That retention of iodine must prove deterimental is suggested by the proportion eliminated. In a case treated by H. C. Wood[178] 265 grains (17 gms.) were recovered daily by Marshall from the urine alone, out of 360 grains (24 gms.) administered. According to Wood, "See states that the elimination is apt to be irregular, so that the drug may accumulate in the system." Cushny[179] says, moreover, that among the conditions "which favor the onset of symptoms, is a slow excretion of the iodine such as is observed in some forms of renal irritation."

As to the quantities of iodine or its salts which produce iodism, the comprehensive research of Briquet[180] in several hundred cases, led to the conclusion that "the greater the dose of any iodide, the greater the likelihood that iodism will appear, and that the symptoms will be severe"—contrary to the prevailing opinion. He cites, moreover, cases reported by Bresgen, Nègre and Petitjean in which large doses would produce it, while smaller doses would not. According to my own interpretation of its effects, the nearer the patient's condition approximates normal health, the greater are the chances of his developing iodism. I have not only observed this fact clinically, but Ricord, Jullien and Wood, according to Briquet, have observed that syphilitics appear, on the whole, to be practically immune to the morbid effects of the iodides as compared to others. There is no doubt, moreover, that very small doses can produce iodism in accord with the prevailing view. In one of my goitrous cases, less than 1 minim (0.065 c.c.) of the tincture of iodine daily produced it; Rilliet[181] observed that even sea-air and cod-liver oil sufficed to awaken morbid phenomena in these cases. Gautier[182] confirmed the observation as to the influence of the sea-shore, and refers to a case in which poisoning followed "the application of iodine dressing to a tooth by a dentist." The reason for this becomes self-evident if interpreted from my standpoint. While Baumann[183] found that the amount of iodine in the thyroid was greatly reduced when this organ was diseased, Ewald[184] observed that in advanced colloid degeneration of the gland only traces of iodine were present. The loss of the body's great storehouse for this halogen accounts for its accumulation in the blood and the readiness with which morbid phenomena are produced. This indicates how the organism resents even minute quantities when they exceed the physiological limit. Indeed, irrespective of the presence of goiter, small doses may also provoke iodism. Hynes[185] reported a case in which 3-grain (0.2 gm.) doses brought on hæmorrhagic rash; and H. C. Wood[186] one in which 6 grains (0.4 gm.) daily brought on violent conjunctivitis with facial œdema.

The presence of iodine in the cutaneous secretions has been shown by R. W. Taylor,[187] and other observers have found it in the saliva, nasal secretion, milk, etc. Its morbid influence in the production of the cutaneous disorders during elimination is generally recognized. Cushny[188] writes: "That a similar action on the skin may be induced by iodine and iodides is shown by the application of iodine to the skin, being often followed by eruptions which are not confined to the point of application, but spread." That toxic wastes must be retained as well as the

[178] H. C. Wood: *Loc. cit.*, thirteenth edition, p. 499, 1906.
[179] Cushny: *Loc. cit.*, fourth edition, p. 508, 1906.
[180] Briquet: Semaine méd., vol. xvi, p. 137, 1896.
[181] Rilliet: Cited by Nothnagel and Rossbach: *Loc. cit.*
[182] Gautier: Rev. méd. de la Suisse Rom., vol. xix, p. 618, 1899.
[183] Baumann: *Loc. cit.*
[184] Ewald: *Loc. cit.*
[185] Hynes: Lancet, Feb. 13, 1904.
[186] H. C. Wood: *Loc. cit.*, thirteenth edition, p. 501, 1906.
[187] R. W. Taylor: Amer. Jour. of Syphilis and Derm., vol. iv, p. 110, 1873.
[188] Cushny: *Loc. cit.*, fourth edition, p. 508, 1906.

iodides in the cutaneous capillaries hardly needs to be emphasized; their influence in the pathogenesis of eruptions is also well-known.

The list of symptoms observed in iodism could be considerably lengthened—sufficiently so, in fact, to show that the three degrees of passive capillary hyperæmia: the simple, exudative and hæmorrhagic, can be provoked by iodine and its preparations in *all* organs. The fact that such an array of phenomena can be explained by this one general mechanism, affords in itself conclusive proof of its soundness as an explanation of iodism—especially in view of the fact that the physiological action of iodine has remained unknown.

Acute Poisoning.—When a poisonous dose of iodine is taken, a sense of severe burning in the pharynx and œsophagus is soon followed by nausea, retching and vomiting, and ultimately by cramps and, in some cases, purging. These are purely local phenomena due to the caustic action of the drug.

When a large quantity of iodine passes into the blood, the general vasoconstriction, described in the preceding pages, becomes such that all functions are inhibited, including those of the heart, owing to narrowing of the coronaries and other cardiac arteries.* The heart-walls being no longer supplied with enough blood to sustain their functional activity,* their contractions weaken, and the pulse becomes frequent, feeble and thready. This condition is aggravated by the concomitant constriction of the arterioles which supply the pituitary body and the inhibition of all the functions carried on by this organ.* Great weakness, anuria and cyanosis appear and death occurs from heart-failure. If the patient survives, the acute vasoconstriction of the arterioles becomes less marked, and the blood, driven to the periphery by the contracted central vessels, floods the superficial capillaries,* causing marked flushing and even blotches resembling exanthematous patches, hæmorrhages, etc., though the temperature remain low. If death does not occur, the acute symptoms may be replaced by those of iodism and the patient lingers for some time, dying more or less suddenly of cardiac inhibition.* Recovery occurs in a large proportion of cases, however, when the dose taken is not excessively large.

The morbid process in acute poisoning differs from that of the fourth group of "iodism" only in that the hyperconstriction comes suddenly and with probably greater violence. I have shown elsewhere[189] that the belief of physiologists that the coronaries are not supplied with vasomotor nerves is erroneous. This question is reviewed in a succeed-

* *Author's conclusion.*
[189] New York Med. Jour., May 14, 21, 1904.

ing chapter, where a microphotograph shows beyond question the existence of such nerves. All the arteries of the body being constricted simultaneously, the caliber of the arteries of the pituitary is not reduced as greatly as it is when their contraction is due to depressor impulses. The morbid effects on the other organs, the heart, for instance, stand out, therefore, more prominently. The secondary hyperæmia, exanthematous patches, etc., referred to have been observed by several clinicians to follow acute poisoning.

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

Therapeutics.—The foregoing interpretation of the physiological action of iodine and the iodides accounts for their marked value in diseases characterized by impaired metabolism, defective nutrition, certain infections and chronic inflammatory process in which resolution is delayed. In *gout, rheumatism, asthma* and disorders of the *menopause,* their beneficial effects are due to the fact that by increasing the auto-antitoxin in the blood, the pathogenic toxic wastes are not allowed to accumulate. In *syphilis, tuberculosis* and *scrofula,* their power to promote phagocytosis also comes into play, the bacteria, their toxins or endotoxins, being combatted by the same constituent—antitoxic and bacteriolytic—which is caused to accumulate by injections of tuberculin or kindered substances. Even parasites may be destroyed by the digestive activity which the blood acquires through iodine and its salts, as shown by its remarkable effects in *actinomycosis.* In torpid processes, such as *chronic bronchitis, pleuritis* or *endocarditis,* the curative action of these valuable agents differs in no way from the above: by increasing the activity of metabolism, they promote nutrition and process of repair, while simultaneously insuring the destruction of the detritus and of any pathogenic germ that may be present—all this, while protecting the body against renewed infection.*

The doses indicated differ in each case, since its action is dependent upon the asset of the organism and the condition of the test-organ. If the patient's asset is up to the maximum, as is often the case in normal subjects, small doses suffice to raise the functional activity of the test-organ and, therefore, the defensive properties to a high degree of efficiency.* If conversely his asset is small, his thyroid poor in

* *Author's conclusion.*

iodine-laden cells, and his test-organ is torpid, conditions essentially present in syphilis and various disorders accompanied by paralysis,* large doses are necessary, first to replenish the thyroid and enable it in turn to supply the red corpuscles and all cells with enough thyroidase to endow them with the normal irritability, and second to awaken the test-organ from its lethargy.*

ADRENAL EXTRACTIVES.

(Adrenal Extract, Adrenalin, Epinephrin, Suprarenalin, etc.)

Physiological Action.—When a therapeutic dose of an adrenal active principle, adrenalin, epinephrin, etc., or that embodied in adrenal extract, is introduced directly into the blood, it increases, in proportion to the quantity administered, the catalytic and oxygenizing properties of the hæmoglobin, and the activity of cellular interchanges—the vital process itself—is thus enhanced.* This effect is shown prominently in conditions such as surgical shock in which all functions are markedly depressed.

The influence of the drug on metabolism is well shown by the rise of temperature it causes. Reichert[190] observed that adrenal extract caused an elevation of 1° F. in rabbits, accompanied by increased metabolic activity. Lépine[191] states that the increase of blood-pressure caused by adrenal extract is always followed by a rise of temperature. Morel[192] noted that it caused in guinea-pigs a rise of from 0.9° to 1.8° F. Again, Kinnaman,[193] in a comprehensive study of the temperature relationship to shock, concluded that as shock increased in severity, the most uniform and progressive factor was the fall in temperature. He states that "in one series [of cases] the fall in temperature was the sole cause of shock." The results of Crile[194] with adrenalin in salt-solution given very slowly and gradually for a considerable time thus find a normal explanation. He supplied the organism precisely with the substance which sustains the vital process in the tissue cells. He also resuscitated animals in this manner—with simultaneous artificial respiration—fifteen minutes after all signs of life had ceased, and was able to keep a decapitated dog alive over ten hours by this same procedure.

By enhancing the catalytic and oxygenizing properties of the blood, and therefore tissue metabolism, adrenal extractives provoke directly effects that are produced indirectly through the adrenals, by drugs and poisons capable of stimulating the

* *Author's conclusion.*

190 Reichert: Univ. of Penna. Med. Bull., Apr., 1901.
191 Lépine: Semaine méd., Feb. 18, p. 53, 1903.
192 Morel: Le progrès méd., Aug. 3, 1903.
193 Kinnaman: Annals of Surgery, Dec., 1903.
194 Crile: Boston Med. and Surg. Jour., Mar. 3, 1903.

test-organ.* The functional activity of all organs—including the leucocytogenic structures and the pancreas—being enhanced, the blood is provided with an increase of phagocytes and of plasmatic auto-antitoxin.* Adrenal extractives thus increase the immunizing properties of the blood.

Byelaventz[195] found experimentally that adrenalin first increased the gaseous interchanges. This shows that it becomes an inherent factor of the blood's oxygenizing constituent. This action is evidently widespread, for Ioteyko[196] noted that adrenalin increased markedly the contractility of muscles under electrical excitation. Battelli, moreover, found that during fatigue the proportion of adrenalin in the adrenals was diminished, while conversely Dessy and Grandis[197] observed that an aqueous solution of adrenal extract injected into the exhausted animal restored the contractility of its muscles in from 2 to 8 minutes, and rendered them more resistant than before the experiment.

That the adrenals cause, in some way, the destruction of blood-poisons has asserted itself so prominently that various investigators, Abelous and Langlois,[198] for example, consider it as their only function. This is the basis of the so-called "auto-intoxication" theory. Indeed, these investigators, and also Albanese, having observed that animals deprived of their adrenals rapidly succumbed to a short exertion, they concluded that it was the secretion of the adrenals which neutralized the muscular toxic wastes. This theory has failed in its main feature, however, for there is no foundation for the belief that the secretion itself destroys these poisons. Interpreted from my standpoint, Abelous and Langlois's theory assumes another aspect: the adrenal secretion being, as adrenoxidase, a constituent of the bacteriolytic and antitoxic triad trypsin, and the one which endows it with its quality as a ferment, the antitoxic power of the blood gradually diminishes after extirpation of the adrenals (since the animal lives a short time on what adrenoxidase his blood happens to contain), and the muscular toxic wastes being less and less destroyed, accumulate in the blood. Hence the fact that exertion after removal of the adrenals hastens, as we have seen, the lethal issue, while the post-operative use of adrenal extract, as first shown by Brown-Séquard,[199] prolongs life. Schäfer[200] states, moreover, that "the transfusion of normal blood into the veins of 'decapsuled' animals tends markedly to prolong their survival of the operation." In other words, in whatever form the active principle of the adrenal secretion is introduced, it increases the antitoxic power of the blood—precisely as is the case when the test-organ is stimulated by a poison. The digestive (antitoxic) power of the blood—including phagocytosis—may be so increased, in fact, that destruction of the blood-cells themselves will occur. Thus Loeper and Crouzon[201] observed that injections of adrenalin into the blood first caused leucocytosis, then hæmolysis. Nor does this apply only to toxic muscular wastes, for Meltzer and Auer[202] found that the intravenous injection of adrenalin renders a rabbit resistant to a surely fatal dose of strychnine.

* *Author's conclusion.*
[195] Byelaventz: Russkii Vratch, vol. ii, No. 7, 1903.
[196] Ioteyko: Jour. de méd. de Bruxelles, July 9, 16, 23, 1903.
[197] Dessy and Grandis: Arch. Ital. de Biol., May 31, 1904.
[198] Abelous and Langlois: C. r. de la Soc. de biol., p. 855, 1891; p. 388, 1892; p. 444, 1893.
[199] Brown-Séquard: C. r. de la Soc. de biol., T. xliv, p. 410, 1892.
[200] Schäfer: "T. B. of Physiol.," vol. i, p. 949, 1898.
[201] Loeper and Crouzon: Arch. de méd. exper., vol. xvi, p. 83, 1904.
[202] Meltzer and Auer: Med. News, June 4, 1904.

When applied locally to mucous membranes, adrenal extractives produce blanching through local ischæmia. This is due to the fact that they excite very active local metabolism in all the tissues into which they penetrate.* The muscular elements of the arterioles and veins being thus caused to contract to their utmost limit, the access of blood to the cellular elements is prevented.* The energetic consumption of cellular materials which this excessive constriction entails,* is sometimes sufficient to cause gangrene by arresting local nutrition. Again, it leaves the cellular elements deprived of nutrient materials for a time,* their restoration occurring in a measure according to the age and general recuperative activity of the patient. Hence* the gaping vessels, the œdematous infiltration, etc., observed after the local use of adrenal extractives, especially in debilitated and aged subjects, and the post-operative hæmorrhages occasionally witnessed.

Local hypermetabolism is well exemplified by the experiments of Herter and Wakeman,[203] in which they found that by painting the pancreas with 1 c.c. of a 1 in 1000 solution of adrenalin, they caused glycosuria. In the light of my interpretation the solution increased markedly the functional activity of the pancreas, and increased the production of amylopsin—the ferment which converts glycogen into sugar. Wolownik-Charkow[204] found that after the administration of large doses to rabbits, the liver contained less glycogen than the control animal. Müller[205] found, moreover, that adrenal extractives produced no morbid changes in the tissues—thus pointing to mere excess of activity—and that it did not interfere with reparative changes.

So intense is this local vasoconstriction that Braun[206] found that a solution of 1 in 1,000,000 of the active principle depleted the tissues as if they had been frozen. Neugebauer[207] and others have, in fact, found that it caused gangrene, the tissues being totally deprived of blood. Taramasio[208] observed a similar effect in experimental animals. This illustrates the activity of the intracellular exchanges it provokes in the muscular elements of the vessels, and for the observations of F. E. Hopkins,[209] Kyle[210] and others, that its use is liable to be followed by post-operative hæmorrhage, the vessels being left gaping when the action of the extractive passes off. Seitz[211] observed sloughing of the nasal tissues. Solomon Solis-Cohen[212] reported an instance of acute œdema of the uvula, palate, pharynx and epiglottis. A similar, though more extended œdema, occurred in a case treated by Bloch.[213] Many instances of this kind have been reported.

* *Author's conclusion.*
[203] Herter and Wakeman: Amer. Jour. Med. Sci., Jan., 1903.
[204] Wolownik-Charkow: Virchow's Archiv, Bd. clxxx, S. 225, 1905.
[205] Müller: Münch. med. Woch., Bd. li, S. 199 u. 262, 1904.
[206] Braun: Berl. Klinik, Bd. xvii, Nu. 1, S. 16, 1904.
[207] Neugebauer: Centralbl. f. Chir., Bd. xxx, Nu. 5, S. 1417, 1903.
[208] Taramasio: Rev. Méd. de la Suisse Rom., Aug. 20, 1902.
[209] F. E. Hopkins: New York Med. Jour., Aug. 25, 1900.
[210] Kyle: Therap. Gaz., July 15, 1902.
[211] Seitz: Jour. of Ophthal., Otol. and Laryn., Mar., 1901.
[212] S. Solis-Cohen: *Ibid.*, May, 1902.
[213] Bloch: Medical Record, July 6, 1901.

In large therapeutic doses given hypodermically or endovenously, the adrenal extractives increase markedly the force of the cardiac contractions. This is the result of two consecutive effects of the drug: the *first* of these is the direct action: as normally the secretion of the adrenals stimulates the right ventricle while passing through it on its way to the lungs with the blood of the inferior vena cava,* the presence of an excess of adrenal principle in this blood increases this action on cardiac dynamism.* This occurs only when the adrenal extractive is not converted into adrenoxidase before reaching the heart.* The *second* action is indirect, but that which prevails in every instance.* The addition of adrenal extractive to the adrenoxidase—oxyhæmoglobin—already in the blood, increases its catalytic and oxygenizing power, and the functional activity of the heart is increased as well as that of all other organs.*

The passage of the adrenal secretion into the inferior vena cava and its action on the heart having been studied in detail in the thirteenth chapter, only a few of the main facts will be rehearsed here. Brown-Séquard, in 1853, found that the blood of the vena cava contributed to the heart's contraction. Oliver and Schäfer,[214] referring to the use of a solution of adrenal extract in saline solution, write: "We have in this way administered large doses of the extract to the dog, thereby producing the most violent cardio-vascular disturbance without causing a fatal result." The fact that extracts powerfully stimulate the heart was confirmed by Cybulski, Seymonowicz, Gottlieb and others. Vincent, Velich, Ott and others having obtained a similar effect after dividing the cord, while Cyon[215] found that it occurred notwithstanding division of the splanchnics, it is evident that the effect was not of central origin, it being well known, moreover, that it is not prevented by section of both vagi. That the action is local is further shown by the fact that Brown-Séquard found that removal of the adrenals greatly enfeebled the cardiac contractions, and that injections of adrenal extract restored them. Again, I (1903) showed that the dynamic agent in the venous blood of the vena cava (which Brown-Séquard thought was CO_2—a fact disproved) was the adrenal secretion. Beaman Douglass (1905) found that an adrenal solution caused a detached heart immersed in it at once to resume beating. The oxidizing activity of the blood on the adrenal secretion is given below.

That a therapeutic dose influences the heart by increasing the activity of its cellular exchanges, as it does that of all other tissues rather than by a direct action, is self-evident. Langlois,[216] and Carnot and Josserand[217] found experimentally that the adrenal active principle disappeared on entering the blood, while Embden and von Furth[218] found that it was oxidized in the latter, though not *in vitro*.

* *Author's conclusion.*
[214] Oliver and Schäfer: Jour. of Physiol., vol. xvii, p. 9, 1894-95.
[215] Cyon: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 541, 1906.
[216] Langlois: Archives de physiol., T. x, p. 124, 1898.
[217] Carnot and Josserand: C. r. de la Soc. de biol., p. 1472, 1902.
[218] Embden and von Furth: Hofmeister's "Beiträge z. chem. Physiol. u. Path.," Bd. iv, S. 421, 1903.

The muscular elements of the vessels being also the seat of excessive metabolism,* another prominent symptom shows itself: viz., elevation of the blood-pressure. This in turn gives rise to a third phenomenon: slowing of the pulse owing to the greater resistance offered by the blood-column to the cardiac muscle.*

That hypermetabolism in the muscular layers of vessels causes vasoconstriction has already been sustained in the foregoing pages by considerable evidence. It is shown, moreover, by the fact that adrenal extractives, when administered during a prolonged period, produce arteriosclerosis, as recently shown by Josué,[219] Erb,[220] von Rzentkowski[221] and others. Oliver and Schäfer[222] showed twelve years ago that adrenal extract caused contraction of the blood-vessels by acting directly on their walls. In the light of the foregoing data, this is readily accounted for by the fact that it enhances excessively intracellular metabolism in the vascular elements, the vessels being thus caused to contract violently. The smaller the caliber of a vessel, therefore, the greater the chance of its lumen being obliterated. Now, the vasa vasorum have long been known to take a prominent part in the pathogenesis of arteriosclerosis. Cowan[223] states, in fact, that the "vasal changes may, in some cases, be the only visible lesion," and refers to cases in which he says "the interference with the vascular supply from the vasal vessels produced medial and intimal necrosis." Councilman's[224] study of 41 autopsies showed that in the nodular form the primary alteration consisted "in a degeneration or a local infiltration in the media and adventitia, chiefly about the vasa vasorum." The manner in which injections of adrenal extract can give rise to the arterial lesions is now plain. By closing the vasa vasorum, they arrest the nutrition of the vascular walls, and the lesions of arteriosclerosis follow. That lesions of the vasa vasorum are actually present was recently confirmed by Scheidemantel,[225] Marini[226] and Papadia.[227]

Poisoning.—In toxic doses, adrenal extractives, by causing excessive metabolism in the muscular elements of all vessels—excepting the capillaries, which are not provided with a muscular coat*—provoke so intense a general vasoconstriction in animals that all the organs are dangerously engorged. When death occurs its direct cause is pulmonary congestion and œdema and the consequent asphyxia.

There is at first more or less irritability, excitement and restlessness, soon followed by stiffness of the muscles, with perhaps spasmodic movements, or tremors. Gradually as the

* *Author's conclusion.*
[219] Josué: C. r. de la Soc. de biol., vol. iv, p. 1374, 1903.
[220] Erb: Wiener med. Presse, Bd. xlv, S. 884, 1904.
[221] von Rzentkowski: Berl. klin. Woch., Bd. xli, S. 830, 1904.
[222] Oliver and Schäfer: Jour. of Physiol., vol. xvi, p. 1, 1894.
[223] Cowan: Practitioner, Mar., 1906.
[224] Councilman: Osler's "Practice of Medicine," third edition, p. 771, 1898.
[225] Scheidemantel: Virchow's Archiv, Bd. clxxxi, S. 426, 1905.
[226] Marini: Gazetta d. Ospedali, Feb. 19, 1905.
[227] Papadia: Riv. di patol. nerv. e mentale, Mar., 1906.

blood-pressure rises all capillaries become so gorged with blood that hæmorrhage from the nose and mouth, hæmaturia, bloody diarrhœa, cutaneous œdema and ecchymosis may occur; the caliber of the arterioles is soon sufficiently reduced, however, to impede circulation* and the symptoms of cutaneous ischæmia appear, viz., marked hypothermia, and anæsthesia. This is accompanied by great prostration, paralysis (beginning in the lower limbs), labored respiration, at first rapid, then slow and shallow, feeble heart action and finally death from asphyxia. This is preceded in some instances by convulsions, due to the accumulation of toxic wastes.

In man, besides the untoward effects produced by the local action of adrenal extractives, referred to on page 1171, any of the morbid effects observed in animals may appear after injections into the tissues or circulation. The usual symptom-complex due to an excessive, though not necessarily fatal, dose is: preliminary restlessness, then weakness and staggering. Gradually as the general vascular pressure increases, the blood-column crowds the heart* and may give rise to marked cardiac pain, the pulse being hard and tense. This is attended by free passive perspiration, also of vasoconstrictor origin.* Gastric, bronchial and other capillaries may be ruptured by the pressure of blood into them,* and hæmatemesis, hæmaturia, etc., may occur. When the arterioles are sufficiently contracted to interfere with the circulation* the extremities and even the body may become very cold. Death may then occur by cardiac arrest from three factors: 1st, owing to the pressure upon it of the blood-column;* 2d, excessive constriction of its arteries, including the coronaries, which, contrary to prevailing teachings, are also supplied with vasomotor nerves;* 3d, arrest of the respiration by vasoconstrictor interference with the progress of the blood to the pulmonary alveoli.*

Swale Vincent[228] states that "the first effect noticeable in dogs is excitement. There is increased muscular activity which passes into a stage of agitation with tremors." The hæmaturia and the bleeding from the mouth and nostrils observed in various animals by the same investigator[229] is, he writes, "probably the expression of the high blood-pressure, brought about by the extract." These phenomena are evidently not of central origin, since he also found that destruction of the spinal

* *Author's conclusion.*
[228] Swale Vincent: Jour. of Physiol., vol. xxii, p. 270, 1898.
[229] Swale Vincent: *Ibid.*, vol. xxii, p. 111, 1897.

cord in frogs did not prevent them. Pellacani,[230] who was the first to study the toxicology of adrenal extract in animals, found that such effects were only produced by very large doses, a fact subsequently confirmed by Swale Vincent.[231]

Pellacani observed congestion of the liver, spleen and kidneys, and other structures, and when death was delayed, atrophy of these organs —a fact which indicates subsequent constriction of the arterioles and the resulting arrest of nutrition. The engorgement of all organs was also witnessed by Taramasio,[232] Cybulski,[233] and others.

Hultgren and Andersson[234] found that sufficient quantities of the extract caused death in the rabbit by provoking pulmonary œdema and sometimes hæmorrhage. These authors and Cybulski ascribe death caused by adrenal extracts to this condition. Gourfein[235] attributed it to asphyxia. Abel[236] and Abbott[237] both observed that epinephrin caused death by arresting the respiration. Indeed, Swale Vincent[238] found that the blood of one of his animals (dog) had become venous throughout the body. This illustrates the extent to which the œdematous lungs prevent aëration of the blood. On the other hand, Cybulski showed that artificial respiration kept the experimental animal alive, normal breathing being subsequently restored.

Therapeutics.—As the uses of adrenal gland have been treated at length in the first volume (pages 748 to 762 inclusive), its main indications will only be mentioned here. Adrenal gland is used in disorders due to a gouty "diathesis," as *hay-fever,* and *asthma*—a result accounted for by its power to enhance metabolism and therefore catabolism of toxic wastes. In asthma due to low vascular tension, suprarenalin or epinephrin, 10 minims of the 1:1000 solution in 1 dram of saline solution intramuscularly, promptly arrests a paroxysm, by supplying the blood with more adrenoxidase, *i.e.,* with oxygen.*

The manifest influence adrenal gland has on nutrition also accounts for its beneficial action in adynamic disorders,* *neurasthenia* and *surgical shock,* for example. This applies also to *cardiac disorders* characterized by weakened systole or dilatation and their complications.

Adrenal gland has been found of value in neurasthenia by many observers, including Huchard, and, as already stated, in shock, saline solution (1 in 50,000) being used as excipient. In cardiac disorders it has been recommended by several clinicians, including Mankowsky,[239] Floersheim,[240] and Deeks.[241] Mankowsky specifies that the most useful

* *Author's conclusion.*
[230] Pellacani: Arch. per le Scienze med., vol. iii, p. 24, 1879.
[231] Swale Vincent: Jour. of Physiol., vol. xxi, p. 25, 1897.
[232] Taramasio: *Loc. cit.*
[233] Cybulski: Wiener med. Woch., Bd. xlvi, S. 214, 255, 1896.
[234] Hultgren and Andersson: Skandin. Arch. f. Physiol., Bd. ix, p. 73, 1899.
[235] Gourfein: Revue méd. de la Suisse Rom., vol. xv, p. 513, 1895.
[236] Abel: Zeit. f. physiol. Chemie, Bd. xxviii, S. 318, 1899.
[237] Abbott: Jour. of Med. Research, vol. iv, p. 329, 1903.
[238] Swale Vincent: Jour. of Physiol., vol. xxii, p. 270, 1898.
[239] Mankowsky: Russian Arch. of Path., Clin. Med. and Bact., Mar., 1898.
[240] Floersheim: New York Med. Jour., Oct. 6, 1900.
[241] Deeks: Montreal Med. Jour., Nov., 1901.

application of adrenal gland is in cardiac weakness and threatening collapse. Floersheim found it effective where our usual remedies had failed. Deeks obtained not only marked improvement in cardiac weakness, but disappearance of attending œdema. Boy-Teissier[242] obtained excellent results in cases of weak heart with general cyanosis and great cardiac dilatation.

Addison's disease, whether due to organic lesions of the adrenals themselves or of the nerves or ganglia through which they receive their impulses, is attended by lowered metabolism, hypothermia, and low blood-pressure. Adrenal gland is indicated *in doses sufficient to raise both the latter and the temperature to normal and keep them so,* i.e., 3 grains during meals.

In this disease, the vitality is so reduced that, as stated by Rolleston,[243] the cases sometimes emit a cadaveric odor. Some clinicians, including Senator,[244] have noted no modification of the nitrogen output; some found that it was increased; others that it was decreased. In literature, these results are recorded as discordant; but this is not warranted in the light of my views. They merely indicate that metabolism is more impaired in some cases than in others, owing to greater destruction of the adrenals or of their nerves, and that where no perceptible effect is obtained from adrenal extractives, it is because the supply is not adequate, both as to quality and quantity, to restore the vital equilibrium—to compensate, in other words, for the loss of those organs which sustain the vital process by supplying the tissues with oxygen. In an analysis of 97 cases reported in literature, by E. W. Adams,[245] in which adrenal preparations were used, 7 cases were made worse; 43 derived no real benefit; 31 showed marked improvement, and 16 were "permanently relieved." The pigmentation waned in most of the cases improved. This affords a marked contrast with Lewin's 800 reported cases treated by other methods,[246] of which 28 cases were improved and 5 cured. (Addison's disease is treated in full in Chapter II.)

In hæmorrhagic disorders, the identity of adrenoxidase as the fibrin or coagulating ferment,* renders adrenal extractives effective as hæmostatics, whether applied externally or given internally. Hence its recognized value in *epistaxis, hæmoptysis, hæmatemesis, intestinal hæmorrhage,* the dose of adrenalin chloride when given orally varying from 5 to 30 drops every three hours, according to the urgency of the case. Even the hæmorrhages of *hæmophilia* can be promptly arrested by the local application of adrenal extractives. The internal use of thyroid gland, which actively stimulates the adrenal center and causes a marked increase of adrenoxidase,* masters the primary disorder itself. (See also Adrenal Opotherapy, vol. i, p. 750.)

* *Author's conclusion.*
[242] Boy-Teissier: Arch. gén. de méd., Aug. 23, 1904.
[243] Rolleston: Allbutt's "Practice of Medicine," vol. v, p. 540, 1897.
[244] Senator: Charité-Annalen, Jahrg. xxii, S. 235, 1897.
[245] E. W. Adams: Practitioner, Oct. 1903.
[246] Lewin: Allbutt's "Practice of Medicine," vol. v, p. 561, 1897.

ANTITOXINS.

Source and Chemical Nature.—None of the prevailing theories of immunity explain the origin or mode of action of antitoxin. This is due to the fact that Ehrlich's side-chain theory—though extremely elucidative in many directions—has diverted the attention of pathologists from the true source of the constituents of this substance: the adrenals and other ductless glands.*

As to the origin of antitoxin, Ritchie in an impartial review as president of the section of Pathology of the British Medical Association,[247] said recently: "We must admit that at present we know of no definite facts which point to the place of origin of antitoxin;" and, moreover, referring to Ehrlich's theory: "The view that the saturation of the side-chains of the cell [the tissue-cell] with toxin made them drop off with their burden of toxin always appeared to me to be hardly tenable, in view of the fact originally put forward by Ehrlich that the reason for the affinity of toxin for the cell was probably to be found in the fact that the toxin closely resembled the normal food of the cell. It would be of little use to the cell if a side-chain should straightway drop off into the serum whenever a food particle became attached to it. *The whole view was too theoretical.*"

The practical side of the question is aptly described by H. C. Wood, Sr. and Jr., in a recent edition of their text-book:[248] "The mode of action of the antitoxin in infectious diseases has been the subject of a large amount of surmise and study, but while a number of interesting theories have been suggested, notably that of Ehrlich, it must be confessed that we have no positive knowledge of the manner in which this substance acts in infectious diseases."

Again, as stated by H. Gideon Wells,[249] according to the side-chain theory, "the antitoxin consists of cell receptors that have been produced in excess and secreted *by the cells into the blood,*" referring to the *tissue*-cells. Ehrlich has failed to demonstrate this fact. On the other hand, considerable evidence is available, we have seen, to show that it is through the intermediary of the leucocytes that the bacteriolytic and antitoxic substances reach the blood. Ainley Walker,[250] for instance, writes: "A definite relation exists between the mass of the leucocytes added [to serum] and the degree of bactericidal power obtained (Bordet). Again, a bacteriolytic pleural exudate has been made *entirely inactive* by the removal of its leucocytes, active again on their replacement (Denys and Havet)." From this and other facts submitted, the author concludes that "the addimentary ferment is definitely associated with the leucocytes, and is not a ferment circulating freely in the blood-plasma as Ehrlich teaches."

Before Ehrlich introduced his side-chain theory, and ever since, numerous investigators have urged the importance of the ductless glands and internal secretions as important factors in the destruction of poisons. "Some years ago," writes Charrin,[251] "the physiology of the

* *Author's conclusion.*
[247] Ritchie: Brit. Med. Jour., Sept. 10, 1904.
[248] H. C. Wood, Sr. and Jr.: "Therapeutics," thirteenth edition, p. 544, 1906.
[249] H. Gideon Wells: "Chemical Pathology," p. 138, 1907.
[250] Ainley Walker: Lancet, Oct. 19, 1901.
[251] Charrin: Semaine médical, vol. xv, p. 147, 1895.