Thus, four agents—as instances of others—fully capable of increasing the auto-antitoxic properties of the blood, and, therefore, its auto-antitoxin, show distinct properties in other directions. These points of divergence are all, as I will show, of great importance in practice.

Another important point emphasized by the analysis of the action of the four remedies studied in this chapter is that *it is the small doses which are the beneficial ones,* because they raise the germicidal and antitoxic properties of the blood to a safe limit; while large doses provoke excessive overactivity of the immunizing substances, and its results, destruction of the blood-cells and, in the case of mercury, of the tissues themselves.

To establish the views I advance on a sound basis, a study of the various *antitoxins* is submitted at the close of the chapter. It shows plainly, I believe, that Ehrlich's theory, as far as the side-chain feature itself is concerned, is defective, and that the ductless glands alone afford a sound foundation for the study of all problems concerned with immunity, a fact which I urged in 1903 in the first volume. Ehrlich to this day (1911) has failed to indicate the nature or source of the blood constituents which carry on the immunizing process—a suggestive fact.

As the subjects to be submitted hereafter bear upon questions related to the above: the physiological action of drugs, the pathogenesis of disease, their treatment, etc., all of which are of special interest to the practitioner, they will be presented in a way calculated to facilitate their study: the general principles introduced will be presented in the usual type and the evidence in small type. This plan, however, has entailed the necessity of introducing in the general text (that in large type) a large number of personal conclusions *based upon the evidence herein submitted,* which are necessarily new, since they refer to functions of the organs I have introduced into the problem, or effects produced by them. In each case, therefore, to obviate the introduction of many personal pronouns and, furthermore, indicate that the conclusions reached do not form part of accepted doctrines, they will be distinguished by an asterisk (*) referring to the words *"author's conclusion"* at the foot of the page.

THYROID PREPARATIONS.

Physiological Action.—A dose of thyroid gland may either be stored by the organ itself, or its thyroiodase may be added to the blood at the time, precisely as if the thyroid and the parathyroids had secreted it.* As a result, the functions that thyroiodase subserves, viz., (1) to increase the sensitiveness of all living cells, including those composing the test-organ; and (2) to sustain by direct stimulation the functional activity of the latter as adrenal center, are correspondingly activated.* The immediate effect is an increase of adrenoxidase in the blood, and, therefore, of general metabolism, and increased sensibility of all cellular elements.* The tissue-cells (as well as pathogenic cells, bacteria, parasites, etc.) being thus rendered more vulnerable to the metabolic process, this process is carried on at a rate exceeding greatly that incited by an agent capable only of stimulating the test-organ.* The phase of metabolism most activated, however, is that of catabolism, since the function of thyroiodase is to facilitate the breaking down of cellular elements by rendering them vulnerable to the digestive action of the auto-antitoxin.* Thyroid gland is mainly, therefore, a stimulant of the catabolic process.

The manner in which the thyro-parathyroid secretion (which thyroid gland represents) sensitizes cellular elements and the test-organ, and the mode of action of this secretion on this organ as a direct stimulant, were studied in the preceding chapter, to which the reader is referred. The actual presence of this colloid secretion—thyroiodase—in the lymph and blood has been urged by Hämig,[45] Ehrich,[46] and others. Cerletti and Perusini[47] found it in the arteries and veins. That the addition of a glandular extract containing the active principle or ferment of the colloid should augment the activity of that already in the blood is obvious.

Considerable evidence as to the influence of the thyroid apparatus on metabolism has already been adduced in the preceding chapters. A few additional facts will therefore suffice. In a general review of the subject, Chittenden[48] states that experiments on dogs show that fresh thyroid and iodothyrin have practically the same action in stimulating metabolism of proteid matter and decomposition of fat. This is obviously the result of increased oxygenation, since, as observed by Robert Hutchison[49] and many others, it promotes "the rapidity of combustion."

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* *Author's conclusion.*

[45] Hämig: Archiv f. klin. Chir., Bd. lx, S. 1, 1897.

[46] Ehrich: Bruns's "Beiträge f. klin. Chir.," Bd. xxviii, S. 97, 1900.

[47] Cerletti and Perusini: Jour. of Mental Path., vol. vii, p. 209, 1906.

[48] Chittenden: Trans. Congress Amer. Phys. and Surgs., p. 96, 1897.

[49] Robert Hutchison: Brit. Med. Jour., July 16, 1898.

All the phenomena that this entails are present, moreover. Thus Georgiewsky[50] found that thyroid extract, whether injected or given with the food, caused, in dogs and rabbits, after some time, a rise of temperature, excessive appetite, increase in nitrogen excretion and sometimes glycosuria.

This evidence is controlled by the fact that thyroid gland increases the output of carbon dioxide. Whitney[51] found that there was a marked increase in the amount of CO_2 eliminated by the body, showing increased oxidation of the carbonaceous materials. Conversely, while Albertoni and Tizzoni demonstrated that after thyroidectomy the proportion of CO_2 in the blood was markedly decreased, Magnus-Levy[52] noted that the gaseous exchanges, the temperature and metabolism were all reduced by removal of the thyroid. The increase of excretory products induced by thyroid extract applies as well to catabolic wastes, since large doses produce marked irritation of the organs concerned with their elimination. Thus Ghedini[53] found in 14 animals the liver, kidneys, spleen, and the axillary and inguinal lymph-nodes greatly swollen, infiltrated and inflamed, and concluded that they acted chiefly on organs which eliminated noxious substances. So marked is the increase of catabolism that as shown by Magnus-Levy[54] overalimentation does not prevent emaciation which large doses of thyroid produce.

On the other hand, impairment of the functions of the thyroid apparatus by reducing the efficiency of catabolism, causes imperfectly broken-down—and therefore toxic—wastes to accumulate in the blood. Lange[55] found that removal of portions of the thyroid affected pregnant animals more severely than normal ones. A remnant sufficient for health in the latter did not protect the pregnant animals from spasms or from renal disorders. In pregnant women Lange observed also that, when the customary enlargement and overactivity of the thyroid did not occur, the likelihood that nephritis would appear was greatly increased. Interpreted from my standpoint, this is because the overactive thyroid insures the destruction of the excess of toxic wastes which the fœtus contributes to the blood; if the organ fails to increase its activity, toxic, *i.e.*, imperfectly catabolized, wastes are secreted in abundance by the kidneys, exposing them to nephritis, or if these wastes are retained, puerperal eclampsia occurs. Hypo-thyroidia under these conditions becomes the main cause of puerperal nephritis and eclampsia. Additional evidence to this effect will be submitted in the section on that disease. This indicates the great rôle the thyroid apparatus fulfills in causing destruction of toxic wastes.

That when used in small therapeutic doses, thyroid gland promotes metabolism, but only sufficiently so to enhance nutrition, growth, and the life process itself, is shown by the results obtained with thyroid extract in myxœdema and cretinism. This is fully confirmed experimentally. Thyroidectomy, as is well known, arrests growth and development in animals. Moussu[56] observed that in such animals, thyroid extract soon caused the animals to resume their normal growth and development until a condition was reached when the comparison with the controls was striking. On the other hand, we have in the use of thyroid gland in obesity, evidence to the effect that it can powerfully stimulate catabolism.

[50] Georgiewsky: Bull. méd., Dec. 1, 1897.
[51] Whitney: Cited by Mosely: Med. News, Sept. 17, 1898.
[52] Magnus-Levy: Zeit. f. klin. Med., Bd. xxxiii, S. 269, 1897.
[53] Ghedini: Centralbl. f. Bakt., Bd. xxxiv, S. 721, 1903.
[54] Magnus-Levy: *Loc. cit.*
[55] Lange: Zeit. f. Geb. u. Gyn., Bd. xl, S. 34, 1899.
[56] Moussu: C. r. de la Soc. de biol., vol. vi, p. 241, 1899.

As thyroid gland promotes catabolism by increasing, through the test-organ and the adrenals, the proportion of adrenoxidase, nucleo-proteid, and trypsin in the blood, it augments its supply of auto-antitoxin.* Being capable also (as opsonin) of sensitizing directly pathogenic germs, thus insuring their destruction by phagocytes and the plasmatic antitoxin, thyroid gland fulfills the two conditions which the body requires to defend itself effectively when infection has occurred.* The blood's antitoxic constituents being, moreover, the bodies which convert the physiological wastes, broken-down cells and all other detritus into benign, eliminable products,* they also prevent the formation of intermediate products, *i.e.*, toxic wastes*—the pathogenic agents in gout and disorders related thereto, including convulsive diseases, eclampsia, tetanus, etc.

Howell,[57] alluding (1905) to the prevailing views as to the functions of the thyroid apparatus and their secretion, writes: "Excision or atrophy of these bodies results in a loss of this secretion and a consequent malnutrition or perverted metabolism in other tissues of the organism. According to the other point of view, less generally held, the function of these bodies is to neutralize or destroy toxic substances formed in the metabolism of the rest of the body." Interpreted from my standpoint, *both* these views are sound, since the identical process which sustains nutrition and metabolism, is that which insures neutralization of toxic substances. We have seen that the rôle of the thyroid in metabolism is supported by a multitude of facts; this applies as well to its function in the destruction of poisons, the latter function being—as I view it—but an exacerbation of the former.

Recent clinical observations have extended the defensive functions of the thyroid to general infections. Thus, Roger and Garnier[58] examined the thyroid glands of 33 cases after death from various infections, scarlet fever, measles, diphtheria, smallpox, typhoid fever, cerebro-spinal meningitis and septic meningitis. Congestion and hypertrophy were found in all. The clinical histories did not include pain in the thyroid. They suggested that these local disorders might be due to overactivity of the gland having for its purpose the destruction of the specific poisons. Odoacre Torri[59] also found that during infectious diseases the gland was overactive and that it secreted an inordinate amount of colloid secretion. He noted, moreover, a marked epithelial proliferation, which, from my standpoint, means an abundance of iodine-laden leucocytes. In common with other investigators, however, he erroneously regards the colloid itself as the bactericidal product and the excessive secretion as a defensive process.

Vincent[60] observed enlargement of the thyroid in rheumatism and regards it as "an expression of increased function to antagonize

* *Author's conclusion.*
[57] Howell: "T. B. of Physiol.," p. 774, 1905.
[58] Roger and Garnier: Presse méd., vol. vi, p. 181, 1899.
[59] Odoacre Torri: Policlinico, vol. vii, pp. 145, 226, 280, 1900.
[60] Vincent: Bull. et mém. de la Soc. méd. des hôpitaux de Paris, 3 série, 23 annee, p. 598, 1906.

infection." He found the organ sensitive and enlarged in 11 out of 17 cases of typhoid fever, in which these signs appear early. The results obtained by Leopold-Lévi and de Rothschild[61] in 100 cases to which they administered thyroid extract also led them to conclude that the thyroid "acted as a regulator of nutritional ferments as well as of the defensive ferments" of pancreatic origin, in accord with the view I had advanced over two years earlier. They point, moreover, to the fact that thyroid insufficiency predisposes to infection and auto-infection. Morin[62] also emphasized recently the defensive rôle of the thyroid as shown by the liability to tuberculosis and other infections of individuals suffering from congenital myxœdema. In 348 ordinary cases of tuberculosis, 192 showed marked atrophy of the thyroid. He regards this phenomenon as the main cause of the prominence of the thyroid cartilage in these cases. Such cases fared badly, as a rule, while those in which the gland was normal or enlarged yielded promptly to remedies. Bonnet[63] has already observed that in cases of athrepsia, the addition of small doses of thyroid extract to the usual remedies and diet measures, promptly turned the tide in favor of the patient, while Reid Hunt,[64] found that thyroid feeding rendered "white mice much less susceptible to the toxic action of acetonitril."

The marked increase of colloid which Roger and Garnier and Torri observed under the influence of infectious diseases corresponds with that of Wright's opsonin formed under the influence of inoculations with tuberculin and kindred bodies. Opsonin and thyroidase, as I have pointed out, being one and the same substance, thyroidase, when we administer thyroid gland, we contribute opsonin directly to the blood. As thyroid gland also promotes active metabolism by stimulating the test-organ, we have precisely the effects produced by inoculations, since it is through a similar process that they cause the appearance in the blood of what Wright has termed "bacteriotropic" substances. Hence the fact that, as I have myself observed, thyroid extract is an effective agent in the treatment of tuberculosis and other infections.

Untoward Effects.—Small doses administered at too short intervals, or large therapeutic doses cause the blood-pressure to fall, although the proportion of auto-antitoxin in the blood may not be sufficient to cause hæmolysis, and thus normally to awaken the protective intervention of the depressor nerve.* This is due to the fact that the thyroiodase which the thyroid preparation introduces into the blood, by accumulating therein, gradually raises directly the excitability of this nerve.* Though stimulated artificially, the nerve fulfills its normal rôle, and by causing vasoconstriction of the arteries of the pituitary and thyroid, inhibits their functions.* Less thyroiodase and adrenoxidase (which jointly aid in sustaining the vascular tone) being secreted, the arteries relax passively.*

* *Author's conclusion.*
[61] L. Lévi and de Rothschild: C.-r. de la Soc. de Biol., vol. lx, p. 971, 1906.
[62] Morin: La Presse méd., vol. xiv, p. 623, 1906.
[63] L. Bonnet: Semaine méd., vol. xxiii, p. 212, 1903.
[64] Reid Hunt: Jour. of Biolog. Chemistry, vol. i, p. 33, 1905-06.

Oliver and Schäfer, Haskovec, Gley, Langlois, and several other investigators have all found that experimental—and therefore large—doses of thyroid extract caused vasodilation and lowered the blood-pressure. Human thyroid extract produces a similar effect as observed by Guinard and Martin,[65] who used the thyroid taken from an executed criminal, immediately after death. The influence on the vessels is very prompt: Béla von Fenyvessy[66] found that it lowered the blood-pressure in rabbits, beginning a few seconds after the injection. Patta[67] found that thyroidin lowered the blood-pressure in a manner directly opposed to suprarenin.

If the use of large doses is persisted in, the excessive vasodilation produced by the remedy becomes such that, in accord with Marey's law,* the rapidity of the heart-beats, *i.e.*, the pulse, is greatly increased. The blood being caused to accumulate in the great central trunks, the splanchnic area, the quantity circulating through the lungs is reduced* and, the absorption of oxygen being inadequate,* dyspnœa ensues, and sometimes cyanosis. General oxygenation, owing to this cause and to the diminution of adrenoxidase,* being lowered, the heart's action becomes irregular. The skeletal muscles being affected in the same way,* general weakness, trembling and muscular pains (owing to the accumulation of toxic wastes) may be complained of. Vertigo, mental depression may likewise occur.

When the cutaneous arterioles are also dilated, they admit an unusual volume of blood into the capillaries;* causing superficial congestion, hyperthermia, pruritus and tingling. A similar condition of the gastric capillaries causes nausea and vomiting; of the intestines, diarrhœa; of the brain, insomnia; of the meninges, headache. These symptoms are usually transitory if the use of the remedy is discontinued, but if it is persisted in, it may produce syncope. The morbid symptoms sometimes persist after withdrawal of the drug. Exertion, when large doses of thyroid gland are being used, is dangerous, owing to the deficient nutrition and weakness of the cardiac muscle.

Various other symptoms have been recorded: transitory aphasia with monoplegia and unilateral anæsthesia (Béclère); epileptoid convulsions (Henry); a condition resembling uræmia (Schmidt), etc. Two fatal results were reported by Murray; two by Vermehrer; one by Foulis; one by Stabel—but all in cases of myxœdema in which the

* *Author's conclusion.*
[65] Guinard and Martin: C. r. de la Soc. de biol., 10 série, vol. vi, p. 161, 1899.
[66] Béla von Fenyvessy: Wien. klin. Woch., Bd. xiii, S. 125, 1900.
[67] Patta: Inaug.-Dissert., Pavia, 1904.

doses were large. Many others have been reported. Popoff,[68] who refers to these cases, states, however, that thyroid preparations produce "deplorable effects capable of causing death not only in myxœdematous subjects, but also in cases of obesity, psoriasis and even in healthy subjects." Georgiewsky,[69] even in animals killed by the drug, found, in accord with Murray's observation, that the thyroid gland was "pale, yellowish and diminished in size," although there was pronounced atrophy of the adipose tissue and of the muscles and intense congestion of other organs, the kidneys, bulb, brain, etc. This points to the sequence of events: (1) violent hypercatabolism of the body constituents which are always the first to yield, the fats; (2) reaction of the depressor; (3) death through the presence of enough thyroidase in the blood to excite violently the depressor and cause it to paralyze the pituitary body and thyroid gland by unduly constricting their vessels.

Therapeutics.—As this feature of the subject has been treated at length in the first volume (pages 708 to 737 inclusive) only a brief reference will be introduced here.

The use of thyroid is deemed dangerous by some. In truth, there are but few remedies whose effects can be controlled with more accuracy, if the symptoms it provokes are watched, and if fresh preparations of thyroid are used. Small doses, ½ to 1½ grains (0.03 to 0.1 gram) of the desiccated gland, seldom prove excessive. The pulse may be raised slightly, and there may be a rise of temperature of ½ to 1° F. (0.3 to 0.6° C.), but this is not due to abnormal action; it is the result of enhanced metabolism—an expression of the remedy's beneficial or "tonic" action. Conversely, when larger doses are given, such as those employed in the treatment of obesity (beginning with 2 grains [0.13 gram] three times daily and gradually increased), the hypercatabolism to which the reduction of flesh is due keeps the patient on the verge of depressor action, and, more or less suddenly, the pulse becomes faster. Instead of being firm or somewhat harder than usual, as is the case when the "tonic" phase of thyroid action prevails, the pulse is softer and yields readily to pressure. The patient may complain of vertigo, weakness and palpitations, etc., altogether a symptom-complex indicating functional torpor—though the face may be flushed by dilatation of the arterioles. The two conditions are radically different, therefore, and the danger signals of depressor action are clearly defined.* It is always best to discontinue the drug when the latter occur, and resume only with smaller doses.

* *Author's conclusion.*
[68] Popoff: Arch. gen. de méd., Oct., 1899.
[69] Georgiewsky: *Loc. cit.*

Murray[70] also states that "the earliest and most common symptom is the increased frequency of the pulse. Other symptoms are violent palpitation, fine tremor of the hands, flushing and moisture of the skin, and, in case of large doses, emaciation." Easterbrook,[71] after using thyroid gland in about 100 cases in sufficient doses to produce thyroidism, concluded that "indubitably" it was "a profound catabolic stimulant."

The principles formulated in the foregoing pages account for the beneficial effects thyroid preparations have afforded in various disorders:—

Their mode of action in *myxœdema* and *cretinism* is self-evident, since by enhancing the irritability of all cells and stimulating the adrenal functions, thyroid preparations supply the organism with precisely the two sources of energy that incite and sustain the vital process. In the various diseases due to lowered catabolism or the accumulation of toxic wastes in the blood, such as *tetany, puerperal eclampsia, epilepsy,* the disorders of *menopause, asthma* and *rheumatoid arthritis,* their beneficial effects are but the counterpart of their action after thyroidectomy: by promoting catabolism, they insure the conversion of the pathogenic elements into readily eliminable end-products. Exaggeration of this process accounts for the emaciation caused in *obesity* and its benefit in Dercum's disease, *adiposis dolorosa.* The nutrition of osseous tissues and the processes of repair being enhanced, the improvement observed in *osteomalacia, rickets, osteomyelitis* and delayed union in *fractures* is also easily accounted for. Their action on the adrenal center leading to the accumulation of adrenoxidase in the blood, explains their efficacy in *hæmorrhages* of various kinds and hæmophilia, since adrenoxidase is the fibrin ferment,* the underlying factor in the formation of the blood clot.

In infections, including *asthenic pneumonia,** the *exanthemata* of childhood, *tuberculosis* and *typhoid fever,* the value of thyroid preparations—in small doses—is readily explained. They attack directly the pathogenic organism by rendering it vulnerable to the attacks of phagocytes and the blood's auto-antitoxin—and insure the work of destruction by stimulating the test-organ, the governing center of the body's defensive mechanism.* (See also Thyroid Organotherapy, vol. i, p. 708.)

* *Author's conclusion.*
[70] Murray: Lancet, March 18, 1899.
[71] Easterbrook: Lancet, Aug. 6, 1898.

MERCURY.

Physiological Action.—Whether administered by the mouth, injected subcutaneously, or rubbed into the skin (dissolved therein by the constituents of the sebaceous secretion), mercury and its salts are taken up by leucocytes and carried to all tissues.

Although toxic effects occur after the ingestion or inhalation of metallic mercury, this metal cannot, as shown by Hermann,[72] penetrate normal epithelium in any part of the body. The metal is found condensed upon the epithelium. This was confirmed by Hoffmann, Rohrig, Bärensprung, Neumann and Fleischer, and others.[73] The reason for this becomes plain in view of the fact that it is taken up by leucocytes. Conti and Zuccola[74] found that mercury, whether administered by the mouth or hypodermically, was always carried to the tissues by these cells. We have seen in the preceding chapter that Stassano, Besredka and Montel had also observed that they ingested mercurial salts, including calomel, introduced into the blood by injections or inunctions. Montel[75] ascertained, moreover, that this rôle was carried on by the neutrophiles and the large mononuclears. This was confirmed by Collet,[76] who found also that lymphocytes and the red corpuscles took no part in the process. Stassano[77] isolated the red corpuscles from the leucocytes and found mercury in the leucocytes only. Carles[78] reached a similar conclusion. Almkwist[79] holds that in the intestine mercury forms a sulphide with sulphuretted hydrogen, and observed leucocytes containing fine yellow granules of the sulphide between the epithelial cells of the intestine. He also found this sulphide in the blood, lymph and tissue fluids. As other observers, including Rindfleisch and Fürbringer[80] and Chittenden[81] have found mercury in solution in the body juices in the form of albuminates, the metal, in the light of the foregoing facts, must be derived from the tissues into which they have been secreted by their normal carriers, the leucocytes. Barthe and Mongour[82] conclude that the mercury must first destroy these cells to be liberated, but the evidence I have submitted sufficiently demonstrates that such destruction is unnecessary.

That mercury does not act directly upon the tissues is shown by the fact that it may accumulate in the organism, and remain practically inert therein. Referring to the labors of Vajda and Paschkis,[83] Schuster,[84] Balzer and Klumpke,[85] and others, Wood[86] states that "the evidence in favor of the storing up of mercury in the system is overwhelming."

[72] Hermann: "Lehrbuch d. exper. Toxikologie," Berlin, 1874.
[73] Hoffmann, Rohrig, Bärensprung, Neumann and Fleischer: Cited by A. A. Chittenden: Bull. Johns Hopkins Hosp., May, 1899.
[74] Conti and Zuccola: Riforma médica, Mar. 17, 1906.
[75] Montel: Gaz. hebd. de méd. et de chir., Apr. 21, 1901.
[76] Collet: Lyon médical, June 14, 1903.
[77] Stassano: C. r. de l'Acad. des sci., 1898.
[78] Carles: *Loc. cit.*, p. 32.
[79] Almkwist: Nord. med. Ark., Afd. 2, No. 6, 1903.
[80] Fürbringer: Virchow's Archiv, Bd. lxxxii, S. 491, 1880.
[81] Chittenden: Bull. Johns Hopkins Hosp., May, 1899.
[82] Barthe and Mongour: Jour. de méd. de Bordeaux; Med. Age, Dec. 26, 1906.
[83] Vajda and Paschkis: "Ueber d. Einfl. d. Quecksilber," Wien, 1880.
[84] Schuster: Zeitsch. f. klin. Med., Bd. vii, S. 80, 1884.
[85] Balzer and Klumpke: Rev. de méd., vol. viii, p. 303, 1888.
[86] Wood: *Loc. cit.*, thirteenth edition, p. 484, 1906.

The various salts of mercury owe their therapeutic value to the energy with which they stimulate the test-organ.* In minute doses they promote nutrition, *i.e.*, act as a tonic, because, by stimulating the test-organ, they increase the secretory activity of the adrenals, and enhance, therefore, general oxygenation and metabolism.* The function of the pancreas, the thyro-parathyroid apparatus and the leucocytogenic organs being correspondingly activated, the quantity of auto-antitoxin in the blood is augmented.*

Its powerful stimulating action on the adrenal center is shown in various ways. Like all lesions of the anterior pituitary attended with local hyperæmia, mercury provokes glycosuria.

Saikowsky[87] found that "mercury diabetes lasts longer than the other artifically-produced diabetes, persisting sometimes eighteen days" after the causative doses. It was also noted by Reynoso, Rosenbach, Bouchard and Cartier.[88] It is commonly observed in rabbits, when too large doses (which paralyze the adrenals) are avoided. As emphasized by Cartier, it is not by causing grave hepatic lesions that mercury evokes diabetes; as I have shown,[89] a marked excess of adrenoxidase in the blood is the cardinal factor in its production, since this greatly enhances the functional activity of the pancreas, and, therefore, the production of amylopsin, the ferment which converts glycogen into sugar. That the adrenals are hyperactive was ascertained by Moulinier,[90] who found the adrenals intensely congested in slow mercurial poisoning, and invariably hypertrophied. He observed, moreover, that in subjects who suffered from slow mercurial intoxication, even minute doses of adrenalin hastened death; and moreover, as a corollary to this fact, that individuals to whom mercury and adrenalin were given simultaneously died sooner than when adrenalin was given alone. He concluded, therefore, that the action of mercury is added to that of adrenalin. The reason for this is obvious: the mercury doing harm by overexciting the adrenals, adrenalin added fuel to the fire, the excess of adrenoxidase—the albuminous hæmoglobin—being of course the harmful agent. Under these conditions mercury should prove useful in conditions attended with deficient hæmoglobin. Semmola[91] noted that in syphilitics, the hæmoglobin rose markedly under mercury, within seven or eight days. As shown by Cervello[92] the same effect is produced in animals.

The stimulating action of mercury on the pancreas is illustrated further on. That on lymphatic organs is sufficiently marked to have led Jullien[93] to ascribe to it the striking effects of this drug in syphilis. That leucocytogenesis is actively stimulated was conclusively shown by the experiments of Koslowsky.[94] Not only was the proportion of older cells reduced, but that of young cells was increased. Kupferwasser[95] found that the number of young leucocytes in the blood was considerably increased in normal subjects, and in syphilitics when the treatment was

* *Author's conclusion.*
[87] Saikowsky: Virchow's Archiv, Bd. xxxvii, S. 346, 1866.
[88] Cartier: Thèse de Paris, 1891.
[89] *Cf.* this vol., p. 1021.
[90] Moulinier: Archives de méd. navale, vol. lxxxiv, p. 265, 1905
[91] Semmola: Presse méd., Sept. 15, 1889.
[92] Cervello: Jour. des practiciens, Jan. 12, 1901.
[93] Jullien: "Maladies Vénériennes," 1886.
[94] Koslowsky: Thèse de St. Petersburg.
[95] Kupferwasser: Arch. des sci. biol. de St. Pétersburg, vol. vi, 1898.

not too prolonged. A contrary effect is produced, however, when the drug is taken in toxic doses, *i.e.*, in sufficient quantities to depress the test-organ.

The experimental investigations upon the influence of mercury on metabolism that have been recorded are worthless in that the ruling element of the problem, the relative influence of dosage, was not taken into account, the animals thus receiving toxic doses which paralyzed the adrenal center in practically every instance. The clinical evidence on the subject is alone instructive, therefore. Levi,[96] in a study of 252 patients suffering from syphilis, "found that the mercurials increase organic combustion and hasten metabolism in this condition," a proof that the blood's asset in auto-antitoxin is increased. That nutrition is enhanced is shown, moreover, by the increase of weight observed by Liégeois,[97] Armaingaud and Martin-Damourette,[98] while Keyes,[99] Wilbouchewitch, Gaillard, Hayem, Robin, and others noted besides this, a marked increase of red corpuscles. Similar results were obtained by Schlesinger[100] in dogs and rabbits.

This accounts for the fact that various preparations of mercury, calomel particularly, have always occupied a high place among the agents known to abort disease. Daly, of Pittsburgh, found calomel of great value in diphtheria, recommending its use until the stools became green. Illingworth[101] found the biniodide or calomel extremely effective for the jugulation of various infectious diseases such as scarlet fever, diphtheria, measles, chickenpox, pertussis, typhoid fever, pyæmia, puerperal fever, etc., and his observations in some of these diseases have been confirmed by Dukes, Neale, Lloyd Brown, and others.

The immunizing process is most active in the liver, an action which becomes manifest when sufficiently large doses of mercury to produce purgation are given. Mercurial purgatives do not, as generally believed, produce their effects by increasing the secretion of bile—which is a mere epiphenomenon when it occurs—but by increasing the germ- and poison-destroying properties of the hepatic blood.* The green stools produced are rich in biliverdin, *i.e.*, adrenoxidase.*

It is believed by many that mercury produces its beneficial effects by increasing the biliary secretion, but the investigations of Pfaff and Balch, and Joslin,[102] have shown that the bichloride and calomel not only do not increase the flow of bile in patients with biliary fistula, but that they tend rather to decrease it. This indicates that the benefit derived from mercury is due to the greater antitoxic activity of the hepatic blood and not to an increase of fluid. Again, when calomel is administered to healthy individuals in suitable doses, green liquid stools, as is well known, are produced. The belief that this was due to an increase of bile was eventually replaced by the view that the color was the result, as suggested by Traube and Stillé, of the presence of a mercurial compound. But the analyses of Simon,[103] Golding Bird,[104]

* *Author's conclusion.*

[96] Levi: Cited by Jour. Amer. Med. Assoc., May 12, 1906.
[97] Liégeois: Gaz. des hôpitaux, vol. xlii, pp. 347, 350, 363, 371, 395, 1869.
[98] Armaingaud and Martin-Damourette: Manquat: *Loc. cit.*
[99] Keyes: Amer. Jour. Med. Sci., Jan., 1876.
[100] Schlesinger: Arch. f. exp. Path., Bd. xiii, S. 317, 1881.
[101] Illingworth: "Abortive Treatment of Febrile Disorders," 1888.
[102] Joslin: Cited by Hare, "Practical Therapeutics," p. 323, 1904.
[103] Simon: Animal Chemistry, Sydenham Soc. Trans., ii, p. 386.
[104] Golding Bird: London Med. Gaz., vol. i, p. 801, 1845.

and Michéa[105] failed to show that the metal was present in any form. The investigations of Simon and Michéa revealed an important fact, however, viz.: the presence in the stools of bile *pigments*, and particularly *biliverdin*, in large quantity. As I have shown in various parts of this work,[106] however, bilirubin is oxidizing substance, *i.e.*, adrenoxidase; the large quantity of bilirubin in the stools is evidently due, therefore, to excessive activity of the adrenals.

The antitoxic process carried on in the liver under the influence of a mercurial purgative is supplemented by a similar process in the intestine.* The excess of adrenoxidase in the blood raises the secretory activity not only of the pancreas, but also of all the intestinal glands.* A large volume of intestinal juice rich in pancreatic juice, nucleo-proteid and adrenoxidase, *i.e.*, in auto-antitoxin similar to that in the blood, is thus produced, which flushes the intestinal canal and sterilizes it.*

The manner in which the various components of the intestinal juice are produced and their physiological function have been reviewed in the fourteenth chapter, to which the reader is referred. The stimulating influence of mercury on the pancreas is generally recognized. Potter,[107] for instance, states that in full doses, continued, the preparations of mercury "overstimulate the glands, especially the pancreas." In a case reported by Copland,[108] in which death occurred during excessive salivation, the pancreas weighed, *post-mortem*, four ounces, was red and congested, while its ducts were dilated. Arnozan and Vaillard[109] observed marked evidences of overactivity in the pancreas of rabbits treated about one month with corrosive sublimate.

The powerful stimulating action of mercury on the test-organ, *i.e.*, on the adrenal center,* renders it a powerful cardiac stimulant. The adrenal secretion not only sustains the functional activity of the right heart, but the improved oxygenation of the entire body increases the nutrition of the organ.* Again, by stimulating catabolism, it also relieves the blood of any excess of wastes,* and thus antagonizes undue arterial tension and vascular resistance.

Murray[110] regards blue pill, 5 grains (0.3 gm.) every night, as "the basis of treatment in all cases of weak, dilated, irritable and irregular heart where there is resistance in the arterial system." Sir William Broadbent, Allbutt, Dickinson, Morison[111] and others have all recommended small doses of mercury to reduce "impedimental conditions of vascular tension." William Pepper has also emphasized the value of mercury in heart failure.

* *Author's conclusion.*

[105] Michéa: L'Union méd., vol. ii, p. 495, 1848.
[106] *Cf.* vol. i, pp. 115, 119, 128, in the first two editions.
[107] Potter: "Materia Medica, Pharm. and Therap.," eighth edition, 1901.
[108] Copland: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 487, 1906.
[109] Arnozan and Vaillard: Jour. de méd. de Bordeaux, 1883.
[110] Murray: Phila. Med. Jour., June 23, 1900.
[111] Morison: Lancet, Oct. 28, 1899.

Mercury is an energetic diuretic. This is due (1) to the fact that it increases considerably the intrinsic metabolism of the kidneys, and, therefore, their functional activity—as it does that of all other organs—and (2) to the passage through the kidneys of an unusual proportion of excretory products, including a portion of the drug itself. Its prolonged use exposes the kidneys to grave disorders.

Rosenheim[112] found, in experiments upon dogs, that when mercury acted as a diuretic, it did so by stimulating the renal epithelium, and by flushing the renal vessels. Bieganski[113] and Stintzing[114] and others also attributed the local lesions directly to the metal. Fürbringer,[115] in a study of the statistics of the subject, found that 8 out of 100 syphilitic subjects suffered from nephritis when under mercurial treatment, but that withdrawal of the drug was usually followed by recovery. Swan[116] reported a case which had reached the stage of parenchymatous nephritis in which the urine, examined at short intervals, was found to contain mercury one year and twenty-nine days after the last dose had been administered. In a case of sublimate poisoning observed by Chauffard[117] there was complete anuria during five days. H. C. Wood, Jr.,[118] observed hæmorrhagic nephritis in several cases of corrosive sublimate poisoning.

Untoward Effects.—The therapeutic dose of mercury *i.e.*, the quantity that will stimulate sufficiently the test-organ to protect the body against infection, is very small.* Beyond this limit excessive oxygenation of the blood occurs and digestive activity of the auto-antitoxin becomes such that it provokes more or less serious disorders.* This is due to the fact that while the adreno-thyroid center is stimulated very actively (through the test-organ) by mercury, the proportion of thyroidase produced is only sufficient to excite the depressor nerve (thus inhibiting the formation of auto-antitoxin) when the metal is taken in very large or toxic doses.*

The earliest indication that mercury is being given in excess is *salivation*, due to undue stimulation of the salivary glands. The intrinsic metabolism becomes such* that enormous quantities of saliva are sometimes voided. The glands often become enlarged and tender. Evidences of increased general metabolism,* slight fever and restlessness may also

* *Author's conclusion.*
[112] Rosenheim: Zeit. f. klin. Med., Bd. xiv, S. 170, 1888.
[113] Bieganski: Arch. f. klin. Med., Bd. xliii, S. 177, 1888.
[114] Stintzing: Münch. med. Woch., Bd. xxxv, S. 1, 1888.
[115] Fürbringer: Med. Week, vol. ii, p. 334, 1894.
[116] Swan: Amer. Jour. Med. Sci., Jan., 1904.
[117] Chauffard: Semaine méd., vol. xxv, p. 13, 1905.
[118] H. C. Wood, Jr.: Amer. Med., Dec. 27, 1902.

appear at this time, accompanied by increase of tendon reflexes, and, in rare cases, by hallucinations.

While the stimulation of the test-organ, which indirectly increases the auto-antitoxin in the blood, is brought about by the mercurial carried directly to that organ by leucocytes, the bulk of the drug which is secreted in the tissues by these cells, is converted, as is well known, into an inert albuminate. Chittenden,[119] for instance, writes as the result of a careful study of the question: "Just how the solution of mercury by the body juices is effected, and what part is played by the albuminous constituents, we cannot say, but that solution is effected and the mercury eliminated as an albuminate seems to be true." As it is this compound which circulates in the pituitary body, the test-organ is not caused to react.

The proteolytic activity, to which the intestinal juice owes its bacteriolytic and antiseptic properties, may be sufficient in cases of poisoning to cause lesions in intestinal mucosa, by a process similar to that of hæmolysis in the blood proper. These lesions are now attributed to a direct action of the mercury, but such is evidently not the case when even large therapeutic doses are taken, for they may be produced when mercury is applied externally. In Sackur's fatal case,[120] for example, a single inunction sufficed to provoke them. In Audry's case[121] hypodermic injections of the metal caused numerous ulcers in the intestine, etc. Interesting in this connection is a case reported by Alfred Berliner[122] in a syphilitic woman, six months pregnant, in whom inunctions caused violent enteritis. On withdrawing the drug the latter disappeared, but recurred at once on resuming its use. After delivery, however, the inunctions produced no ill effects. The use of mercury has often been pointed out as dangerous in pregnant and puerperal women. The reason for this is self-evident, in view of the fact that during pregnancy, "the *anterior lobe* of the pituitary body" as shown by Comte, Launois and Mulon,[123] is "in a manifest condition of hyperactivity." As mercury violently stimulates precisely the anterior pituitary (the test-organ), and the symptoms of mercurial poisoning are those of excessive activity of the adrenals, it is only normal that mercury, during pregnancy or parturition (the anterior pituitary remaining active until all toxic wastes in the body are destroyed), should cause poisoning.

As to salivation, the rôle of adrenoxidase in the process of excessive auto-antitoxin formation is well illustrated by the fact that adrenal extract in toxic doses was found by Gourfein[124] to cause salivation, among other symptoms, in animals. Taramasio[125] also observed frothing. As mercury acts by stimulating the adrenal mechanism, the cause of this symptom is obvious. Cushny,[126] who refers to the fact that many liters of saliva are sometimes poured out in twenty-four hours, states that "the salivation and stomatitis which are so frequently seen under mercurial medication are obviously not due to the local action of the drug on its way to the stomach, for they occur equally readily when it is applied by hypodermic injection or by inunction." Nor are salivation and stomatitis due to a local effect of the remedy while being ingested, since they occur as readily when mercury is used by hypodermic injection or by inunction. Indeed, Bockhart,[127]

[119] Chittenden: *Loc. cit.*
[120] Sackur: Berl. klin. Woch., Bd. xxix, S. 618, 1891.
[121] Audry: Lyon méd., Apr. 15, 1888.
[122] Alfred Berliner: Allg. med. Centr. Zeit., vol. lxxiii, p. 612, 1904.
[123] Comte, Launois and Mulon: Ann. de gynéc. et d'obstét., Jan., 1904.
[124] Gourfein: Rev. de la Suisse rom., vol. xv, p. 513, 1895.
[125] Taramasio: *Ibid.*, vol. xxii, p. 589, 1902.
[126] Cushny: *Loc. cit.*, p. 643.
[127] Bockhart: Monats. f. prakt. Derm., Aug., 1885.