adrenals was singularly obscure. The foresight of Brown-Séquard, the interesting researches of Langlois, Abelous, and those of Albanese, Zucco, etc., akin to our own, have brought these structures within the group of organs endowed with antitoxic functions. With Langlois, I ascertained that a given quantity of these organs weakened the action of certain alkaloids, especially nicotine." Other organs are referred to in the same sense. "As to the antitoxic functions," writes Charrin, "one may depend upon a series of viscera, first of all, the liver, the pituitary body, the adrenals, the pancreas, the kidneys, the spleen, etc."

The most recent writers speak in the same trend. While Ritchie, alluding to the side-chain theory in the address previously referred to, concludes that "we must keep an open mind for admitting that the cells pathogenically affected by a toxin may not be the cells of origin of antitoxin," Gruber and von Pirquet[252] urge that the formation of antibodies, contrary to Ehrlich's view, occurs in an entirely different place than the action of the toxins, and that they had the character of internal secretions. Sir A. E. Wright[253] also emphasized this kinship, though asserting that "their origin in the body was unknown," by the statement, "all the protective substances which were involved in the cure of disease were to be regarded as produced by internal secretions," urging that "if the laws by which such substances were produced were known," we could "call forth" their production.

This is not intended to imply that the side-chain theory has contributed nothing to our knowledge; Ehrlich's own labors in this connection and those of the many investigators who have taken up his views have done much to elucidate the relations between the various bodies which take part in the immunizing process. Moreover, Ehrlich has himself forever set aside the erroneous view that antitoxin is nothing but transformed toxin, and placed on a solid foundation the fact that the protective bodies were products of cellular activity. What I claim is that the cells in general are not, as Ehrlich believes, the source of antitoxin, and that the substances of which it is composed are the products of the organs referred to below.

Antitoxin is blood-plasma containing adrenoxidase, nucleoproteid and digestive triads (trypsin, etc.), and thyroiodase. It is produced in animals under the effects of injections of various toxins, as a result of the stimulating action of the latter upon the test-organ, and through it upon the adreno-thyroid center. The resulting excess of adrenoxidase excites, in turn, an overproduction of pancreatic ferments and leucocytes, by increasing metabolic activity in the pancreas and leucocytogenic tissues. The thyroiodase is due to direct excitation of the thyroid. Antitoxin is the homologue of auto-antitoxin formed in the blood under the influence of mercury, iodine, and other drugs.*

Although, as stated by Gideon Wells,[254] the chemical nature of antitoxins "is as entirely unknown as is the nature of the toxins," the few facts available point to the presence of all the constituents which compose what, in the preceding articles, I have referred to as "auto-antitoxin."

* *Author's conclusion.*

[252] Gruber and von Pirquet: Münch. med. Woch., Bd. l, S. 1259, 1903.
[253] A. E. Wright: Brit. Med. Jour., Mar. 19, 1904.
[254] Gideon Wells: *Loc. cit.*, p. 139.

That antitoxin is blood-plasma unusually rich in its normal immunizing constituents is suggested by various facts. A careful chemical study led Viquerat[255] to the conclusion that, barring the presence of lactates in antitoxin and other sera, the latter differed in no way qualitatively from normal serum. F. Warren White[256] studied the germicidal action of serum taken from healthy persons; from patients suffering from various diseases and from the body just before and after death. All showed marked bacteriolytic properties on the typhoid bacillus. This was completely destroyed, however, by heating the serum to 55° C. Thus, the blood-serum during health and disease is qualitatively similar to antitoxin. In fact, as stated by B. Meade Bolton,[257] horses used for the production of diphtheria antitoxin, often "possess antitoxin normally in their blood."

As to *adrenoxidase*, the principle increased is, of course, the adrenal secretion, to which Auld and others refer as "a colloid." Gideon Wells,[258] alluding to antitoxins, remarks: "In any event they behave as colloids"—a fact which suggests that in keeping with the evidence previously submitted, the plasma and red corpuscles are correspondingly richer in oxyhæmoglobin. Again, we have seen that adrenoxidase is a globulin. William H. Park, of the New York Health Department,[259] refers to the fact that "recent investigations have connected antitoxins and *globulins* so closely" that "we may consider it a probability that the antitoxins are globulins or globulin-like substances:" he was led experimentally to confirm this fact. I have pointed out, furthermore, that the adrenal principle is the general catalytic of the organism and the "ferment of ferments." Now, Ehrlich has shown that a given quantity of antitoxin will not only neutralize a fixed quantity, say 100 lethal doses of toxin, but that it will keep on neutralizing until very large quantities are rendered harmless. Bashford[260] also observed that "the poisonous action of the lethal dose of toxin may be abolished within the time limit by the addition of a very small quantity of antitoxin." This, of course, is due to the presence of a ferment—trypsin, perhaps; but this in itself proves the presence of the adrenal active principle, since it is to this principle that every trypsin owes its activity as such, while we have seen that, as stated by Moore,[261] "ferment actions" are "catalytic reactions."

Finally, it becomes a question whether toxins (by stimulating the test-organ and through it the adreno-thyroid center) can provoke an increase of this globulin, as they do of adrenoxidase. This is well shown in the following lines by W. H. Park:[262] "Horse numbered 137 when first obtained contained 3.2 per cent. globulin and 3 units of antitoxin in each c.c. It is of some interest to note that this is the largest amount of normal antitoxin ever noted by us in an *untreated* horse. Three months later, after repeated *injections of toxin*, the *globulin*, as tested by Mr. Atkinson, was 8.2 per cent., and the antitoxin 1200 units per c.c. Three weeks later toxin injections having been *omitted*, the globulin was 5.9 per cent. and the antitoxin 650 units per c.c. Still ten days later the globulin was 4.7 and the antitoxin 400 units." The importance of adrenoxidase in the process now asserts itself. "As investigations progressed," writes Park,[263] "it has become more and more evident that the antitoxic substances in the blood are closely combined

[255] Viquerat: Centralbl. f. Bakt., Parasit. u. Infekt., Bd. xxi, S. 581, 1902.
[256] F. Warren White: Boston Med. and Surg. Jour., Feb. 23, 1899.
[257] B. Meade Bolton: Jour. of Exper. Med., July, 1896.
[258] Gideon Wells: *Loc. cit.*, p. 140.
[259] W. H. Park: Archives of Pediatrics, Nov., 1900.
[260] Bashford: Lancet, Oct. 17, 1903.
[261] Moore: Schäfer's "T. B. of Physiol.," vol. i, p. 317, 1898.
[262] W. H. Park: *Loc. cit.*
[263] Park: Pediatrics, Aug. 15, 1900.

with the globulins of the blood, and that whatever precipitates them precipitates the antitoxin also. In fact, without globulin there appears to be no antitoxin, and wherever antitoxin exists, globulin does also."

Antitoxin contains *nucleo-proteid* besides nuclein. As to nuclein, Szontagh and Wellmann[264] found that it was present in antitoxin as well as in horse-serum, as nucleo-albumin. E. W. Walker[265] noted that "the bacteriolytic power of a fresh serum [antitoxin] rapidly diminishes both in the immune and normal sera, and ceases to be recognized within a few days from the time of bleeding." I have shown that this is due to the presence of the phosphorus-laden nuclein, *i.e.*, the body (Pflüger's "reducing substance") which promptly takes up the oxygen in shed blood. As to proteids, Wells[266] concludes, that "taken altogether, the evidence indicates a closer resemblance of antitoxins to proteids than has been shown for the toxins, and all attempts to separate antitoxins from proteids have so far failed." As shown below (Park and Throne) these bodies, nuclein and proteid, can be isolated from antitoxin as nucleo-proteid.

The various *hydrolytic triads*, including trypsin, secreted in the plasma by leucocytes, represent, from my standpoint, we have seen, Ehrlich's "complement" or "addiment," which Ehrlich and Morgenroth[267] define as "the unstable (labile) *ferment-like* body which effects the solution of the blood-cells," *i.e.*, hæmolysis. These investigators state that a serum described by Bordet and their own, derived from goats, "lost its hæmolytic power when heated for half an hour to 56° C." This they state has been shown by Buchner to be true of all normal hæmolytic sera. Whether the temperature be 56° or 55° is evidently immaterial, for Wassermann, alluding to Ehrlich and Morgenroth, says that they made hæmolytic serum "inactive by heating to 55° C., so that," he adds, "it contained only the substance sensibilisatrice." Having shown[268] that this latter substance is adrenoxidase plus thyroidase, it is evident that the trypsin alone was destroyed. Now, since as shown above, blood-serum and antitoxin are similar qualitatively, if antitoxin also contains the ferment, it should likewise be destroyed at this temperature. Wells[269] writes, "If we heat bactericidal serum made by immunizing an animal against bacteria, say the cholera vibrio, at 55° for fifteen minutes, it will be found to have destroyed the power of destroying these organisms." We have seen, moreover, under "adrenoxidase" that antitoxin, as noted by Ehrlich and Bashford, acts as a ferment. The formation of thyroiodase (opsonin) was described in the preceding chapter.

Although the various germicidal and antitoxic constituents of the blood are included in antitoxin, they are not all required to produce its beneficial effects. The latter are due to the large proportion of adrenoxidase that antitoxin contains.*

It was in the course of experiments to prevent the untoward effects sometimes produced by injections of antitoxin: eruptions, hæmolysis, etc., that William H. Park, of New York, observed the fact, mentioned above, that "without globulin there appears to be no antitoxin," and "that wherever antitoxin exists globulin does also." Inasmuch as adrenoxidase is the only globulin among the constituents of antitoxin,

* *Author's conclusion.*

[264] Szontagh and Wellmann: Deut. med. Woch., Bd. xxiv, S. 421, 1898.
[265] E. W. Walker: Lancet, Jan. 4, 1902.
[266] Wells: *Loc. cit.*, p. 141.
[267] Ehrlich and Morgenroth: "Collective Studies of Immunity," Bolduan's Transl, p. 11, 1906.
[268] *Cf.* preceding chapter.
[269] Wells: *Loc. cit.*, p. 144.

it follows that it is to adrenoxidase that we must ascribe the curative action of antitoxin. That such is the case is shown in another way. We have seen that the power of normal serum to destroy the red corpuscles of another animal (hæmolysis), *i.e.*, its digestive power, and also that of bactericidal serum derived from an immunized animal—and, therefore, antitoxin—were destroyed when these sera were heated from fifteen to thirty minutes at 55° C. An important feature of these experiments, however, is that they were conducted *in vitro*, and that as far as the antitoxin is concerned, heating to 55° C. does not destroy its germicidal and antitoxin effect when injected into the living body. This was shown in the course of experiments by Atkinson.[270] He found that when a solution of globulin (precipitated from antitoxic serum as well as ordinary serum by magnesium sulphate) was saturated with sodium chloride and then gradually heated to 72° C., precipitates were formed which, in the *various antitoxins, remained antitoxic.* Now, as 55° C. destroys the digestive triads (complement), and even thyroidase (opsonin), which is destroyed at from 60° to 65° C., there was nothing left in the precipitate as active agent but adrenoxidase, which, we have seen, resists all temperatures up to 100° C., and even that several hours.

Physiological Action.—The various antitoxins, when administered subcutaneously during health or disease, increase the bacteriolytic and antitoxic properties of the blood by augmenting, in proportion with the quantity administered, its content in auto-antitoxin, the homologue of all antitoxins.* As is the case when thyroid extract or adrenal extractives, adrenalin, epinephrin, etc., are used, metabolism is increased,* sufficiently so in some instances, to produce fever, leucocytosis, rheumatic pains due to accumulation of wastes, and even renal disorders.

There is ample evidence to the effect that antitoxin injections increase metabolism, while the febrile phenomena point directly to the presence of an excess of adrenoxidase in the blood. A few illustrations will emphasize these facts.

Coldefy,[271] for example, out of 400 cases in which antidiphtheritic serum was injected as a prophylactic measure, observed six in which there was pyrexia, which appeared and disappeared rapidly. In eight, the pyrexia lasted a short time, while in a tuberculous patient it was very marked, and lasted several days. Rolleston[272] states that muscular and joint pains occurred in 10.24 per cent. and pyrexia in 15.01 per cent. of 600 cases treated in the Metropolitan Asylums. He states, moreover—thus unconsciously contributing testimony to the curative value of the enhanced metabolism—that in the 600 cases treated in the Metropolitan Asylums upon which his conclusions are based, that as a general rule, the more marked the antitoxin reaction, the better the prognosis. Mongour[273] found that the excretion of nitrogen wastes was increased, and also that the chances of recovery were greater when the urea output was marked.

J. Ewing[274] observed that antitoxin caused an increase of multinuclear leucocytes within thirty minutes. In severe cases hyperleuco-

* *Author's conclusion.*

[270] Atkinson: Jour. of Exper. Med., vol. v, p. 67, 1900.
[271] Coldefy: Birmingham Med. Review, Feb., 1905.
[272] Rolleston: Practitioner, May, 1905.
[273] Mongour: Jour. de méd. de Bordeaux, vol. xxv, p. 217, 1895.
[274] J. Ewing: New York Med. Jour., Aug. 10, 17, 1895.

cytosis and fever occur. Kucharzewski[275] also found that moderate doses of diphtheria, tetanus, or antistreptococcus serum produced a leucocytosis lasting several days.

The albuminuria, following the use of antitoxin, is sometimes ascribed to the disease, but Adae,[276] having examined the urine in 25 cases before using antitoxin, found albuminuria in only one instance, while in all it appeared at once after the injection. This symptom was observed to follow injections of antitoxin in 42.5 per cent. of the cases by Bokai,[277] in 64 per cent. by Fürth,[278] and 72 per cent. by Soltmann,[279] and 64.8 per cent. by Schröder.[280] In animals Vissmann[281] ascertained that doses in the relative strength given to children caused nephritis.

Untoward Effects.—The morbid phenomena that follow large therapeutic doses of diphtheria antitoxin are as follows: fever, due to increased metabolic activity,* attended, if metabolism becomes excessive,* with diminution of the red corpuscles, sometimes to 3,000,000, and albuminuria. When metabolism is excessive, it causes, owing to involvement of the vascular walls, correspondingly marked vasoconstriction* and the arterioles of the pituitary body and heart, among others, being almost closed, the functions of these organs are inhibited,* giving rise to faintness, coldness with feeble and irregular cardiac action. In rare cases, death occurs. When constriction of the peripheral arterioles persists there occurs, after a few days, accumulation of waste products of various kinds* in the cutaneous tissues, and eruptions,* especially urticaria and erythema, may appear, along with increased nitrogen and phosphoric acid secretion and albumin. This may last several days and be attended with œdema, bloody diarrhœa, acute joint pains, myalgias and neuralgia due to intense congestion of the various structures involved.* The inordinate consumption of chromatic elements in the nervous elements attending this excessive metabolism,* may give rise to paresis or paralysis of muscles in different regions, especially those of the palate.

These morbid symptoms are familiar to all practitioners. They obviously correspond with those of the agents previously reviewed and indicate further the similarity of their action. The capillary engorgement also affects the internal organs. Thus Kossorotoff[282] found that

* *Author's conclusion.*

[275] Kucharzewski: Arch. intern. de pharmacod. et de thérap., T. xii, p. 117, 1903.

[276] Adae: Med. Correspondenzblatt des wurttemb. Aerzt. Landesv., Nu. 12, 1895.

[277] Bokai: Deut. med. Woch., Bd. xxi, S. 233, 1895.

[278] Fürth: Münch. med. Woch., Bd. xlii, S. 689, 1895.

[279] Soltmann: "Ueber die Erfolge mit Diphtherie Heilserum," 1895.

[280] Schröder: Münch. med. Woch., Bd. xlii, S. 327, 351, 1895.

[281] Vissmann: Med. Record, Sept. 14, 1895.

[282] Kossorotoff: Praktitcheskoï Medicini, Dec., 1895.

in rabbits, injections of antitoxin caused a marked hyperæmia of the liver, kidneys and spleen, and marked leucocytosis. As instance of excessive constriction of the arterioles I may mention a case reported by J. P. Marsh,[283] in which 1500 units caused in 10 minutes intense dyspnœa, cyanosis and a comatose state, during which the patient, a woman of 39 years, was practically blind and complained of general numbness. This was followed by severe itching and "stinging rash," due here to secondary overdilation of the arterioles and hyperæmia of the skin and its sensory nerve endings. The vasoconstrictor action may occur immediately. Thus E. R. Houghton[284] observed an instance in a pregnant woman, to whom another practitioner administered a protective injection. "At once she felt faint and very cold, but after a few moments rallied and went home." Her 8-months fœtus, which had shown vigorous movements until then, no longer gave evidence of life and was macerated when born two weeks later. Rolleston[285] states that the eruptions, the principal varieties of which are: the scarlatiniform, the urticarial and the circinate erythematous, depend directly upon the size of the dose.

When an antitoxin divested by heat or other physico-chemical procedures of its trypsin (complement) is employed, the digestive activity of the blood's auto-antitoxin is not reduced, since it is adrenoxidase (the specific immune body) which endows all ferments with their power as such.* The proferment fibrinogen is in reality alone destroyed in the antitoxin;* and, as it confers on the ferment merely its specific character (proteolysis), its absence does not affect the result, as considerable trypsin, and therefore trypsinogen, is available in the blood.* This proves, however, that *adrenoxidase is the active agent in all antitoxins.**

R. B. Gibson,[286] in reference to the antitoxin submitted to temperatures which destroyed their ferment or complement, states that "Park studied the possibility of eliminating serum rashes by treating a considerable number of cases with an antitoxic globulin prepared by Atkinson. Rashes were still produced." Recently Park and Throne[287] reported a series of cases in which antitoxin from "the *nucleo-proteids* and insoluble globulins present in the Atkinson preparation were eliminated." They obtained somewhat better results (due probably to the loss of 30 per cent. of units during the process), but found that "the antitoxic effect was identical with that of the whole serum." In fact, they "could not detect the slightest evidence that any desirable substance in the antitoxic serum is lost by the refining process." Thus, the elimination of nucleo-proteid does not affect the action of the globulin antitoxin any more than the destruction of the trypsin by heat. It is evident, therefore, that the active body in antitoxin is the only remaining one, adrenoxidase.

* *Author's conclusion.*

[283] J. P. Marsh: Amer. Jour. Med. Sci., Dec., 1903.

[284] E. R. Houghton: Med. Record, Apr. 4, 1903.

[285] Rolleston: *Loc. cit.*

[286] R. B. Gibson: Jour. of Biol. Chem., vol. i, p. 161, 1905-06.

[287] Park and Throne: Amer. Jour. Med. Sci., Nov., 1906.

Therapeutics.—All the disorders—*diphtheria, tetanus* and others—in which antitoxins are indicated being infections, it is perhaps needless to state that the physiological action I describe in the foregoing pages accounts clearly for the beneficial effects obtained.

Another feature upon which some stress must be laid is that the physiological action of the antitoxins, as I interpret it, is identical with that provoked by the various drugs described in the present chapter—each of which likewise introduces its own array of evidence. *If,* therefore, *we grant life-saving properties to antitoxin*—which is undoubtedly the case in so far as diphtheria antitoxin is concerned—*we must concede the same value to drugs which are capable of evoking in the blood the formation of the same substance, i.e., auto-antitoxin.*

CHAPTER XIX.

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

THE SYMPATHETIC CONSTRICTORS AND THE CRANIAL STRICTO-DILATORS IN ORGANIC FUNCTION.

We have seen in the sixteenth chapter that the sympathetic system is autonomous as a functional entity, and that its governing center is located in the posterior pituitary, with the centers of motor nerves.

According to prevailing teachings, the sympathetic carries on several different functions. In a succinct review of the subject, W. S. Hall[1] states, for example, that the "more important functions" of the sympathetic system are the following: "(*a*) cardio*acceleration* and cardio*augmentation* through the branches from the cervical ganglia. (*b*) *Secretory* impulses to the salivary glands, the stomach, the pancreas, the liver, the small intestine, the large intestine, the kidneys. (*c*) *Vasomotor* impulses, *both constrictor and dilator,* to all arteries and arterioles. (*d*) *Motor* impulses to the *muscular coats* of the stomach and intestines, causing peristalsis and controlling the pylorus and the cardia of the stomach. (*e*) *Motor* impulses to the *muscularis mucosa* of the alimentary canal, causing movements of the mucosa."

Another function ascribed by physiologists to the sympathetic, is that of *inhibition.* In the heart, as is well known, this is believed to be the physiological function which counteracts cardiac acceleration; in the intestine it is thought by some to oppose peristalsis; it is also believed by many to inhibit the contraction of certain vessels, etc. As this inhibition is produced by stimulating the sympathetic nerves distributed to these various organs, we are brought to the conclusion, in view of the fact that a sympathetic nerve can awaken function by causing vasodilation, that it can also inhibit that

[1] Hall: *Loc. cit.,* p. 106, 1905.