

in our hands a lever by means of which we can control the vital activities through the thyroid apparatus and enhance, as we will see presently, the functional efficiency of the processes through which the body protects itself against disease.

On the whole, the following conclusions appear warranted:

(1) *the thyroid and parathyroids are not, as now believed, true glandular organs; (2) they are composed of a capsule containing a sponge-like connective-tissue reticulum, the meshes of which form closed tubular cavities lined with a basement membrane, the follicles; (3) the follicles are not supplied, as now believed, with a secreting epithelium; (4) their secreting cells are leucocytes derived from the alimentary canal or the circulation, which enter the organ with its blood, migrate through the walls of the capillaries in the interfollicular septa and the septa proper, and fix themselves to the follicular basement membrane more or less evenly side by side; (5) the granules of these leucocytes are secreted in the follicular fluids and represent the active constituents of the colloidal secretion; (6) the secretions of both organs (thyroid and parathyroids) leave them through their lymphatics and ultimately reach the superior vena cava, the heart, and the pulmonary alveoli.*

What is the rôle of the secretion formed by the joint action of the thyroid and parathyroids?*

THE ADRENAL SYSTEM (THE THYROID APPARATUS, ANTERIOR PITUITARY AND ADRENALS COMBINED) AS THE AUTO-IMMUNIZING MECHANISM OF THE ORGANISM.

In the first volume, which appeared in January, 1903,⁸¹ I pointed out that the physiological function of the thyroid gland was "to sustain the functional efficiency of the anterior pituitary body up to a certain standard, by means of its secretion." Considerable evidence was also submitted, showing that the thyroid secretion, by stimulating the anterior pituitary, sustained the secretory activity of the adrenals, and therefore the activity of the metabolic processes in all tissues; and furthermore, that the three organs thus functionally related—

⁸¹ Cf. also Monthly Cyclo. of Pract. Med., Jan., 1903; Philadelphia Med. Jour., Mar. 7, 1903.

the thyroid, the anterior pituitary and the adrenals—constituted what I termed the "adrenal system."

Although four years have elapsed since I advanced these views, and the organs involved have received greater attention than ever before, my position has not been weakened, while conversely, all solidly established experimental or clinical facts that have come to my notice have only served to demonstrate the strength of the doctrines I have urged.

In the present volume, I have submitted so far considerable additional evidence to the effect: (1) that the adrenal substance on being converted into adrenoxidase, is the oxygenizing agent of the entire organism, and (2) that the anterior pituitary body—its test-organ—governs the functional activity of the adrenals and, therefore, general oxygenation. The third organ of the adrenal system, the thyroid (including the parathyroids, the secretion of which is included in that distributed to the pituitary, and also in the thyroid extracts we use), will now be shown to fulfill the rôle I had originally ascribed to it.

The cardinal rôle of the anterior pituitary body, as the governing center of the adrenals, being to regulate oxygenation, diminution of its functional activity must entail a corresponding reduction of the oxygen supplied to the body at large and, therefore, a reduction of the general temperature. We have seen that removal of the pituitary body or of the adrenals is attended by a steady decline of the temperature, and that this is a characteristic symptom of Addison's disease. On the other hand, I have shown that the anterior pituitary body was the general heat center and that it raised the general temperature by stimulating the adrenals and, therefore, the oxygenation of the body at large. Under these conditions, if, as I hold, the functional activity of the anterior pituitary body is sustained by the secretion of the thyroid gland, overactivity of this organ, or thyroid extract, should cause a rise of temperature, while conversely, removal of the gland or disorders capable of reducing its efficiency as a secreting organ should cause a fall of the temperature. Ample physiological and clinical testimony is available to demonstrate that these conditions are satisfied.

From the standpoint of physiology, Geo. R. Murray,⁸²

⁸² G. R. Murray: Brit. Med. Jour., Jan. 25, 1896.

after describing the morbid phenomena that occurred in a rabbit after incomplete removal of the thyroid, refers to the "similarity between the condition developed and that which develops in man and in monkeys after thyroidectomy, as shown by the hebetude, swelling, loss of hair, dryness of skin and low temperature." J. Lorrain Smith⁸³ observed "a steady fall of body temperature" in every animal (cats) in which he had performed thyroidectomy. Edmunds⁸⁴ states that after removal of goiters the temperature is "generally subnormal." In the cat, Jeandelize⁸⁵ noted a fall of nearly 3° C. (5.4° F.) though the animal was not then moribund, three days after "parathyroidectomy," meaning thereby the careful removal of the thyroid and parathyroids. In a kitten in which he had left two parathyroids, he also observed "lowering of the temperature," though the post-operative life was prolonged. Referring to experiments by Gley, Rouxeau and Hofmeister in rabbits, in which removal of the thyroid was followed somewhat later by that of the parathyroids, Jeandelize states that "paralysis, hypothermia and chronic phenomena seemed to dominate the scene." Rouxeau⁸⁶ in fact states that in his animals "hypothermia was practically constant and often rather accentuated from the start." This applies to all animals, including man.

Conversely, the effects of thyroid extract on the temperature are well known. Thus Chantemesse and Marie, and Ballet and Enriquez (Popoff⁸⁷) observed a rise of temperature in animals after the administration of thyroid extract. Similar observations have been recorded by Guéorguievsky,⁸⁸ Bourneville⁸⁹ and others. Lewis C. Bruce,⁹⁰ having used it in 60 cases, found that it caused fever. In an experimental study Ott⁹¹ was also led to conclude that thyroid produced a rise of temperature, *i.e.*, that it was "a pyrogenic agent." "That thyroid overdosage does quicken the pulse, raise the temperature and cause loss of weight," says F. C. Shattuck,⁹² "admits of no

⁸³ J. Lorrain Smith: *Jour. of Physiol.*, vol. xvi, p. 378, 1894.

⁸⁴ Edmunds: *Practitioner*, April, 1901.

⁸⁵ Jeandelize: *Loc. cit.*, p. 45.

⁸⁶ Rouxeau: *Archives de physiologie*, T. xxix, p. 136, 1897.

⁸⁷ Popoff: *Arch. gén. de méd.*, Oct., 1899.

⁸⁸ Guéorguievsky: *Thèse de St. Petersburg*, 1896.

⁸⁹ Bourneville: *Arch. de neurol.*, Sept., 1896.

⁹⁰ Lewis C. Bruce: *Jour. Mental Science*, Oct., 1895.

⁹¹ Ott: *Medical Bulletin*, Oct., 1897.

⁹² F. C. Shattuck: *Boston Med. and Surg. Jour.*, June 30, 1904.

doubt." He refers to a case in which, under the influence of excessive doses, the temperature from subnormal rose to 103° F.

Additional evidence from the standpoint of clinical medicine is afforded by the fact that the two diseases now generally ascribed to inadequate activity of the thyroid, myxœdema and cretinism, both present hypothermia as a prominent symptom. Thus while Osler and Norton⁹³ state that the temperature of cretins is "invariably subnormal" and that "they suffer from cold," Tyson⁹⁴ says that in myxœdema "subnormal temperature is characteristic, though in the early stages the temperature may be normal or slightly above. In winter the patient always feels cold and hugs the stove." Lévi and de Rothschild⁹⁵ have shown recently, moreover, that aside from these diseases, a large number of disturbances attended with hypothermia, objective and subjective, and often accompanied by vasomotor disorders, cyanosis, neuralgia, chilliness, etc., are in reality due to hypothyroidia and yield to thyroidal treatment. Hertoghe⁹⁶ refers to a case in which recurrent chills had suggested the use of quinine in large quantities; then, on the plea that hysteria was present, to the equally fruitless use of the bromides. The chills yielded promptly to thyroid extract, but returned as soon as its use was discontinued.

Suggested in this connection is the fact that the process through which the temperature is raised or depressed by the thyroid apparatus or its extracts has remained obscure, though many tentative theories unsupported by evidence have been vouchsafed. This is a normal result of the fact that, as recently stated by Laulanié (1905),⁹⁷ physiologists ("we") "are absolutely ignorant of the mechanism of organic oxidation." With the adrenal secretion as the basis of oxygenation, the test-organ of the anterior pituitary body as the adrenal center, and the secretion of the thyroid apparatus as the physiological stimulus of the test-organ, we have an explanation sustained not only by physiological and clinical evidence, but also, we have

⁹³ Osler and Norton: *Sajous's "Cyclo. of Pract. Med."* vol. iii, p. 485, 1905.

⁹⁴ Tyson: *"Practice of Medicine,"* third edition, p. 678, 1903.

⁹⁵ Lévi and de Rothschild: *C. r. de la Soc. de biol.*, Oct. 26, 1906.

⁹⁶ Hertoghe: *La méd. pratique*, Nov., 1906.

⁹⁷ Laulanié: *"Éléments de physiologie,"* Paris, 1905.

seen, by the teachings of comparative zoölogy and physiological botany.

Again, I have pointed out that, owing to its rôle as the governing center of the adrenals, and, therefore, of general oxygenation, the test-organ of the pituitary governed tissue metabolism. If the thyroid gland sustains, by its secretion, the functional efficiency of this organ, and, through it, oxygenation, it should also influence metabolism. Here again, physiology and clinical medicine harmonize in showing that this influence is very marked.

Removal of the thyroid, we have seen, causes a steady fall of the temperature. This should, if my view that this organ influences oxygenation through the adrenals is sound, reduce the proportion of secretion in the blood and cause a corresponding reduction of its power to take up oxygen. Albertoni and Tizzoni⁹⁸ observed that after thyroidectomy "the blood showed less power to fix oxygen." Again, as I have shown that the adrenal secretion formed part of the hæmoglobin molecule, the latter should show diminution: Masoin⁹⁹ found that "the relative quantity of oxyhæmoglobin in the blood was diminished in proportion as the morbid results of thyroidectomy progressed." That the thyroid should be able to influence metabolism under these conditions is evident; that it does so is made apparent by the following testimony:—

Swale Vincent¹⁰⁰ published recently (1906) such a succinct and withall comprehensive review of the subject that excerpts from his text will be submitted as evidence:—

"The discovery of iodine in the thyroid gland by Baumann¹⁰¹ and the isolation of thyroiodin as the probable active principle led observers to test the action of this last upon metabolism. Treupel,¹⁰² Grawitz,¹⁰³ David,¹⁰⁴ and Dinkler,¹⁰⁵ by observations on the human subject, and Roos,¹⁰⁶ who used a small dog, came to the conclusion that thyroiodin influenced

⁹⁸ Albertoni and Tizzoni: Cited by Maragliano: *Gaz. degli Osped.*, Oct. 20, 1894.

⁹⁹ Masoin: *Bull. de l'Acad. de méd. de Belgique*, No. 1, p. 88, 1895.

¹⁰⁰ Swale Vincent: *Lancet*, Aug. 18, 1906.

¹⁰¹ Baumann: *Zeit. f. physiol. Chemie*, Bd. xxi, S. 319, 1895.

¹⁰² Treupel: *Münch. med. Woch.*, Bd. xliii, Nu. 6, S. 117, 1896, and Nu. 38, S. 884.

¹⁰³ Grawitz: *Ibid.*, Bd. xliii, Nu. 14, S. 312, 1896.

¹⁰⁴ David: *Zeit. f. Heilkunde*, Bd. xvii, S. 439, 1896.

¹⁰⁵ Dinkler: *Münch. med. Woch.*, Bd. xliii, Nu. 32, S. 513, 1896.

¹⁰⁶ Roos: *Zeit. f. physiol. Chemie*, Bd. xxi, S. 19, 1895.

metabolism in the same way as the thyroid gland substance itself, in that the body weight diminished and the nitrogen secretion increased.

"Some experiments of short duration are recorded, directed to the estimation of the oxygen taken in and the carbon dioxide given out during thyroid administration. These respiration experiments were carried out after the Zuntz-Gepfert method. Magnus-Levy¹⁰⁷ found in a normal man during the exhibition of thyroid glands a not very distinct increase of the oxygen intake and the carbonic acid output. Later experiments by the same author¹⁰⁸ on a myxœdematous patient gave, on the other hand, an increase of 80 per cent. in the oxygen intake under the influence of thyroid, and 43 per cent. under the influence of iodothylin.

"The experiments of Stüve¹⁰⁹ on a healthy man showed an increase of oxygen intake of 20-23 per cent., and a somewhat smaller increase of carbon dioxide excretion. Thiele and Nehring¹¹⁰ also found an increase of oxygen intake amounting to 20 per cent.; the carbon dioxide output was smaller and irregular. . . . Schöndorff¹¹¹ has performed a series of very careful experiments of long duration upon dogs, and has reached the conclusion that metabolic processes are distinctly increased by the administration of thyroid substance. There is at first no influence on proteid metabolism, but an increase in nitrogenous excretion from increased elimination of nitrogen-holding extractives already present in the body. The body fat is first used up. After a certain period, however, the proteid is also attacked. On stopping the thyroid administration, the metabolism returns to normal, while renewed administration leads to increased nitrogenous excretion."

This occurs likewise when the thyroid gland is overactive, as in exophthalmic goiter. Hirschlaff¹¹² found the "metabolic processes most surprisingly active." In one case the gaseous interchange was found 77 per cent. greater than that of a nor-

¹⁰⁷ Magnus-Levy: *Berl. klin. Woch.*, Bd. xxxii, S. 650, 1895.

¹⁰⁸ Magnus-Levy: *Deut. med. Woch.*, Bd. xxii, Nu. 31, S. 491, 1896.

¹⁰⁹ Stüve: *Festschrift des Städtischen Krankenhauses in Frankfurt am Main*, Sept., 1896.

¹¹⁰ Thiele and Nehring: *Zeit. f. klin. Med.*, Bd. xxx, S. 41, 1896.

¹¹¹ Schöndorff: *Pfüger's Arch.*, Bd. lxxvii, S. 395, 1897.

¹¹² Hirschlaff: *Zeit. f. klin. Med.*, Bd. xxxvi, Hft. 3-4, S. 200, 1898-99.

mal girl of about the same weight. Salomon¹¹³ also found the O intake decidedly increased. Scholz¹¹⁴ found that when thyroid extract was administered to such a case the excretion of phosphoric acid was increased tenfold, while in a normal subject the increase was only 25 per cent. The great increase of O intake is often such as to cause considerable discomfort, which the patient describes as "flushings," "hot waves," etc. The emaciation, rapid breathing, duskiness, muscular cramps, etc., also point to excessive oxygenation.

Easterbrook,¹¹⁵ after a careful study of the influence of thyroid extract in a large number of cases of various kinds, concluded that "thyroid is a profound catabolic stimulant," and that "it greatly accelerates the splitting up and oxidation of the tissues." Administered in exophthalmic goiter (before the cachectic or breaking-down period) thyroid extract should prove harmful. Tyson,¹¹⁶ referring to Greenfield, states that "thyroid in excess produces tachycardia, tremor, headache, sweating, and prostration, symptoms of Graves's disease," and that "when administered during the disease, it aggravates the symptoms." This applies also to parathyroid extracts. James J. Walsh¹¹⁷ concludes, after using the latter, "I do not think that parathyroid extract produces any benefit in cases of Graves's disease, and that if employed in large doses, even for a few days, or in small doses for many days, it will produce an exacerbation of symptoms not unlike those which are produced by the ingestion of a certain amount of thyroid substance."

All this shows clearly the marked influence of the thyro-parathyroid apparatus upon the intake of oxygen, the output of carbon dioxide, phosphoric acid, nitrogen, etc., *i.e.*, upon metabolism—precisely the function carried on by the adrenals through the intermediary of the anterior pituitary.

That overactivity of the anterior pituitary is capable of causing excessive metabolism and overnutrition, is emphasized by the osseous and muscular overgrowth that occurs in the erethic stage of acromegaly. Marie termed this disease a "systemic dystrophy" of pituitary origin, while Tamburini, Harlow

¹¹³ Salomon: Berl. klin. Woch., Bd. xli, S. 635, 1904.

¹¹⁴ Scholz: Centralbl. f. inn. Med., Bd. xvi, S. 1041, 1069, 1895.

¹¹⁵ Easterbrook: Lancet, August 27, 1898.

¹¹⁶ Tyson: "Practice of Medicine," third edition, p. 672, 1903.

¹¹⁷ James J. Walsh: Amer. Med., May 20, 1905.

Brooks, and Mitchell and Le Count, as stated in the first volume, and more recently by D. D. Lewis¹¹⁸ have shown, not only that the anterior lobe was the seat of the lesion, but that the latter was due to "hyperplasia of the chromophile cells"—a suggestive condition in view of my interpretation of the functions of this organ. Benda's¹¹⁹ conclusion (1891) that this probably indicates "an excessive activity of the gland," Woods Hutchinson's¹²⁰ belief that the pituitary "is the growth center or at any rate the proportion regulator of the skeleton," indicate that, although unaware of the nature of the process, investigators have connected the pituitary with nutrition. This applies as well to the question in point: Fuchs's¹²¹ remarks in a study of the tumors of the pituitary: "Very important in this connection is the influence exerted by the pituitary upon the bodily metabolism."

It is plain, therefore, that the thyroid secretion can, through the anterior pituitary, sustain metabolism through the body at large. Here again, the prevailing obscurity as to the manner in which thyroid extract influences metabolism affords in itself cogent testimony in favor of an interpretation which accounts so readily for recorded experimental and clinical facts. This becomes all the more evident when we realize that physiologists have failed to explain metabolism, as shown by Foster's previously quoted conclusion that, after all, it "consists of guesses and gaps." With the thyroid apparatus as the source of a secretion which sustains the functional activity of the anterior pituitary, *i.e.*, of the sensory test-organ which governs the adrenals, and with the adrenal secretion as the active factor in metabolism, we have a chain composed of solidly forged links.

The functional relationship between the thyroid, the anterior pituitary body, and the adrenals is further shown by the fact that each of these organs, when overactive, can provoke glycosuria. I pointed out this fact in the first volume¹²² and submitted additional evidence in the present volume¹²³ as to

¹¹⁸ D. D. Lewis: Johns Hopkins Hosp. Bull., May, 1905.

¹¹⁹ Benda: Cited by Lewis: *Ibid.*

¹²⁰ Woods Hutchinson: Osler's "Practice of Medicine," p. 1143, 1898.

¹²¹ Fuchs: Wien. klin. Woch., Bd. xvi, S. 151, 1903.

¹²² Cf. vol. i, pp. 362 to 420, in the first three editions.

¹²³ Cf. this vol., p. 1021.

the rôle of the pituitary and adrenals. The supplementary evidence concerning that of the thyroid need alone, therefore, be adduced.

That overactivity of the thyroid can cause glycosuria is shown by the fact that it is commonly observed in exophthalmic goiter, a disease in which the thyroid is admittedly overactive. In some cases, in fact, glycosuria occurs prior to the development of the more typical symptoms of the disease, exophthalmos, enlargement of the thyroid, etc. Cases in which the sugar occurs as a symptom of the general disease—those which interest us in the present connection—have been reported by Lauder Brunton,¹²⁴ Barnes,¹²⁵ Launois,¹²⁶ who refers to twenty-six cases reported by others, including two by Lépine, Souques and Marinesco,¹²⁷ Kleinwächter,¹²⁸ Pitres,¹²⁹ and many other clinicians.

That irrespective of such diseases, overactivity of the thyroid can provoke glycosuria has moreover been pointed out by Arnold Lorand,¹³⁰ who found that thyroid extract exceeded adrenal extract in activity in this particular, and that it could bring on glycosuria, "and even its higher degree, true diabetes." Bosanquet¹³¹ observed a case of combined "diabetes and myxœdema." Many such have been reported; but this is not true diabetes: it is the form in which, as I have previously shown,¹³² the ingested sugar is absorbed and eliminated without first becoming converted into glycogen. It may also occur, in fact, in the terminal or cachectic stage of acromegaly.¹³³ But this does not, in the least, invalidate the fact that overactivity of the thyroid also evokes glycosuria by causing indirectly a too active conversion of glycogen into sugar. Lorand found that "by giving thyroid extract all the symptoms of true diabetes could be produced," and refers to cases recorded by Ewald¹³⁴

¹²⁴ Lauder Brunton: St. Bartholomew's Hosp. Reports, vol. x, p. 253, 1874.

¹²⁵ Barnes: Brit. Med. Jour., June 1, 1889.

¹²⁶ Launois: Lyon méd., vol. xxix, p. 46, 1897.

¹²⁷ Souques and Marinesco: Bull. méd., June 16, 1897.

¹²⁸ Kleinwächter: Centralbl. f. Gynäcol., Bd. xvi, S. 181, 1892.

¹²⁹ Pitres: Le bull. méd., Aug. 18, 1897.

¹³⁰ Arnold Lorand: Ann. de la Soc. roy. d. sc. méd. et nat. de Bruxelles, T. xii, fasc. 4, 1903; Trans. Pathol. Soc. of London, vol. lvii, Pt. 1, 1906; Monthly Cyclo. of Pract. Med., Aug., 1906.

¹³¹ Bosanquet: Lancet, June 10, 1905.

¹³² Cf. vol. 1, p. 418, in the first three editions.

¹³³ Cf. also vol. 1, pp. 154, 197, 365, in the first three editions.

¹³⁴ Ewald: Berliner klin. Woch., Bd. xxxii, ii, S. 25, 55, 1895.

and Bécclère,¹³⁵ in which diabetes was brought on by "treatment with large doses of thyroid extract."

That a functional link exists between the thyroid and the anterior pituitary body in this connection is well shown by the fact that in cases of acromegaly (the true form of which is due to hypertrophy of the anterior pituitary only, as shown by Tamburini,¹³⁶ Harlow Brooks,¹³⁷ Lewis and others) in which diabetes is present, the thyroid is also found "hypertrophied, with much colloid," as illustrated by cases reported by Pineles,¹³⁸ Hansemann,¹³⁹ Ferrand,¹⁴⁰ Harlow Brooks,¹⁴¹ Dallemagne,¹⁴² and others.¹⁴³ Indeed, Lancereaux¹⁴⁴ and others have reported cases in which acromegaly, exophthalmic goiter and glycosuria were present simultaneously.

Once more are we confronted with a condition, the pathology of which has remained obscure. Tyson,¹⁴⁵ for example, states, referring to diabetes, that "there is no disease concerning which so much accurate knowledge has been arrived at, and of the true pathology of which we are so thoroughly in the dark." An overactive thyroid, by exciting the anterior pituitary and through its test-organ, the adrenals, accounts clearly for at least one way in which it can be produced. (We will see elsewhere that many drugs and poisons can cause it by exciting directly the test-organ.) As previously shown, the investigations of Blum, Croftan, Herter and others have demonstrated that adrenal extractives produce glycosuria.

Now that the relationship between the thyroid and tissue metabolism, *i.e.*, the vital process—through the intermediary of the anterior pituitary and the adrenals—has been shown, many clinical facts find a logical explanation which so far have only been accounted for by tentative hypotheses devoid of foundation.

Osler and Norton¹⁴⁶ state that "thyroid extract has revo-

¹³⁵ Bécclère: Gazette méd. de Paris, 1899; cited by Lorand: *Loc. cit.*

¹³⁶ Tamburini: Riv. Sperm. de Fren., p. 559, 1894; p. 414, 1895.

¹³⁷ Harlow Brooks: Arch. of Neurol. and Psych., vol. i, p. 485, 1898.

¹³⁸ Pineles: Jahrbuch der Wiener Krankenanstalten, pp. 256, 268, 1897; cited

by Lorand: Monthly Cyclo. of Pract. Med., Sept., 1906.

¹³⁹ Hansemann: Berl. klin. Woch., Bd. xxxiv, S. 417, 1897.

¹⁴⁰ Ferrand: Revue neurologique, T. ix, p. 271, 1901.

¹⁴¹ Harlow Brooks: *Loc. cit.*

¹⁴² Dallemagne: Archives de méd. expérimentale, etc., T. vii, p. 539, 1895.

¹⁴³ Cited by Lorand: *Loc. cit.*

¹⁴⁴ Lancereaux: La semaine médicale, Feb. 3, 1895.

¹⁴⁵ Tyson: *Loc. cit.*, p. 797.

¹⁴⁶ Osler and Norton: *Loc. cit.*, p. 496.

lutionized the treatment of cretinism," and that such "children show a most astonishing rapidity of growth during the first months or a year of treatment," after which "growth proceeds gradually as in healthy children," along with development of the intelligence, the adjustment of functions to the normal, etc. Now, in this disease, as in myxœdema, its kindred disorder in adults, the vital processes are not carried on with sufficient activity, and—in the light of my views—thyroid extract, by stimulating the adrenal center, raises all vital functions to their normal standard by promoting general nutrition. Hence also, the value of thyroid extract: in arrested growth, irrespective of cretinism, as shown by Hertoghe,¹⁴⁷ Schmidt,¹⁴⁸ and others; for delayed union in fractures by Gauthier,¹⁴⁹ Bayon,¹⁵⁰ and others; chronic osteomyelitis by W. J. Taylor,¹⁵¹ etc., and other conditions in which the vital and reparative processes are sluggish.

All this is further emphasized by the influence of thyroid extract upon accumulated wastes, fats, etc. In enhancing metabolism, it naturally promotes destruction of these substances; in other words, as stated by Easterbrook, thyroid extract is "a profound catabolic stimulant"; hence its marked action in obesity as shown by Charrin,¹⁵² Magnus-Levy,¹⁵³ and many other clinicians, and its special efficacy as observed by French physicians in subjects that are also "pale, soft and flabby." By stimulating metabolism, the fats are caused to break down—the first manifestation of adequate oxygenation.

This applies as well to toxic wastes which accumulate when metabolism is inadequate—a fact which accounts for the relief afforded by thyroid extract in the tetany that follows removal of the thyroid gland. The absence of thyroid secretion which this operation entails, by depriving the test-organ of its normal stimulus, reduces the secretory activity of the adrenals in proportion; the oxygenation of the entire organism being correspondingly impaired, the food and tissue wastes are inadequately

¹⁴⁷ Hertoghe: Bull. de l'Acad. roy. de méd. de Belgique, p. 897, 1895.

¹⁴⁸ Schmidt: Therap. Woch., Nov. 15, 1896.

¹⁴⁹ Gauthier: Lyon méd., vol. lxxxv, pp. 296, 359, 1897.

¹⁵⁰ Bayon: Verhandlungen des phys. méd. Gesellsch. zu Würzburg, Bd. xxxv, S. 249, 1903.

¹⁵¹ W. J. Taylor: Monthly Cyclo. of Pract. Med., July, 1905.

¹⁵² Charrin: Semaine méd., Jan. 2, 1895.

¹⁵³ Magnus-Levy: Zeit. f. klin. Med., Bd. xxxiii, Hft. 3-4, S. 269, 1897.

catabolized and accumulate in the blood, finally causing convulsions. Herbivora, rabbits, sheep, oxen, horses, etc., whose food contains much less nuclein and other substances capable of forming toxic wastes, suffer less from tetany than carnivorous animals, cats, dogs, foxes, men, etc., whose food contains considerable of these noxious and spasmogenic bodies. Even in the latter animals, however, thyroid extract arrests the convulsions.

The thyroid gland has long been known to neutralize or destroy toxic wastes, its secretion being thought to do so while circulating in the blood by some authorities, while others hold that this process is carried on in the organ itself. These views, however, have not been satisfactorily sustained. On the other hand, excitation of the adrenal center in the anterior pituitary—the test-organ—and the resulting increase of the blood's oxygenizing (and therefore, catabolic) activity, accounts clearly for the beneficial effects observed *as long as the extract is administered*.

This explains also the beneficial and sometimes curative effects of thyroid extract in the tetany of gastroenteritis, especially in children, and idiopathic tetany as shown by Gottstein,¹⁵⁴ Maestro,¹⁵⁵ Levy-Dorn,¹⁵⁶ and other observers. While the spasmogenic toxics here are derived directly from imperfectly digested food-stuffs, the fact that toxic waste products are likewise destroyed under the influence of thyroid extract is shown by its marked action in puerperal eclampsia. This was first shown by Nicholson,¹⁵⁷ whose aim was to antagonize "auto-intoxication," thyroid proving curative when given in large doses. Nicholson's results have been corroborated by other observers.

Here again we have evidence of concomitant overactivity of the anterior pituitary. Lange¹⁵⁸ found in a study of 133 cases, that the thyroid gland begins to enlarge during the fifth or sixth month of pregnancy and that eclampsia and albuminuria occurred most frequently among cases (22) which did not

¹⁵⁴ Gottstein: Deut. Zeit. f. Nervenheilk., Bd. vi, S. 177, 1895.

¹⁵⁵ Maestro: Riforma Medica, vol. xii, ii, p. 468, 1896.

¹⁵⁶ Levy-Dorn: Berl. klin. Woch., Bd. xxxiii, S. 88, 1896.

¹⁵⁷ Nicholson: Scottish Med. and Surg. Jour., vol. viii, p. 503, 1901; vol. xii, p. 204, 1903.

¹⁵⁸ Lange: Zeit. f. Geburts. u. Gynäk., Bd. xl, S. 34, 1899.

show this enlargement. This indicates—in the light of my views—overactivity of the organ at a time when the wastes of the foetus are such as to increase materially those of the mother, the object being to enhance the catabolic activity of the blood correspondingly. Hence the beneficial influence of thyroid extract observed by Nicholson and others. That the anterior pituitary is the seat of a corresponding overactivity during pregnancy is shown by Comte,¹⁵⁹ who specified that “the hypertrophy affected the glandular lobe alone.” Launois and Mulon¹⁶⁰ confirmed these observations and emphasize “the disproportion between the two lobes of the gland, the epithelial lobe being much larger, in comparison with the neural lobe, than under normal conditions.” Histological examination of the organs showed, moreover, that they were “in a manifest state of hyperactivity.”

As will be shown under their respective headings, thyroid extract has also proven beneficial in such disorders as epilepsy, tetanus, rheumatoid arthritis, etc., in which, as in eclampsia, toxic wastes are the pathogenic elements—all through its stimulating action upon the test-organ, *i.e.*, the adrenal center.

Adrenal extract, adrenalin, etc., have also proven effective—due allowance being made for its ephemeral action—in disorders characterized by deficient oxygenation, hypocatabolism, etc.

We have seen that adrenal extract and adrenalin provoked glycosuria: the increase of metabolic activity in the pancreas, and the resulting overproduction of amylopsin—the ferment which acts on glycogen—account for the phenomenon. The familiar action of adrenal on the tissues is also explained by the intense metabolic activity which it excites in the cellular elements, owing mainly to its identity as a catalytic—a fact which explains also the observation of Herter that glycosuria could be produced by applying a solution of adrenal into the pancreas. The vascular contraction it produces—thus insuring a bloodless field for operation—is also a normal outcome of the excessive metabolism it induces in the muscular elements of the vessels. This accounts for the production of arteriosclerosis by adrenal

¹⁵⁹ Comte: Thèse de Lausanne, 1898.

¹⁶⁰ Launois and Mulon: Ann. de gynéc. et. d'Obstét., Jan., 1904.

extractives, as shown by Josué,¹⁶¹ Erb,¹⁶² von Rzentkowski,¹⁶³ and others, since excessive constriction of the vasa vasorum must normally produce denutrition of the vascular coats, with degeneration and fibrosis as results. Thus Councilman,¹⁶⁴ in a study of forty-one autopsies, found 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 usefulness of adrenal extract and adrenalin in conditions due to depression of vital activity, hypocatabolism, etc., likewise finds a logical explanation. In shock, a condition in which, as stated by Kinnaman,¹⁶⁵ “the most uniform and progressive factor” is “the fall in temperature,” adrenalin, as shown by Crile,¹⁶⁶ is of great value when judiciously employed. This investigator resuscitated animals by its use—with simultaneous artificial respiration—fifteen minutes after life had ceased—a normal result in the light of my opinion, since the adrenal secretion sustains the vital process in the tissue cells. In cases of asthma with lowered vasomotor tone S. Solis-Cohen¹⁶⁷ and Bullawa and Kaplan¹⁶⁸ found it effective; so did Mankovsky,¹⁶⁹ Floersheim,¹⁷⁰ and others, in cardiac weakness and threatening collapse—especially, according to Boy-Teissier,¹⁷¹ when there is dilatation and cyanosis. These are but few of the conditions in which adrenal extractives have been tried successfully. Here, however, as in other disorders, they have proven effective only where the life-processes were more or less in abeyance.

On the whole, we have now seen that the thyroid gland, the anterior pituitary and the adrenals influence temperature and metabolism in the same way, and that they awaken homologous phenomena in many directions. That each of these structures is capable of provoking individually such parallel effects would be illogical; indeed, no experimentally-sustained explana-

¹⁶¹ Josué: C. r. de la Soc. de biol., vol. lv, p. 1374, 1903.

¹⁶² Erb: Wien. med. Presse, Bd. xlv, Nu. 18, S. 884, 1904.

¹⁶³ von Rzentkowski: Berl. klin. Woch., Bd. xli, S. 830, 1904.

¹⁶⁴ Councilman: Osler's "Practice of Medicine," p. 771, third edition, 1898.

¹⁶⁵ Kinnaman: Annals of Surg., Dec., 1903.

¹⁶⁶ Crile: Boston Med. and Surg. Jour., Mar. 5, 1903.

¹⁶⁷ S. Solis-Cohen: Jour. Amer. Med. Assoc., May 12, 1900.

¹⁶⁸ Bullawa and Kaplan: Med. News, Oct. 24, 1903.

¹⁶⁹ Mankovsky: Russian Archives of Path., Clin. Med. and Bact., Mar., 1898.

¹⁷⁰ Floersheim: N. Y. Med. Jour., Oct. 6, 1900.

¹⁷¹ Boy-Teissier: Arch. gén. de méd., Aug. 23, 1904.