oxidase circulates in nerves as it does elsewhere, accounts for these results. Again, the increase of pulsation in a painful area and the relief afforded by elevating the part in which it lies, point distinctly to a common cause—a fact further sustained by the relief afforded by morphine, whatever be the source of suffering.

The so-called "toxic" form of pain might appear to constitute an exception, but analysis of the question soon shows that even here hyperæmia must be taken into account. In auto-intoxications of intestinal origin, we often have, as is well known, a rise of vascular tension, *i.e.*, a cause of congestion in nerves predisposed to neuritis, in aural structures previously diseased; in old pleural or peritoneal adhesions. In the pains due to mercury, lead, arsenic, alcohol, etc., the influence on vascular tension is also marked, some causing them by provoking active and others passive hyperæmia. The influence of increased vascular tension is well shown by the fact that, as shown by Richet, the sensibility to pain is reduced in idiots, imbeciles, and senile dements. Ioteyko[29] found the sensibility to heat decreased in melancholic women, and the initial sensibility to cold markedly increased. All these subjects bear the stigma of deficient peripheral circulatory activity.

Reducing the whole question to its simplest expression, a prominent fact asserts itself, viz., that *given the presence in any area of nerve-endings capable of transmitting pain impressions, congestion of that area from whatever cause, direct or indirect, will provoke pain.* As viewed from my standpoint, these minute sensory elements are the seat of metabolic processes in which adrenoxidase fulfills the function it does in all other cells: an increase of adrenoxidase here means increased metabolic activity and, therefore, increased acuity of the pain-impulses transmitted to the posterior pituitary.

THE SYMPATHETIC CENTER AS THE INTERMEDIARY THROUGH WHICH ANALGESICS PRODUCE THEIR EFFECTS.

In the light of the conclusions submitted in the two foregoing sections, any drug capable of reducing the blood circulating in the peripheral tissues, including the central nervous system, and of inhibiting metabolism in these tissues, should be

[29] Ioteyko: Jour. de neurol., Oct. 5 to 20, 1905.

capable of causing sleep and of arresting pain. Again, inasmuch as we have seen that it is the sympathetic center which governs the caliber of the arterioles, and, therefore, the blood supplied to these tissues, drugs capable of causing sleep and of subduing pain should do so through the intermediary of this center. That such is the case will be illustrated by the action of three of our main analgesics—morphine, antipyrin and acetanilid.

Both *opium* and *morphine* produce a temporary exhilaration, visions, etc., by augmenting the propulsive activity of the arterioles—a condition supplemented by a direct excitation of the vasomotor center and peripheral hyperæmia when *large* doses are taken. Under the influence of therapeutic doses this is soon succeeded by the typical action of the drug: constriction of the arterioles, and diminution of the blood supplied to capillaries and nervous elements in general, including those of the brain and spinal system and of any region which may be the seat of pain; this condition being brought about by the stimulating effect of the drug upon the sympathetic center. Both analgesia and sleep are produced by *therapeutic doses* because they influence this center only and the arterioles only, and the supply of arterial blood to the neurons, capillaries, etc., is reduced.

As produced by opium and morphine, sleep is caused indirectly, *i.e.*, artificially. We will see in the next chapter, in which the drugs that depress the adrenal and other centers are studied, that we have several agents (the bromides, chloral, etc.) which provoke sleep by a process approximating closely that of Nature.

Antipyrin and *acetanilid* arrest pain as does morphine, but an important feature deprives these analgesics of soporific properties; even in therapeutic doses they stimulate the vasomotor center and thereby keep the neurons of the central nervous system and the capillaries in general more or less engorged, thus defeating an essential condition of sleep. This blood, when the drug proves toxic either in small or large doses, may be detained in the peripheral capillaries through circulatory torpor and, becoming partly venous, cause cyanosis. Another feature illustrated by these drugs is that their action is prevented by section of the tissues immediately below the pitu-

itary body (and, therefore, above the bulb), a procedure involving, therefore, division of the sympathetic fibers derived from the posterior pituitary.

OPIUM AND MORPHINE.

Physiological Action.—A small therapeutic dose of opium or morphine excites sufficiently the sympathetic center to cause slight contraction of the arterioles—that degree of constriction which, we have seen, provokes at each pulsation a reflex dilation of these vessels.* The alternation and exaggerated constriction and reflex dilation of the arterioles increases their propelling power, and an excess of blood is projected with each pulse-wave into all capillaries, including those of the cerebro-spinal system.* Hence,* the period of mental vigor and excitement, visions, hallucinations sometimes witnessed, and which in subjects habituated to the use of the drug may attain the proportion of wild delirium.

In normal individuals, however, the mean caliber of the arterioles is, on the whole, reduced by a small dose, and the average volume of blood thrust into the capillaries being diminished,* a feeling of torpor, general and cerebral, is experienced sometimes accompanied by a semiconscious condition or light sleep, a good part of which is taken up by dreams.

If the dose be large, the general and cerebro-spinal hyperæmia* manifests itself in a correspondingly more active way, and symptoms of actual cerebral congestion appear: the face is reddish or suffused and may even be cyanosed; the skin is warm and dry, the pulse strong and full.

The influence of opium and its preparations on the vascular system are generally recognized. Guinard[30] studied graphically the changes in the blood-pressure provoked by morphine in the higher mammals, the horse, ox, goat, sheep, pig and cat, and found that in all these animals the pressure was increased when the limits of therapeutic doses were not exceeded, and however introduced. The rise was always very marked. Gscheidlen[31] also observed primary vasoconstriction; having injected morphine in animals, he saw the *arterioles* of the mesentery contract. The primary rise of blood-pressure occurs under these conditions in the arteries behind the arterioles, owing to the obstruction which the latter present to the blood-stream. The venous engorgement which this should entail is likewise present. Picard[32] observed, after he had

* *Author's conclusion.*

[30] Guinard: C. r. de la Soc. de biol., 10 série, vol. ii, pp. 551, 572, 1895.

[31] Gscheidlen: Untersuch. aus dem physiol. Lab. zu Würzburg, 2ter Theil, 1869.

[32] Picard: C. r. de l'Acad. des Sci., May 6, 1878.

injected from 0.06 to 0.08 gms. (1 grain to 1⅓ grains) in a dog and opened a vein in an exposed submaxillary gland, that the blood-flow was increased, notwithstanding division of the chorda tympani. This shows that the gland's secretory nerve, which normally causes the increased blood-flow when stimulated, played no part in the production of this phenomenon under the influence of morphine, and that it was due to the general vasoconstriction which this drug provoked. Cushny[33] states that the "blood-pressure remains high" under the influence of morphine.

The influence of partial contraction of the arterioles may be illustrated by the action of morphine upon certain animals. We have seen that Guinard observed powerful vasoconstriction in the horse, ox, goat, sheep, pig and cat. In all these animals morphine causes excitement, but not narcosis. In the dog, rabbit, guinea-pig, white rat and mouse, on the other hand, he also observed general vasoconstriction, but with narcosis. Yet, this does not mean that the horse cannot be made to sleep by morphine: Harley,[34] for instance, found that large doses, 12 grains (0.8 gm.), produced very great excitement in this animal, not only cerebral, but general, as indicated by frothing at the mouth, muscular tremors, great restlessness, etc. In another experiment he gave a horse 36 grains (2.4 gms.) of morphine acetate. This powerful dose caused the animal to sleep three hours, but on awakening he passed through the stage of excitement, and this continued some seven hours. Again, in the mouse, which is readily put to sleep by adequate doses, Harley caused tonic spasm of the trunk, abnormal sensitiveness to sounds, etc., without narcosis by giving small doses. This clearly shows that the *caliber* of the vessel determines the character of the cerebral phenomena provoked, *i.e.*, *excitement* when an inordinate quantity of blood is admitted to the cellular elements; *sleep* when a smaller quantity than usual reaches them, owing to marked constriction of the arterioles. Manquat[35] deems it remarkable that the more intellectual Europeans should show more particularly the narcotic effects of the drug, while others, the Malays for instance, are rendered wildly delirious by it. This assumes a normal aspect when the sympathetic center is regarded as the intermediary of the drug's action—that of the European being more sensitive, the arterioles are sufficiently constricted to induce sleep; in the less sensitive races, they remain sufficiently patent to admit an unusual amount of blood in the brain, *i.e.*, to induce excitement.

Action as Analgesic.—Opium and morphine reduce or arrest pain when the arterioles are sufficiently constricted under its influence to diminish the volume of blood supplied to the painful area.* The sensory end-organs of this area, previously overstimulated through local hyperæmia, are thus freed of the excess of blood to which the pain is due.* This process is further enhanced by the fact that the constriction of the arterioles tends to produce capillary stasis; the blood being reduced by the tissues as usual, it tends to become venous, and thus to reduce sensibility in the sensory terminals it supplies.*

* *Author's conclusion.*

[33] Cushny: *Loc. cit.*, fourth edition, p. 213, 1906.

[34] Harley: Cited by Wood: *Loc. cit.*, eleventh edition, p. 124, 1890.

[35] Manquat: *Loc. cit.*, vol. ii, p. 437, 1903.

The general constriction of the arterioles, by slowing the circulation and diminishing the volume of blood supplied to all tissues, must necessarily lower the rate of metabolism. E. T. Reichert[36] found in twelve experiments in dogs that general metabolism, as determined by heat-production, falls on an average 26 per cent. below the normal during the first hour, 62 per cent. during the second hour, and 40 per cent. during the third hour, with an average temperature fall in the rectum of 1.76° C. (3.17° F.). This harmonizes with the observation of Boeck and Bauer[37] and Chittenden and Cummins,[38] that the elimination of carbon dioxide is reduced during the narcotism induced by the drug. Guinard ascertained that both the intake of oxygen and the output of carbon dioxide were reduced. Wood and Cerna[39] also found experimentally, as did Guinard, that morphine acted as a depressant of the respiration. Heger,[40] moreover, showed that the slowing of the respiration caused by the drug was closely related with the diminution in the respiratory exchange, the animal consuming less oxygen and producing much less carbon dioxide than normally.

That reduction of the blood supplied to the skin, and other structures containing end-organs, should, under these conditions (especially in view of the capillary stasis which it entails), diminish their relative sensibility is self-evident. Moreover, experimental testimony points in the same direction. Cushny,[41] for instance, referring to several observers who have studied the relative sensibility of the skin by measuring the smallest distance at which two points could be distinctly recognized, states that "in every case it was found that the ability to do this was lessened by morphine." The analgesia produced is not due to a direct action of the drug upon the sensory organs themselves, for Gscheidlen found that when applied locally to a sensory nerve during strychnine-poisoning, morphine increased its excitability and prolonged it. Manquat[42] states that while "the contact of morphine irritates mucous membranes and skin deprived of its epidermis, causing an unpleasant pricking sensation, this is soon replaced by lowering of the sensibility." This represents about the only tangible fact in favor of the prevailing view that morphine produces analgesia and sleep by acting directly upon the cerebral and other nervous elements after stimulating them. But we cannot logically compare the local effects of a solution of morphine of 1 to 400,000—such as a $^1/_4$ grain (0.016 gm.) dose makes with the thirteen pounds of blood in the body—with those of the alkaloid itself applied to mucous membranes or to denuded tissues. Even here, proof of the fallaciousness of the present conception asserts itself. Morphine is a reducing agent, and, as shown by Landsberg and Marmé, it is converted in the tissues into oxydimorphine. It is, therefore, because it deprives the tissues to which it is directly applied *of their oxygen* that it obtunds sensibility. It does so, in other words, merely by inhibiting metabolism in those tissues precisely as would any other equally active reducing agent, and not *as* morphine. But this proves also that diminished tissue-oxidation is the underlying cause of analgesia, and morphine, by so stimulating the sympathetic center as to reduce the blood-supply in a congested and therefore overstimulated structure, does nothing else.

[36] E. T. Reichert: Phila. Med. Jour., Mar. 9, 1901.
[37] Boeck and Bauer: Zeit. f. Biol., Bd. x, S. 339, 1874.
[38] Chittenden and Cummins: Studies from the Lab. of Physiol. Chem. of Yale Univ., vol. ii, p. 200, 1887.
[39] Wood and Cerna: Jour. of Physiol., vol. xiii, p. 870, 1892.
[40] Heger: Bull. de l'Acad. de med. de Belg., 4 série, T. xiv, p. 137, 1900.
[41] Cushny: *Loc. cit.*, fourth edition, p. 211, 1906.
[42] Manquat: *Loc. cit.*, vol. ii, p. 437, 1903.

Action as Hypnotic.—Sleep is also induced by morphine because it provokes general constriction of the arterioles.* By thus reducing the blood supply to the brain and spinal cord, it lowers their functional activity, as it does that of other organs.* Morphine thus incites artificially a condition very similar to normal sleep, since the latter is likewise due to diminished irritability of the cerebro-spinal system.* Morphine sleep differs from normal sleep only in that the irritability of the nerve-cells is reduced by a diminution of the volume of blood, and, therefore, of adrenoxidase supplied to them, while in normal sleep the blood's oxygenizing properties are reduced through a diminution of the proportion of adrenoxidase in the blood, the result in turn of a physiological depression of the adrenal center.*

That the sleep induced by morphine is due to diminution of the blood circulating in the brain has been determined experimentally. Thus Kauffmann[43] observed "slowing of the capillary circulation with stasis," while Stcherbach[44] found that there was "diminution of the blood flowing to the brain"—a normal consequence of contracted terminal arterioles. This evidently applies to the entire circulation, for Guinard also found a diminution in the speed of the carotid current, which, by diminishing the blood supplied to various organs, checks the various secretions of the body, *i.e.*, *inhibits* their functions. Both Nothnagel[45] and Isaac Ott[46] found that opium checked peristalsis in animals as it is known to do in man. On the whole, the changes of vascular caliber which endow morphine with its analgesic properties are also those which render it a soporific. The only difference between the two phenomena is that a larger dose is required to cause sleep *besides* analgesia, than it does to obtain analgesia alone. Thus, as stated by Cushny,[47] "in man, it is often found that comparatively small quantities are sufficient to deaden or even entirely remove the pain of disease without rendering the patient unconscious." This is simply because pain is caused by so slight an exacerbation of local metabolic activity that a slight vasoconstriction will counteract it, while the production of sleep requires a greater degree of vasoconstriction to induce the state of "diminished irritability of the nervous system" which, according to Landois,[48] exists during sleep.

The *after-effects* of morphine are due to a depression of the sympathetic center which lasts in proportion as the recuperative power of the center is marked.* Usually this is sufficiently great to prevent appreciable untoward effects after small doses; otherwise, even these may cause: lassitude, owing to the loss of tone of the arterioles in the skeletal muscles; nausea or vom-

* *Author's conclusion.*
[43] Kauffmann: Cited by Guinard: *Loc. cit.*
[44] Stcherbach: *Ibid.*
[45] Nothnagel: Virchow's Archiv, H. 1, S. 1, 1882.
[46] Isaac Ott: N. Y. Med. Jour., Aug. 18, 1883.
[47] Cushny: *Loc. cit.*, fourth edition, p. 210, 1906.
[48] Landois: *Loc. cit.*, p. 778, 1905.

iting, because of a similar condition in the gastric mucous membrane and muscles; and headache, owing to cerebral hyperæmia.*

In neurasthenic individuals, especially women, the morbid effects of this secondary vasodilation may assume alarming proportions. The lassitude lapses into prostration with a low peripheral temperature, due to depletion of the cutaneous capillaries.* Vertigo and fainting replace the headache when this occurs, both due to inadequate supply of blood to the brain.* Nausea and vomiting are usually very marked in these cases, the effusion of blood-fluids into the stomach, and the dilation of this viscus because of the relaxation of its muscles, being correspondingly great. The heart's action is also morbidly influenced by the relaxation of its nutrient arterioles* and its action becomes feeble. As a result of this cardiac adynamia, the blood is not propelled with adequate vigor into the lungs, causing dyspnœa, nor into the vascular system. A vicious circle is thus established* which may culminate in syncope and death.

The explanations given in the text are self-evident. The corresponding effects in animals are very marked. Wood[49] states that "after awaking, the dog shows unmistakable signs of nervous and psychical depression. In walking, the hind legs are dragged, as though semi-paralyzed; the eyes are haggard; the naturally brave animal cowers in a corner or seeks to hide himself, no longer recognizing his master. After smaller doses, the effects are proportionally less intense. It has been shown by Harley," says the same author, "that in some dogs, precisely as in some people, morphine fails to exert its usual hypnotic action, but produces great depression, as evinced by faintness, prolonged nausea and retching, interrupted only by intervals of dreamy, delirious somnolency."

Morphinism.—In this condition the morbid phenomena witnessed are due to a condition differing from the foregoing only in that the sympathetic center, overtaxed by the continuous use of the drug, finally becomes unable to preserve the tone of the arterioles throughout the organism, unless stimulated by steadily increasing doses.* This entails the development of *morphinomania,* since the craving for the drug is prompted by the pleasurable sensation that relief of the suffering provoked by general vasodilation procures.

The symptoms betray plainly the loss of vascular tone:* weak and sometimes irregular pulse and heart-beat; light sleep,

* *Author's conclusion.*
[49] Wood: *Loc. cit.*, thirteenth edition, p. 128, 1906.

disturbed by unpleasant dreams or distressing insomnia, both due to passive hyperæmia of the cerebral capillaries and cells; hallucinations, day-dreams, and occasionally delirium, due to the same cause; sensory disorders, hyperæsthesia, formication, etc., due to fluctuations of vascular tension; anæsthesia when, on the other hand, the central trunks are widely dilated at the expense of the peripheral vessels and, therefore, of those which supply the cutaneous sensory endings; diminution of the reflexes and disorders of locomotion from the same cause; atonic dyspepsia, nausea, vomiting, diarrhœa—all due to dilation of the gastro-intestinal vessels, and the resulting relaxation of muscles and mucosa.

Complications incident upon the loss of vascular tone soon appear.* Pustular and urticarial eruptions betoken the inadequate conversion of toxic wastes,* both in the liver and the blood—a morbid factor for which simple vasodilation does not account. The lowered oxygenation of the peripheral tissues may also give rise to abscesses, gangrene, progressive emaciation, and muscular atrophy and loss of sexual powers. As the case progresses, the circulation in both lobes of the pituitary body also becomes inadequate* and general collapse occurs. The test-organ and adrenal center are the first to feel the effects of this condition, owing to the great vascularity of the anterior lobe; as this organ constitutes, with the adrenals, the thermogenic mechanism, inhibition of its functions entails a corresponding decline of oxygenation and metabolism throughout the entire organism,* a condition soon followed by dissolution.

The familiar clinical facts recited, the exaltation produced by the drug followed by marked depression, asserts itself also experimentally. Thus Kraepelin,[50] in a study of the action of morphine upon the brain, found that it caused first marked excitation of the sensory functions and a subsequent marked and rapid depression of the same. He noted, moreover, that it produced a decided and persistent paralysis of the motor functions. The great depression of the adrenal system, which may occur at any time, is shown by the fact that bronzing is sometimes witnessed. Thus, in a case successfully treated by Sollier,[51] the skin of the entire body had acquired the Addisonian hue. That the adrenal center—the thermogenic center, in the light of my views—is depressed, is indicated not only by the marked fall of temperature, but also by the experiments of Reichert,[52] which showed that the hypothermia caused by a toxic dose of morphine was due to "depression of the thermogenic centers in the

* *Author's conclusion.*
[50] Kraepelin: Riforma medica, July 11, 1892.
[51] Sollier: Le progrès médical, May 12, 1900.
[52] Reichert: Phila. Med. Jour., Mar. 9, 1901; Univ. of Penna. Med. Bull., Nov., 1903.

caudate nucleus" and to the resulting heat-production. Confirmatory also in this connection is the fact that the drugs which have been found most beneficial in morphinism are those which improve the vascular tone or which stimulate the adrenal center. Norman Kerr,[53] for example, recommends digitalis and strophanthus, which combine both properties. Hunter Wells,[54] in fact, found adrenalin strikingly effective in the treatment of a large number of cases in Korea.

Acute Poisoning.—All the phenomena enumerated in the foregoing pages occur in more or less rapid succession when a large dose of morphine is taken. The sympathetic center bears the brunt of the action of the poison, but the vasomotor center is also excited at first, so that a large quantity of blood is forced into the capillaries.* So marked is the general vasoconstriction—both arteries and arterioles—in the first stage, that all the blood is practically transferred to the capillaries and veins.* The circulation being thus greatly hampered and slowed, the arterial blood is rapidly reduced, *i.e.*, deprived of its oxygen, by the surrounding tissues, and becomes dark and even absolutely venous in the capillaries.* Hence* the suffused, bloated and deeply cyanosed face and the labored and sometimes stertorous respiration, the contracted pupil, and the slow and forcible action of the heart, mainly due to the marked resistance of the blood-column.

The sleep of a toxic dose of opium or morphine differs from that produced by a therapeutic dose of these agents in that it is stuporous, and due to the venous condition of the blood circulating in the cerebro-spinal system.* It occurs soon after the ingestion of the poison, and deepens to a condition from which the patient can only be roused with the greatest difficulty.

The relative arterial constriction is so great that the accumulation of blood in the veins can sometimes be discerned after death. Thus J. Ewing[55] found in a case of acute poisoning that "there was extreme œdema of the lungs, and marked *venous* congestion of all viscera." The œdema further indicates the extreme tension to which the vessels submitted—serum having been evidently forced through capillary walls. Both Kauffmann and Guinard found, we have seen, that the blood-stream was slowed, owing to this vasoconstriction.

The case may, under appropriate treatment, recede at this stage, the morbid phenomena disappearing gradually, or it may proceed on its lethal course to the stage of collapse.

Collapse is due here to a combination of two factors: the

* *Author's conclusion.*
[53] Norman Kerr: Sajous's "Analyt. Cyclo. of Pract. Med.." vol. v, p. 37, 1900.
[54] Hunter Wells: W. Va. Med. Jour., Dec., 1906.
[55] J. Ewing: Arch. of Neurol. and Psycho-Path., vol. i, p. 263, 1898.

extreme general vasoconstriction, due to direct irritation of the vasomotor center, and, as a result of the interference with the circulation, a venous condition of the blood.* This venous blood is the cause of the lethal trend, however, since the lack of oxygen first depresses, then paralyzes, the test-organ, the adrenal center, and the adrenals themselves.* The adrenal center being both the respiratory and thermogenic center,* death is caused by respiratory failure.

The symptoms observed are quite in keeping with this morbid process: the respirations grow steadily weaker, slower, shallower, and more distant. The skin, being supplied with blood deficient in oxyhæmoglobin, is at once pale and cyanotic. The heart and pulse become gradually weaker, smaller, and irregular, until, shortly after cessation of respiration, they can no longer be discerned.

Dott and Stockmann[56] found that after *large* doses morphine lowered the vascular pressure, owing, they thought, to "depression of the respiratory center." Reichert[57] also published records which show that "morphine is not only a *powerful thermodepressant*, but that it has also, coupled with this action, one of some potency of the opposite character, as is indicated by the fact that the profound rapid fall of temperature may be preceded by a rise, or may be checked by a secondary rise, or both." The interpretation I submit in the general text accounts for these antagonistic phenomena: the rise of temperature occurs when the adrenal system has the upper hand; and the fall when the venous blood is depressing its action. Now, Reichert[58] pointed out a very important fact in this connection, viz., that cocaine antagonized morphine-poisoning, and clinical observations have sustained his conclusion. On the other hand, I have called attention, in the article on cocaine, to the fact that this alkaloid exceeded others greatly in power as a stimulant of the test-organ and adrenal center. The value of cocaine as a direct antagonist of morphine is thus accounted for: by powerfully exciting the adrenal center it sustains its functions notwithstanding the venous condition of the blood, and, by thus enforcing a rapid production of adrenal secretion, increases in proportion the volume of adrenoxidase in the blood. This affords the precise weapon needed to save the patient's life, since by endowing his blood with oxygenizing properties, its venous quality, the deadly feature of the process, is simultaneously eliminated.

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

Therapeutics.—Opium and morphine have not been superseded by any of the more modern agents for the relief of pain. This cannot be said of their use in *insomnia,* for we have better

* *Author's conclusion.*
[56] Dott and Stockmann: Proceedings of the Royal Soc. of Edinburgh, 1891.
[57] Reichert: Univ. of Penna. Med. Bull., Nov., 1903.
[58] Reichert: Therap. Gaz., July, Aug., 1902.

hypnotics, though none can replace morphine when pain and insomnia are present simultaneously. The manner in which opium and morphine produce both these effects (according to my interpretation) suggests, however, a number of *contraindications:* in disorders of the brain, cerebral congestion, meningitis, mental excitement, delirium, etc., the use of large doses of morphine, by causing cerebral hyperæmia, tends to aggravate the symptoms. Morphine is sometimes used in tetanus, epilepsy, eclampsia, etc., but the convulsions being due to an accumulation of toxic wastes, the slowing of the capillary circulation and the venous condition of the blood tend to inhibit catabolism and thus to increase the proportion of these wastes,* the result being, in the end, an augmentation of the spasms. Their use in fevers is open to the same objection, since the febrile process is a protective one, carried out by an excess of auto-antitoxin in the blood.* To prevent the access of this blood to the capillaries of the liver and skin, where the pathogenic organisms and toxins are mainly destroyed, by provoking constriction of the arterioles is to defeat Nature's protective efforts. In intestinal disorders, the same protective function is carried out in a different way, *i.e.,* by the copious secretion of the constitutents of auto-antitoxin into the intestinal fluids, peristalsis being likewise enhanced to insure elimination of the offending materials.* Opium and morphine, by causing undue constriction of the intestinal arterioles, arrest both the antitoxic flushing and peristalsis.* This applies as well to the copious expectoration which serves to eliminate pathogenic materials and detritus from the respiratory tract. All these contraindications are sustained by clinical observation. To this may be added the marked susceptibility of very young children, of debilitated individuals of all kinds to its effects, and the danger of morphinism—which precludes its prolonged use.

There are many conditions, however, in which its value is firmly established. After the vomiting and purging of *cholera morbus* have insured elimination of the toxic materials, morphine checks the severe abdominal pain by causing constriction of the intestinal arterioles, thus inhibiting the excessive peristaltic action and the intestinal flux.* A similar action on

* *Author's conclusion.*

the intestines promptly relieves the marked suffering of *lead colic.* In *hæmorrhage,* and especially the intestinal hæmorrhage due to *intestinal perforation,* morphine promptly stops the blood-flow by the same process,* since it is through the arterioles that the bleeding area is supplied with blood. By inhibiting the peristaltic movements, moreover, it tends materially to prevent recurrence. In *asthma* of nervous origin, in which the face is pale—a condition due to a marked lowering of the blood-pressure—morphine will often arrest a paroxysm by causing a rise of the latter and thus increasing the volume of blood exposed to the air in the pulmonary alveoli.* In *diabetes,* morphine proves useful by depressing the excessive functional activity of the adrenal center, thus reducing the proportion of adrenal secretion, *i.e.,* of adrenoxidase, in the blood, a frequent cause of this disease.

DRUGS WHICH RESEMBLE MORPHINE IN THEIR PHYSIOLOGICAL ACTION.

Codeine differs from morphine only in that it is considerably less active and, therefore, less poisonous. Such being the case, the stage of stimulation is more marked, and the propulsive activity of the arterioles is kept up much longer than under morphine,* the constriction of the arterioles, which endows the latter with its analgesic and hypnotic properties, coming on much later.* Hence the value of codeine in *irritative coughs, mild bronchitis,* etc., since by increasing the supply of blood to the bronchi, it enhances (when given in small doses) the activity of the local curative process. In large doses, its action resembles that of morphine, but it does not as actively excite the sympathetic center. All the properties due to abnormal constriction of the arterioles* are therefore less evident: the sleep produced is light and not restful; the effect on pain is also slight and fugacious; it does not inhibit peristalsis materially, nor cause constipation as readily as does morphine. For reasons submitted under "Tuberculosis" I do not advocate the use of opiates in the treatment of cough.

Heroin acts much as does codeine, and its value in *irritative coughs* is also due to the fact that it increases the propulsive

* *Author's conclusion.*