and perhaps anxious and confused. The pulse is accelerated, the respiration rapid, the mouth and throat dry, and the pupils dilated. Gradually as the general vasoconstriction increases these symptoms become more marked, and profuse perspiration, creeping sensations in the skin, convulsive movements and præcordial distress appear; the cardiac action becomes extremely rapid and irregular, the respiratory movements likewise, dyspnœa becoming steadily more marked. If the toxic dose be not too large, these phenomena may gradually disappear, leaving the patient extremely weak, especially in the lower extremities. Otherwise violent tonic and clonic convulsions appear, and death occurs in the midst of a paroxysm. In such cases the heart is found tightly contracted. Its diastoles become more and more restricted, and the volume of blood raised is gradually lessened until finally it ceases to dilate. This mode of death is due to excessive stimulation of the adrenal center and to paralysis of the heart by excessive contraction of its ventricles.*

In some cases, especially when the toxic dose is very large, the convulsive stage does not appear; the patient, after a few of the preliminary symptoms, lapses into a state of profound collapse, the pulse being weak, small and intermittent, and sometimes slow. The heart here, though still active, is unable, owing to the cramped condition of its walls, to dilate sufficiently, and, too little venous blood being sent to the lungs during each contraction, respiratory failure occurs.* The respirations become increasingly slow and shallow; the skin grows cold, clammy and cyanotic, and death follows, but due in this case to respiratory paralysis.

Death from cocaine-poisoning is evidently not due to inhibition of the heart. Pachon and Moulinier[166] found the ventricles tightly contracted and the auricles dilated. That a relatively small dose may produce such effects is well shown by the following case reported by Tivy[167] —one of urethral stricture with retention of urine. He states: "I resolved to get a small catheter or bougie into his bladder if possible, and, to save the patient some of the pain and so facilitate the process, I decided to inject some solution of cocaine into the urethra beforehand. I therefore injected half a drachm of a 10-per-cent. solution of cocaine hydrochloride with a glass syringe into the urethra in the ordinary way, telling the patient to hold the penis in his fingers to prevent escape. I

* *Author's conclusion.*
[166] Pachon and Moulinier: *Loc. cit.*
[167] Tivy: Brit. Med. Jour., Oct. 6, 1906.

then left the patient with the wardsman who was attending me, and turned to wash my hands; but before I could get to the end of the ward the man called to me, and I returned immediately. I then found the patient in a state of clonic convulsion, with his back arched, and jumping up off the bed. His jaws were moving spasmodically, and he had bitten his tongue. His face was somewhat cyanosed and his breathing very spasmodic and slightly stertorous. The eyeballs were fixed and the lids half closed. I could not feel a pulse at the wrist, but his arms were jerking so forcibly that it was not easy in any case. I put my ear to the chest and heard the heart beating. His breathing rapidly became shallower and convulsions lessened in force, and in about a minute respiration ceased, the cyanosis increasing; I put in a gag, pulled out his tongue, and began artificial respiration, and the Sister brought me a hypodermic syringe of brandy, which she injected while I continued the respiration. I also had a hot stupe put over the heart, but when I listened again the beats had ceased. I persevered with artificial respiration for a quarter of an hour and had the brandy repeated, but with no effect, as the patient never rallied, and was, I believe, dead in about three minutes from the time of injection. I made a post-mortem examination the next day and found all the organs fairly healthy. The kidneys were congested but not diseased, the spleen was enlarged and fleshy, and the liver showed signs of cirrhosis. The heart had apparently stopped in systole, as all the chambers were empty." The participation of the entire muscular system in the morbid process and the influence on the heart are clearly shown.

The second mode of death is really but a slight modification of the first. The "cramped" heart, instead of stopping outright, continues its functions in an imperfect manner; it necessarily fails to satisfy the needs of the respiratory process, and the function, as a whole, sooner or later comes to a standstill. A suggestive fact in this connection is the observation of Dujardin-Beaumetz[168] that doses no larger than 0.01 or 0.02 gm. ($\frac{1}{6}$ to $\frac{1}{3}$ grain) never caused syncope in his cases when the patient was either standing or sitting. In the recumbent position the heart's tendency to become arrested in systole, *i.e.*, in the cramped state, is increased, since the upright position, by augmenting the intra-ventricular resistance of the blood-column, tends to prevent contraction of the ventricles.

Chronic Cocainism.—The stimulating action of cocaine upon the adrenal and sympathetic centers is attended, when any but very small doses penetrate the blood-stream, by an unusual expenditure of local latent energy, followed by a period of depression and recuperation. Gradually, as the doses are repeated, the recuperative power of the centers decreases and the depression experienced not only persists, but tends to lapse into prostration, especially in neurotic subjects. Soon the discovery is made that this prostration, which entails apathy, apprehension, inability to do satisfactory work, etc., is at once antagonized by the drug itself. Strength, agility, self-confidence, etc., return, but continue only as long as the effects of the drug last. Stimulated, the adrenals have temporarily

[168] Dujardin-Beaumetz: Manquat: *Loc. cit.*, vol ii, p. 399, 1903.

enriched the blood's supply of oxidizing substance; stimulated, the sympathetic centers caused the enriched blood to be driven vigorously into the tissues and the entire nervous system. Yet the centers, having sacrificed a correspondingly great amount of their energy, become increasingly less responsive to the exciting influence of the drug, and gradually, as the prostration augments after each exacerbation of activity, the dose must be increased in order to insure satisfactory effects. Finally the patient shows evidences of rapidly-developing marasmus—the result of the general vasodilation and the deficiency of adrenoxidase which the debility of the adrenal center entails. The skin assumes a pale yellowish color, the extremities are cold; digestive disorders, due to relaxation of the gastro-intestinal muscular elements and deficiency of digestive ferments, appear, with anorexia and emaciation as normal sequences. The sympathetic center also losing its hold upon the arterioles, there occur hallucinations of vision, hearing, taste, smell and cutaneous sensibility—the patient imagining that foreign bodies, creeping bugs, etc., are present in his skin—insomnia, delirium and delusions of persecution, sometimes attended with furor, during which the patient may injure himself or others, convulsions, general paralysis and insanity.

The experiments of Reichert[169] in dogs clearly illustrate another fact, *i.e.*, the depression which the active effects of cocaine produce: the 0.0025 gm. dose (per kilo weight) increased the temperature 0.55° C., but caused no subsequent depression; the 0.01 dose raised it 1.81° C., but it became *subnormal* during the third hour; in the two succeeding experiments with still larger doses the temperature, after a marked rise, also became subnormal and continued so throughout the experiment. In man, as stated by Norman Kerr:[170] "When the dose taken has been relatively immoderate, the depression and nervous debility may remain for days or till the next dose."

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

Therapeutics.—Apart from its local action (a feature of its use, which does not enter within the limits of this work) cocaine is of great value in all disorders in which *general adynamia* prevails. Unfortunately, the vigor with which it overcomes the symptoms, *i.e.*, by stimulating the adrenal center, whose debility underlies the morbid process,* is so gratifying to the

* *Author's conclusion.*

[169] Reichert: *Loc. cit.*

[170] Norman Kerr: Sajous's "Annual and Analytical Cyclo.," vol. ii, p. 318, 1898.

patient, if adequate doses are taken, that he is exposed to the danger of indulging inordinately in its use, *i.e.*, acquiring the cocaine habit. To avoid this, small doses or, better still, preparations of the coca plant should be prescribed, the aim being to raise *gradually* the functional efficiency of the adrenal center to its normal standard. This measure avoids also the depression which follows the use of large doses.

I have not given cocaine itself internally since the first two years of its appearance on the market, over twenty years ago; two experiences having shown me its dangers. I use a preparation of uniform strength, the Mariani coca wine, which contains $^1/_{10}$ grain (0.006 gm.) of cocaine to the ounce (as one of the constituents of the coca leaf), and prescribe it in the regular way, avoiding the word "cocaine" (Vinum Erythroxylon C. Mariani), and directing that it be put up in an ordinary pharmaceutical bottle. While ordering one ounce to be taken three times daily, however, I give simultaneously digitalin ($^1/_{10}$ grain—0.006 gm.), or strychnine ($^1/_{60}$ grain—0.001 gm.), and lay stress on the importance of the last-named drugs. The patient's attention is thus diverted from the cocaine, and experience has shown that he is not exposed to the danger of becoming a cocainomaniac. Mariani wine has of late contained no cocaine, however, and the uncertain U. S. P. wine of coca is alone available.

Coca and cocaine have been found of especial value in *neurasthenia, debility* and *retarded convalescence,* owing to its effects on general metabolism not only upon the muscular tissues, but also the nervous elements proper.* This accounts also for their value in all forms of *paralysis* dependent upon general asthenia, and in *melancholia* due to cerebral ischæmia. In *cardiac disorders* in which functional atony and dilation prevail, they serve much the same purpose as digitalis, strophanthus and kindred drugs.* Their beneficial effects are especially marked in the weak heart of delayed convalescence from debilitating diseases, influenza, for example. This applies also to *torpid catarrhal processes* and *particularly* to *chronic bronchitis,* the increased vigor of cardiac contractions and the greater oxygenizing power of the blood serving to increase the circulatory activity in the bronchial mucosa* and to incite and hasten resolution. In disorders of the gouty series, *migraine, asthma,* etc., they tend to prevent the recurrence of accesses by increasing the oxygenizing and antitoxic properties of the blood and,* therefore, its power to break down the toxic products* of imperfect metabolism, while simultaneously, by activating the metabolic process itself, preventing the formation of toxic wastes.* They

* *Author's conclusion.*

also afford material aid in the asthenic stage of infectious diseases, *typhoid fever, yellow fever* and *smallpox* especially, by increasing the blood's asset in auto-antitoxin* and by sustaining the contractile power of the heart. Coca is one of the most efficient agents at our disposal in the treatment of *alcoholism;* by stimulating directly the test-organ, and through it the adrenal center,* it counteracts the debilitating action of alcohol on this center and the craving for alcoholic stimulation.

QUININE.

Physiological Action.—Moderate doses of quinine stimulate the general vasomotor center and cause general vasoconstriction. Contraction of the central vascular trunks being thus produced, the blood supplied the peripheral vessels is increased,* and the reflex sensibility of the cutaneous sensory nerves is correspondingly influenced.

"Quinine," says Manquat, "always causes, in the state of the vessels, modifications related to those of the pressure. Weak doses give rise to vasoconstriction and large doses to a vasodilation." This was conclusively demonstrated experimentally by H. A. Hare,[171] who observed that in frogs under the influence of quinine, the vessels were much more contracted (their walls being also thicker) than those of normal frogs. Von Schroff,[172] in accord with this observation, had found that quinine caused a preliminary rise of blood-pressure, an effect also noted experimentally by Schlockow,[173] Block, Neissner,[174] Jerusalimsky,[175] Sée and Bochefontaine[176] and others. It is further confirmed by the fact that the peripheral congestion caused by the constriction of the central vascular trunks becomes sufficiently marked to greatly increase the sensibility of the cutaneous nerve-endings. This was first observed by Schlockow, who found that quinine increased the skin's reflex activity. Heubach[177] and Cerna[178] reached similar results experimentally, but found that this was produced only by very small doses; they also conclude that since it was prevented by ligation of the abdominal aorta, it was to be ascribed to overactivity of the peripheral sensory nerves.

This indicates that the general vasoconstriction is of central origin, for, as we have seen, convulsions are caused in frogs by excessive stimulation (*i.e.*, hyperæmia) of the cutaneous sense-organs, such as that produced by quinine and other alkaloids of cinchona. Albertoni[179] found that the convulsions thus produced by cinchonidin in pigeons occurred, even though the cerebrum had been removed, provided the drug were injected after the animal had been given time to recover from the shock of the operation. This shows that the indirect cause of the convulsions

* *Author's conclusion.*
[171] Hare: Phila. Med. Times, Oct. 18, 1884.
[172] von Schroff: Med. Jahrb., S. 175, 1875.
[173] Schlockow: "De Chinii Sulfurici, etc.," Vratislaviæ, 1860.
[174] Block, Neissner: Nothnagel et Rossbach: "Mat. méd. et thérap.," French edition, p. 635, Paris, 1889.
[175] Jerusalimsky: Centralbl. f. med. Wissen., Bd. xiv, S. 476, 1876.
[176] Sée and Bochefontaine: C. r. de l'Acad. de sci., vol. xcvi, p. 267, 1883.
[177] Heubach: Centralbl. f. med. Wissen., Bd. xii, S. 674, 1874.
[178] Cerna: Phila. Med. Times, July 3, 1880.
[179] Albertoni: Arch. f. exper. Path. u. Pharm., Bd. xv, p. 278, 1882.

originated not in the cortex, but in structures below the brain. Indeed, they occurred also in dogs after destruction of the cortex. Moreover, Jerusalimsky found that the rise of blood-pressure caused by quinine did not occur after transection of the spinal cord, which, of course, contains the vasomotor paths.

Larger therapeutic doses likewise stimulate the general vasomotor center, but this action is soon supplemented by another, *i.e.*, direct stimulation of the *sympathetic* center, and, as a result, by increased propulsive activity of the terminal arterioles.* The peripheral vessels are thus not only supplied with an unusual volume of blood, but the pressure to which the terminal arterioles submit the latter as it passes through them forces the blood into the cutaneous capillaries with sufficient violence, generally, to cause marked flushing.* A sensation of fullness in the head and ears, due to cerebral hyperæmia, may be accompanied by more or less severe headache, tinnitus and deafness, the latter being sometimes permanent, especially when the use of the drug is continued.

Occasionally hæmaturia, purpura, erythema and subdermal swelling appear, the latter phenomenon being due to the fact that the blood or its serum is forced through the walls of the capillaries, owing to the centrifugal pressure exerted upon them by the blood-stream.*

The cardiac action is accelerated and strengthened under these conditions, the heart-muscle receiving a greater influx of blood.

The intense hyperæmia of the capillaries is well shown by the investigations of St. John Roosa[180] and Kirchner,[181] the first-named investigator having found that in adequate doses the drug caused congestion of the middle ear. Kirchner not only confirmed this observation, but found that it produced, in cats, hæmorrhages in the middle and internal ears and in the fourth ventricle. The latter phenomenon shows that the aural symptoms are due to a *general* excessive engorgement of the capillary system, the blood, as in hæmaturia and the cutaneous vascular lesions, causing often actual rupture of the vessels. This is illustrated by the familiar fact that quinine often provokes epistaxis, with considerable relief, sometimes, of the severe headache caused by the drug.

Quinine is poisonous to many organisms, including amœboid cells. So marked is this action that adequate doses check the amœboid movements of the leucocytes themselves and prevent their migration from the vessels. The tissues failing to receive their usual proportion of nucleo-proteid

* *Author's conclusion.*
[180] St. John Roosa: Amer. Jour. Med. Sci., Oct., 1874.
[181] Kirchner: Berl. klin. Woch., Bd. xviii, p. 725, 1881.

granules,* nutrition is lowered. Hence* the decreased elimination of urea caused by excessive doses of the drug.

It is to its direct action as a toxic upon the plasmodium malariæ that quinine produces its beneficial effects in the various malarial fevers. It destroys not only the amœba, but its spores, and thereby breaks up the morbid cycle. The activity of this process is enhanced by the stimulating action of the drug upon the vasomotor center; the blood being driven in greater quantities into the capillary system and the liver, a fever-like process is awakened, in which the drug acts as the immunizing agent.* The volume of blood in transit through the capillaries is sufficiently increased in some instances to produce a rise of temperature reaching sometimes 105° F. (40.6° C.). In such cases the adrenal center is also stimulated by the drug.*

The toxic action of quinine upon the leucocytes was first shown by Binz[182] in 1867. So marked was its action in this particular that areas of inflammation in the mesentery of frogs produced by the local application of mustard failed to be invaded by leucocytes when quinine had been given to the animal, while they were present in great number in the untreated animals. This has been confirmed by Maurel,[183] Pouchet[184] and others. Fitch[185] found that in animals poisoned with quinine the polymorphonuclear leucocytes are considerably reduced in number. These leucocytes are the neutrophiles—those which, as I have shown,[186] take up the food-products from the intestine. The result of this destruction of leucocytes, which necessarily diminishes the supply of granulations to the tissue-cells and metabolism is self-evident: deficient nutrition of the entire organism. That quinine produces, in fact, a marked diminution of urea excretion has been noted by many observers. Referring to this evidence, and particularly to Prior's,[187] Wood, Sr. and Jr.,[188] write, "we are warranted in believing it established that quinine powerfully depresses the elimination of the nitrogenous excretory principles."

The direct action of the drug on the plasmodium is generally recognized. As to the febrile process sometimes awakened by quinine, cases have been reported in which the temperature rose several degrees. Thus, A. L. Goodman[189] refers to a case in which the drug raised the temperature from 99° to 103.2° F., twice, the temperature receding when the drug was withdrawn, and he refers to many reported cases, including nineteen by Prof. Tomasselli, of Catania, in some of which the temperature reached 105° F. (40.6° C.).

Luca,[190] in a study of the relative value of the administration of the drug by the mouth or by hypodermic injection, ascertained that the

* *Author's conclusion.*

[182] Binz: Archiv f. micros. Anat., Bd. iii, S. 383, 1867.

[183] Maurel: Rev. inter. de Bibliogr., Sept. 25, 1892; Arch. de méd. expér. et d'anat. path., vol. xv, p. 37, 1903.

[184] Pouchet: "Leçons de Pharmacodynamie," p. 250, 1902.

[185] Fitch: Yale Med. Jour., June, 1905.

[186] *Cf.* this vol., p. 1027.

[187] Prior: Archiv f. d. ges. Physiol., Bd. xxxiv, S. 237, 1884.

[188] Wood, Sr. and Jr.: *Loc. cit.*, thirteenth edition, p. 570, 1906.

[189] Goodman: Med. Rec., Dec. 1, 1906.

[190] Luca: Archives Ital. de Biol., Mar., 1905.

quantity in the blood is at first very minute, but that it increases gradually, the maximum being reached in an hour. This is doubtless due to the fact that, as held by Lombard and Carles,[191] leucocytes ingest quinine and are poisoned by it. The alkaloid then passes out into the blood again or is promptly secreted by these cells. Luca found also that the parasite of malaria was susceptible to a minute proportion of the drug.

Untoward Effects and Poisoning.—In subjects unduly susceptible to its effects, owing to hypersensitiveness of the sympathetic center,* very small doses of quinine have caused untoward effects. Under normal conditions, even moderate doses (15 to 30 grains—1 to 2 grams), by unduly stimulating the sympathetic center,* become harmful. They provoke such powerful contraction of the arterioles that the penetration of blood into the capillary system is interfered with.* As a result, the peripheral hyperæmia caused by the smaller doses is replaced by anæmia of the cutaneous capillaries.* This naturally entails lowering of the temperature of the surface; hence the antipyretic effects of the drug, when administered in large doses.

The arterioles of the various structures of the eye being likewise excessively constricted,* the quantity of blood supplied to them is correspondingly diminished. The vision may thus become impaired, or total blindness may occur, sometimes quite suddenly. Quinine amblyopia usually disappears gradually, however, after the use of the drug is discontinued. The light reflex is usually absent and accommodation may also become impossible. Nystagmus, strabismus and anæsthesia of the conjunctiva have also been observed. The pupils are dilated when the constriction of arterioles* of the sphincter muscles of the iris is sufficiently marked.

The corresponding constriction of the terminal arterioles* in various other organs also interferes with their functions: the cerebral (capillary) anæmia gives rise to vertigo; that of the spinal system and the skeletal muscles to marked muscular weakness and a tremor resembling that of paralysis agitans; that of the lungs and in the body at large to marked dyspnœa; that of the myocardium to slowing and weakening of the heart's action. Collapse may then occur, death being sometimes preceded by convulsions. Such an issue, however, is extremely rare.

* *Author's conclusion.*

[191] Carles: "Rôle des Leucocytes," p. 94, Paris, 1904.

All these morbid effects are aggravated, when very large doses are taken, by the destruction of leucocytes which such doses provoke.

The transition from hyperæmia to anæmia of the cutaneous capillaries is well illustrated by the fact that in frogs very small doses produce, as stated by Wood,[192] "a permanent palsy of reflex activity." The cause of this has remained obscure. This may be said also of the antipyretic action of quinine. "While no solution of this dilemma has been offered as yet," says Cushny,[193] "it seems extremely probable that the antipyretic action of quinine is due to its retarding metabolism." He characterizes as a "paradox" also the fact that while "on the one hand, there is no question that the temperature falls," "the combustion is certainly not reduced to any notable extent." Another unexplained fact is that noted by de Mussy in 1871, and more recently by Huchard,[194] that large doses of quinine arrest hæmorrhage. All these effects are readily explained when excessive (sympathetic) constriction of the terminal arterioles is taken into account: the palsy of reflex activity is due to the reduced volume of blood in the capillaries; the temperature falls for the same reason, though combustions are not materially reduced; hæmorrhages are controlled because the constricted vessels no longer allow the blood to pass freely, and thus favor the formation of obturating clots.

The constriction of the ocular arterioles under the influence of large doses was directly observed by De Bono[195] in dogs. The vessels of both the iris and choroid were markedly contracted in most instances—those of the optic nerves always. He found the "quinine-amblyopia ischemia" in the retina of all cases, whether cured or not. As stated by Wood,[196] "the ophthalmoscopic examination commonly, but not always, has revealed pallor of the optic disks, with excessive lessening in the size of the retinal vessels." The exceptions are, obviously, those in which the doses were not large enough to provoke ischæmia. Indeed, smaller doses may induce the opposite effect—the hyperæmia to which I have referred. Thus, Dickinson "has seen the optic disks swollen and having the appearance of an ordinary choked disk." The presence of quinine ischæmia is further emphasized by the fact that de Schweinitz found that "the continuous administration of the drug may finally cause a true atrophy of the optic nerve"—a normal result of inhibited nutrition. Both Brunner[197] and de Schweinitz[198] ascribe the loss of retinal function to a vasomotor spasm probably of centric origin, but such a spasm would mean the presence of general vasoconstriction, a condition which would entail engorgement and not depletion of the peripheral vessels. Again, vasomotor spasm does not exist under such conditions. "When the doses of quinine are large (1.5 to 2 gms. [23 to 30 grains]),"write Nothnagel and Rossbach, "whether in man or animals, during disease or health, the contractions of the heart and the vascular pressure is *lowered;* most observers (Briquet, Duméril, Reil, Schlockow, Lewitzky, Schroff, Jr., Liebermeister) consider this as an indubitable and constant fact." Indeed, we are dealing, not with vasomotor spasm, but with spasm due to excitation of the *sympathetic* center, the terminal arterioles of the eye being throttled, as it were, as are those of the body at large.

[192] Wood: *Loc. cit.*, thirteenth edition, p. 563, 1906.
[193] Cushny: *Loc. cit.*, third edition, p. 365, 1899.
[194] Huchard: Jour. des Praticiens, Dec. 8, 1900.
[195] De Bono: Arch. d. Ottal., vol. ii, fasc. 3 to 6, 1895.
[196] Wood: *Loc. cit.*, thirteenth edition, p. 562, 1906.
[197] Brunner: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 563, 1906.
[198] de Schweinitz: *Ibid.*

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

Therapeutics.—The use of quinine as an antipyretic is now obsolete, other remedies and measures being preferable when hyperpyrexia (above 105° F.) is to be reduced to prevent hæmolysis. Its tendency to produce destruction of the red and white corpuscles in large doses also argues against its employment in the febrile diseases. In *all forms of malarial fever,* and conditions due to malaria, *neuralgia, enlargement of the spleen,* etc., however, quinine is invaluable, its power exceeding that of any other remedy. It is customary to precede its use by a mercurial purgative: the powerful stimulating action of mercury upon the test-organ and adrenal center[199] accounts for the increased effect thus obtained.* On the other hand, the production of *malarial hæmaturia,* sometimes witnessed when quinine is given in intermittent fevers, is explained by the intense capillary hyperæmia to which the drug gives rise,* and points to the need of moderation in its use. As a *prophylactic* against malarial infection, quinine is now of recognized value. This property is due to the cutaneous hyperæmia which the drug produces* and to the fact that the parasite or its spores, when introduced into the tissues by the mosquito, at once meet blood which is toxic to them, owing to the presence of quinine in solution.

It is also by producing capillary hyperæmia, especially of the cutaneous tissues,* that quinine is beneficial in many other conditions. It can thus* abort *acute coryza, tonsillitis, subacute bronchitis,* etc., if taken early and in sufficient quantities: 3 grains (0.2 gram) every two hours until slight headache or flushing of the face occur, when the dose is reduced.* The toxic wastes liberated in the blood through exposure to cold are thus promptly destroyed* where they have accumulated, *i.e.,* in the superficial tissues.* Suppurative processes, *boils,* for instance, are promptly arrested by this treatment. In asthenic disorders, *neurasthenia,* quinine is of value by causing the nerve-elements, which are in reality all capillary blood-channels,* to receive a greater volume of blood-plasma.*

* *Author's conclusion.*
[199] *Cf.* this vol., p. 1147.

DRUGS WHICH RESEMBLE QUININE IN THEIR PHYSIOLOGICAL ACTION.

A number of drugs act much as does quinine, the variations consisting in their action upon the different centers. Thus *eucalyptus* stimulates the adrenal, vasomotor and sympathetics centers, but mainly the latter. Indeed, when toxic doses are given, death is due to excessive constriction of the arterioles of the heart and failure of the respiration. Eucalyptus is much less effective than quinine, or, in fact, any preparation of cinchona, as antiperiodic.

DRUGS WHICH BECOME CONSTITUENTS OF THE TISSUE-CELLS.

Closely associated with the drugs described in the foregoing pages is the class of agents generally known as "nutrients," in the sense that they are actual components of the tissues. They are of great value, therefore, as adjuncts to these drugs in appropriate cases, since the latter only stimulate function without contributing directly to the body's resources.

Iron owes its therapeutic value to several concomitant properties. Being a normal constituent of tissue and blood-cells, its beneficial effects appear only when it is actually required. It stimulates the adrenal center only incidentally—probably before it has assumed an assimilable form. Its specific action, however, is to take part in the elaboration of hæmatin, of which it is the chief component, and to stimulate the bone-marrow—thus increasing the production of red corpuscles. Its purpose in hæmatin being, as I have shown, to act as storage material (the link being its own affinity for oxygen) for adrenoxidase, pending the distribution of the latter to the tissues, iron thus enhances directly the blood's all-important function, oxygenation.

In *phosphorus* we have another constituent of tissue-cells even more widespread than iron, and fully as important to the vital process. The various rôles I have ascribed to it in all organic functions, *e.g.*, in the maintenance of the blood's temperature, in the body's auto-protective processes, in the intrinsic exchanges of the tissue-cells, including the nerve-cells, and the genesis of the nerve-impulse, etc., emphasize sufficiently its

therapeutic indication in adynamic disorders, especially those in which the nervous system has borne the brunt of the original pathogenic factor. Being, like iron, a component of the tissues, it affects the nerve-centers morbidly only when given in toxic doses. In therapeutic doses, especially when it forms part of an organic compound, phosphorus is building material, and is essentially beneficial as such when given with such agents as digitalis, coca, strychnine, etc., which activate metabolism and the mechanism of nutrition, without, however, as stated above, contributing directly to the body's assets.

IRON.

Physiological Action.—Iron being an important constituent of the blood and tissues, its effects become manifest only when the quantity available in the body is inadequate to satisfy the needs of the functions in which it takes part.* The earliest beneficial influence obtained is an increase of general oxygenation, and, therefore, of general metabolic activity. This is due to an incidental stimulation of the test-organ and adrenal center by the iron carried thereto by the leucocytes.* As iron is likewise an active stimulant of the hæmatopoietic cells of the bone-marrow, the red corpuscles are increased in number concomitantly with the volume of adrenoxidase in the blood.*

The physiological action of iron is at present unknown. The increase of general oxygenation has been noted by various observers, and by some after the first dose. Wood[200] says: "The studies of Pokrowsky[201] have shown that, in cases of anæmia, after the exhibition of iron the temperature does rise, even when in the beginning it was not below normal, and that simultaneously there is an increase in the daily elimination of urea"—experiments confirmed by Botkin in healthy men. "The increased oxidation cannot be due simply to an increase in the number of corpuscles," continues Prof. Wood, "for while the latter accrue slowly, Pokrowsky found that the temperature sometimes rose within five hours after the exhibition of the first dose." Von Noorden[202] also states that "the salts circulating in the blood (medicinal iron) exert a powerful stimulus upon the hæmatopoietic cells of the bone-marrow, and the result of this stimulation is an improvement of the blood."

A second important effect of iron is to increase the proportion of hæmoglobin. This metal is the main component of hæmatin, the coloring constituent of hæmoglobin that remains

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* *Author's conclusion.*
[200] Wood: *Loc. cit.*, thirteenth edition, p. 446, 1906.
[201] Pokrowsky: Virchow's Archiv, Bd. xxii, S. 476, 1861.
[202] von Noorden: "Nothnagel's Encyclo.," vol. on the Blood, p. 487, 1905.