nels; (2) accumulation of hypocatabolized wastes in the peripheral and cerebro-central capillaries; (3) excessive excitation of the general vasomotor center and general vasoconstriction; (4) lethal vasomotor inhibition of the pituitary and heart.

H. C. Wood,[202] many years ago, and again recently with H. C. Wood, Jr.,[203] found that when given hypodermically in toxic doses, veratroidine "caused an enormous rise of blood-pressure." This could not be ascribed to a direct action of the drug on the vasomotor center, but to deficient oxidation, since the author found that "it did not occur when artificial respiration was maintained"—a procedure which greatly increases the air intake. He ascribes it to "centric asphyxia," but we have seen that the phenomena ascribed to the inert CO_2 are in reality due to toxic waste products. Again, the cardiac inhibition was evidently the cause of the lethal phenomena, for H. C. Wood and H. C. Wood, Jr., referring to the former's earlier articles state that "in these it was noted that the veratroidine was an extremely powerful stimulant to the inhibitory nerves, so that it was possible to produce by it a cardiac arrest which was immediately put an end to by section of the vagi." Finally, if the lethal vasodilation is due to inhibition, and not to the vasomotor depressor jervine, a dose of the violent vasomotor stimulant veratroidine should counteract it. Wood states that "an animal, apparently dead, could be restored to life by vagal section, or by giving *more of the poison*," referring to veratroidine.

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

Therapeutics.—In the incipient stage of *pneumonia* when excessive general vasoconstriction* tends to asphyxiate the patient by gorging his lungs with blood, veratrum viride in small therapeutic doses, given frequently until dyspnœa is relieved and the pulse is less tense, is a life-saving measure by causing general vasodilation and relieving the heart of undue resistance. It is of especial advantage in plethoric subjects. Veratrum viride is also of value in convulsive disorders, such as *puerperal eclampsia* and *epilepsy*, to prevent convulsions, which are due in part to excessive vasoconstriction and hyperæmia of the cerebro-spinal system.* It should be regarded only as a palliative, however, since it tends to encourage hypocatabolism and the accumulation of spasmogenic toxic* wastes in the blood. Veratrum viride is also of value in localized inflammatory processes such as *cerebritis, meningitis, pleurisy,* and *peritonitis,* to antagonize excessive hyperæmia. By causing general vasodilation it is also advantageous in *aneurism,* especially when there is danger of rupture.

* *Author's conclusion.*
[202] H. C. Wood: Phila. Med. Times, Aug. 22, Sept. 12, 1874.
[203] H. C. Wood and H. C. Wood, Jr.: Amer. Jour. Med. Sci., May 9, 1899.

ACONITE.

Physiological Action.—In therapeutic doses, aconite depresses the sympathetic center and causes general dilation of the arterioles.* An excess of blood being admitted into the capillaries, passive* hyperæmia is produced. Small doses infrequently repeated may thus cause a slight feeling of warmth; if frequently repeated, or if full doses are given, a characteristic symptom appears, viz., tingling, or prickling, felt at first either in the nose, lips, tongue, or finger-tips, and due to hyperæmia of the sensory terminals of the skin and mucous membranes.*

The prevailing view that aconitine causes the characteristic tingling by a local action of the remedy on the sensory terminals involves the assumption that—inasmuch as $^1/_{60}$ grain (0.001 gm.) of aconitine caused Dr. Meyer's death, and also that of a case reported by Lépine[204]—a solution of 1 in 8,000,000 (basing the calculation on only 16 pounds of blood and disregarding the lymph-vessels into which the plasma is constantly flowing) is the active factor in the process. Granting even that it has run safely the gauntlet of the antitoxic substances of the blood, this view does not appeal to reason. Especially is this the case when we take into account the fact that the tingling develops into hyperæsthesia, as it does at times in experimental animals, who jump about to avoid contact of their feet with the floor and show evidences of severe pain by their cries, and the fact that severe neuralgic pains occur in some cases of poisoning. These effects are obviously out of all proportion with the strength of the solution. On the other hand, we have a thoroughly logical explanation of these phenomena—and concurrently of all the other symptoms enumerated in the general text—in the sudden flooding of sensory elements with arterial blood. The dilation of the arterioles is generally recognized; Shoemaker,[205] for instance, states that "owing to the lowering of the blood-pressure and the dilatation of the arterioles caused by the aconite, the heat of the body is at first brought, with the increased blood-flow, to the surface."

Untoward Effects and Poisoning.—When a large dose of aconite or aconitine is taken, this passive hyperæmia provokes a sensation of warmth throughout the body, including the skin, mouth, pharynx, and stomach, and redness of the face. This is accompanied by the characteristic symptom, tingling, which may now spread over large areas—owing to flooding of the sensory terminals with adrenoxidase-laden plasma.* The nerves themselves, especially the upper division of the fifth pair, may also become hyperæmic,* and cause acute lancinating pain. Among other symptoms observed that are ascribable to this

* *Author's conclusion.*
[204] Lépine: Semaine med., vol. xii, p. 117, 1892.
[205] Shoemaker: "Therapeutics," sixth edition, p. 148, 1906.

cause* are cephalalgia, tinnitus aurium, photophobia, dilation of the pupil, increase of cardiac power and of respiratory activity, salivation, nausea, vomiting, and pruritus.

Such a dose may introduce another morbid factor, *i.e.*, depression, then paresis of the test-organ, and through it of the adrenal center. The proportion of adrenoxidase being correspondingly reduced, general hypometabolism follows in all tissues, including the walls of the arteries and heart.

"In the very beginning of aconite poisoning," writes Wood, "the bodily temperature may rise slightly, but in severe poisoning a very pronounced fall occurs." The relationship of paralysis of the adrenal functions with this phenomenon is not only suggested by the rôle of their secretion in general oxygenation, but also by the concurrent "fall of the arterial pressure, which," as stated by Wood, "progressively increases to the end." Now, Strehl and Weiss[206] found that after removal of one adrenal, the blood-pressure fell 4 or 5 m.m. Hg., but that when the second adrenal was removed, the blood-pressure fell at once 20 or 30 m.m. and continued to fall till death ensued. Moreover, clamping of the adrenal veins—through which the secretion passes to the blood—caused the pressure to fall, while their release at once caused it to rise. What paralysis of the adrenal center means under such conditions is self-evident.

Several investigators, Boehm and Wartmann,[207] Guilland[208] and others hold that aconite causes a rise of the blood-pressure. But, as stated by Wood,[209] the stimulating action of the drug on the vasomotor system is not proved by their researches. Interpreted from my standpoint, these investigators observed the intercurrent rise which precedes convulsions. But as the latter are due to toxic waste products of hypocatabolism (owing to their imperfect elimination from the spinal system, an incident of the local ischæmia), we cannot incriminate the drug. Another misleading factor is the supposed physiological inhibition of the heart by the vagus. We have seen that this phenomenon is a morbid one, and that the nerves the vagus supplies to the heart are vasomotor. Hence the preliminary slowing by an excess of blood admitted into the heart and the subsequent tachycardia due to general vasodilation. (Marey's law).

When the dose is sufficiently large to prove fatal, the capillary hyperæmia is promptly succeeded by capillary ischæmia, caused by retrocession of the blood from all capillaries, and its accumulation in the deeper and widely dilated trunks, especially those of the splanchnic area.* This is due to the arrest of adrenal functions and the resulting depression of metabolic activity in the muscular layer of all vessels.*

This inaugurates the stage of general depression and finally

* *Author's conclusion.*
[206] Strehl and Weiss: Pflüger's Archiv, Bd. lxxxvi, S. 107, 1901.
[207] Boehm and Wartmann: Arbeit physiol. Würzburger Hochschule, Bd. i, S. 93, 1872.
[208] Guilland: Arch. de physiol. norm. et path., 2 série, vol. ii, p. 766, 1875.
[209] Wood: *Loc. cit.*, thirteenth edition, p. 382, 1906.

collapse. The patient complains of great weakness, and of feeling cold and numb, the peripheral sensitive organs being now depleted of their blood. The surface is generally bedewed with sweat, the pupil is dilated, vision and hearing become impaired and towards the close may be lost, though the intellect remains clear.

The pulse, at first slow, becomes rapid when the greater arteries are dilated (Marey's law).* Any exertion at this time, such as sitting up, etc., may cause cardiac arrest. The irregular action finally lapses into *delirium cordis,* and the heart's intrinsic circulation* soon becomes sufficiently reduced to paralyze its functions.

The respiration, slightly increased in activity at first, soon becomes slow and shallow, expiration being followed by a long pause. Cyanosis and other signs of asphyxia, often preceded by a feeling of tightness about the throat and convulsions, then appear, the precursors of death.

All this entails the conclusion that it is upon the centers that the drug acts. Laborde and Duquesnel,[210] Liégeois and Hottot[211] long ago furnished experimental evidence of this effect. Cushny[212] also refers repeatedly to a central action of the drug. Thus, he states that "the respiratory symptoms are certainly of central origin, though their explanation is still unknown." Again: "Death is due to paralysis of the respiratory center from the direct action of the poison." The "respiratory center" being, from my standpoint, the adrenal center, and the adrenals ceasing to produce their secretion, respiration becomes impossible. Cushny states that "the paralysis advances much more rapidly in the respiratory center than elsewhere, and death occurs from asphyxia." Cash and Dunstan[213] state that death in mammals is due "to central respiratory failure."

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

Therapeutics.—Aconite has been used considerably for the arrest of *colds.* Its value in this connection is accounted for by the fact that it dilates the peripheral arterioles, and thus allows a greater volume of blood to penetrate the capillaries and to exercise more effectively its antitoxic action.* It is also beneficial in *neuralgia* and *migraine* when the blood-pressure is ele-

* *Author's conclusion.*
[210] Laborde and Duquesnel: "Des Aconits et de l'Aconitine," p. 103, 1883.
[211] Liégeois and Hottot: Brown-Séquard's Jour. de physiol., vol. iv, p. 520, 1861.
[212] Cushny: *Loc. cit.*, fourth edition, pp. 329 et seq., 1906.
[213] Cash and Dunstan: Proceedings Royal Soc. of London, vol. lxii, p. 338, 1898.

vated, thus driving the blood into the diseased nerves;* under the influence of aconite the general lowering of the vascular tension, which the dilation of all the arterioles of the body entails,* thus relieves the pain.

Aconite has been used in *sthenic pneumonia* to diminish the threatening asphyxia and relieve the heart, but veratrum viride is a better remedy for this purpose, since it depresses the vasomotor center* and relieves the pressure more effectually. It has been used in *fevers* of various kinds, but a better knowledge of the immunizing value of the febrile process has caused its use to be largely abandoned.

AMYL NITRITE.

Physiological Action.—Amyl nitrite, by stimulating the sensory end-organs of the fifth pair in the upper respiratory tract, while inhaled, causes reflexly a slight rise of the arterial tension by stimulating the sympathetic center;* but this effect is almost immediately replaced by general vasodilation beginning with the arterioles, due to the characteristic physiological effect of the drug: depression of the sympathetic center.*

Cushny[214] states that "in the beginning" and "from irritation of the nasal sensory terminations" . . . . . "the blood-pressure may rise and the heart be slowed from reflex action on the inhibitory and vasoconstrictor centers respectively." Reichert[215] also noted a primary stimulation. Wood[216] states that "our present physiological evidence justifies the belief that very small quantities of amyl nitrite primarily stimulate the heart, although it is demonstrated that in moderate or large amounts the drug respectively depresses or paralyzes the heart-muscle." Conversely, Vaquez[217] observed that a small dose inhaled by an individual whose arterial tension is moderate reduces the arterial tension by from 40 to 50 m.m. Hg., while a large dose lowers it by from 70 to 80 m.m. The primary stimulation is, therefore, but a preliminary incident due to the drug's irritating action upon the respiratory passages and independent, therefore, of its true physiological effect.

When a full or excessive dose of amyl nitrite is inhaled, the relaxation of the arterioles produced causes the capillaries of all organs, including the central nervous system, to become overfilled with arterial blood, *i.e.*, passive'y congested. The face, neck, and upper portion of the body become flushed; severe and sometimes violent headache, with confusion and perversions

* *Author's conclusion.*
[214] Cushny: *Loc. cit.*, fourth edition, p. 467, 1906.
[215] Reichert: N. Y. Med. Jour., July, 1881.
[216] Wood: *Loc. cit.*, thirteenth edition, p. 255, 1906.
[217] Vaquez: La presse méd., vol. ii, p. 702, 1904.

of color sense (objects appearing yellow), is complained of; the heart beats forcibly, the respiration is likewise accelerated and deepened. When moderate doses are used these phenomena gradually subside.

This stage of peripheral hyperæmia could not occur if the larger vessels, especially those of the splanchnic area, were likewise dilated, since the blood would accumulate therein, and cause ischæmia of the peripheral capillaries.* This is what takes place under the influence of large doses, those which likewise depress the vasomotor center. Another factor is superadded under these conditions, however: depression of the adrenal center either through direct depression of its functions or through ischæmia of the pituitary body.* The blood being thus rendered poor in adrenoxidase while the capillary streams are greatly reduced in volume, their blood is rapidly reduced, *i.e.*, rendered venous by the tissues.* Hence the fact that marked hypothermia and cyanosis occur under the influence of large doses.

The effects of the drug appear very promptly. Within a minute of the inhalation, according to Hale White,[218] the arterioles "may actually be seen to widen in the ear of a rabbit or in the retina." Similar observations have been recorded by Amez-Droz,[219] Gaspey,[220] Aldridge,[221] Bader and others. Francis Hare[222] also ascribes the action of amyl nitrite to "widespread, if not general, peripheral vasodilation," and holds that "this action is alone sufficient to explain the therapeutic effects which have been or may be observed in a number of clinically diverse affections." This is doubtless true in so far as the average dose is concerned.

The effects of large doses on the general blood-pressure are well shown in the following quotation: Nothnagel and Rossbach[223] state that the cutaneous vessels are not alone dilated; one may also see the vessels of the deeper organs, those of the pia mater, for example, are dilated, and may thus become twice or three times their normal diameter (Schüller, Schramm)." Cushny[224] states that both the arteries and veins are widened "very considerably under the influence of the drug," and that "the vessels of the abdominal organs and the brain are more affected than those of the extremities." Again, as will be shown under Nitroglycerin, dilation of the arterioles only does not cause an appreciable fall of the blood-pressure, while, as stated by Nothnagel and Rossbach, amyl nitrite may cause one of 50 m.m. and considerably below that as shown recently by Vaquez.[225]

The promptness with which cyanosis occurs is not fully accounted for by the cutaneous ischæmia, since other drugs which depress the

* *Author's conclusion.*
[218] Hale White: "Materia Medica," London, 1892.
[219] Amez-Droz: Archiv de physiol., vol. v, p. 467, 1873.
[220] Gaspey: Virchow's Archiv, Bd. lxxv, S. 301, 1879.
[221] Aldridge: West Riding Lunatic Rep., vol. i, p. 71, 1871.
[222] Francis Hare: Clinical Journal, Aug. 29, 1906.
[223] Nothnagel and Rossbach: *Loc. cit.*, p. 406.
[224] Cushny: *Loc. cit.*, fourth edition, p. 465, 1906.
[225] Vaquez: *Loc. cit.*

vasomotor center do not produce this effect. The fact that the adrenal functions are likewise inhibited is suggested in various ways. According to Wood,[226] amyl nitrite "reduces most remarkably animal temperature"—as much as 13° F. (7° C.) in one of his experiments. Bourneville[227] observed in one of his experiments a reduction of 9° C. (16.2° F.). Wood ascertained that the excretion of carbon dioxide was reduced. The actual absence of a substance capable of taking up the oxygen of the air is shown by the fact that Gamgee[228] found "that amyl nitrite blood had lost its power of absorbing oxygen or of yielding oxygen to the air-pump." Devoid of adrenal secretion, the blood cannot absorb this gas, and what remained in it having been taken up by the tissues, none was available for the tissues.*

Acute Poisoning.—The toxic effects are, in addition to the blood-changes described below, the cyanosis and the general vasodilation; excessive muscular weakness and great pallor, a slow, weak and irregular pulse, shallow and irregular respiration, loss of reflexes, wide dilation of the pupils, arrest of the respiratory movements, and asphyxia, sometimes preceded by tetanic convulsions.

All these effects are due to paralysis of the adrenal center.* Small doses obtund its sensibility temporarily; but poisonous doses paralyze its functions sufficiently to allow morbid changes to occur in the blood, which render it unsuitable for the continuation of life.*

The blood, under the indirect influence of toxic doses (in man) of amyl nitrite, assumes a nearly uniform chocolate-brown color, owing to the presence therein of methæmoglobin. This substance is hæmatin, the iron-laden constituent of hæmoglobin, which normally remains in the red corpuscles, and serves to hold therein the adrenoxidase (the albuminous constituent of the hæmoglobin molecule), pending its gradual distribution to the tissues. When, under the influence of amyl nitrite, too little adrenoxidase is available in the blood to supply the needs of tissue respiration, the hæmatin is not only deprived of the greater part of the adrenoxidase linked to it, but it is itself (in part), owing to its firm hold upon the last remnants of the latter substance, withdrawn from the red corpuscles into the plasma.* Hence the term "methæmoplasma." This symptom is not nearly as marked in man, however, as it is in animals.

* *Author's conclusion.*
[226] Wood: *Loc. cit.*, thirteenth edition, p. 256, 1906.
[227] Bourneville: Cited by Manquat: *Loc. cit.*, vol. ii, p. 121.
[228] Gamgee: Philos. Trans. of Royal Soc. of London, vol. xvi, p. 339, 1868.

The usual picture of adrenal insufficiency promptly appears when the dose administered is excessive. "After poisonous doses," says Professor Wood, "the symptoms have been great pallor, usually dilatation, but sometimes contraction of the pupils, excessive muscular relaxation, slow, scarcely perceptible pulse, hæmoglobinuria and irregular respiration."

We have just seen that Gamgee found that amyl nitrite blood no longer yielded oxygen to the air-pump. Hammarsten[230] states that "methæmoglobin does not contain any oxygen in molecular or dissociable combination." The causative absence of oxidizing substance relegates the whole process of methæmoglobin formation to a corresponding diminution of oxygen, and invalidates the prevailing view that amyl nitrite and other drugs cause methæmoglobinæmia by acting directly on the blood.* Referring to a mouse killed in 2 minutes by amyl-nitrite inhalations, Haldane, Makgill and Mavrogordato[231] state that "the symptoms were those of asphyxia from *want of oxygen.*" In another experiment the animal was placed in oxygen with a 0.3 c.c. capsule, and the oxygen pressure raised to 80 c.m. This mouse only died in 14 minutes. A third animal was placed in pure oxygen at atmospheric pressure and an 0.18 c.c. capsule. At the eleventh minute the air was removed; in a few seconds life had ceased. The blood in all was chocolate-colored. The authors also ascertained during experiments upon themselves that air deficient in oxygen or carbonic acid poisoning caused symptoms identical to those evoked by amyl nitrite. That methæmoglobin may be formed irrespective of any direct action upon it, and simply through abstraction of oxygen, is also shown by the following experiment, as described by Hammarsten: "If arterial blood be sealed up in a tube, it gradually consumes its oxygen and becomes venous, and by this absorption a little methæmoglobin is formed." Gamgee, however, found that the spectrum bands of methæmoglobin corresponded with those of *acid* hæmatin. "According to Rabuteau," writes Manquat,[232] "in animals poisoned with amyl nitrite, the blood becomes neutral and even acid." Again, if methæmoglobin is hæmatin *plus* a remnant of oxidizing substance, it should itself be reducible by the tissues after leaving the red corpuscles. The conversion into methæmoglobin "does not entail," says Cushny,[233] "the destruction of the red corpuscles, and the compounds are eventually *reduced* by the *tissues*, although the reduction progresses much more slowly than that of ordinary oxyhæmoglobin." Finally, Vulpian[234] found that in methæmoglobinæmia due to venom, the blood-corpuscles are almost all, when death did not occur promptly, deprived of their hæmoglobin. In the animal poisoned with amyl nitrite by Haldane, Makgill and Mavrogordato, the proportion of "hæmoglobin" converted varied from 80 to 92 per cent.

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

Therapeutics.—The vasodilator action of amyl nitrite upon the arterioles, owing to the lowering of the vascular tension it involves, accounts for its beneficial action in *angina pectoris*, a disorder due to excessive arterial tension, and claudication of the heart. In the continuous hyperconstriction which keeps up

* *Author's conclusion.*
[230] Hammarsten: *Loc. cit.*, p. 171.
[231] Haldane, Makgill and Mavrogordato: Jour. of Phys., vol. xxi, p. 160, 1897.
[232] Manquat: *Loc. cit.*, vol. ii, p. 121, 1903.
[233] Cushny: *Loc. cit.*, fourth edition, p. 468, 1906.
[234] Vulpian: C. r. de l'Acad. d. sci., vol. xciv, p. 613, 1882.

the convulsions of *status epilepticus,* and the corresponding though temporary condition in *tetanus, puerperal eclampsia* and kindred disorders, the drug is of recognized value. An elevation of the blood-pressure, as will be shown, likewise prevails in *migraine* and *neuralgia,* a fact which accounts for the analgesic effect of amyl nitrite in this disorder. In *dysmenorrhœa,* the condition of the uterus and adnexa resembles closely that which prevails in angina pectoris; hence the benefit derived from the drug. In the *chill of intermittent fever,* due to hyperconstriction of the cutaneous arterioles, a few whiffs (about five minims) of amyl nitrite suffice to cause its cessation.

NITROGLYCERIN.

Physiological Action.—Nitroglycerin causes dilation of all arterioles,* by depressing directly the sympathetic center.* The capillaries of all organs being thus caused to receive an influx of arterial blood,* full therapeutic doses give rise to a sensation of fullness of the head with throbbing, more or less violent headache, vertigo, congestion of the conjunctiva, tingling or itching in the throat and tongue, salivation, muscular stiffness and spasmodic jerks, tinnitus aurium, flushing of the face and sometimes of the neck and trunk, and a feeling of constriction about the throat and precordial region. The cardiac contractions are more powerful, sometimes dicrotic, and, owing to the vasodilation, more frequent, the increased cardiac power extending up to and being discernible in the carotids.

Various investigators, including Hénocque,[235] Lauder Brunton and Tait,[236] and Hay[237] hold that nitroglycerin and amyl nitrite act similarly, notwithstanding the disparity in their chemical composition. The primary vasoconstriction due to irritation of the respiratory passages is not provoked by nitroglycerin, however, a fact ascertained experimentally by Haldane, Makgill and Mavrogordato.[238] Hence dilation of the arterioles is the first effect of the drug, irrespective of any intervention of the "inhibitory" or depressor mechanisms, which have introduced confusion in the study of amyl nitrite.

When the doses taken are administered too often, or when they are large, the dilation of the arterioles is supplemented by dilation of the larger vessels, caused by a similar depressing

* *Author's conclusion.*
[235] Hénocque: C. r. de la Soc. de biol., 7 série, T. v, p. 669, 1883.
[236] Lauder Brunton and Tait: St. Bartholomew's Hosp. Rep., vol. xii, p. 146, 1876.
[237] Hay: Practitioner, vol. xxx, p. 422, 1883.
[238] Haldane, Makgill and Mavrogordato: *Loc. cit.*, p. 183.

effect of the drug upon the bulbar vasomotor center and its subsidiary centers in the cord.*

The prevailing view is that nitroglycerin in therapeutic doses produces *general* vasodilation, but, as recently shown by H. P. Loomis,[239] such is not the case. By means of the sphygmomanometer used in a number of cases, some of which were observed until recovery, he ascertained that even when given in full therapeutic doses repeatedly, the drug did not lower the blood-pressure. It was only when given to dogs in doses which would have proved toxic to man that the blood-pressure fell, the heart being extremely weakened. The fall of pressure lasted only five minutes, however, though the heart remained feeble. The retrocession of blood from the capillaries was rendered evident by marked diminution of the volume of the kidney, as shown by an oncometer placed upon this organ.

This points clearly to the sympathetic center as the one depressed by the drug at first, since dilation of the arterioles *alone,* such as that produced by therapeutic doses, does not suffice to cause an appreciable fall of blood-pressure. Indeed, did such occur, there would not be flushing of the face and other signs of hyperæmia, but pallor and other signs of capillary anæmia, owing to recession of the blood to the deeper vessels. When large therapeutic doses are taken, however, the vasomotor center is also depressed by the drug. This is shown not only by the cardiac weakness in Loomis's dogs, and the dose required to produce it and reduce the pressure, but also, in man, by the fact that Von Noorden[240] found that by using very large doses, *e.g.*, "daily doses of 10 milligrams, and even 12 milligrams" ($^1/_6$ to $^1/_5$ grain), (the initial doses having been small and gradually increased) the blood-pressure could be reduced from 180 and 220 to 100 and 120, and even less, in his service in the Frankfort Hospital.

Untoward Effects and Poisoning.—The untoward phenomena produced by nitroglycerin are all those enumerated above which exceed a slight frontal fullness, tingling, itching, or formication in the throat and tongue and a slight quickening of the pulse, and, perhaps, a feeling of warmth about the face.

When the blood-pressure is reduced by depression of the vasomotor center, the arterial pressure falls and all the symptoms are those of collapse—the reverse of the erethic condition produced by the smaller doses, which affect only the sympathetic center. There is marked failure of the heart's action, and its beats may become weak, irregular and intermittent, the pulse being correspondingly feeble. The resulting retrocession of the blood from the surface, including that of the pulmonary alveoli, engenders inadequate oxygenation,* but another factor promptly aggravates the morbid process under these conditions: ischæmia of the anterior pituitary body and inhibition of the adrenal

* *Author's conclusion.*
[239] H. P. Loomis: Med. Rec., Mar. 18, 1905.
[240] Von Noorden: Verh. des Congress f. innere Med., Bd. xxi, S. 152, 1904.

functions.* Hence the marked dsypnœa, hypothermia, anæsthesia, and cyanosis.

The various stages of this process are explained in the foregoing general text.

The sequence of events caused by large doses may be illustrated by Demme's[241] experiments on himself with a 1 in 10 alcoholic solution. Two or three drops caused formication or itching (also mentioned by Vohl[242]) in the mouth and tongue, salivation, an increase of 10 to 12 beats in the pulse. After 6 to 10 minutes, dull, constrictive pains in the forehead, vertigo, cerebral fatigue. With *five* or *six* drops, these phenomena occurred sooner and were more marked; choreic movements of the masseter then appear, which may spread to other muscles when *ten* drops are given. Although these doses should not be taken as guide in practice, Loomis[243] states that the usual dose, $^1/_{100}$ grain (0.00065 gm.), is too small to produce any effect in pathological conditions, and that $^1/_{50}$ grain (0.0013 gm.) is a minimum dose. He regards it as a safe drug—in opposition to prevailing view—even large and repeated doses having never produced ill effects. D. D. Stewart[244] states that an excessive tolerance to nitroglycerin can be readily acquired if care is not taken to avoid a too rapid increase of the dose; hence the drug, though intelligently employed, is often of little service. He refers to a case in which 50 minims of a 10-per-cent. solution were taken daily without any very marked effects. Binz,[245] of Bonn, states that man "offers, as a rule, energetic resistance to nitroglycerin when the doses are not excessive," and refers to others who advocate larger doses than those generally administered.

Still we must not overlook the fact that nitroglycerin is capable of producing violent symptoms. Wood refers to an observation of Noer's,[246] in which ten-drop doses of an alcoholic solution (usually $^1/_{100}$) in a woman caused violent toxic phenomena.

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

Therapeutics.—The beneficial effects of nitroglycerin are due to the fact that it lowers excessive arterial tension in the organs themselves, by dilating only the extremities of the vascular tree, *i.e.*, the arterioles.* In *angina pectoris,* for example, the pallor and ashen gray appearance of the surface observed not only during the paroxysm in some, but at all times, points to excessive vasoconstriction. Here, one minim of the 1-100 alcoholic solution, three times daily, suffices at first, but gradually, as the patient becomes habituated to the drug (the sympathetic center becoming less and less sensitive to its action*), it must be increased until three or four times the original dose is taken.

* *Author's conclusion.*
[241] Demme: Cited by Albers: Deut. Klinik, Bd. xvi, S. 407, 1864.
[242] Vohl: Cited by Eulenburg: Berl. klin. Woch., Bd. ii, S. 251, 1865.
[243] Loomis: *Loc. cit.*
[244] D. D. Stewart: Jour. Amer. Med. Assoc., May 27, 1905.
[245] Binz: Revue de thérap. medico-chir., vol. lxxii, p. 656, 1905.
[246] Noer: Therap. Gaz., July 15, 1887.

The best rule for giving the drug for its effects on blood-pressure is, in Stewart's opinion,[247] to administer it four times a day in dose just sufficient to produce the slightest feeling of fullness in the head or to slightly quicken the pulse. If more than that is given, an undesirable tolerance is likely to be established. When a rather rapid increase seems needed to keep up a constant effect, it is best to discontinue the drug for two or more days, at intervals, and to resume its use with a smaller initial dose. By so doing the use of very large doses and strong solutions, which are not exactly safe to handle, will be avoided. Nitroglycerin, Stewart thinks, has not met expectations as a remedy in conditions of persistent high tension, and he now uses it in such cases less frequently than formerly, endeavoring at first, at least, to relieve by limiting the nitrogenous intake and maintaining free action of the skin and bowels. Aconite is often substituted for nitroglycerin in these cases with advantage.

It has been used to advantage in *epilepsy, puerperal eclampsia,* and kindred disorders in which the arterial tension is high. This phenomenon is also present in *uræmia.*

DRUGS WHICH RESEMBLE NITROGLYCERIN IN THEIR PHYSIOLOGICAL ACTION.

Erythrol tetranitrate is somewhat less active than nitroglycerin, but its effects endure much longer and begin earlier after its ingestion. Its physiological action differs in no way from that of nitroglycerin. Being also a violent explosive, tablets should alone be prescribed.

CREOSOTE, CREOSOTE CARBONATE, GUAIACOL AND GUAIACOL CARBONATE.

Physiological Action.—Creosote is primarily a depressant of the sympathetic and vasomotor centers.* If the patient be markedly asthenic, as the result (1) of the disease from which he is suffering; (2) of a congenital hypersensitiveness of the two vascular centers mentioned;* (3) of a temporary hypersensitiveness of these centers, brought on by shock, pain, etc., even a small dose may provoke sufficient general vasodilation* to cause an accumulation of blood in the great central vessels, and by depleting the peripheral vessels cause marked hypothermia.

This is a very important feature of the action of creosote, which should be borne in mind when it is prescribed in tuberculosis. Its depressing action on both vascular centers is illustrated by its effects on the temperature. Thus R. Simon[248] states that in some subjects, hypothermia lasts as long as creosote is employed; in one of his cases it remained 1.1° C. (2° F.) below normal during the two months that

* *Author's conclusion.*
[247] Stewart: *Loc. cit.*
[248] R. Simon: "Créosote Tolérance et Intolérance," Paris, 1899.

it was used. Burlureaux[249] states that after injections of creosote "the patient may complain of a most unpleasant sensation of internal cold; his extremities are icy, and his lips cyanosed. . . . ." Desplats[250] found that, like guaiacol, it caused "a general and intense vasodilation with all its consequences." Even a small dose may cause death under such conditions. Zawadzki[251] reported a death in a young woman who was taking 18 minims daily.

The production of a temporary vulnerability of the vascular centers to the morbid effects of creosote is well shown by various instances reported by Simon. In several cases "the drug was tolerated perfectly before and after an attack of influenza, but not during this disease." In another, large doses could be taken excepting during menstruation. In some, the untoward effects came only after the injections had caused severe pain. In one of Burlureaux's cases, it came on immediately after a painful traumatism, etc. That advanced cases of tuberculosis cannot bear creosote, and that certain persons are very susceptible to its effects, is well known.

When marked general asthenia is not present, the arteries and arterioles are only sufficiently dilated to admit a greater volume of blood than usual into all capillaries,* and to reduce excessive vascular tension. This action is supplemented by another which endows creosote with its curative properties in appropriate cases, viz., it excites a protective reaction of the test-organ.* The adrenal center being stimulated, the quantity of adrenoxidase in the blood is increased and its proportion of auto-antitoxin likewise.* The volume of arterial blood circulating in the capillaries—of the lungs, for example—is thus not only increased, but its bacteriolytic and antitoxic properties are also enhanced.

Arloing[252] found that creosote, as well as eucalyptol, guaiacol and mercury, when injected repeatedly into goats, caused their blood to acquire the property of "agglutinating rapidly and completely Koch's tubercle bacilli suspended in homogeneous emulsions." He found that in equal volume this goat serum "agglutinated somewhat less energetically than the serum of goats which had received tuberculin." The connection between this condition of the blood and the preliminary depression of the vascular centers produced by the drug is illustrated by the *hyper*-thermia which occurs when the *hypo*thermia ceases. Thus, Simon states that in cases of intoxication the temperature becomes steadily lower until the seventh hour, when (under the influence of the adrenoxidase, which has been accumulating all this time*) a reaction occurs, the temperature gradually rising up to 39° C. (102.2° F.) or 40° C. (104° F.), the latter coinciding with free sweating. This indicates, as Desplats says, "a sudden and general vasoconstriction, which should not be considered as a sign of intoxication. Indeed, such a reaction is the sign of recovery even after enormous doses, as shown by several cases on record. In a case of Faisans's[253] a dose of 9.5 gms. (146 grains) taken

* *Author's conclusion.*

[249] Burlureaux: "Traitement de la Tuberculose par la Créosote," 1894.
[250] Desplats: Jour. des sc. méd. de Lille, vol. xvii, pp. 1, 25, 1894.
[251] Zawadzki: Centralbl. f. innere Med., Bd. xv, S. 401, 1894.
[252] Arloing: C. r. de l'Acad. des sc., T. cxxvi, May 9, 16, 1898.
[253] Faisans: Bull. gén. de thérap., Feb. 8, 1896.

surreptitiously by the patient to hasten his cure, the hypothermia was succeeded by a temperature of 38° C. (100° F.) and hyperæsthesia, showing that the peripheral capillaries were hyperæmic.

Untoward Effects and Poisoning.—As shown by the above analysis, the untoward symptoms are due to depression of the sympathetic and vasomotor centers,* and the resulting general vasodilation. The blood accumulating in the deeper vessels, the subjective signs are progressive hypothermia with sensation of intense cold, cold sweats, contracted pupil, vertigo, marked adynamia, cyanosis, and unconsciousness with involuntary emesis and micturition—on the whole a cholera-like syndrome—due to ischæmia of the peripheral organs. In markedly debilitated individuals collapse may occur, and death follow respiratory failure.

In the majority of cases, however, after a period of six or seven hours, the drug is sufficiently modified by the blood's auto-antitoxin* (especially adrenoxidase, which by oxidizing it turns it black*) to lose its depressing power over the vascular centers,* and the tide turns. The blood-vessels not only resume their normal caliber, sometimes suddenly, but the reaction of the test-organ, which the presence of the drug in the blood has excited all along,* having caused overactivity of the adrenal center and, as a result, an accumulation of adrenoxidase in the blood,* evokes the hyperthermia referred to, which may reach 104° F. (40°C.). The cutaneous and cerebro-spinal vessels being now overfilled with blood, general hyperæsthesia, hallucinations, talkative delirium, dilation of the pupil, restlessness and trismus may occur. The urine is usually smoky, owing to its content in oxidized creosote*—the oxidation* continuing in some instances when the urine is exposed to the oxygen of the air. The patient soon recovers completely.

The untoward effects are not necessarily caused by large doses only. Simon refers to cases in which doses as small as $^1/_{12}$ minim (0.0012 c.c.) and 5 minims (0.3 c.c.) brought them on. It depends entirely upon the condition of the patient, *i.e.*, from my standpoint, of the sensitiveness of his vascular centers. In such cases these centers are on the verge of collapse, and this may occur in persons who have been taking the drug right along, owing, we have seen, to the debilitating action on the patient's *sensorium commune* of some intercurrent influence, menstruation, grippe, pain, etc. Neither sex nor age influences the production of these phenomena. Lamplough,[254] who treated 100 cases without meeting with untoward effects, gave children from two

* *Author's conclusion.*

[254] Lamplough: Brit. Med. Jour., May 28, 1898

to five years of age 30 minims (2 c.c.) daily. He followed strictly a rule which should never be set aside when creosote is used, viz., to begin with very small doses so as to test the patient's sensitiveness. Schoull[255] used it safely in patients ranging from two months old to ninety-one years of age. This does not mean that extreme ages are free from its toxic effects. Marcard[256] observed a fatal case of poisoning in an infant four weeks old, in which the most prominent symptom was cyanosis.

The identity of creosote as a derivative of wood-tar accounts for the fact that it may become oxidized in the blood. Wood[257] states, in fact, that "it occurs in the urine probably in part as oxidized educts." We have seen that, as shown by Bertrand, Loew and many others, plants contain a ferment which becomes oxidized and black on exposure to oxygen. That the process of distillation liberates such a ferment is probable. Simon, referring to instances of poisoning, states that "the urine may be already black on leaving the bladder, or it may blacken very rapidly on being exposed to the air." This suggests that the vegetable ferment might prove active in the blood, but many facts indicate that such is not the case.

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

Therapeutics.—*Creosote carbonate* which contains ninety per cent. of creosote is preferable to pure creosote. It is an oily, tasteless liquid which can be readily administered in capsules. In *lobar pneumonia* creosote is of very great value during the early stages, when the diseased area is engorged. A dangerous feature of this stage is the excessive vascular tension. The drug not only counteracts this condition, but it opens the channels through which the auto-antitoxin-laden blood can penetrate to the diseased lobes.* The pneumococcus being readily killed, creosote often becomes a life-saving measure. This applies as well to *broncho-pneumonia*. In *pulmonary tuberculosis*, the slight vasodilation produced likewise enables the arterial blood laden with antitoxin to reach more freely the diseased portions of the lung,* and thus to enhance the local reparative process. The manner in which it is to be used is indicated under the headings of these various disorders.

Guaiacol may be used instead of the foregoing, but the *guaiacol carbonate* is less toxic and should be given the preference. A curious property of guaiacol is to produce, when painted on the skin, a more or less marked hypothermia. It does this by depressing reflexly the vasomotor and sympathetic centers.*

* *Author's conclusion.*

[255] Schoull: Jour. des praticiens, vol. xi, p. 373, 1897.

[256] Marcard: Vjhrsch. f. gericht. Med. u. S., Supp.-Hft., S. 20, 1889; Schmidt's Jahrbücher, Bd. ccii, S. 269, 1889.

[257] Wood: *Loc. cit.*, thirteenth edition, p. 843, 1906.

Vasodilation thus produced is of advantage as an emergency measure, as will be shown, but not in the treatment of the disorders in which, on the other hand, creosote and creosote carbonate are of great value.*

Carbolic acid acts much as does creosote, but it is more active as a stimulant of the adrenal mechanism, and the depressing action on the sympathetic and vasomotor centers is antagonized almost from the start by a large increase of adrenoxidase.* Toxic doses, however, likewise paralyze the vascular centers, and produce marked hypothermia. The internal use of carbolic acid is especially interesting on account of Baccelli's success with it in *tetanus*. His results are accounted for by the fact that, the proportion of auto-antitoxin in the blood being greatly increased by the drug, the spasmogenic poison is actively destroyed.*

* *Author's conclusion.*