cells of the cerebro-spinal axis. "During sleep," says Landois,[178] "there is diminished irritability of the entire nervous system." . . . . . "During sleep stronger irritation is required in order to excite reflexes."

Untoward Effects.—Death may be caused in two ways, (1) by cardiac arrest, owing to the resistance imposed upon the cavities of the heart by the excessively constricted arteries,* (2) by respiratory failure owing to the nonconversion of the adrenal secretion into oxidizing substance.*

Oliver and Garrett[179] found in dogs killed with nitrous oxide, that the arteries were empty and the veins engorged. This is readily accounted for by the marked vasoconstrictor action of adrenal secretion which, as stated, penetrates the arteries without being converted into the adrenoxidase.* The blood was necessarily forced into the veins. The same experimenters found all the heart cavities distended—a normal result of the intense back-pressure imposed upon this organ. As to the second cause of death, *i.e.*, the non-formation of the adrenoxidase, Wood states,[180] referring probably to his experiments, that "death always occurred from respiratory paralysis, the heart continuing to beat powerfully after respiration had ceased and the arterial pressure had fallen very low." The heart is not deprived of adrenal secretion, hence its powerful resistance; the respiratory process loses its aid, however, hence its failure. Oliver and Garrett found the lungs collapsed.

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

Danger Signals.—The mortality of nitrous oxide is practically *nil* (about 1 in 150,000), owing mainly to the fact that it is used only for minor operations, the extraction of teeth, etc. As it unquestionably produces asphyxia, its prolonged use is contraindicated. This drawback is partly overcome, however, by Cryer's apparatus, which enables the patient to inhale a certain proportion of oxygen along with the nitrous oxide gas, and also to administer at once nothing but oxygen when danger signals appear.

* *Author's conclusion.*
[178] Landois: *Loc. cit.*, tenth edition, p. 778, 1905.
[179] Oliver and Garrett: *Loc. cit.*
[180] Wood: *Loc. cit.*, thirteenth edition, p. 86, 1906.

CHAPTER XXI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*).

REMEDIES WHICH DEPRESS THE FUNCTIONS OF THE ADRENAL, VASOMOTOR AND SYMPATHETIC CENTERS.

All the drugs analyzed so far which were shown to produce their effects by influencing nerve-centers, were found to do so by stimulating those centers. Evidence will now be submitted to the effect that by means of other remedies we can produce a contrary action, *i.e.*, depress these identical functions —profitably where excessive erethism prevails—each agent described being likewise capable of doing so in a characteristic manner.

Even the test-organ and the adrenal center can thus be controlled through our drugs. Indeed, Nature seems to have provided a substance, *arsenic*, which, merged in with the thyroidase probably, tends to reduce markedly its sensitiveness. Whether we are dealing with a physiological constituent of the body or not, the fact remains, that it is found normally in greatest quantity in the thyroid gland and that it antagonizes directly the action of thyroid extract. Whereas the latter promotes catabolism and emaciation, arsenic prevents wear and tear of the tissue-cell. Thyroid breaks down fats; arsenic conserves them. The many beneficial effects it produces in cutaneous, nervous, and blood diseases are, we will see, accounted for by this one central action.

Another, though of course artificial, agent of this class is *chloral*, which causes sleep by rapidly depressing the test-organ, and through it therefore, general metabolism. The muscularis of all vessels being the seat of less active exchange, it becomes relaxed, and the brain being deprived of some of its blood owing to accumulation of the latter in the great channels of the splanchnic area, sleep is promoted not only because of the diminution of blood in it, but because the blood itself is defi-

cient in adrenoxidase. Here, again, marked general phenomena are due not to action on peripheral structures, but upon a general center.

Another form of depression, the converse, as it were, of the vital erethism procured by adrenal extractives and antitoxin, is that caused by *alcohol*. The stimulating property with which it is credited is an artificial and ephemeral phenomenon, as we will see, due to the sudden excess of heat energy developed while it is being oxidized by the oxygen-laden adrenoxidase. The process itself brands alcohol as a depressant, however, since it is at the expense of the tissues that it robs the blood of this gas. It is because of the misinterpretation of the rôle of energy in the organism and of the prevailing misconception of the nature of the vital process, that it is regarded as a food. As a remedy it has but little claim to recognition: beyond the spurt of proteolytic activity acquired by the blood's trypsin which a small dose of ethyl alcohol procures by liberating heat-energy, its trend is to paralyze the body's protective functions, as shown in various ways.

The test-organ is not, however, the only center whose functions may be depressed directly or indirectly by drugs. As stated by Professor Charles Richet,[1] "all toxics (with rare exceptions, CO_2, for instance, and a few other hæmoglobin toxics) are hardly poisonous otherwise than through their action upon the *nerve-cell*. In the organism, the nerve-cell, to the detriment of other cells: muscular, glandular, epithelial, is the most sensitive to toxic action. These laws of excitation, then of depression of the nerve-cell by poisons, are, therefore, very general and applicable to almost all poisons." This does not necessarily mean that nerve-centers are alone influenced in this manner, but it is self-evident that being the most highly organized of nervous structures, they should prove more sensitive to the action of toxics than either subsidiary centers or ordinary nerve-cells.

Richet refers, however, to the secondary depression produced by excitants, having shown in 1881 that even strychnine could be converted into an anæsthetic if the animal's life were prolonged sufficiently long. It is probable that all depressants

[1] Chas. Richet: "Dictionnaire de Physiol," T. iv, 1900.

stimulate primarily, though so slightly in some instances, that the effects of this stimulation are not perceived.

The mode of action of depressants on vascular centers is illustrated by the effects of *bromides* on the vasomotor center, and concomitantly, doubtless, upon the subsidiary spinal centers. Being depressed directly by these salts, the general center allows the vessels of the entire organism to dilate. The blood being thus caused to recede from all peripheral structures, the skin, cerebro-spinal system, etc., to collect in the great central channels, the "depressomotor" influence of these salts becomes self-evident. By this depletion of the peripheral structures, including the pituitary body, the functions of all centers, including the adrenal center, are likewise depressed, and the production of adrenoxidase being correspondingly reduced, general nutrition is impaired. Hence the trophic disorders of bromism. We have here much the same process as that awakened by chloral, but brought about in a different way. The therapeutic kinship of these two drugs is well known.

In *veratrum viride* we have a drug very similar in action to the bromides. By its direct and depressing action on the vasomotor center, it lowers the arterial tension to such a degree, that it "bleeds the patient into his own vessels." The ischæmia of the pituitary body and the skin produced by large doses, so inhibits catabolism, however, that toxic wastes accumulate in the blood, including that circulating in the cerebro-spinal system, an action which causes a rise of the blood-pressure. We thus have the curious example of a drug which in therapeutic doses lowers the blood-pressure and in toxic doses raises it, thus counteracting its own physiological action—with threatened pituitary and cardiac inhibition if prolonged.

Depression of the sympathetic center is illustrated by three well-known agents, prominent among which is *aconite*. The general dilation of the arterioles thus produced allows an excess of arterial blood to enter the capillaries in general. When full doses are given, this marked though passive capillary hyperæmia excites the peripheral end-organs of sensibility and tingling is caused, besides flushing, headache, etc. In poisonous doses, aconite also depresses, then paralyses, the test-organ and

through it the adrenal center. The formation of adrenoxidase being arrested, the patient dies asphyxiated.

Amyl nitrite likewise depresses the sympathetic center, and by thus causing dilation of the arterioles causes the familiar flushing, increased heart-action, etc. It differs from aconite in that when given in large doses it depresses the vasomotor center, thus causing ischæmia of the peripheral organs and, therefore, the hypothermia and cyanosis sometimes witnessed. The remarkable benefit amyl nitrite affords in angina pectoris finds its explanation in the reduction of vascular tension which dilation of all the arterioles of the body produces, for while the volume of blood admitted into the capillaries of the heart is augmented, the pressure behind the blood-columns as a whole is decreased. *Nitroglycerin* is the counterpart of amyl nitrite as to physiological action, and affords an admirable means for the perpetuation of the beneficial, though fugacious, effects obtained with the latter remedy.

Creosote and kindred agents are shown to combine two seemingly antagonistic actions, viz., to depress the sympathetic and vasomotor centers and excite the adrenal center. In truth, this is but a normal result of the fact that these remedies are treated as foreign and harmful agents by the test-organ, and that it incites a protective reaction which entails the appearance of an excess of adrenoxidase, and, therefore, of auto-antitoxin, in the blood. The beneficial effects of therapeutic doses are readily accounted for by these two properties: by causing a vascular relaxation, creosote not only counteracts excessive vascular tension—a deadly phenomenon in lobar pneumonia, for instance—but the blood which penetrates through the dilated arteries into the diseased areas being unusually bactericidal and antitoxic, the curative process is directly activated.

ARSENIC.

Physiological Action.—Arsenic, which, like other remedies is taken up by leucocytes, is the direct (and probably the physiological) antagonist of thyroidase as far as the stimulating influence of the latter on the test-organ is concerned.* By depressing, through this organ, the functional activity of the

* *Author's conclusion.*

adrenal center, it restrains the production of adrenal secretion and, therefore, the formation of adrenoxidase.* This reduces general oxygenation correspondingly.*

Besredka[2] found that the trisulphide of arsenic when injected into the peritoneum of rabbits was taken up by leucocytes, in the interior of which these yellowish-red grains could readily be seen to break up into smaller granules, and then to disappear. Gautier[3] found arsenic in various structures, the thyroid, thymus, mammary gland, the skin, hair and nails containing the most, and incorporated with the nucleoproteids and iodine. It will doubtless prove to be a component of thyroidase.*

The constitutional effects of arsenic are evidently of central origin. "There is accord between the experimenters in regard to the cause of the final arsenical paralysis," writes Wood, "all finding that it is produced by a direct action of the poison upon the nerve-centers." As stated by Cushny, paralysis is elicited in frogs by arsenic "much sooner than by arrest of the circulation by excision of the heart." The drug must, therefore, act on the nerve-centers from the start.

That it is the adrenal center which it depresses is shown by the fact that, as stated by Cushny, "arsenic lessens oxidation of the tissue." This is further emphasized by the observation of Bédart and Mabille[4] and Ewald[5] that it antagonizes the effects of thyroid extract, which, as we have seen, powerfully enhances oxidation. According to Hutchison,[6] for instance, the effect of thyroid extract is "to increase oxidation in the body; it makes the tissues, as it were, more inflammable, so that they burn away more rapidly," a conclusion amply sustained by evidence adduced in the first volume. Conversely, as observed by Lauder Brunton,[7] arsenic interferes with normal metabolism. This is also shown by the fact that Chittenden and Cummins[8] and others found that it reduced the excretion of carbon dioxide.

The physiological action of thyroidase being to enhance catabolism both by stimulating the test-organ and the adrenal center, arsenic, as the antagonist of thyroidase, opposes catabolism, *i.e.*, a too rapid consumption of the cellular elements.* While, therefore, thyroid extract in sufficient doses causes emaciation, as shown by its action in obesity, arsenic provokes the opposite effect, gain in flesh.

The general effects of arsenic on nutrition are illustrated by the use to which the peasants of Styria, Tyrol and Lower Austria put it—the men to increase their physical activities, the women to enhance their charms, round off their shape, clear their complexion, etc. Their habitual use of the drug, however, engenders tolerance, *i.e.*, habituation of the adrenal center to its presence in the blood,* and increasingly large doses becomes necessary to obtain the desired effects. They thus

* *Author's conclusion.*

[2] Besredka: Ann. de l'Inst. Pasteur, T. xiii, pp. 49, 209, 1899.
[3] Gautier: Trans. 13th Inter. Med. Congress, Sect. Gen. and Exp. Pathol., p. 545, 1900.
[4] Bédart and Mabille: C. r. de la Soc. de biol., 10 série, T. v, p. 556, 1898.
[5] Ewald: Die Therap. d. Gegenwart, Sept., 1899.
[6] Hutchison: Brit. Med. Jour., July 16, 1898.
[7] Lauder Brunton: Lancet, May 4, 1901.
[8] Chittenden and Cummins: Studies Lab. of Physiol. Chem., Yale Univ., vol. ii, p. 200, 1887.

become "arsenic-eaters." As shown by Cloetta, however, much of the arsenic ingested is not absorbed, but passes out with the fæces.

Knapp[9] has witnessed, and brought before a medical meeting a peasant who took in their presence, without apparent discomfort, 0.33 gm. (5 grains) of arsenous acid. This does not seem to influence the mortality of Styrian peasants, who, in fact, live to old age. Gies[10] found that fowl could also be made to ingest large doses, if gradually habituated to the drug. He also administered minute doses to some young rabbits several weeks, leaving others of the same litter untreated. The treated animals became larger than the controls, the muscles, bones, and fat being better developed. Others have made similar observations. Stockman and Greig,[11] however, noted only an increase in the size of the bones. It is well known, however, that animals given arsenic, lay on fat. Lardelli[12] confirmed this observation experimentally, but he found also that the increase in weight was due, "in great part," to the nitrogenous constituents.

In skin disorders, arsenic is beneficial because, by reducing the metabolic activity in the muscularis of arteries it causes, in small therapeutic doses, slight general vasodilation.* As the caliber of the cutaneous arterioles is likewise increased, the capillaries of the skin, among others, receive a greater influx of auto-antitoxin-laden arterial blood. This serves not only to free mechanically the cutaneous intercellular spaces of toxic wastes, cellular débris and other pathogenic substances that may be present, but also to hasten their destruction and insure their freer transmission to the general blood-stream where they are finally broken down and thus converted into benign and eliminable excretory products.*

The physiological action of arsenic thus interpreted, indicates that it should not be used when the cutaneous disorder present is attended with acute inflammation; the greater influx of blood in the capillaries of the skin cannot but aggravate such a condition and the disease itself.

This coincides with the clinical results recorded by dermatologists. Many have found arsenic harmful during the earlier stages of cell proliferation. Duhring, for instance, states that "it should not be prescribed where there is great heat, burning, intense itching, or rapid cell-change. It is not only of no benefit at this stage, but in most cases it is positively injurious, tending to augment the activity of the morbid process." Brocq[13] emphasizes the importance of avoiding its use in the forms of eczema and other disorders attended by the least inflammatory phenomenon. Shoemaker[14] deems it valuable only in the absence of irritation and inflammation. In chronic, sluggish processes, however, it is of great value.

The vasodilation produced is well shown by the fact that even therapeutic doses will cause, as is well known, œdema, *i.e.*, effusion of blood-serum through the walls of the capillaries.

* *Author's conclusion.*
[9] Knapp: Manquat: *Loc. cit.*, vol. i, p. 934.
[10] Gies: Arch. f. exper. Path. u. Pharm., Bd. viii, S. 175, 1877.
[11] Stockman and Greig: Jour. of Physiol., vol. xxiii, p. 376, 1898.
[12] Lardelli: Münch. med. Woch., Bd. liii, S. 2388, 1906.
[13] Brocq: "Traité d. mal. de la Peau," 1890.
[14] Shoemaker: "Mat. Med. and Therap.," fifth edition, 1901.

Untoward Effects.—When therapeutic doses are proving toxic, the cutaneous capillaries become overburdened with blood,* serous effusion into the connective tissue occurs, and œdema appears, at first under the eyes, then elsewhere.

The morbid effects of salvarsan (dioxydiamidoarsenobenzol), as described by Hoffman, Jaffé and Moirowsky, blue-red swelling of the face, lips and eyes, dyspnœa, severe diarrhœa and anuria, death being threatened,[14a] illustrate the paresis of the sympathetic control over the arterioles. This is further proven by the fact that, as first shown by Milian of Paris, the free use of adrenal, which, as is well known, contracts these arterioles, counteracts the morbid effects of salvarsan.

Chronic Poisoning.—The chronic form of arsenic poisoning, due to the absorption of very small particles from wall-paper, arsenical paints, stuffed animals, factories, mines, beverages, etc., illustrates the gradual development of lesions incident upon lowered general metabolism. Increasing weakness, gastric dilation, headache, lachrymation, congestion of the conjunctiva, coryza, sneezing, cough, cardiac dilation, enlargement of the liver, swelling beneath the eyes or of the face and extremities, all point to a general relaxation of the muscles, including those of the cardiovascular system. Imperfect cleavage of toxic wastes causes the appearance of eruptions of various kinds, some attended by intense itching. Bronzing is often witnessed in these cases, the skin falling off in brownish scales or in large flakes. Pallor and slight cyanosis may be observed.

Nervous disorders appear in practically all cases—sensory affections especially, varying from slight paræsthesia to complete anæsthesia due to imperfect oxygenation of the peripheral end-organs, to intense headache, neuralgia, muscular tenderness, pains in the joints, formication of the lower extremities, and perversions of the temperature sense. Erythromelalgia, *i.e.*, swelling, redness, and hyperæsthesia of the palms and soles, may also appear. Motor paralyses are met with in a large proportion of cases, in the lower extremities especially, recalling locomotor ataxia, and are often preceded by the sensory phenomena. They usually begin in the toes or fingers and are generally symmetrical. The knee-jerks may be exaggerated early in the history of a case, but when paralysis and atrophy

* *Author's conclusion.*
[14a] Ehrlich: British Medical Journal, May 9, 1914.

appear, they are absent. Prolonged intoxication has given rise to insanity and epilepsy, and to a state of mental torpor simulating idiocy.

All these morbid phenomena gradually disappear when the patient is no longer exposed to the effects of the poison and judiciously treated, provided disintegration of the muscular tissue has not occurred.

The pathology of chronic arsenic poisoning, as stated by Cushny, is "still obscure," but its nature—in the light of the foregoing analysis—is plainly suggested in view of the fact that, as observed by Wood,[15] "a peculiar brown pigmentation of the skin," *i.e.*, a light bronzing, "is almost pathognomonic of chronic arsenicalism." This pigmentation may even be generalized as shown by a case reported by J. Sobél,[16] some regions, the anterior and posterior surfaces of the neck, the inner sides of the thighs, etc., being "dark brown." Arsenic inhibits the functions of the adrenal system, and causes general vasodilation.

The lesions found in the spinal cord are usually ascribed to a "neuritis," a "myelitis," or the cord is said to be "inflamed." When, however, we consider that these conditions are said to be observed immediately after death from acute experimental poisoning, it becomes evident, in view of the data just submitted, that the condition present is misunderstood. What we see under these conditions is not an "inflamed" cord but an organ the vessels of which are dilated precisely as they are throughout the entire body.* In more protracted cases the vessels are said to be surrounded by an "exudation" ascribed to a so-called "inflammatory process;" but we are obviously dealing with an accumulation of blood-fluids. The walls of the vessels are said to be "thickened" and the cellular nervous elements "degenerated," but these are merely morphological alterations due to engorgement of the vasa vasorum and of the cellular elements themselves, including the multipolar cells, due to the one morbid effect of the drug: general vasodilation. Even the widespread "fatty degeneration" so-called is naught else, as we have seen in the first volume, but blood-serum converted into myosin. Wonder is expressed in text-books that in practically all cases, whether due to acute or chronic poisoning and even in paralytics showing the "reactions of degeneration," recovery occurs after discontinuing the use of the drug. This result becomes a normal one, however, when absorption of extravasated fluid devoid of physiological value and resumption of vascular tone are taken into account.

Acute Poisoning.—Arsenic, *i.e.*, arsenous acid, when in contact with the fluids of living tissues, *i.e.*, the blood-serum, becomes converted into arsenic acid, owing to the presence of the oxygen-laden adrenoxidase in these fluids.* Therapeutic doses of arsenic on reaching the stomach become, therefore, markedly active and may excite gastro-intestinal irritation.

Adrenoxidase is a constituent, we have seen, of the blood-serum, and therefore of the various secretions. Binz and Schulz[17] found that

* *Author's conclusion.*

[15] Wood: *Loc. cit.*, p. 451, eleventh edition, 1900.

[16] J. Sobel: Archives of Pediatrics, Jan., 1907.

[17] Binz and Schulz: Arch. f. exper. Path. u. Pharm., Bde. xi, S. 200, 1879; xiv, S. 345, 1881; xxxvi, S. 275, 1895.

albumin, fibrin and blood could convert arsenous to arsenic acid, and *vice versa*, the brain, liver, pancreas and kidney exercising marked activity in this process, and fats none. Cushny[18] also deems it probable "that the oxides of arsenic alone are capable of modifying vital functions." The avidity of arsenic for oxygen is satisfied as soon as it reaches the oxygen-laden fluids and tissues, and the violent abstraction of this gas from the latter accounts for its corrosive action.

It is owing to the presence of adrenoxidase in the fluids of the entire alimentary canal that a poisonous dose of arsenic may cause severe pain in the throat, œsophagus, stomach, and abdomen, nausea and vomiting, and organic lesions, *i.e.*, congestion, ecchymoses, erosions attended sometimes by hæmorrhages.* Purging is likewise the result, though only in part, of the violent intestinal irritation. Although the discharges may be merely loose, greenish, or yellow, they often assume the aspect of the rice-water stools of Asiatic cholera, and contain minute flakes of mucous membrane. The excessive loss of fluid may then entail diminution or suppression of urine.

The general or secondary effects of the poison are of another order. Arsenic is readily absorbed and the functional activity of the adrenal center is soon depressed and finally inhibited. Owing to the more or less advanced adrenal insufficiency thus engendered, the heart's action and the pulse become weak and small, and because of the marked general vasodilation, very rapid. The respirations are painful, labored, and frequent—an effort to compensate for the paucity of adrenal secretion available. As a result of the diminution of adrenoxidase in the blood and tissues the temperature gradually recedes, the extremities and body become very cold—recalling, with the concomitant symptoms, cramps, etc., the algid stage of cholera. Gradually as the blood loses its oxygenizing properties, the surface becomes dark and cyanosed, coma, and sometimes convulsions, supervene, and death ends the patient's intense suffering.

The functions of the adrenal center are evidently inhibited. Thus, arsenic may, as we have seen, provoke the characteristic symptoms of Addison's disease—progressive wasting, asthenia, hypothermia, general vasodilation, etc., including the characteristic pigmentation, *i.e.*, *bronzing*—all of which often disappear when the use of arsenic is discontinued. The case of Enriquez and Lereboullet,[19] Hutchinson,[20] Förster,[21]

* *Author's conclusion.*

[18] Cushny: *Loc. cit.*, p. 616, fourth edition, 1906.

[19] Enriquez and Lereboullet: Gaz. hebd. de méd. et de chir., July 6, 1899.

[20] Hutchinson: Arch. of Surg., vol. v, p. 339, 1894.

[21] Förster: Berl. klin. Woch., Bd. xxvii, S. 1150, 1890.

Richardière,[22] Heuss,[23] Leszynsky,[24] and many others reported, afford evidence to this effect.

Subserous ecchymoses in the endocardium, confined to the left ventricle in eight out of ten cases of acute arsenical poisoning, was observed by Powell,[25] police surgeon in Bombay.

Moreover, arsenic, by causing ischæmia of the pituitary, deprives it of its reflex activity.*

Boehm and Unterberger[26] found that both the *sensory* and *motor* paths of the upper spinal cord failed to cause the usual vasoconstriction. Such was also the case after Cyon and Massolongo had removed the pituitary body. This cannot be due to inability of the paths themselves or of the muscular coats of the arteries (owing to inhibition of their metabolism) to react under the influence of the stimulus, since the authors found that the arteries of the ear of the same animals were still constricted sufficiently to cause pallor when the cervical sympathetic was stimulated. Hence, we are dealing with a central paralysis, in accord with the prevailing view among therapeutists—but of a center located in the pituitary body, that of the adrenals. Pistorius[27] recently argued that it was the vasomotor center which lost it control over vessels, but as shown by Boehm and Unterberger, arsenic is first of all a respiratory poison—a view sustained by the marked inhibitory effect of arsenic on oxygenation, a process governed by the adrenal center, *i.e.*, the thermic center.*

After large doses, collapse and death may occur suddenly within twenty-four hours, the case lapsing almost from the start into the advanced stage. When the quantity ingested is not great, or when a part of it has been eliminated by vomiting, the primary symptoms may cease and the patient apparently improve. In many instances, however, this is only temporary; a recrudescence of the symptoms occurs, more intense perhaps than the first, but often accompanied (as a result of the corrosive action of the poison on the alimentary canal) by fever, a dry tongue, and considerable tumefaction of the abdomen. Eruptions, which may be pustular, papular, vesicular, or petechial, are often witnessed in these cases. The algidity, the intense dyspnœa, cyanosis, muscular trembling, cramps, and other characteristic symptoms of a primary acute attack nevertheless prevail and death may take place between the second and sixth day.

Recovery in such cases is slow and is usually attended by disorders of various types: of the stomach and intestines owing to the local lesions; of the nervous system or of limited portions thereof, sensory or motor, due mainly to trophic changes during the whole process; of the liver and kidneys owing to excess of toxic substances in the blood, etc.

* *Author's conclusion.*
[22] Richardière: Ann. d. derm. et syphil., 3 série, T. v, p. 1296, 1894.
[23] Heuss: Corr. f. schweitz. Aerzte, Bd. xxiv, S. 301, 1894.
[24] Leszynsky: N. Y. Med. Jour., Mar. 23, 1889.
[25] Powell: Bombay Med. and Phys. Soc., vol. ix, 1905.
[26] Boehm and Unterberger: Arch. f. exp. Path. u. Pharm., Bd. ii, S. 89, 1874.
[27] Pistorius: Arch. f. exp. Path. u. Pharm., Bd. xvi, S. 188, 1882.

In the epidemic of arsenical poisoning which occurred in Manchester a few years ago among beer-drinkers, E. S. Reynolds[28] found a large number of cases of peripheral neuritis, especially among women. In many of the cases the skin of the armpits, the nipples and the genital organs "was deeply pigmented, as in Addison's disease." Out of a series of 253 cases of neuritis collected by W. Janowski,[29] 136 were found to be due to acute arsenical poisoning. As observed by Boehm and Unterberger, and Pistorius, in poisoned animals even such large trunks as the splanchnic, which at first transmitted impulses, failed to do so later on. Impaired metabolism in their structure is a normal result of adrenal insufficiency caused by arsenic. It is, in fact, the main initial feature of the post-acute nervous disorders, when all nervous elements are regarded as channels for oxygen-laden blood-plasma.*

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

Therapeutics.—The manner in which arsenic produces its beneficial effects in certain *skin diseases* was explained on page 1302. It has proven equally efficacious in *pernicious anæmia*, a disorder due, as will be shown elsewhere, to hæmolysis through excess of auto-antitoxin and adrenoxidase in the blood.* By reducing the activity of the adrenal center and the production of adrenoxidase, arsenic counteracts this morbid phenomenon.* It is also a specific in *chorea*, another disorder due to excessive metabolic activity resulting in uncontrollable muscular activity.* In *diabetes*, the manner in which arsenic produces its beneficial effects is almost self-evident: we have seen that this disorder is due to excessive activity of the anterior pituitary, manifested through the test-organ and the adrenal center;* arsenic by depressing the activity of the adrenal center* counteracts the morbid process. In *torpid catarrhal processes*, chronic rhinitis, chronic gastritis, etc., and in persons who readily "take cold" and whose extremities are usually hypothermic, arsenic is also of value, owing to its action on the arterioles of the mucous membrane and skin. The excess of the arterial blood admitted into the capillaries enhances the curative process by introducing an excess of auto-antitoxin in the diseased tissues, and relieves the superficial hypothermia and ten-

* *Author's conclusion.*
[28] E. S. Reynolds: Brit. Med. Jour., Nov. 24, 1900.
[29] W. Janowski: Zeit. f. klin. Med., Bd. xlvi, S. 60, 1902.

dency to "colds" in debilitated individuals.* It is also because the cutaneous hyperæmia thus produced insures an increased supply of auto-antitoxin in the superficial tissues* that arsenic, as stated in the first volume,[30] protects the body against *malaria, and other diseases* in which the pathogenic agent is introduced into the blood by the sting or bite of insects, infection under these conditions depending upon the antitoxic activity of the cutaneous blood.* The curative action of arsenic in *intermittent fever* is likewise due to the accumulation of auto-antitoxin in the cutaneous capillaries*—the minute channels which Nature utilizes as a powerful adjunct to the liver when an exacerbation of defensive activity, "fever," becomes necessary.*

CHLORAL.

Physiological Action.—Chloral causes sleep by depressing directly the functional activity of the test-organ and, through it, of the adrenal center. The quantity of adrenal secretion produced being diminished, less adrenoxidase is formed and the metabolic processes in general become less active.* The brain, owing to the great volume of blood it contains, is one of the first organs to feel the influence of lowered oxygenation; the gemmules of its cellular elements are retracted and comparatively normal sleep is produced when the dose is not excessive.* The respirations, the cardiac action and the pulse are somewhat slowed and the temperature is slightly lowered, but on awakening from four to eight hours after ingesting the dose, the patient feels about as usual, though perhaps a little weary and confused.

That chloral is absorbed unchanged in the blood and circulates as such is now generally recognized. Liebreich's view, that it is split into chloroform and sodium formiate, has been shown by Labbée,[31] Tomascewicz[32] and others to be erroneous. It is not, however, by a direct action on the blood itself that it acts, for Rajewsky[33] found that the drug produced its typical effects on a frog whose blood had been replaced by salt solution. Nor is it by a direct action on the motor nerves, for the same investigator and Labbée found that even fatal doses had no influence on these structures. Both these investigators traced the phenomena witnessed to the spinal centers.

* *Author's conclusion.*
[30] *Cf.* vol. i, p. 769.
[31] Labbée: Arch. gén. de méd., vol. xvi, p. 330, 1870.
[32] Tomascewicz: Arch. f. d. ges. Physiol., Bd. ix, S. 35, 1874.
[33] Rajewsky: Centralbl. f. d. med. Wissen., Bd. viii, S. 211, 1870.

The prevailing view is that chloral paralyzes the respiratory center. Although, as observed by Loewy,[34] there is practically no difference between normal sleep and the effect of a therapeutic dose in this particular, Cushny[35] states that "as the dose is increased . . . . . , the respiration becomes very slow and weak, and finally ceases from paralysis of the center." Even therapeutic doses, as observed by DaCosta[36] and others, reduce the temperature. When the doses are large, this reduction may become very marked. Thus, B. Ward Richardson[37] observed a reduction of 10.8° F. (6° C.) in the rabbit. Hammarsten[38] obtained a similar reduction in one hour, "though the animals were well wrapped up and laid in a warm place." This is evidently due to deficiency of oxygen-absorbing power of the blood, for the air utilized is considerably reduced. Thus Wood and Cerna[39] found experimentally that the reduction in the amount of inspired air produced by large doses was, in many instances, 50 per cent., and that sometimes it amounted to 75 per cent. These experiments demonstrated, in their opinion, that in the dog, chloral was a true respiratory depressant. Again, the effects of chloral in man being similar to those exerted upon the dog, they conclude that in human beings chloral likewise paralyzes the respiratory centers. H. W. Mitchell[40] refers to a case in which the oxygenation of the blood was sufficiently impaired to produce cyanosis. Wood concludes,[41] in view of Rajewsky's experiments, that "the influence of chloral must be exerted upon the respiratory center at the *base* of the brain." All these observations harmonize with those of Richet,[42] who found that chloral greatly reduced the excretion of carbon dioxide, and with those of Germain Sée[43] and others, who ascribe to chloral a paralyzing action on the "thermic centers"—also thought to be at the *base* of the brain. As I have pointed out,[44] the thermic center is the adrenal center.

As the paralysis of the adrenal center becomes more marked gradually as the dose is increased, the oxygenization of the tissues is correspondingly lowered and the functional activity of all organs, including the muscular layer in the walls of the vessels and the cardiac muscle, is lowered in proportion.* General vasodilation occurs as a normal result.* This feature of the action of chloral renders the use of large doses dangerous.

Large therapeutic doses, by augmenting the adrenal insufficiency and causing marked general vasodilation,* produce a deep sleep which lasts twelve to eighteen hours, and from which the patient can only be awakened with considerable difficulty. All functions being to a certain extent impaired by the paucity

* *Author's conclusion.*
[34] Loewy: Pflüger's Arch., Bd. xlvii, S. 601, 1890.
[35] Cushny: *Loc. cit.*, p. 188, fourth edition, 1906.
[36] DaCosta: Cited by Wood: *Loc. cit.*, p. 149, thirteenth edition, 1906.
[37] B. Ward Richardson: Med. Times and Register, Sept. 4, 1869.
[38] Hammarsten: Cited by Wood: *Loc. cit.*, p. 149, thirteenth edition, 1906.
[39] Wood and Cerna: Jour. of Physiol., vol. xiii, p. 870, 1892.
[40] H. W. Mitchell: Boston Med. and Surg. Jour., Jan. 31, 1907.
[41] Wood: *Loc. cit.*, p. 149, thirteenth edition, 1906.
[42] Richet: Arch. de Physiol. norm. et path., 5 série, T. ii, p. 221, 1890.
[43] Germain Sée: C. r. de l'Acad. de méd., July 22, 1890.
[44] *Cf.* this volume, p. 1008.