Another prominent physiological effect of purgatives is to increase the peristaltic movements of the intestines, in addition to their stimulating influence upon the secretory activity of the intestinal mucosa. Saline purgatives do not increase intestinal peristalsis, however, when given in therapeutic doses—an important practical fact when it becomes necessary to asepticize by purgation* and flush the intestinal canal without increasing the movements of its walls, as during the onset of peritonitis, appendicitis, etc.

Nothnagel and Rossbach[42] conclude that "the principal cause of purgation lies in an increase of the peristaltic movements of the intestine." The experiments of Legros and Onimus,[43] Houckgeest[44] and others have shown, however, that this does not apply to saline purgatives. Vulpian, in the course of the experiments referred to above, found, in fact, that while jalap and other vegetable cathartics increased peristalsis, the salines did not. Radziejewski[45] found that purgatives in general increased the peristaltic movements of the small and large intestine, but that it was mainly by enhancing those of the colon that the alvine dejections were rendered more frequent. Lauder Brunton teaches that there can be no doubt as to the fact that purgatives increase both the secretory activity and the peristaltic movements of the intestine. Wood, Sr. and Jr.,[46] adduced a number of facts which are, they state, "incompatible with any other belief than that purgatives cause both increased secretion and increased peristalsis in the alimentary canal." Experimental evidence shows clearly, however, that an exception must be made as to the salines.

Mercurial purgatives do not produce their effects through either of the two mechanisms described above.* After being taken up from the intestinal canal they act as ordinary drugs by exciting the test-organ, and through it the adrenal center.* By thus increasing the proportion of adrenoxidase in the blood, they raise the secretory activity of the pancreas and of the intestinal glands by enhancing their intrinsic metabolism.* They also augment the proportion of adrenoxidase that traverses the liver, this substance appearing in the stools as biliverdin and giving them the familiar green color.* Mercurial purgatives enhance the bacteriolytic antitoxic properties of the blood (especially in the liver), besides that of the intestinal canal.*

The physiological action of mercury was reviewed at length under the heading of that drug, to which the reader is referred. We have seen that mercury, even when rubbed into the skin, sufficed to provoke

* *Author's conclusion.*
[42] Nothnagel and Rossbach: *Loc. cit.*, p. 564, 1889.
[43] Legros and Onimus: Jour. de l'anat. et de physiol., vol. vi, pp. 37, 163, 1869.
[44] Houckgeest: Archiv f. d. ges. Physiol., Bd. vi, S. 266, 1872.
[45] Radziejewski: Arch. f. Anat., S. 37, 1870.
[46] Wood, Sr. and Jr.: *Loc. cit.*, thirteenth edition, p. 646, 1906.

violent irritation of the intestinal mucosa and diarrhœa by increasing excessively the proteolytic property of the blood. This shows that primary contact is not a *sine qua non* of purgation. Podophyllotoxin was found by Neuberger[47] to purge when given hypodermically and to cause intestinal hyperæmia. Apocodeine, introduced by Guinard, has also been found effective as a cathartic, when given subcutaneously, by Raviart, Heinze[48] and others. These, and other agents used in a similar way, markedly irritate the tissues at the site of injection and are used no longer. It is probable that all cholagogues act much as do the mercurials, by a central action, but no evidence to that effect is available.

Therapeutics.—*Castor oil* acts mildly as a stimulant of the intestinal mucosa, when therapeutic doses are used, though quite active as a purgative. It provokes just enough local hyperæmia to enhance the germicidal and antitoxic activity of the intestinal fluids.* Hence* its value in *diarrhœa* and *dysentery* due to the presence of pathogenic organisms. It is, in fact, effective in all mycotic disorders of the alimentary canal, especially in children. In the *bronchial catarrh* of infants it is very efficacious as revulsive.

Croton oil, owing to the violence with which it acts, in very small quantities, is of great value as a drastic purgative in *apoplexy, acute mania, uræmic coma,* etc. By causing a copious outpour of intestinal fluid, it relieves the blood-pressure. In *impacted fæces,* or *intestinal obstruction,* the large quantity of fluid with which the canal is flushed increases materially the chances of recovery. In *lead colic* it is especially advantageous, owing to the rapidity of its action.

Salines.—These salts include sodium sulphate, magnesium sulphate, magnesium citrate, potassium tartrate and bitartrate, and potassium and sodium tartrate. Of these the citrate and sulphate (Epsom salts) are of especial value in inflammatory disorders of the abdomen, *peritonitis, enteritis* and threatening *appendicitis,* and in many *acute fevers,* not only because they do not cause peristalsis while flushing the bowel, but also owing to the intestinal antisepsis they tend to promote.* The purgative mineral waters, Seidlitz, Hunyadi Janos, Friedrichshall, Pullna, etc., owe their properties mainly to magnesium sulphate.

Mercurials.—The therapeutic value of mercurials in this connection was reviewed in the article on Mercury.

* *Author's conclusion.*
[47] Neuberger: Archiv f. exper. Path. U. Pharm., Bd. xxviii, S. 32, 1891.
[48] Heinze: Psychiat-neurol. Woch., Bd. v, S. 297, 1903.

The numerous other purgatives at our disposal present nothing of special interest in connection with the internal secretions, other than those referred to under "Physiological Action."

EMETICS.

Physiological Action.—Certain emetics, such as mustard and zinc sulphate, produce their effects by irritating the gastric mucosa. Afferent impulses being transmitted to the vagal center (in the posterior pituitary body*), the various muscles, gastric and thoracic, which take part in the act, are reflexly stimulated, and the irritant is vomited.

When such emetics as ipecac and apomorphine are employed, they are absorbed, and produce their effects by depressing the functional activity of the sympathetic and vasomotor centers.* All arterioles and larger arteries being relaxed, the glandular elements of the entire body are passively congested and secrete vicariously.* The passive congestion of the gastric mucous membrane being supplemented by a more or less great outpouring therein of serous pseudo-secretion,* the same process that prevails when irritants are ingested occurs, *i.e.*, the stomach is emptied through reflex vagal action.

Although emetics which are first absorbed, ipecac, apomorphine, etc., appear to influence only the stomach and the muscles that the act of vomiting brings into play, such is evidently not the case. Manquat,[49] for instance, states, referring to tartar emetic, "a dose of 0.01 gm. ($^1/_6$ grain) causes nausea, a general malaise, salivation, exaggeration of the gastro-intestinal secretions, and at the same time sweating and exaggeration of the bronchial secretion." He states also[50] that ipecac causes prostration, coolness of the skin, salivary hypersecretion, sweating, "hypersecretion of all the glands of the digestive apparatus (liver, pancreas, mucous follicles), this giving rise to a moderate diarrhœa." Even the nasal secretion is increased. Wood[51] states that the vomiting caused by apomorphine is accompanied by "excessive secretion from the salivary, nasal and lachrymal glands." It is evident, therefore, that emesis is but one of the phenomena awakened by an emetic, and that these agents, as do most drugs, produce their effects by acting upon a center. Indeed, Wood[52] distinguishes emesis produced by local irritation of the stomach (mustard, sulphate of zinc, etc.) from that of "centric" origin. Gianuzzi[53] found that after the cervical portion of the spinal cord had been divided in the dog, tartar emetic failed to produce emesis. Foulkrod[54] obtained the same result with emetin, the active principle of ipecac.

* *Author's conclusion.*
[49] Manquat: *Loc. cit.*, vol. i, p. 575, 1903.
[50] Manquat: *Loc. cit.*, vol. i, p. 388, 1903.
[51] Wood: *Loc. cit.*, thirteenth edition, p. 640, 1906.
[52] Wood: *Loc. cit.*, thirteenth edition, p. 632, 1906.
[53] Gianuzzi: Cited by Manquat: *Loc. cit.*, vol. i, p. 577, 1903.
[54] Foulkrod: Phila. Med. Times, vol. viii, p. 551, 1878.

That it is the vascular centers, *i.e.*, the sympathetic and vasomotor centers, which are influenced by this class of drugs, and, moreover, that it is by depressing these centers that emesis is caused, is shown by the fact that the blood-pressure is markedly lowered by ipecac, as observed by Pécholier,[55] Reboul,[56] Podwyssotzki,[57] Grasset and Amblard[58] and others, as well as by apomorphine as shown by Harnack[59] and Reichert.[60] The concomitant hypothermia which occurs under such conditions through recession of blood from the surface is likewise present. Thus, Radziejewski[61] found that the temperature could drop 6.6° C. (11.8° F.). Hayem[62] observed that in the rabbit 0.005 gm. ($^1/_{12}$ grain) brought the temperature down 1° C. (1.8° F.) in one hour. Manquat states that emesis is usually attended with a fall of 1° C. Apomorphine does likewise, according to Nothnagel and Rossbach,[63] the temperature declining "little by little."

The rôle of the vagus as the direct factor in the production of emesis is well shown by the fact that, as stated by Manquat, "the experiments of Chouppe, Polichronie and Dyce Duckworth have shown that emesis does not take place when emetine is injected after division of both vagi." The fact that emesis occurs while the emetic is being eliminated by the gastric membrane (Radziejewski) being also established, we have three sources of irritation of the vagal sensory terminals in the gastric mucosa: passive congestion, the serous secretion, and the excreted (and probably chemically transformed) emetic.

Untoward Effects and Poisoning.—Toxic phenomena may be produced by emetics, especially in infants, feeble and aged subjects, the symptoms being those of collapse, with marked muscular weakness and a steady lowering of the temperature. This is due to increasing paresis of the sympathetic and vasomotor centers.* In apomorphine poisoning, unconsciousness, failing respiration, and profound depression and convulsions (due to accumulation of toxic wastes*) are the main symptoms, death being due to asphyxia.

Both the sympathetic and vasomotor centers being depressed, accumulation of blood in the great vessels of the splanchnic area occurs. This is shown by the fact, "attested by Pécholier, Dyce Duckworth and d'Ornellas, that in emetine poisoning, although there is a distinct fall of temperature in the mouth and on the surface of the body, in the intestine the temperature remains stationary, or more commonly rises." Wood[64] also states that "Dyce Duckworth especially noted intense hyperæmia of the lungs, which were in some places emphysematous, but in other portions collapsed"—the typical *passive* hyperæmia of sympathetic paralysis. The recession of blood from the periphery produced by large doses is also well shown by Wood's additional statement that Magendie and d'Ornellas had "also seen cases in which ischæmia of the pulmonary tissue was found after death."

* *Author's conclusion.*
[55] Pécholier: Gaz. méd., vol. xxxiii, p. 744, 1862.
[56] Reboul: Cited by Manquat: *Loc. cit.*, vol. i, p. 589, 1903.
[57] Podwyssotzki: *Ibid.*, p. 589.
[58] Grasset and Amblard: Montpellier méd., vol. xl. pp. 101. 197, 293, 1881.
[59] Harnack: Archiv f. exper. Path. u. Pharm., Bd. iii, S. 44, 1875.
[60] Reichert: Phila. Med. Times, vol. x, p. 109, 1879.
[61] Radziejewski: Arch. f. Anat. u. Physiol., S. 472, 1871.
[62] Hayem: Cited by Manquat: *Loc. cit.*, vol. i, p. 581, 1903.
[63] Nothnagel and Rossbach: *Loc. cit.*, p. 726, 1889.
[64] Wood: *Loc. cit.*, thirteenth edition, p. 637, 1906.

There is considerable analogy between the action of emetics as described above, and that of hypnotics, previously submitted. Tartar emetic and other emetics have long been known to possess soporific properties. C. J. Douglas[65] has shown recently that this applied also to apomorphine.

Therapeutics.—*Ipecac* as an *emetic* is given to adults in 20-grain (1.3 gm.) doses, repeated at intervals of twenty minutes if necessary. In children 5-grain (0.3 gm.) doses suffice. Its action is aided by drinking lukewarm water freely. The value of ipecac in *dysentery* is accounted for by the fact that by enhancing vicariously the activity of all glands, including the pancreas and intestinal glands, it increases the sterilizing properties of the succus entericus.* This serves not only to destroy pathogenic organisms that may be present, but also to hasten the resolution of lesions of the mucosa—a process further aided by the local hyperæmia awakened. In *hæmoptysis* it acts very favorably by diminishing general blood-pressure,* even when given in small doses. In *chronic bronchitis,* the same mechanism and the fact that it increases the secretory activity of the bronchial mucosa renders it particularly effective where the secretion is viscid and raised with difficulty, notwithstanding hard and exhausting paroxysms of cough.

Apomorphine as an *emetic* may be given hypodermically to adults in $^1/_{10}$ grain (0.006 gm.) doses at fifteen minutes interval until vomiting occurs, reducing the dose in weak or aged subjects. It may be given in larger doses by the mouth. In a child of eighteen months $^1/_{50}$ grain (0.0013 gm.) and in one of eight years $^1/_{25}$ grain (0.0026 gm.) suffice. In the cough of *bronchitis* it is of marked value in small doses, repeated every three hours, to increase the bronchial secretion and hasten the process of resolution. In *hysteria,* it is of great value to counteract the muscular rigidity by relaxing the arterioles.* The hyperæmia of the central nervous system being also relieved,* the patient falls into a refreshing sleep.

DIAPHORETICS.

Physiological Action.—The physiological action of diaphoretics is well exemplified by *jaborandi* and its alkaloid, *pilocarpine.*

* *Author's conclusion.*
[65] C. J. Douglas: N. Y. Med. Jour., Mar. 17, 1900.

These agents produce sweating by depressing markedly the sympathetic center.* The diaphoresis represents only, however, an epiphenomenon of the effects of jaborandi, all glands being affected in the same manner as the sweat-glands.* The depression of the sympathetic center, by causing dilation of the arterioles of all these organs, causes functional hyperæmia of their capillaries;* hence the increase of secretory activity. Hence also* the flushing of the face, the salivation, lachrymation and, in some instances, the diarrhœa and vomiting observed.

That sweating is but one of the phenomena of a drug which affects all glands as well as the sweat-glands is sustained by considerable evidence. Thus, Tzistovitch[66] ascertained experimentally that pilocarpine stimulates *gastric* secretion, and that the gastric juice appears early in proportion as the dose is large. Edkins[67] and Masloff[68] found that pilocarpine administered caused *intestinal* secretion. Heidenhain[69] found that it caused intense secretory activity in the crypts of the colon. This applies to the muscular coat as well. Morat[70] and others have found that it caused very active peristalsis in experimental animals. Bayliss and Starling[71] note that pilocarpine increased the *pancreatic* secretion, the latter being rich and thick. In all cases the gland seemed to tire rapidly and to become insusceptible to the drug. Lauder Brunton and Delépine[72] found that pilocarpine stimulated glandular activity of the liver-cells. It increases the functional activity not only of the sweat-glands, but also of all cutaneous glands. Thus, Langley[73] observed that in the frog the skin became covered with a thick, viscid secretion.

That these phenomena are due to depression of the sympathetic center is suggested not only by the facial hyperæmia, but also by the nausea and vomiting which, as I have shown, are due partly to sympathetic depression. Even the average dose may cause these symptoms. Thus, H. C. Wood,[74] referring to the effects of a therapeutic dose of the infusion of jaborandi, states that "there is not rarely nausea, and sometimes vomiting," of "large quantities of glairy mucus" he adds elsewhere in his text. Again, the increased functional activity of various organs provoked points in this direction. Horbaczewski,[75] for instance, found that pilocarpine produced, in man, a leucocytosis, and a proportionate increase in the uric acid excretion, a fact which shows that general metabolism is increased. Again, Murrell observed that in the frog, $^1/_{20}$ grain (0.003 gm.) of pilocarpine gave rise to a marked increase of reflex activity and convulsion—phenomena which point to excessive hyperæmia of the skin and central nervous system. Even the nerves are hyperæmic. C. R. Marshall,[76] in the course of experiments with pilocarpine, noted

* *Author's conclusion.*
[66] Tzistovitch: Bolint Gazeta Botkina, July 13, 1902.
[67] Edkins: Schäfer's "T. B. of Physiol.," vol. i, p. 555, 1898.
[68] Masloff: Untersuch. a. d. physiol. Inst. d. Univ. Heidelberg, Bd. ii, 1882.
[69] Heidenhain: Hermann's "Handbuch," Bd. v, i, S. 171, 1883.
[70] Morat: Lyon méd., vol. xl, pp. 289, 335, 1882.
[71] Bayliss and Starling: Jour. of Physiol., vol. xxx, p. 61, 1903.
[72] Lauder Brunton and Delépine: Proceed. of the Royal Soc. of London, vol. lv, p. 424, 1894.
[73] Langley: Jour. of Physiol., vol. i, p. 339, 1878.
[74] H. C. Wood: *Loc. cit.,* thirteenth edition, p. 721, 1906.
[75] Horbaczewski: Bull. du Comité agric. du Départ. de l'Aube, France, B. 100, Sect. 3, p. 101, 1892.
[76] C. R. Marshall: Jour. of Physiol., vol. xxxi, p. 120, 1904.

that it increased the sensitiveness of the vagus to electrical stimulation. Finally, that it is by causing *dilation* of the arterioles that pilocarpine causes sweating is shown by the fact, demonstrated by Langley[77] in 1875 and confirmed since by many observers, that absolute antagonism exists between this drug and atropine. Now, as I have shown, atropine *constricts* the arterioles.

The peripheral hyperæmia is augmented through the fact that the arterioles of the adrenals are relaxed, as are those of all other glands, and that the increase of adrenal secretion produced causes general vasoconstriction, the blood being driven towards the periphery, *i.e.*, the skin.*

The prevailing belief that pilocarpine increases the activity of all the glands of the body, including those of the skin, by acting *directly* upon them, is, to say the least, illogical when we consider that $^1/_8$ to $^1/_4$ grain (0.008 to 0.016 gm.) will produce marked effects. The only proof of any weight, the fact that Luchsinger,[78] and subsequently Nawrocki, found that division of the nerves of a cat's leg did not prevent the paws from sweating when jaborandi was injected into the animal, fails when analyzed from my standpoint. All the vessels of the leg being dilated by the section of the vasomotor nerves, any general rise of the blood-pressure would cause a flood of blood to invade these dilated vessels and the sweat-glands, and provoke sweating. Now, Wood, alluding to Reichert's[79] experiments, states that "immediately after the injection of the alkaloid [pilocarpine] into the jugular vein the arterial pressure falls, but in a few moments the characteristic phenomena of a slow pulse with *increased arterial pressure* come on." It becomes a question, however, as to how this rise of pressure is produced, but we have the solution of this problem in the fact that A. Pettit[80] found the adrenals greatly congested and swollen in experimental animals poisoned with jaborandi. As this means hyperactivity of these glands, and as the adrenal secretion raises the blood-pressure, not through the vasomotor center, but, as I have shown, by enhancing me abolic activity in the muscularis of all vessels the cause of the rise of blood-pressure is self-evident.

Untoward Effects and Acute Poisoning.—The symptoms which follow a toxic dose include the following: copious sweating, vertigo, marked salivation, rhinorrhœa, vomiting, diarrhœa, strangling, dimness of vision, myopia, more or less marked cardiac oppression and metrorrhagia—all due to what amounts to paralysis of the arterioles.* Sudden death has also been produced by a small dose ($^1/_3$ grain—0.021 gm.) pilocarpine given hypodermically. As it is the sympathetic center which is depressed by this drug,* it should be given with especial care in debilitated and aged subjects.

* *Author's conclusion.*
[77] Langley: Brit. Med. Jour., Feb. 20, 1875.
[78] Luchsinger: Archiv f. d. ges. Physiol., Bd. xv, S. 482, 1877.
[79] Reichert: Univ. Med. Mag., Apr., 1893.
[80] A. Pettit: C. r. de la. Soc. de biol., vol. iii, p. 535, 1896.

Lanphear[81] recommends caution in the use of pilocarpine. Its continued use may also give rise to papulo-exudative dermatoses. Thus, in a case observed by Hallopeau and Vielliard,[82] the histological examination revealed an inflammatory exudate about the excretory ducts of the sweat-glands.

Therapeutics.—*Jaborandi and Pilocarpine.*—The latter drug is to be preferred, since it is less likely to provoke vomiting. It has been found of value in *uræmia, chronic Bright's disease* and *dropsical conditions*; the benefit is due to the lowering of the blood-pressure which general dilation of arterioles insures,* and to the increased elimination of fluids and retained excrementitious wastes. It is of use in *erysipelas*, owing to the fact that the cutaneous hyperæmia means the presence in the affected area of an increased volume of auto-antitoxin.* *Chronic eczema* and other cutaneous disorders, especially those due to deficient secretion of the sweat-glands, are also improved by pilocarpine. In ophthalmic disorders associated with *intra-ocular pressure*, it is also valuable, owing to the general lowering of the blood-pressure it insures.* In *orchitis* it tends, through the same process,* to relieve the intense pain.

Sweet Spirit of Nitre.—This agent, an alcoholic solution of amyl nitrite, acts, as does pilocarpine, by depressing the sympathetic. It is milder, however, and acts both as diuretic and diaphoretic. It is considerably used in *febrile disorders* of children when excitement, startings, etc., occur. By lowering slightly the blood-pressure it controls these phenomena.*

OXYTOCICS.

(Ergot, Hydrastis, Hydrastinine.)

Physiological Action.—*Ergot* in ordinary doses causes contraction of the uterus by augmenting the blood-supply of its walls*—a condition due primarily to the fact that it excites directly the vasomotor center. All the arteries of the body (with the exception of the arterioles, which are governed by the sympathetic center*) being constricted, the blood is driven into the smaller vessels and capillaries of all organs, including the uterine muscle. The contractile power of this muscle being

* *Author's conclusion.*
[81] Lanphear: Kansas City Med. Index, Nov., 1888.
[82] Hallopeau and Vielliard: Ann. de derm. et de syph., 4 série, vol. v., p. 233, 1904.

proportionate, as in all organs, with the activity of its intrinsic metabolism, its sensitiveness to the reflex motor impulses which the uterus receives periodically during parturition is correspondingly enhanced.*

As stated by Manquat,[83] "it is generally admitted that ergot has a vasoconstrictor action upon the vessels; this opinion rests upon a large number of experiments." Holmes[84] observed the constriction of the arteries in the frog and in the albino rabbit, marked anæmia of the ears of this animal being noted. A rise of the general blood-pressure (preceded by a short period of depression) was also obtained experimentally by Köhler,[85] Eberty,[86] H. C. Wood,[87] Kobert and by Jacobi.* Wood,[88] who refers to these experiments, states that "the rise in pressure, which is to be regarded as the characteristic effect of ergot upon the circulation, is due to a constriction of the blood-vessels," and that "Holmes, Wernich,[89] Vogt,[90] Kersch,[91] Schüller[92] and Briesemann[93] assert that they have seen invariably diminution in the caliber of the arteries under the influence of ergot."

The more recent experiments point in the same direction. Plumier[94] found that the intravenous injection of the fluid extract of ergot produces in the dog a marked elevation of the blood-pressure in the pulmonary artery. H. H. Dale[95] observed "a stimulant constrictor effect upon certain organs composed of plain or unstriated muscle-fibers, among which are the arteries, the uterus and the sphincter of the iris." The 300 painstaking experiments of Sollmann and Brown,[96] which seem to controvert all this evidence, are unfortunately of no value. They overlooked the fact that the anæsthetic they administered to their dogs, ether, caused a very marked rise of pressure, and that the ergot could not raise it beyond this level. Hence their erroneous conclusion that "there is no evidence of strong vasoconstriction." The slowing of the pulse is readily accounted for by the increased resistance of the blood-column to the cardiac contractions, produced by the general vasoconstriction.

That the rise of blood-pressure is due to a centric action was shown experimentally by J. C. Hemmeter,[97] who found that the rise did not occur when the spinal cord was severed, and, in accord with Wernich,[98] that after this operation ergot could no longer provoke uterine contractions.

Full therapeutic doses of ergot cause such marked constriction of the arteries that the lumen of the smaller vessels becomes sufficiently narrowed to interfere with the circulation.* The blood-stream being slowed in the arterioles and capillaries,

* *Author's conclusion.*
[83] Manquat: *Loc. cit.*, vol. i, p. 71, 1903.
[84] Holmes: Thèse de Paris, 1870.
[85] Köhler: Virchow's Archiv, Bd. lx, S. 384, 1874.
[86] Eberty: Cited by Köhler: *Ibid.*
[87] H. C. Wood: Phila. Med. Times, vol. iv, p. 518, 1874.
[88] Wood: *Loc. cit.*, thirteenth edition, p. 748, 1906.
[89] Wernich: Virchow's Archiv, Bd. lvi, S. 505, 1872.
[90] Vogt: Berl. klin. Woch., Bd. ix, S. 115, 1872.
[91] Kersch: Betz's Memorabilien, Bd. xviii, S. 202, 1873.
[92] Schüller: Berl. klin. Woch., Bd. xi, S. 294, 305, 1874.
[93] Briesemann: Inaug.-Dissert., Rostock, 1869.
[94] Plumier: Jour. de physiol., vol. vii, p. 13, 1905.
[95] H. H. Dale: Jour. of Physiol., vol. xxxiv, May, 1906.
[96] Sollmann and Brown: Jour. Amer. Med. Assoc., July 22, 1905.
[97] J. C. Hemmeter: N. C. Med. Jour., Aug., 1891.
[98] Wernich: *Loc. cit.*

the opposite condition to that described above is produced, viz., ischæmia of the organs which these small vessels supply.* The peripheral temperature is then reduced and the patient complains of cold—a danger signal which indicates that an excess of the drug is being administered.*

Before I had realized this fact, I caused complete—though temporary—inertia of the uterus by the use of excessive doses in a case requiring prompt delivery. I blamed the ergot at the time. Wood[99] states in the lower animals the symptoms of intoxication "are mainly paralytic, and that the only ones which are in any sense characteristic are the *anæsthesia* and the *coldness* of the surface. As this coldness of the surface has been noted in various women in whom the drug has caused fatal abortion, it is probably characteristic of the poisoning." Ringer and Sainsbury[100] found that ergotin slowed markedly the rate of flow through the arterioles. Hemmeter[101] noted that in poisoning the temperature sometimes fell more than 2° C. (3.6° F.) in human beings and 5° C. (9° F.) in animals.

Untoward Effects and Poisoning.—The earlier effects of ergot-poisoning are due to the great accumulation of blood in the peripheral vessels, which a large dose of the drug provokes by violently stimulating the vasomotor center,* viz., formication, tingling, giddiness, delirium, flushing, purpura, tinnitus, dilation of the pupil, colic, spasmodic contractions of the muscles, opisthotonos or emprosthotonos, and even epipleptic convulsions. The constriction of the vessels increasing rapidly, this hyperæmia is soon replaced by ischæmia* of the tissues: the skin then assumes an earthy hue, the surface becomes cold, there is great muscular weakness and fatigue and numbness particularly of the extremities, nausea, vomiting, and the respiration is labored. More or less suddenly collapse occurs, due to hyperconstriction of the cardiac coronaries* and of the arteries of the anterior pituitary and thyroid.* The pulse then becomes very rapid and weak, the blood-pressure falls rapidly and death follows.

In *chronic ergotism,* which does not occur in this country, all these symptoms may develop gradually, but here another typical symptom of excessive constriction of the arteries occurs, viz., dry gangrene, beginning at one of the extremities, especially the toes, or the nose, lips and ear.

* *Author's conclusion.*
[99] Wood: *Loc. cit.*, thirteenth edition, p. 747, 1906.
[100] Ringer and Sainsbury: Med.-Chir. Trans., vol. lxvii, p. 67, 1884.
[101] Hemmeter: *Loc. cit.*

The explanations submitted of these various symptoms are self-evident when the vasoconstrictor action of the drug is taken into account. Wood[102] states that "ergotic gangrene can readily be produced in the comb and tongue of chickens" and "von Recklinghausen asserts that the essential lesions in these cases are hyaline thrombi in the arterioles and capillaries"—an obvious proof that it is not these two kinds of vessels that are hyperconstricted, but the arteries behind them. Again, Wood states that "by toxic doses the rapidity of the heart's action is increased, and, according to Boreischa, galvanization of the par vagum has at this time little or no effect upon the pulse." The cause of this is also quite plain when interpreted from my viewpoint: the coronaries are already so constricted that stimulation of the vagi can contract no farther. Hence the cardiac arrest.

Therapeutics.—In the light of the above facts, a very small dose of ergot (10 minims of the fluid extract) is alone efficacious in the *uterine inertia* of parturition. Such a dose has also the advantage of avoiding tetanic contraction of the uterus, a condition which tends to cause retention of the placenta. Ergot is also useful in *post-partum hæmorrhage;* here a full dose may be given, and it may be administered hypodermically to obtain more rapid results. It has been used to prevent hæmorrhage from the lungs, stomach, intestines, etc., but the marked rise of blood-pressure it provokes before causing sufficient contraction to arrest the flow renders it a dangerous remedy in these conditions. In uterine hæmorrhage due to the presence of *fibroids* or other neoplasms, however, it has given excellent results, and tends to cause shrinking of the growth when given in full doses. In *chronic dysentery* and *chronic diarrhœa* ergot sometimes proves curative by causing hyperæmia of the small and large intestine and hastening resolution. It is of value also in *adynamic depression, melancholia* and neuropathies in which *hypochondria* is a prominent symptom, the benefit being due to the increased volume of blood which the cerebro-spinal system receives.*

DRUGS WHICH RESEMBLE ERGOT IN THEIR PHYSIOLOGICAL ACTION.

Hydrastis.—The physiological action of hydrastis and of its alkaloid hydrastine is similar to that of ergot. It stimulates the vasomotor center less violently, however, and its action in therapeutic doses is limited to the stage of hyperæmia of all

* *Author's conclusion.*

[102] Wood: *Loc. cit.*, thirteenth edition, p. 755, 1906.

organs, including the mucous membranes.* It has been used advantageously, therefore, in various disorders of the latter, viz., *chronic gastro-intestinal catarrh, chronic rhinitis, otorrhœa, dysmenorrhœa, chronic vaginitis, gonorrhœa,* etc.

Hydrastinine, an alkaloid obtained by the oxidation of hydrastine, has been employed with considerable success in uterine hæmorrhages, *menorrhagia,* and *metrorrhagia,* being more active than hydrastis or hydrastine as a vasoconstrictor. It is also useful in the same disorders as hydrastis, especially *dysmenorrhœa.*

DIURETICS.

The diuretics most used at the present time are drugs which have been treated in full in the preceding pages. Their property as such need alone be referred to.

Saline solution has been thought to act as an "hæmocathartic," the excrementitious products of tissue and other wastes, detritus, etc., being, it was believed, simply washed out of the blood by the excess of water introduced therein. I have shown in the earlier portion of this chapter that the process is really a nobler one, so to say, and that the introduction of saline solution into the organism enhances greatly the efficiency of the body's auto-protective processes. The proteolytic activity of the auto-antitoxin being greatly augmented,* there is soon thrown into the lymphatic channels an unusual quantity of products of catabolism which must be eliminated, partly by the urine. A prominent cause of diuresis is now present, viz., reflex stimulation of the secreto-motor center (located in the posterior pituitary) which governs renal action.* The kidneys are thus activated and a freer flow of urine follows—carrying along with it the excess of wastes. We need not inject a quart of saline solution to produce this effect; much smaller quantities will evoke it; but if at least a pint is employed the action will be greatly facilitated, since the organism promptly rids itself of the fluids that are useless to it. *Plain water* is an excellent diuretic for this reason, as is well known.

Digitalis.—When the infusion is used the fluid aids the process, and, as suggested by Huchard, it is probable that the min-

* *Author's conclusion.*

eral salts the leaves contain contribute somewhat to its diuretic effects. Diuresis may be obtained with digitalin, however, a fact which shows that the drug is itself active in this connection. Its mode of action becomes plain, in view of its main general property, that of a potent stimulant of the adrenal center.* As this stimulates metabolism in all tissues, we have again an unusual production of tissue-wastes and the same central excitation (reflex) of the renal functions that saline solution affords,* though caused in a different way. Of material aid to the process is the increased vascular tension which the drug causes by activating indirectly metabolism in the muscular coat of all arteries.* A rise of blood-pressure is a recognized cause of diuresis. Digitalis is especially efficient in cardiac dropsy—a result readily accounted for by the above-described physiological action.

Squill acts much as does digitalis, including its action on the cardiac muscle, the arteries and general metabolism induced by a stimulating action on the adrenal center through the test-organ.* In large doses it stimulates the kidneys violently, causing sometimes hæmaturia. It is used in *dropsy, pleural* and *pericardial effusions* and the *cardiac dropsy,* but any form of nephritis is a contraindication to its use.

Calomel.—We have seen that this salt is an active diuretic also by enhancing general metabolism, thus causing rapidly an excess of waste-products in the blood.* When its use is prolonged it is also capable of causing grave renal disorders, including hæmorrhagic nephritis. It is very efficient in *cardiac dropsy,* however, and in *anuria* of asthenic origin in which the blood-pressure is low.

* *Author's conclusion.*

CHAPTER XXIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS.

THE ADRENAL SYSTEM AS IMMUNIZING MECHANISM, AND CANCER.

In the first edition (which appeared in January, 1903) of the present work,[1] the following lines appear: "Certain growths, particularly the more malignant forms, sarcoma and carcinoma, seem closely connected with adrenal insufficiency and its normal consequences. We have seen that *trypsin,* fibrinogen [a nucleoproteid compound] and the oxidizing substance were simultaneously necessary to insure the destruction of cells *in vitro,* and furthermore, that this process required, in addition, the presence of alkaline salts. That the destruction of worn-out or degenerated cells is a function of these very elements in the blood, is evident. Insufficiency of the adrenals, therefore, by reducing the relative proportion of these four constituents in the blood-stream, must correspondingly inhibit this physiological process in all parts of the organism." Thus, any region "may become the seat of this malignant growth, or rather of a local accumulation of the aberrant or worn-out cells which enter into its formation. The great vascularity of these growths suggests *an effort* of Nature to cause their elimination, but mitotic proliferation is alone induced, the blood being deficient in the four constituents which should insure destruction of the morbid cellular elements."

I pointed out also in this connection, in the same volume,[2] and under the caption "The Internal Secretions in their Relation to Immunity," that these "four constituents" were "the active immunizing agents of the organism," and that they owed their immunizing properties "to trypsin."

Over two years after I had done so, the close relationship between immunity and cancer was emphasized by several investi-

[1] *Cf.* vol. i, p. 785, 1st Ed., 1903.
[2] *Cf.* vol. i, pp. 609 to 666 incl., 1st Ed., 1903.