paralysis of the terminations of the motor oculi, the radiating fibers cause an *active* dilatation without any stimulation of the nerve ends being necessary." The prevailing misinterpretation of the functions of the sympathetic and the multiplicity of functions erroneously attributed to this nerve account for the vulnerability of the views Cushny criticizes. If, setting aside assumptions, we accept the only actually demonstrated function of sympathetic terminals, that of constricting arterioles, as a foundation for deductions, the ground for criticism disappears, since the only solidly established fact concerning the *local* action of atropine, paralysis of nerve-endings, also comes into play. By paralyzing the sympathetic constrictors, therefore, the vessels are allowed to relax and to influence the muscular fibers differentially—a process which necessarily brings in the antagonistic action of the muscular fibers of iris referred to by Cushny. The hyperæmia produced by the dilation of the arterioles not only accounts for the dilation of the pupil, but the fact that hyperæmia is likewise the mode of action when atropine is given internally, and that the phenomenon is explained by a process provoked by the drug in all other organs, indicates that the explanation I submit must be the correct one.

Untoward Effects and Poisoning.—When a large dose is taken, the symptoms of a therapeutic dose, dryness of the mouth and throat, thirst, and dysphagia, rapidly increase in intensity, the propulsion of blood by the arterioles into the capillaries assuming greater violence.* The cutaneous flush then becomes very marked; the congested brain and cord cause violent excitement, delirium, spasmodic choreiform movements of the face and extremities, and also convulsions, during which the patient may die.

When large toxic doses are taken, the sympathetic center is more violently irritated than the others, and hyperconstriction of the arterioles follows.* Those of the anterior pituitary and heart being contracted with the rest, inhibition of their functions occurs,* and collapse is brought on more or less suddenly. Intense muscular weakness which soon lapses into paralysis, particularly of the lower extremities, a rapid, then slow, weak and irregular pulse and heart-beat, shallow and irregular respirations, stupor and coma then follow in quick succession, the patient dying of respiratory failure.

Autopsies of cases in which death occurs during the period of intense vascular engorgement show this condition very clearly in all tissues, including the brain and cord. "At the autopsy of a subject poisoned by belladonna," writes Manquat,[58] "no characteristic lesion is found; the changes witnessed are limited to a considerable hyperæmia of the cerebro-spinal meninges and of the cortex, congestion of the par-

* *Author's conclusion.*
[58] Manquat: *Loc. cit.*, p. 760, 1903.

enchymatous organs and of the mucous membranes, dryness of the throat, and a few ulcerations or sphacelous areas of the stomach." Wood[59] says the post-mortem lesions are "congestion of the lungs and of the membranes, and even of the substance of the brain and cord," and refers to Lematre's[60] observation that "congestion of the retina is an almost characteristic lesion."

The *treatment of belladonna and atropine poisoning* is described in a special section at the end of this volume.

Therapeutics.—The many therapeutic virtues that have been credited to belladonna are sustained by the foregoing analysis. Not only does it provide the blood with an excess of adrenoxidase, and, therefore, of auto-antitoxin, but it stimulates also the centers which augment the circulatory activity of the blood where its antitoxic properties can be productive of the best results.* In short, belladonna, owing to its alkaloid, atropine, produces an artificial fever.*

It is principally in disorders of the respiratory system that belladonna and its preparations are most efficaciaus. The various disorders due to *exposure to cold* and damp, are brought about by the sudden depression of catabolic activity* in the tissues, the trypsin, which plays the active rôle in the process, requiring the normal temperature of the body to break down waste products adequately. Cold, by inhibiting this process, causes the accumulation of imperfectly catabolized wastes in the blood and its consequences—*coryza, pharyngitis, tonsillitis,* or *bronchitis,* the location of the disorder corresponding usually with one which previously has been the seat of catarrhal congestion. Here, belladonna by increasing the antitoxic activity of the blood in all capillaries and raising the temperature therein, not only antagonizes directly the morbid effects of cold, but causes prompt destruction of all toxic wastes.*

In *bronchial asthma, neuralgia, migraine* and *hay-fever,* ascribed to the gouty "diathesis," which means the presence of alloxuric bases or intermediate waste products in the blood, belladonna is beneficial through a similar process.* In *asthma* due to hypotension of the arteries, it is also efficacious by increasing the blood's asset in adrenoxidase and causing thereby a rise of blood-pressure and more perfect oxygenation, thus meeting the two morbid factors of the disorder. Spasm, such as that of *rheumatic torticollis, dysmenorrhœa, enuresis* due to cystic irritability, etc., are also due to hypocatabolism in many instances, and atropine, by promoting the destruction of spasmogenic wastes, causes muscular relaxation.

The reported beneficial effects from the use of atropine in infectious *erysipelas, scarlet fever, typhus,* etc., are doubtless due to the fact that it increases the antitoxic properties of the blood. Its tendency to cause dryness of the mouth and skin, however, is a contraindication to its use.

In asthenic disorders atropine is of great value. In *shock,* which is due mainly to paresis of the sympathetic center,* it is the best drug at our disposal; not only does it act directly upon the paretic center,* but it raises the blood-pressure and restores the capillary circulation of the heart and skin to its normal vigor*—provided alcohol is avoided. This applies as well to *collapse* in the asthenic stage of any disease, including the acute infections, especially when the heart is showing evidences of weakening. It is also one of the most effective remedies at our disposal for the relief of *night-sweats* in phthisis or the *colliquative sweats* that attend the advanced stages of many diseases. This symptom is likewise due to general vasodilation and to relaxation of the sudoriferous mechanism. Atropine not only tends to correct this condition, but also to counteract any toxæmia that may be present.*

DRUGS WHICH RESEMBLE BELLADONNA IN THEIR PHYSIOLOGICAL ACTION.

The physiological action of *homatropine hydrobromide, hyoscyamus, hyoscyamine sulphate* and *stramonium* is similar to that of belladonna, though their effects are less marked, their stimulating influence on the various centers mentioned being less violent.

DIGITALIS.

Physiological Action.—In therapeutic doses digitalis increases the nutrition of the heart and its functional power.

* *Author's conclusion.*

[59] Wood: *Loc. cit.*, thirteenth edition, p. 170, 1906.

[60] Lematre: Cited by Tardieu: "Etude médico-legale et clin. sur l'Empoisonnement," p. 752, Paris, 1867.

* *Author's conclusion.*

This is due to the concurrent influence of three effects produced by the drug.* Two of these are direct and energetic stimulation of the test-organ and through it the adrenal center, and also, but with less violence, the sympathetic centers, which enhances the propulsive action of the arterioles. As a result of the first action, the proportion of adrenoxidase in the blood is increased and general metabolism is enhanced throughout the body.* The muscular elements of the blood-vessels and of the cardiac muscle being influenced similarly,* their contractile power is increased, though the heart's action is slowed by the augmented resistance which the reduced caliber of the vessels entails.

"In our experiments upon the exposed mammalian heart," writes H. C. Wood,[61] "we have seen in the final acts of digitalis drama happenings so curious and unexpected that at present no proposed theory as to the action of the drug is sufficient." This is mainly due to the belief that the drug acts directly upon the heart as it does experimentally. That it does not, however, is shown by the following facts: The weakest solution that will act on the isolated heart at all is that of 1 to 50,000. To produce any effect in an adult man supplied with but 13 pounds of blood, therefore, at least 1 grain (0.06 gm.) of digitalin would have to be given orally, since $^1/_4$ grain, "the full therapeutic dose" (Wood), would only make a solution of 1 to 200,000. The hypodermic use of the drug shows a still greater discrepancy, since Deucher[62] found tnat a dose of digitalis thus given produced the effects of a dose four times larger administered orally. A solution of digitalin in the blood-mass of 1 to 800,000 (equal to $^1/_{16}$ gr.—0.004 gm.) thus becomes active, though totally inadequate experimentally, *i.e.*, though sixteen times weaker than the weakest solution that will affect the isolated heart. And this allows nothing for the antitoxic action of the blood, wnich further reduces the strength of the drug, or for any dispersion in the lymph mass, which is twice greater than that of the blood. Nor does it allow for the fact that an isolated heart does not have to overcome the resistance of the blood-column which it must raise each time it contracts.

This is further emphasized by the fact that division of the adrenal and vasomotor nerve-paths from the pituitary annuls the effects of digitalis. Thus, transection of the *upper* part of the spinal cord was found by Bezold and Boehm[63] to cause a very marked fall of blood-pressure in an animal under the influence of digitalis, while Traube and Boehm and others[64] found "that after section of the cord high up the arterial pressure is either elevated not at all, or not nearly so much, by digitalis as in the normal animal." Wood (Sr. and Jr.) regard this as "a strong indication that the drug increases the arterial pressure largely by increasing the peripheral resistance without centric vasomotor stimulation." This points also to adrenals as the source of the vasoconstricting influence, for Langley[65] found, in a series of experiments with adrenal

* *Author's conclusion.*
[61] Wood: *Loc. cit.*, thirteenth edition, p. 318, 1906.
[62] Deucher: Deut. Archiv f. klin. Med., Bd. lviii, S. 47, 1897.
[63] Boehm: Archiv f. d. ges. Physiol., Bd. v, S. 153, 1872.
[64] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 319, 1906.
[65] Langley: Jour. of Physiol., vol. xxvii, p. 237, 1901.

extract, that its action "runs parallel with the action of the sympathetic nerves on the blood-vessels," and that "in many cases the effects produced by the extract and by electrical stimulation of the sympathetic nerve correspond exactly." Now, as the peripheral arterioles are governed by the sympathetic, the adrenal secretion corresponds in its action with that of this nerve, because its action (as adrenoxidase) on the arterioles is the first to manifest itself, owing to their diminutive size. Now, digitalis, acting mainly *through the adrenal secretion*, also increases the peripheral resistance—but not by a direct action of the drug as is generally believed.

The effects of digitalis on metabolism, in consequence of its action on the adrenal center, is well shown in the following lines by Manquat:[66] "The exchanges are increased, and oxidations augmented, and urea is excreted in greater abundance. According to von Broeck, the modifications of urea and carbon dioxide correspond with that of the blood-pressure: the elimination of urea and carbon dioxide increases as long as the pressure remains high; it diminishes when the blood-pressure recedes." The effect of therapeutic doses under these conditions suggests itself. "There occurs," says Cushny,[67] "an improved nutrition of the whole body," while after the use of digitalis and its allies in dilation of the heart, this organ "is found better nourished and has more of a tendency to hypertrophy." This applies also to the marked rise of blood-pressure. Thus, Wood[68] states that after a full dose of suprarenal capsules, "there is developed a slow, full pulse, followed very shortly by a great rise of the blood-pressure,"—precisely the action of digitalis.

The nutrition of the heart-muscle, along with that of all other structures, is aided materially by the slight (only when the average therapeutic dose is given) stimulating action which the drug has upon the sympathetic center, and therefore upon the blood-propelling activity of the arterioles.* Hence,* the fact that besides the rise of blood-pressure and the greater power of the contractions referred to above, the pulse-waves become larger, fuller and harder.

The action of the drug on the sympathetic center is illustrated by the concordance between the effects of direct stimulation of the pituitary body and those of digitalin on the blood-pressure. The only two centers in the pituitary which, on excitation, can produce such an effect are the adrenal center and the sympathetic center. That it is the latter is shown by the fact that the pressure begins to recede *at once* (reaching, in fact, below the normal within one minute) when the stimulation ceases—which would not occur if the adrenals were also stimulated, since the excess of secretion would not only cause a rise of pressure, but sustain it for a time. The similarity of the effects referred to are shown by the following comparative tables prepared by independent experimenters: Arnold and H. C. Wood, Jr.,[69] and Masay:[70]—

* *Author's conclusion.*
[66] Manquat: *Loc. cit.*, vol. ii, p. 17, 1903.
[67] Cushny: *Loc. cit.*, fourth edition, p. 452, 1906.
[68] Wood: *Loc. cit.*, eleventh edition, p. 513, 1900.
[69] Arnold and H. C. Wood, Jr.: Amer. Jour. Med. Sci., Aug., 1900.
[70] Masay: Annales de la Soc. roy. des sci. méd. et natur. de Bruxelles, T. xii, p. 1 to 30, 1903.

DIGITALIN.
(*Arnold and H. C. Wood, Jr.*)

Dog: 9.5 kilograms.	PRESSURE.
Prior to injection.....	80 mm. Hg.
1 hour 10 min. after 0.02 gm.	104 " "
30 min. after injec. of 0.04 gm.	122 " "
After division of both vagi:—	
Dog: 8 kilograms.	
Prior to injection.....	167 mm. Hg.
50 min. after 0.04 gm.	200 " "
1 hours 40 min. after.	140 " "
4 hours 20 min. after.	240 " "

PITUITARY, EXCITATION OF.
(*Masay.*)

Dog: 2.6 kilograms.	PRESSURE.
Prior to excitation....	81 mm. Hg.
First excitation	144 " "
Second excitation	200 " "
After division of both vagi:—	
Dog: 5 kilograms.	
Prior to excitation....	162 mm. Hg.
First excitation	280 " "
After 15 seconds.....	270 " "
Second excitation	252 " "

On the digitalin side the pressure is sustained, of course, because the stimulation of the adrenal and sympathetic centers persists until the blood rids itself of the poison. This accounts for a feature of the problem which so far has escaped notice, *viz.*, that the effects of digitalis are practically identical with those of suprarenal extract. Wood[71] describes (under separate headings) these effects in the following words:—

DIGITALIS.

"During the first stage there is marked slowing of the heart's beat, with large, full, hard pulse-waves and pronounced rise in the arterial pressure."

SUPRARENAL EXTRACT.

"When to an animal the full dose of suprarenal capsules is given there is developed a slow, full pulse, followed very shortly by a great rise of the blood-pressure."

The third effect of digitalis is also due to its stimulating action on the adrenal center.* The adrenal secretion being considerably increased, it enhances the contractile power of the right ventricle while in transit through it on its way to the lungs.* Hence the dicrotism and other phenomena which point to loss of parallelism between the action of the ventricles when large doses are administered.*

As to the third factor, *i.e.*, the direct action of the adrenal secretion on the right ventricle, we have seen,[72] that Brown-Séquard, over fifty years ago, emphasized the importance of the *venous* blood in cardiac dynamism, and that his belief that CO_2 was the active agent in the process caused his observations—all solidly established experimental facts—to be set aside. I pointed out, however, in the first volume that the effects observed were due to the presence of the adrenal secretion in the blood of the inferior vena cava, Oliver and Schäfer having shown that adrenal extract could cause marked contractions of the cardiac muscle. Digitalis being a powerful adrenal stimulant, it should normally increase the contractile power, *not* of the left ventricle, with which it does not come into contact, but *only* of the right—an important point in practice. Now, Germain Sée[73] has laid stress on the fact that digitalis acts mainly on the right ventricle. Openchowski,[74] who had also found, in 1889, that the action of digitalis was greatest on the right side of the heart, recently noted diminution of the activity of the left ventricle—a true functional dissociation. Cushny likewise[75] states that digitalis, strophanthin and helleborein all "increase the output of the right ventricle."

* *Author's conclusion.*
[71] Wood: *Loc. cit.*, eleventh edition, pp. 297, 513, 1900.
[72] *Cf.* this vol., p. 807.
[73] Germain Sée: Sajous's "Annual and Analyt. Cyclo.," vol. ii, p. 526, 1898.
[74] Openchowski: Berl. klin. Woch., Bd. xli, S. 1045, 1904.

The kidneys being subjected to all the conditions which digitalis awakens in other organs, their functional activity is enhanced by doses sufficiently large to increase the propelling power of the arterioles and the intrinsic metabolism of their functional elements.* Hence the *diuresis* produced by digitalis.* Conversely, when the dose is excessive, the renal arterioles become so constricted that functional inhibition, *i.e.*, *anuria*, occurs.

The first action is self-explanatory in view of the evidence adduced above. As to the constrictor effects, Lauder Brunton[76] writes: "Digitalis contracts the arterioles of the kidney sooner than those in other parts of the body. The renal vessels may contract so much as to arrest the secretion of urine altogether, although the general blood-pressure is high."

Untoward Effects and Poisoning.—Digitalis, especially when administered during a prolonged period and in small doses, may cause a variety of untoward phenomena. In some cases, these are mainly due to what has been termed "*cumulative action*"—which, from my viewpoint, means hypersensitiveness of the sympathetic center, a condition due to the persistent excitation to which the drug submits it. At first the sympathetic center is overstimulated and undue propulsive activity of the arterioles* causes headache, hallucinations and delirium, dryness of the throat through crowding of the lumina of the acini, dilation of the pupil, abdominal cramps, digestive disorders, pains in the limbs recalling those of rheumatism. These symptoms may be accompanied by disturbance of the cardiac rhythm, dicrotism, etc., due to excessive stimulation of the right ventricle.* After a time, however, the sensitiveness of the sympathetic center being greater than that of its fellow,* its own phenomena take the lead:* hyperconstriction of the arterioles is produced, and signs of collapse may appear, including weakness and irregularity of the cardiac action, due to impending arrest of cardiac functions, the case culminating perhaps as one of acute poisoning.

* *Author's conclusion.*
[75] Cushny: *Loc. cit.*, fourth edition, p. 448, 1906.
[76] Lauder Brunton: Trans. of the 13th Inter. Med. Congr., Sect. on Therap., p. 263, 1900.

In acute poisoning, the patient passes through the stage of hyperæmia—which may include violent headache, flushing, muscular pains, vomiting, delirium, etc.—more or less rapidly, then into the stage of depression, just referred to. The heart action becomes irregular, and on exertion, such as sitting up or rising, extremely weak; the ventricles and auricles may no longer beat synchronously; the two ventricles likewise, or portions of the myocardium, may dilate, while others still contract. Hence the irregular action, the occasionally observed blowing systolic murmur, the dicrotic, rapid, weak, irregular and broken pulse. The vascular pressure suddenly drops, concomitantly with general relaxation of the entire muscular system, as shown by the intense muscular prostration, the anuria—due, in part, to inaction of the bladder—the lowered reflex activity (François-Franck[77]) and the widely dilated pupil. Paroxysms of suffocation occur, the adrenal secretion and its carrier, the venous blood of the inferior vena cava, being no longer propelled to the pulmonary alveoli by the cardiac muscle.* Hence* the steady fall of temperature, the cold extremities, the growing pallor and the stupor.

A symptom of another order may appear in this connection towards the end of this stage: the gradual diminution of the blood's antitoxic attributes preventing the adequate conversion of toxic wastes into benign and eliminable products,* convulsions appear. A recurrence of very elevated blood-pressure then occurs, followed by a very rapid fall and death.

That the arterioles play the cardinal rôle in these morbid phenomena has been observed by various investigators. Wood[78] refers to the experiments of Fothergill,[79] Gourvat and Ackermann,[80] who found microscopically that "the *arterioles* of the frog's web or of the mesentery of the rabbit undergo very marked contraction, even to the *obliteration of their lumen,* after the exhibition of digitalis." Weil[81] also noted that the reflex activity of the spinal cord practically disappeared when large doses were given. The drug caused such intense vasoconstriction that the central and peripheral circulations were impeded, and the nervous elements, deprived of blood, lost their irritability. Porter,[82] after an exhaustive physiological study of the *cumulative* action of digitalis, found that it was the result of excessive contraction of the heart's arterioles and of the consequent arrest of the nutrition of the myocardium. Suggestive in this connection is the fact that transection of the upper part of the cord by Traube, Bezold and Boehm (a procedure which, we have seen, arrests the effects of digitalis) at once restored normal conditions in poisoned animals—obviously by causing relaxation of the arteries. This result could not have occurred if the vasoconstriction had, as is now believed, been due, even in part, to a direct action of the drug upon the vascular walls.

A fatal issue occurs rarely, according to Potain,[83] death from digitalis being most frequently met with in subjects suffering from Bright's disease, a rheumatic diathesis, anæmia or delirium tremens. Hence the need of special watchfulness in such cases. The prevailing opinion at present is that the dangers of digitalis have been greatly exaggerated. Henry Beates, Jr.,[84] who uses digitaline (Merck's Germanic) in relatively large doses, and obtains excellent results, is of this opinion.

The *treatment of digitalis poisoning* is described in a special section at the end of this volume.

Therapeutics.—The foregoing interpretation of the physiological action of digitalis accounts fully for its beneficial action in certain cardiac disorders. Thus, in *uncomplicated dilation,* in which the heart-muscle fails to contract adequately, a condition usually occurring as a result of general adynamia, digitalis, or better digitalin, not only enhances markedly the nutrition of the body at large, but that of the heart in particular, increasing greatly its dynamic power. In *dilation due to a valvular lesion,* mitral in most cases, and due to the increased resistance of the blood-column, digitalin is of great value to aid the heart in overcoming the obstruction. Even when the *valves of both sides* are diseased the drug is of value; here the passive resistance to the admission of blood to the right heart causes hyperæmia and venous stasis, and the excess of adrenal secretion causing a rise of blood-pressure, more blood is projected towards the heart, and slows cardiac action, thus giving the organ more time to dilate and to admit more blood.

Conversely, the use of any preparation of digitalis is obviously *inadmissible* when the heart has reached the stage of full compensation, *i.e.*, hypertrophy; when a cardiac disorder is due to, or accompanies, arteriosclerosis, in cases of aortic regurgitation, since the drug would in the latter case, by slowing the cardiac action, lengthen the diastole and afford more time for regurgitation. Moreover, by causing general vasocon-

* *Author's conclusion.*

[77] François-Franck: Sajous's "Annual and Analyt. Cyclo.," vol. ii, p. 526, 1898.

[78] Wood: *Loc. cit.*, thirteenth edition, p. 318, 1906.

[79] Fothergill: "Digitalis, Its Mode of Action and Use," Phila., 1871.

[80] Gourvat, Ackermann: Berl. klin. Woch., Bd. ix, S. 27, 1872.

[81] Weil: Archiv f. Anat. u. Physiol., S. 252, 1871.

[82] Porter: American Medicine, Apr. 27, 1901.

[83] Potain: Jour. de méd. et de chir., vol. lxxi, p. 248, 1900.

[84] Henry Beates, Jr.: Monthly Cyclo. of Pract. Med., Jan., 1905.