striction, it would increase the resistance to the blood-current and help to detain the blood in the ventricle.

In *syncope* and *collapse* of asthenic origin, digitalin is of very great value, since it influences very soon, when administered hypodermically, the centers and organs which underlie the whole vital fabric. In *neurasthenia*, its action on general nutrition, besides that on the heart, renders it invaluable in some cases. In acute adynamic diseases, especially *pneumonia*, it aids powerfully to sustain the heart. It is not indicated during the stage of early pulmonary engorgement, however, since it augments the vascular tension. When the heart is yielding to the resistance of the blood-column, it is far better to relieve the pressure itself by means of the bromides or veratrum viride.

STROPHANTHUS.

Physiological Action.—Like digitalis, strophanthus increases the power of the cardiac contractions and reduces their frequency. The pulse-waves become larger and fuller and the blood-pressure is raised when sufficiently large doses are administered. This action is less marked, but it occurs sooner than under the influence of digitalis, and does not last as long.

Strophanthus likewise owes its action to the fact that it stimulates actively the test-organ, and through it the adrenal center.* A greater quantity of adrenal secretion being produced, the contractile power of the right ventricle is enhanced.* The increased volume of the adrenal secretion insuring a corresponding augmentation of adrenoxidase in the blood, the metabolic activity of all organs is raised.* As this includes the heart-muscle, the latter is also better nourished and its contractile power is thus increased from another direction.*

This applies as well to the arteries. Their walls being supplied with blood richer than usual in adrenoxidase, their tonic activity is raised, and when the dose of the drug is sufficiently large they contract.* As is the case under the influence of digitalis, the arterioles are the first vessels (owing to their diminutive lumen) to show evidences of constriction.* An important difference between strophanthus and digitalis asserts itself in this connection, however, *viz.*, strophanthus does not

* *Author's conclusion.*

excite the sympathetic center even when administered in large doses.* Hence the fact that, although almost as active as an adrenal stimulant as digitalis,* strophanthus does not influence the arterioles as energetically as does the former.

Cushny[85] states that "in the pulmonary circulation, the pressure is not raised by some of the [digitalis] series, such as strophanthin and helleborein, while after digitalis a very distinct rise in the pressure in the pulmonary artery is sometimes seen. Yet," he adds, "*all* of them increase the output of the *right* ventricle." He characterizes these phenomena a "paradox," but their cause is self-evident when we take into account the fact that it is this ventricle alone which receives the surplus of contractile impetus afforded by the adrenal secretion.

The fact that strophanthus does not excite the sympathetic center as does digitalis, is shown plainly by its relatively feeble action on the arterioles. Fraser[86] estimated that it was fifty times less active in this particular than digitalis. Balfour[87] states that, although its action is very much more marked on the heart than digitalis, it acts "one hundred times less powerfully than digitalis on the muscles of the arterioles." Pisani[88] also found clinically that strophanthus acted but slightly upon the vasomotor system, though he observed increased arterial pressure and reduction in the pulse-rate from 5 to 20 beats per minute. Fraser, Delsaux and Yeo[89] observed but little change in the caliber of the blood-vessels. The arterial contraction does not even become very marked under the influence of large doses. Popper, and Gottlieb and Magnus[90] found that division of the cervical cord or of the splanchnic does not prevent the rise of pressure, but these procedures, by causing relaxation of the arteries in the adrenals, increase the functional activity of the latter and cause a rise of pressure even apart from the drug. Günther,[91] after studying the action of the drug upon various kinds of animals, great and small, reached the conclusion that although strophanthus was a vasoconstrictor, this action "was not marked in overdosage."

Strophanthus also provokes diuresis, but less actively than digitalis, owing to the fact that the absence of all influence on the sympathetic center deprives it of any action on the propelling power of the arterioles.* The kidneys are merely stimulated, therefore, because they are rendered hyperæmic with blood unusually stimulating in character, owing to the excess of adrenoxidase it contains.*

The presence of hyperæmia is made evident by the fact that Drasche[92] and other observers found the secreting structures congested and hæmorrhagic in experimental animals after moderate doses of strophanthus.

* *Author's conclusion.*

[85] Cushny: *Loc. cit.*, fourth edition, p. 448, 1906.

[86] Fraser: Jour. of Anat. and Physiol., vol. vii, p. 141, 1872; and Brit. Med. Jour., Nov. 14, 1885.

[87] Balfour: Lancet, May 23, 1896.

[88] Pisani: Gaz. med. di Torina, No. 32, 1899.

[89] Cited by Wilcox: Amer. Jour. Med. Sci., May, 1897.

[90] Gottlieb and Magnus: Archiv f. exp. Path. u. Pharm., Bd. xlvii, S. 135, 1901; Bd. xlviii, S. 262, 1902.

[91] Günther: Therap. Monatshefte, Bd. xviii, S. 285, 1904.

[92] Drasche: Cited by Wood; *Loc. cit.*, thirteenth edition, p. 335, 1906.

Untoward Effects and Poisoning.—Large doses, or small doses given during a prolonged period, may produce nausea, vomiting, diarrhœa and marked diuresis, the heart's action and pulse being greatly slowed and strengthened. Muscular twitchings and abnormal reflex irritability may also occur. The heart muscle being likewise rendered overactive, and therefore oversensitive, it is prone, like the other muscles, to excessive activity, *i.e.*, contraction, and its diastoles become increasingly smaller; it finally fails to dilate at all, being found contracted after death. A general arrest of the vital functions follows at once: the temperature and the blood-pressure fall rapidly, muscular weakness lapses into paralysis, and death follows.

Fürbringer[93] and Hochhaus, out of 120 cases in which they used the drug, also observed three cases of sudden and unexpected death in which the drug had been used "in large doses and throughout a rather long time." As in every instance no post-mortem lesions capable of accounting for the untoward result were found, the authors ascribe them to the drug. Mayeur,[94] Lemoine[95] and others have noted cumulative effects resulting in death in some instances after giving small doses of strophanthus during a prolonged period. If we were dealing with cardiac paralysis incident upon excessive vasoconstriction, as in digitalis poisoning, the heart would be found dilated, *i.e.*, in diastole; but such is not the case. Fraser, Paul Bert, Gley[96] and others have found experimentally that strophanthin arrested the heart in systole. Other investigators have noted that it could arrest the heart in diastole, but this was obtained by applying the drug directly to the isolated heart—a procedure which, as we have seen, does not portray the behavior of drugs in the system. The sudden arrest of function this entails is exemplified by Wood's[97] reference to the experiments of Gley,[98] that "after poisonous doses the pressure immediately or secondarily falls gradually to zero."

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

Therapeutics.—Strophanthus is indicated in the same conditions as digitalis. Unfortunately, it cannot be used hypodermically, owing to its marked irritating action on the tissues. Its oral use is of advantage to replace digitalis for a time, though less effective and more ephemeral in its action. As it does not affect the sympathetic center,* it will usually be borne without trouble by patients who cannot use digitalis.

* *Author's conclusion.*
[93] Fürbringer: Deut. Medizinal-Zeitung, Jan. 23, 1888.
[94] Mayeur: Thèse de Lille, 1888.
[95] Lemoine: C. r. de la Soc. de biol., 8 série, vol. v, pp. 495, 533, 1888.
[96] Gley: Semaine médicale, vol. ix, p. 424, 1889.
[97] Wood: *Loc. cit.*, thirteenth edition, p. 336, 1906.
[98] Gley: *Loc. cit.*

DRUGS WHICH RESEMBLE STROPHANTHUS IN THEIR PHYSIOLOGICAL ACTION.

The physiological action of *apocynum* and *convallaria* is similar to that of strophanthus, the rise of blood-pressure provoked being also due to the increased metabolic activity in the vascular and cardiac muscles.* *Sparteine* stimulates the same centers as digitalis, but with less vigor as to the adrenal center.* The action on the sympathetic constrictors becomes paramount sooner, with the resulting hyperconstriction of the cardiac arterioles and depression.*

STRYCHNINE.

Physiological Action.—A prominent feature of the action of strychnine is that it stimulates the test-organ, and, therefore, the adrenal center.* By thus increasing the volume of adrenoxidase in the blood, it enhances oxygenation, and thereby the activity of the metabolic processes of the entire organism.*

Wood and Cerna[99] obtained experimentally concordant results in dogs, showing that "the injection of strychnine produces an extraordinary increase in the respiratory air-movement, the increase varying from 75 to 300 per cent." Identical effects were obtained in morphinized and chloralized animals. This is sustained by Reichert's[100] observations that the increase in heat production caused by the drug was a constant factor, favorable to an increase of temperature. Kionka[101] found that the drug caused a marked elevation of temperature, and Mosso[102] observed that this occurred even in a curarized dog. All this is confirmed by the fact ascertained by Obermeier,[103] that the production of carbon dioxide was greatly increased. It is evident, therefore, that strychnine powerfully enhances oxygenation.

The central origin of these phenomena was demonstrated experimentally by Stricker and Rokitansky.[104] Both these investigators concluded that strychnine was a stimulant of the respiratory centers. The identity of this center is suggestive by the fact shown by Schiff in 1859, Claude Bernard and others, that strychnine gives rise to glycosuria. Langendorff[105] having found lactic (sarcolactic) acid in the urine, it was believed that glycosuria was due to excessive catabolism due to the convulsions provoked by the drug, but Demant[106] showed that small doses, totally incapable of causing spasm, also caused glycosuria. Langendorff reached the same conclusion after experiments in frogs. Now, we have seen, that as observed by Loeb, Lorand, Caselli, Launois and Roy and others, lesions which stimulated the pituitary body gave rise to the symptom, and that it was produced by increasing the activity of the

* *Author's conclusion.*
[99] Wood and Cerna: Jour. of Physiol., vol. xiii, p. 870, 1892.
[100] Reichert: Therap. Gaz., Mar. 15 to June 15, 1892.
[101] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 218, 1906.
[102] Mosso: Arch. ital. de Biol., vol. vii, pp. 306, 340, 1886.
[103] Obermeier: Inaug. Diss., Erlangen, 1891.
[104] Cited by Manquat: *Loc. cit.*, vol. ii, p. 700, 1903.
[105] Langendorff: Archiv f. Physiol., Suppl. Band., S. 269, 1886.
[106] Demant: Zeit. f. Chemie, 1886.

oxidation processes, *i.e.*, the production of adrenoxidase, through excitation of the adrenals. Indeed, we have seen that Blum, Herter and others caused glycosuria by injections of adrenal extract, and that Bernard prevented toxic glycosuria by dividing the splanchnic nerves, which contain the secretory nerves of the adrenals. It is by stimulating the adrenal center, therefore, that strychnine increases general oxidation.

Strychnine also stimulates directly the bulbar vasomotor center and thus raises the blood-pressure throughout the entire body.

That strychnine stimulates the vasomotor center is recognized by all experimenters. Referring to the experiments of Richter,[107] S. Mayer[108] and Vulpian, Manquat[109] states that it causes "a considerable elevation of the arterial pressure, which may attain the double of the normal level." Reichert[110] was also led to conclude by a large number of experiments, that the drug raised the blood-pressure by an action on the vasomotor center, but he found also, as had Vulpian, Mayer and Klapp,[111] that after division of the upper portion of the spinal cord (the path also of the adrenal secretory nerves), strychnine could no longer raise the arterial pressure.

Small therapeutic doses of strychnine, by thus increasing the oxygenizing property of the blood and simultaneously the vascular tone, enhance general metabolism and nutrition in all organs.* When the therapeutic doses are large, however, undue engorgement of the capillary system occurs,* and is manifested mainly by slight stiffness of the muscles, restlessness, formication and other cutaneous sensations, the other senses becoming also more acute.

Large therapeutic doses evoke the typical effects of the drug, *i.e.*, twitchings and "startings," provoked by slight excitations of the surface, beginning usually with the muscles of the jaw, throat, neck and chest and extending to other muscles. This culminates into tetanic convulsions when toxic doses are taken; but in the genesis of these convulsions a new factor asserts itself, *i.e.*, a marked exaltation of reflex activity due to the highly oxygenized condition of the blood* and the raised vascular tension. The morbid process involved in man is as follows:—

The general vasoconstriction caused by strychnine begins in the great central vascular trunks and affects only vessels supplied with a muscular coat,* excepting the arterioles (governed by the unaffected sympathetic center), which yield to the centrifugal pressure of the blood-stream.* The capillaries not being supplied with such a coat, the passively dilated arterioles thus become engorged with the blood forced into them by these deeper vessels and are dilated.* This general capillary congestion (with highly-oxygenized blood) increases, as stated, the functional activity of all organs;* but prominent among these are (1) the cutaneous sensory end-organs whose sensibility to external excitation is exalted; (2) the spinal cord, whose sensibility to afferent impulses is also enhanced; (3) the skeletal muscles, which are rendered overexcitable to impulses received from the spinal cord.*

Hence, the convulsion produced by strychnine is a reflex phenomenon due to the interaction of three sets of organs, and is produced in the following manner: the morbidly sensitive (hyperoxygenized) sensory end-organs of the skin send unusually violent afferent impulses to the (hyperoxygenized) overexcitable spinal cord, and this organ in turn sends exceptionally energetic stimuli to the overexcitable (hyperoxygenized) muscles.*

Alluding to the action of strychnine on the vasomotor system and the manner in which the vessels are influenced, Cushny[112] states that "the constriction seems to affect mainly the internal vessels, while those of the skin and perhaps of the muscles are dilated, and the blood-current is, therefore, deflected largely from the internal organs to the skin and limbs." Dastre and Morat and Wertheimer[113] found that strychnine produced such an energetic dilation of the peripheral vessels in doses of 0.002 to 0.004 gms. ($^1/_{32}$ to $^1/_{16}$ grain) that it caused a marked blush of the mucous membranes of the lips, gums and tongue. Delézenne[114] also noted that strychnine was a powerful dilator of the peripheral vessels—a fact accounted for by the absence of a muscular layer in capillaries; for, as Manquat[115] says, it is the vessels supplied with a "contractile tunic" which are constricted by the drug, since these are the only ones which are supplied with vasomotor nerves. Indeed Wertheimer observed that the peripheral dilation was most manifest after the blood-pressure had attained its maximum and disappeared together with the fall of pressure. The gravitation of blood towards the periphery is also emphasized by the clinical facts mentioned by Manquat, that "strychnine causes a painful exaltation of the sensibility of the organs of special sense, especially those of sight and hearing," and that "in medium doses (0.005 to 0.01 gm.—$^1/_{12}$ to $1^1/_2$ grains) tactile sensibility is augmented."

* *Author's conclusion.*
[107] Richter: Zeit. f. ration. Med., Bd. xviii, 1863.
[108] S. Mayer: Jahrb. d. k. k. Gesellschaft d. Aerzte zu Wien, S. 112, 1872.
[109] Manquat: *Loc. cit.*, vol. ii, p. 699, 1903.
[110] Reichert: *Loc. cit.*
[111] Klapp: Jour. Nerv. and Mental Dis., Oct., 1878.

* *Author's conclusion.*
[112] Cushny: *Loc. cit.*, fourth edition, p. 202, 1906.
[113] Wertheimer: Semaine Méd., vol. xii, p. 345, 1892.
[114] Delézenne: Arch. de physiol. norm. et path., 5 série, vol. vi, p. 899, 1894.
[115] Manquat: *Loc. cit.*, vol. ii, p. 699, 1903.

The rôle of the cutaneous sensory organs in the genesis of convulsions is illustrated by the experiment of Poulsson,[116] who found that when a frog was poisoned with strychnine the convulsions did not occur after the animal had been dipped in a solution of cocaine. Obviously, as stated by Cushny in reference to this experiment, the cocaine used "was sufficient to paralyze the sensory terminations." Moreover, we know that a draught of air, the slightest touch or a loud noise is sufficient to provoke a convulsion in strychnine poisoning.

That the spinal cord is the source of the spasmogenic impulses is well known. But is its overactivity due, as generally believed, to direct irritation by the strychnine, or to local hyperæmia with overoxygenized blood? Various irritants applied to the bulbar cord, *i.e.*, physical irritants (Magendie), can provoke convulsions. As shown by Van Deen,[117] Valentin and Spence,[118] strychnine will diffuse itself in the blood of the brain and cord when placed on these organs, and provoke convulsions from muscle to muscle as it advances in the cord. Yet this does not prove that a dose, when ingested or injected, quite able to provoke convulsions, will act in the same way; it only shows that strychnine is, as elsewhere, a local irritant. Cushny,[119] in fact, adduces evidence which led him to conclude that tetanus "can be produced in parts whose motor cells are unpoisoned." Again, Brown-Séquard and Martin-Magron and Buisson divided the cord below the fore-legs, and isolated the lower or detached segment of the cord from the circulation by dividing its blood-vessels. On injecting strychnine convulsions occurred only in the portion of the body connected with the upper, *i.e.*, normal, segment of the cord. Nor does this prove that it was because the vessels could no longer carry strychnine to the spinal cells of the lower segment that convulsions did not occur in the lower portion of the body, since destruction of the vessels prevented the hyperæmia of the source of the spasmogenic impulses, the corresponding area of the cord. Such a condition evidently exists in strychnine poisoning, for Wood refers to "indications of spinal hyperæmia" observed at times *post-mortem*, while Cushny[120] states that the local cellular changes seem "to indicate hyperactivity of the cell, which need not necessarily be due to direct action of the poison on it."

The rôle of the adrenoxidase in the cord is exemplified in experimental results recently recorded by Burdon-Sanderson and Buchanan.[121] These investigators (in refutation of views advanced by Baglioni) showed that "when the cord of a strychnized preparation is alternately cooled and warmed by a stream of cold or warm water, the rest of the body being protected as far as possible from the influences of the changes of temperature, the frequency of the responses *varies* according to the *temperature* to which the cord is exposed." As we have seen,[122] the rôle of the adrenoxidase in the organism is to combine with the nucleo-proteid in order to liberate heat energy and thus enhance metabolism. The presence of an excess of adrenoxidase in the blood of the cord by raising metabolism in the cell-elements does, therefore, what immersion in warm water produced in Burdon-Sanderson and Buchanan's experiments, *i.e.*, it increases its activity as the source of the stimuli transmitted to the muscles. That such an excess of adrenoxidase, and therefore a large reserve of oxygen, obtains is also shown by the fact that Meltzer and

[116] Poulsson: Archiv f. exp. Path. u. Pharm., Bd. xxvi, S. 22, 1889.
[117] Van Deen: Physiol. de la Moëlle épinière, iii, 130, 1860.
[118] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 215, 1906.
[119] Cushny: *Loc. cit.*, fourth edition, p. 199, 1906.
[120] Cushny: *Loc. cit.*, fourth edition, p. 200, 1906.
[121] Burdon-Sanderson and Buchanan: Jour. of Physiol., vol. xxviii, No. 5, p. xxix, 1902.
[122] *Cf.* this vol., p. 885 *et seq.*

Salant[123] kept an animal poisoned with strychnine alive thirty minutes, and free from cyanosis, dyspnœa or asphyxia, by insufflating pure hydrogen. This gas delayed death by interfering with the intake of oxygen and reducing the excess of vascular tension, the animal living all the while on the large volume of oxygen in his blood. Moreover, Evenhof[124] observed that an injection of strychnine enabled the patient to bear greater quantities of chloroform—another fact which the presence of a greater quantity of oxygen in the blood explains.

Vulpian[125] long ago concluded that "all spasmodic phenomena caused by strychnine are reflex in nature." Claude Bernard[126] cut all the posterior roots of the spinal nerves, in the frog. Having injected strychnine, convulsions occurred *only* when the segments of the nerves connected with the cord were stimulated. Obviously the cord required this exogenous excitation to produce spasm. According to Wood,[127] this experiment "demonstrates that the reflex motor ganglionic cells are incapable of originating an impulse, and in strychnine-poisoning are simply in such a *condition of overexcitability* as renders them exceedingly sensitive to slight irritations and causes them to respond most energetically to the feeblest stimulus, the convulsions always being therefore a reflex phenomenon." Cushny[128] also concludes that convulsions "follow only on the passage of an impulse *from without* to the spinal cord." Finally, that the convulsions are due to impulses from the cord to the muscles is shown by a simple experiment of Vulpian's, *i.e.*, division of the nerves to any one extremity. This procedure prevents strychnic spasm in that extremity, though all other muscles take part in the convulsion.

Poisoning.—A poisonous dose of strychnine evokes with more or less rapidity the symptoms caused by a large therapeutic dose: stiffness of the face, neck and chest; involuntary twitches; heightened reflex irritability; hypersensitiveness of the special senses, etc. More or less suddenly—sometimes within a quarter of an hour after taking the dose—the convulsions begin, the patient falling with the legs rigidly extended, the body being so bent backward as to rest upon the head and heels (opisthotonos). The facial muscles are strongly contracted, the corners of the mouth being drawn out—the so-called *risus sardonicus*. All the morbid processes described are clearly discernible in this sequence of phenomena. The paroxysm finally lapses into tremor and intermittent muscular contractions, then ceases, leaving the subject in a state of intense exhaustion and calm. The slightest external excitation, a current of air even, suffices to bring on another paroxysm similar to the first, and this may be followed by a third.

[123] Meltzer and Salant: Jour. of Exp. Med., vol. vi, p. 107, 1902.
[124] Evenhof: Russky Vratch, June 18, 1905.
[125] Vulpian: "Leçons sur l'action physiol., etc.," Paris, 1882.
[126] Claude Bernard: "Leçons sur les effets des substances toxiques et méd.," Paris, 1857.
[127] Wood: *Loc. cit.*, thirteenth edition, p. 216, 1906.
[128] Cushny: *Loc. cit.*, fourth edition, p. 198, 1906.

In man, a favorable termination is probable when the convulsions gradually become less intense and shorter, while the intervals become longer. Conversely, in unfavorable cases, the paroxysms become more intense until the vasoconstriction is such as to interrupt the circulation, as shown by the cyanosis of the lips and face. This interruption of the circulation is the main lethal factor, for it not only interferes with functions of the adrenals, but so reduces the *vis a tergo* motion of the blood-current that the venous blood laden with adrenal secretion is not driven past the pulmonary alveoli with sufficient speed to form the minimum quantity of adrenoxidase required by the vital process at large.* The normal issue under such conditions is death from asphyxia—that observed in strychnine poisoning.

The steady increase of the vascular tension which ultimately leads to the fatal issue is well shown by the observations of Santesson,[129] that the action of strychnine on the terminal ramifications of the nerves in the frog increases slowly and progressively with the dose until a maximum is reached. Finally there comes a time when their action is paralyzed. Vulpian and Poulsson[130] also observed this paralyzing action of strychnine on motor nerves. This is readily explained, however, by the intense vasoconstriction caused by the drug, for inasmuch as motor nerves incite functional activity merely, as we have seen,[131] by acting as stricto-dilators, *i.e.*, by admitting a greater volume of blood in an organ, complete obstruction of the channels containing that blood must render the motor nerves useless, *i.e.*, paralyze their action.* Indeed, after injecting a large toxic dose into the jugular of a dog, "the motor nerves," as stated by Wood, were found "to have entirely lost their power of responding to galvanic or other stimulation." Further proof that this is merely due to excessive contraction of the arteries is afforded by the fact that it may be, as shown by Vulpian, only temporary, the motor nerves regaining the functional efficiency even before the effects of the drug have passed off.

The inhibition of the adrenal functions is a normal consequence of the excessive constriction. The pituitary body and the heart, receiving finally a volume of blood quite inadequate to sustain their functions, can no longer continue its functions.

Therapeutics.—The foregoing study of the action of strychnine justifies the great confidence it has earned. In *functional atony*, the increase of adrenoxidase and the simultaneous stimulation of the vasomotor center provide not only the vital principle, but also the mechanism to increase the supply of this substance to the enfeebled organs.* In the various forms of *paralysis, neurasthenia*, etc., an important feature of its action imposes itself, viz., the increased circulation of adrenoxidase-laden plasma *in* the nervous elements themselves, axis-cylinders, the network of the cell-bodies, the dendrites,* etc., in addition to that supplied to the nerves through their nutrient arteries. In *cardiac disorders*, attended with local debility and vascular relaxation, strychnine, by stimulating the adrenal center, increasing metabolic activity in the muscular layer of the vessels and in the heart-muscle proper,* affords precisely the conditions required to counteract the asthenic process. In *alcoholism*, strychnine, by enhancing the production of adrenoxidase, antagonizes precisely its evil effects,* since, as will be shown, it is by robbing the blood of its oxygen that alcohol produces its main toxic action.* In *amblyopia* due to alcoholism, the marked benefit strychnine affords is due to a similar action. In *shock*, a condition mainly due to paretic vasodilation, it strikes directly the depressed center,* increases oxygenation of the vascular walls* and restores the vascular tone to its normal state. Finally, in *chronic bronchitis* and other torpid processes, strychnine is of great value by increasing the oxygenizing power of the blood,* and stimulating thereby all the reparative functions.*

* *Author's conclusion.*

[129] Santesson: Archiv f. exper. Pathol. u. Pharm., Bd. xxxv, S. 57, 1895.
[130] Poulsson: *Loc. cit.*
[131] *Cf.* this vol., p. 1115 *et seq.*

DRUGS WHICH RESEMBLE STRYCHNINE IN THEIR PHYSIOLOGICAL ACTION.

The physiological action of *brucine* differs in no way from that of strychnine. It is less active as a spasmogenic agent, and less reliable.

Caffeine acts much as does strychnine. It activates the adrenal center with even more vigor, however, thus increasing markedly the proportion of adrenoxidase in the blood.* Although its action on the vasomotor center is less marked, it is sufficient to raise the tone of the vessels and heart, the nutrition of these organs being materially aided by the increased oxygenizing property acquired by the blood under its use.* Its indications are practically those of strychnine. Its marked action on the vascular system and the heart has also caused it to be used as a substitute for digitalis.

* *Author's conclusion.*

COCA AND COCAINE.

Physiological Action.—Cocaine owes its therapeutic properties to the fact that it stimulates (1) the test-organ and through it the adrenal center,* and (2) the vasomotor center. Its action on the adrenal center is very powerful, the adrenal secretion and its product adrenoxidase being increased in the blood even by small doses, while general metabolism is augmented in proportion as the therapeutic dose is increased.* This is the characteristic action of nontoxic doses of cocaine.*

Cocaine is more powerful as an adrenal stimulant than either belladonna, digitalis or strychnine. E. T. Reichert[132] refers to it as "a thermogenic of extraordinary power." He found[133] that in dogs "general metabolism is distinctly increased even by small doses, and that the extent of the increase is proportional to the size of the dose." In two series of experiments, for instance, the heat-production was increased 40 per cent. by a dose of 0.0025 gm. per kilo of body weight, and 146.9 per cent. by one of 0.01 gm. per kilo, the mean temperature rise in the first series being 0.55° C. (1° F.) and 1.81° C. (3.26° F.). With still larger doses the rectal temperature rose beyond this (2.19° C.—4.94° F.) before the experiment ceased. Indeed, Wood[134] states that "the rise of rectal temperature in cocaine-poisoning sometimes amounts to as much as 8° F." (4.44° C.), and moreover that the drug "is a powerful stimulant to the respiratory centers"—a conclusion based on the investigations of von Anrep, Mosso and others. That the adrenal center—the respiratory center—is the source of the impulses which provoke these effects is shown by the fact pointed out by von Anrep, Berthold[135] and Reichert,[136] that preliminary division of the upper portion of the spinal cord prevents all the effects of cocaine. By increasing the secretion of the adrenals its action on the heart may become sufficient to arrest it in systole—the characteristic final effect of cocaine on this organ, according to Pachon and Moulinier.[137]

Similar effects are obtained from the coca plaint itself. Gazeau found that coca leaves taken daily increased the respiratory activity, the temperature, and the excretion of urea: 18 gm. (4½ drachms) taken daily increased the output of urea 11 per cent., and 20 gm. (5 drachms), 16 per cent. The latter dose accelerated the pulse and the respiratory rate. These observations were confirmed by Espinosa. Montegazza had previously observed an increase of temperature. Gazeau, Morton,[138] Haig[139] and Mortimer,[140] all assert that it frees the blood of products of tissue-waste—a property due, as is well known, to increased oxidizing power.

* *Author's conclusion.*
[132] Reichert: Therap. Gazette, July 15, 1902.
[133] Reichert: Univ. Med. Mag., May, 1889.
[134] Wood: *Loc. cit.*, thirteenth edition, p. 204, 1906.
[135] Berthold: Centralbl. f. med. Wissen., Bd. xxiii, S. 435, 1885.
[136] Reichert: Amer. Lancet, May, 1891.
[137] Pachon and Moulinier: C. r. de la Soc. de biol., 10 série, vol. v, p. 566, 1898.
[138] Morton: Jour. of Nerv. and Mental Dis., Oct., 1879.
[139] Haig: "Uric Acid as a Factor in the Causation of Disease," London, 1897.
[140] Mortimer: "Peru, History of Coca," p. 425, New York, 1901.

The direct action of cocaine upon the vasomotor center is much less pronounced than that of strychnine.* Though it raises markedly the blood-pressure, this is mainly due to the fact that its powerful stimulating influence upon the adrenal center and the general increase of metabolic activity this entails, affect likewise the heart-muscle and muscular elements of the blood-vessels, arteries and veins.* The volume of blood driven into the capillaries of all organs is therefore increased (by the contraction of the larger vessels), but not excessively, as it is by drugs which excite violently the vasomotor center.* The increase of volume, however, plus the marked gain of oxygenizing power acquired by the blood, represent the immediate effects to which coca and cocaine owe their therapeutic action.*

That cocaine raises the blood-pressure has been shown by von Anrep,[141] Vulpian,[142] Laborde, Nikolsky, Danini, Reichert[143] and others. The fact that the arterioles take part in the general constriction is indicated by the observation of Durdufi[144] that the narrowing of the arteries of a rabbit's ear, which occurs after cocaine has been ingested into this animal's blood, is prevented if the cervical sympathetic of the corresponding side is severed. According to Mortimer,[145] coca, given internally, also "contracts the peripheral arteries." That all these effects are originally of central origin is shown by the fact that when the adrenal and vasomotor paths are severed, they cease. Thus, Danini, Berthold[146] and Reichert found that after section of the spinal cord alone or with the vagi, cocaine no longer distinctly increases the blood-pressure.

The crowding of the highly oxygenized blood into the peripheral tissues causes the effects of cocaine to resemble those of belladonna. Thus, Cushny[147] states that "the pulse is accelerated, the respiration is quick and deep, the pupil generally dilated," and that "headache and dryness of the throat are often complained of." The fugacious preliminary slowing of the heart's action, also observed under atropine, was noted by both Vulpian and Arloing, while dilation of the pupil has been noted by Koller, Terrier,[148] Laborde,[149] von Anrep and others. It occurs also fifteen to twenty minutes after a solution of cocaine has been applied. Cocaine also, as stated by Manquat, causes a slight paresis of accommodation and increases pain in glaucoma, thus showing that it increases intra-ocular tension—as does atropine.

The effects of the coca plant are evidently similar. Shuttleworth[150] noted that it caused dryness of the throat; Mantegazza[151] and Gazeau[152]

* *Author's conclusion.*
[141] von Anrep: Archiv f. d. ges. Physiol., Bd. xxi, S. 38, 1880.
[142] Vulpian: C. r. de l'Acad. d. sci., Nov. 24, 1884.
[143] Reichert: Amer. Lancet, May, 1891.
[144] Durdufi: Deut. med. Woch., Bd. xiii, S. 172, 1887.
[145] Mortimer: *Loc. cit.*, p. 413.
[146] Berthold: *Loc. cit.*
[147] Cushny: *Loc. cit.*, fourth edition, p. 299, 1906.
[148] Terrier: Bull. de la Soc. de chir., vol. x, p. 825, 1884.
[149] Laborde: Tribune méd., Nov. 30, 1884.
[150] Shuttleworth: Can. Pharm. Jour., Aug., 1877.
[151] Mantegazza: "Sulle virtu della Coca," Milan, 1859.
[152] Gazeau: Thèse de Paris, 1870.

both observed acceleration of the pulse. Mortimer[153] says that "after mastication of a *great* quantity of coca, the eye seems unable to bear light," and that "there is marked distention of the pupil," referring to the observations of Tschudi,[154] Schroff[155] and others.

It is owing to its powerful stimulating action upon the adrenal center and its less marked, though effective, action on the vasomotor center, that coca and cocaine owe their energetic excito-motor properties.* The volume of blood supplied to the tissues is not only greater, but, its oxygenizing virtues being unusually high, the intrinsic metabolism of all cellular elements is correspondingly enhanced.* It is through this property that coca activates the nutrition of all muscles.* The muscle fiber is also enriched in those substances which serve to cause its contraction, since the surplus of adrenoxidase in the blood likewise augments the functional activity of the liver and of the leucocytogenic organs.* The carbohydrate reserves (the most important of which is glycogen) are thus supplied to the muscles in greater quantities (though commensurate with the supply of adrenoxidase), and the potential energy which the increased nutrition supplies can thus be converted into a correspondingly greater amount of muscular work.*

Mosso found that in warm-blooded animals, including man, muscular excitability was increased by small doses. Fuster, in experiments upon himself, experienced marked muscular agitation and tremors, with impulses to physical movements. Benedicenti[156] also found ergographically that cocaine raised not only the contractile energy of the muscles, but also their power to resist fatigue. Ott showed that the contractions were prolonged. The convulsions caused by toxic doses occur, as observed by Grasset,[157] five or six minutes after the drug has been injected, and may be brought on by peripheral excitation, thus showing, in accord with the conclusions of Mosso, von Anrep, and Soulier and Guinard,[158] that the reflex activity of the spinal axis is markedly increased. This is not due, as generally believed, to a local action of the drug, but to the excess of adrenoxidase in the plasma of the nerve-cells.*

The leaves of the coca plant have been extensively used by the natives of Peru, Bolivia and other South American countries, to increase their muscular strength and endurance. According to various medical authors, Tschudy,[159] Unamié,[160] Moreno y Maïz[161] and others, who witnessed its use in these countries, the plant undoubtedly possesses this

* *Author's conclusion.*
[153] Mortimer: *Loc. cit.*, p. 413.
[154] Tschudi: Reiseskissen aus Peru, S. 42, 1838.
[155] Schroff: Wochenbl. d. k. k. Ges. d. Aerzte zu Wien, 1862.
[156] Benedicenti: Untersuchungen zur Naturlehre des Menschen u. d. Thiere. Moleschott, Bd. xvi, S. 170.
[157] Grasset: C. r. de l'Acad. des sci., Feb. 9, 1885.
[158] Soulier and Guinard: Lyon méd., vol. lxxxviii, p. 465, 1898.
[159] Tschudy: *Loc. cit.*
[160] Unamié: "Dict. d'Histoire nat.," Paris, 1803.
[161] Moreno y Maïz: Thèse de Paris, 1868.

property. Sir R. Christison[162] observed experimentally upon himself that it removed extreme fatigue and prevented it, suspending also hunger and thirst. Reichert[163] also found that under restricted diet, and even in the absence of food, coca enables its user to do more work than under normal conditions.

Mortimer[164] concludes that the increased muscular power is caused by coca "through the excitation of the hypothetical ferment of the contractile element." That such an action prevails—though indirectly—is evident from the facts I have submitted. Indeed, the function of adrenoxidase is dual here, as it is in all tissues: it takes part in the intrinsic metabolism of the muscular protoplasm as it does in that of all cells, a function which, in its catabolic phase, utilizes the ferment or hydrolytic triad.[165] This is the trophic element of the process, however—that through which the life of the muscle-cell is sustained as well during repose as during contractile activity. This does not mean that coca or cocaine supplies nutriment to the muscle, but that it augments its functional activity by raising its power to utilize the nutrient materials that are available.

The anæsthesia produced by the local application of cocaine is due, as is well known, to a marked vasoconstrictor action. The tissues, including their sensory terminals, being deprived of blood, lose their sensibility. This property of cocaine differs entirely from that of the same agent when it is used internally—the only action which enters within the scope of this work.

Untoward Effects and Poisoning.—An excessive dose of *coca* produces mental excitement and an exacerbation of muscular power, but this is apt to be followed by general weakness, especially of the legs, cutaneous horripilation, coldness and difficult locomotion. These are obviously the after-effects of excessive intrinsic muscular metabolism.

Cocaine, in toxic doses—which include small as well as large doses—gives rise to symptoms due in practically all cases to excessive excitation of the adrenal center. This is aggravated, however, by a concomitant rise of the blood-pressure through supranormal metabolism in the muscular layers of the blood-vessels, a corresponding overaction of the cardiac muscle from the same cause and excitation of the sympathetic center. As a result, blood excessively rich in adrenoxidase is forcibly driven into all organs. The following phenomena are produced: the cerebral hyperæmia provokes marked excitement and hallucinations, the patient being very talkative, wakeful,

[162] Sir R. Christison: Brit. Med. Jour., Apr. 29, 1876.
[163] Reichert: Univ. Med. Mag., Oct., 1890.
[164] Mortimer: *Loc. cit.*, p. 420.
[165] *Cf.* this vol., p. 851.