CHAPTER V.

DISEASES OF THE THYROPARATHYROID APPARATUS (*Continued*).

DISORDERS DUE TO EXCESSIVE ACTIVITY OF THE THYROPARATHYROID APPARATUS.

Overactivity of the thyroparathyroid apparatus, in keeping with the opposite state, described in the preceding chapter, has been identified by numerous terms, the most used of which are pseudo-Graves's disease, aberrant or larval exophthalmic goiter, incomplete Basedow's disease, forme fruste de la maladie de Basedow, hyperthyroidism, and thyroidism. The first five of these were based upon the fact that all of the phenomena were reproduced in exophthalmic goiter, of which the disorder is, in truth, a mild type. The absence of the major symptoms: exophthalmus and goiter, however, so readily misleads the clinician into erroneous diagnoses that the tendency of modern observers is to distinguish this milder type from true exophthalmic goiter, *i.e.*, to regard it as an autonomous syndrome, in which the cardinal symptoms mentioned above are not suggested. Hence the terms "hyperthyroidism" and "thyroidism." As stated in the preceding chapters, however, the terminal "ism" appears to me to suggest the presence of a habit rather than a morbid process subject to treatment. I prefer the term "hyperthyroidia," therefore, which, besides covering this feature, harmonizes with the terminals previously used. To simplify the term, it is not made to include the parathyroids, though, as in hypothyroidia, it must be understood that these glandules are deemed functionally associated with the thyroid proper in the process to be described.

HYPERTHYROIDIA.

(Pseudo-Graves's Disease; "aberrant" or "larval" Exophthalmic Goiter; forme fruste de la Maladie de Basedow; Incomplete Basedow's Disease; Hyperthyroidism; Thyroidism.)

By the above term is meant the aggregate of symptoms which excessive activity of the thyroparathyroid apparatus

awakens when the cardinal symptoms of exophthalmic goiter, *i.e.*, exophthalmus and goiter, are missing. There are still, particularly in Europe, a few observers who deny that exophthalmic goiter is due to excessive activity of the thyroid. But their opinion is based only on a few experimental facts which do not stand close scrutiny. Clinical medicine and surgery, on the other hand, backed up by many expermental data, plead overwhelmingly, however, in the opposite direction. "The whole structure of the surgical treatment of Graves's disease," writes A. E. Elliott,[1] "rests upon the theory of hyperthyroidism, and, if it be not true, then the hundreds of thyroidectomies which are now matters of record remain without justification. The striking influence over the disease, which follows a well-executed partial thyroidectomy, furnishes evidence in favor of the theory of hyperthyroidism, which is so direct as to be apparently irrefutable. The results of thyroid feeding supply evidence which is hardly less conclusive. The administration of thyroid gland substance, or thyroid extract, is capable, if given in sufficient amount, of inducing a toxic state which in almost every essential is similar to Graves's disease." That it can thus be caused both in man and in the lower animals, has been observed by Notthaft, Edmunds, and others. "An artificial state of hyperthyroidism is thereby produced," also writes Elliott, "which duplicates almost in full the morbid syndrome. Even the characteristic exophthalmic symptoms have been observed after thyroid feeding by Auld, Béclère, and others, and Edmunds was able to induce proptosis, widening of the palpebral fissure, and dilatation of the pupils in six monkeys by this means, even after excision of a portion of the cervical sympathetic." That it is the iodine of the thyroiodase which produces it, is also shown by the statement of Kocher that excessive iodide treatment is responsible for the development of exophthalmic goiter in more cases than is generally recognized, the form produced being a severe one.

As to the manner in which such marked phenomena as those witnessed in hyperthyroidia and its aggravated form, exophthalmic goiter, by an excess of thyroid secretion, it must be frankly stated that the existing confusion is eliminated when

[1] Elliott: Amer. Jour. Med. Sci., Sept., 1907.

the functions of the thyroparathyroid apparatus are interpreted, in keeping with the conclusions submitted in the third chapter, (1) that the thyroiodase sustains oxidation and both phases of metabolism—anabolism and catabolism—by sensitizing or increasing the inflammability of the phosphorus of all tissues—including the adrenals and their center and nerves—to the action of adrenoxidase, and (2) that it participates through this same sensitizing action upon all wastes and other eliminable refuse materials in the blood and scavenger cells, in the auto-protective functions of the body, both in health and disease. These two functions once thoroughly apprehended, we shall find that the clinical history of these cases is not difficult to understand. It is perhaps unnecessary to state that the symptomatology of hyperthyroidia illustrates only the phenomena due to exaggeration of metabolism, and that the increased immunizing activity which it entails gives rise to no individual phenomena.

While, as conceded above, there is ground for the recognition of hyperthyroidia as a separate syndrome, the fact remains that its etiology, pathology, symptomatology, and medicinal treatment are practically the same as those that obtain in exophthalmic goiter. It is unnecessary, therefore, to treat the former under a separate head, the reader being requested to look upon hypothyroidia as less severe symptomatically than true exophthalmic goiter, and as presenting neither its two cardinal signs: exophthalmus and goiter, nor its progressive lethal trend, unless, as is often the case, it lapses into this severe form.

EXOPHTHALMIC GOITER.

(Parry's Disease; Graves's Disease; Basedow's Disease.)

Referring to this disease, in the earlier editions of this work,[2] I advanced the view that it was in conjunction with the adrenals that the overactive thyroid gland provoked what I regarded as the *sthenic or first stage* of the disease, my conclusion to this effect being: "Exophthalmic goiter is due to overactivity of the thyroid and adrenal glands, and to the exaggerated tissue oxidation this entails." We have seen that the labors of Kraus and Friedenthal, Kostlivy, and Hoskins have

[2] Sajous: "Internal Secretions," etc., vol. i, p. 164, 1903.

sustained this view. I also concluded at the time, that the stage of the disease (not always reached because of recovery or death) which simulates myxœdema entailed also adrenal insufficiency, the conclusion submitted being: "The *asthenic* or *second stage* of exophthalmic goiter is due to exhaustion and functional insufficiency of the thyroid and adrenal glands, as a result of their prolonged overactivity during the sthenic stage." Here we have familiar clinical facts besides those of myxœdema, to sustain my position. Thus, referring to a case in which the skin had assumed "a peculiar bronze color," W. Macphan Semple[3] expressed the opinion that there might "possibly be some more intimate connection between Graves's disease and Addison's disease than has been so far acknowledged"; Hirschlaff[4] also reported a case due to fright in a girl, in which "there was extensive brownish pigmentation"; von Schrötter[5] likewise observed a case in which "patches of dark-brown pigmentation were found over the entire body." In truth, we are dealing with a not-infrequent symptom of the disease, and recognized as such by classics, which clearly points to involvement of the adrenals.

We must not, however, as has been done, construe this as meaning that I "consider Graves's disease to be the result of excessive suprarenal activity, while myxœdema is due to the opposite condition, adrenal insufficiency." My position is specified in the two conclusions quoted above. Were the adrenals alone active in Graves's disease, its symptoms could not be distinguished from those evoked by adrenal overactivity, treated in the preceding chapter. Acting conjointly with the thyroid, however, the latter introduces factors that are directly traceable to it: the marked emaciation, for example, due to the rapid consumption of the body fat in this disease, as well as in certain adipose subjects treated with thyroid. I have pointed out the influence of the adrenals on oxidation. Now Magnus Levy, Salomon and also Steyrer found that the respiratory exchanges were increased from 50 to 80 per cent.[5a] in Graves's disease.

Yet this does not mean that the influence of either organ may not predominate in proportion as its *relative* efficiency is

[3] Semple: Bristol Medico-Chirurgical Journal, June, 1898.
[4] Hirschlaff: Zeit. f. klin. Med., Bd. xxxvi, H. 3-4, 1898.
[5] Von Schrötter: Medizinische Klinik, April 5, 1908.
[5a] Biedl: "Internal Secretory Organs," p. 98, 1913.

superior. Thus, Washburn,[6] in a test of my contention that the adrenals take part in the process, writes: "Then we should expect high blood-pressure during a considerable part of the clinical course, that is, during the period of adrenal overactivity," and he gives 160, 170, 160, and 200 mm. Hg observed by him in four cases as proof of the correctness of my postulate. While this is perfectly true, and, as observed by Spiethoff,[7] Morris and Edmunds,[8] and others, there is a tendency toward a moderate rise of blood-pressure, the fact remains that in severe or advanced cases, contrary to what we should expect under the influence of a marked excess of adrenal secretion in the blood, there is a remarkable dilatation of the arteries of the entire organism with pulsation in the liver, spleen, capillaries, etc. Why should this occur? As we shall see, this is due to the action of the thyroid secretion, which, exaggerated, offsets that of the adrenal secretion.

And it is between the thyroid and the adrenals that the symptomatology finds its elements. The exaggerated secretory activity of both organs being synchronous, we have merely a correspondingly exaggerated expression of their normal functions. Thus, if the thyroid functions exceed those of the adrenals, we have vasodilation and a more or less marked depression of the blood-pressure, while if the adrenals predominate there is a rise of blood-pressure such as that observed by Washburn. The presence in the blood of an excess of adrenalin, in fact, has, since I urged the participation of the adrenals in Graves's disease, been demonstrated by Kraus and Friedenthal,[8a] and also by A. Fraenkel.[8b]

When fully developed, however, it appears to me that:—

Exophthalmic goiter is a constitutional disease due to excessive functional activity of the thyroparathyroid apparatus, and to the resulting dilatation of all arteries which the excess of thyroparathyroid secretion causes by producing excessive phosphorus oxidation (and elimination as P_2O_5) in all tissues, including the vascular muscles and the depressor nerve.

Pathogenesis and Symptomatology.—As recently stated by Biedl[8c] "Graves's disease is the direct outcome of the flooding

[6] Washburn: Wisconsin Medical Journal, March, 1907.
[7] Spiethoff: Zentralblatt f. innere Med., Bd. xxiii, S. 849, 1902.
[8] Morris and Edmunds: Medical News, vol. lxxxvi, p. 62, 1905.
[8a] Kraus and Friedenthal, Berliner klin. Wochen., S. 1709, 1908.
[8b] A. Fraenkel: Archiv f. exp. Path. u. Pharm., June, 1909.
[8c] Biedl: "Internal Secretory Organs," p. 102, 1913.

of the organism with thyroid substances." But from my viewpoint, the clinical and therapeutic sides of the question render it advantageous to recognize three stages: 1, the *sthenic* or *erethic* stage, during which the overactive thyroparathyroid apparatus causes excessive sensitization of the phosphorus of all tissues to oxidation, and, therefore, abnormally active cellular metabolism; 2, the *transitional* stage, during which the overworked thyroid is beginning to be restrained by the gradual formation of sclerotic areas and atrophy and, 3, the *asthenic* or *myxœdematous* stage, during which progressive fibrosis and atrophy increasingly inhibit the functions of the organ and finally cause the patient's death. The general vasodilation, though an important feature of the process, is incidental, and, as previously stated, subject to fluctuations.

Sthenic or First Stage.—Under "hyperthyroidia" we have seen how clearly the excess of thyroiodase enhances all cellular activities—driving the cell to death, as it were. That the thyroid secretion and extracts increase tissue oxidation is generally recognized, but unlike the oxidation produced by an excess of adrenal secretion or extract there occurs, under the influence of the thyroid secretion, phosphoric acid metabolism and excretion, upon which Chittenden[9] had laid stress. This is a feature of the action of thyroid products upon all phosphorus-containing structures, which stand out even more prominently in the clinical history of exophthalmic goiter than in the milder hyperthyroidia. The brain and nervous system are especially rich, as well known, in this element. The influence of the excessive thyroid activity, therefore, is shown by the greater agitation, restlessness (children being unusually irritable), hallucinations of sight and hearing, capriciousness or unusual gayety in the sthenic stage, which not infrequently includes also pseudo-hysteria, delirium, and even mania. Nervous disorders are so evident in the disease that the latter has been considered by many excellent authorities, including Putnam, as a neurosis. Tremors, especially marked in the upper extremities, but not infrequently involving even the muscles of the back and of the whole body—felt, as indicated by Maude, by placing the hands on the patient's shoulders while he is standing—are practically ubiquitous in

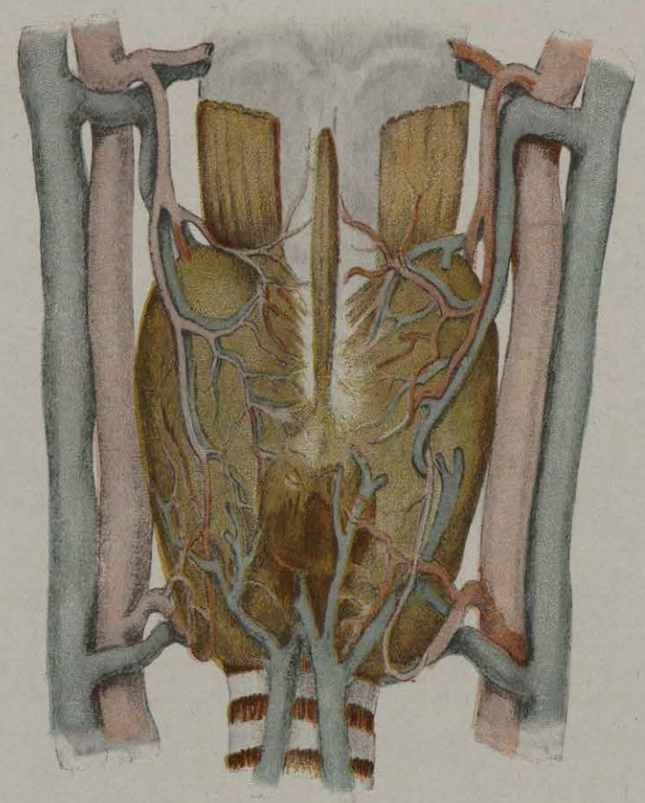
[9] Chittenden: Trans. Cong. Amer. Phys. and Surg., vol. iv, p. 87, 1897.

these cases. Even the voice may become strident and tremulous. Choreic movements (which may replace tremors in children), local cramps, muscular spasms, and even epileptic convulsions are classic, and by no means rare, symptoms of the disease. They denote undue erethism in the cerebrospinal axis and the peripheral nerves, and explain the excessive excretion of P_2O_5. The undue carbohydrate metabolism noted by Kraus, Ludwig, Chvostek, and others are but additional expressions of the same factor.

We cannot ascribe to the thyroid secretion *per se* any more than to the thyroid preparations in common use the powerful oxidizing power this denotes. It is here that "oxidizing ferment" of the blood, *i.e.*, the adrenal secretion converted into adrenoxidase, comes into play. Indeed, concomitantly, we find the evidences of increased oxidation. While a rise of temperature to 100° or 101° is the rule, some cases show a tendency to an acute febrile state, as observed by Gilman Thompson in a series of 70 cases, the fever reaching 104° F. and continuing sometimes several weeks, and recurring every now and then. Few diseases, in fact, furnish examples of such temperatures. In a case observed by Rendu,[10] it reached in the course of one of these exacerbations 110° F., remaining two days between 107° and 110° F. The patients often complain bitterly of a sensation of warmth, of "burning flushes," especially when pruritus and sweating, both due to excessive metabolism in the skin and sweat-glands, are present. The increased demand for food and fluids betokens the intense rate of metabolism to which the tissues are subjected; indeed, polydipsia and boulimia are common. Yet, emaciation proceeds; the thyroiodase, by increasing the vulnerability of the nucleus—also rich in phosphorus—of all fat cells to oxidation by the adrenoxidase, finally consumes all reserve fats; then follow nitrogenous tissues, whose cell nuclei are likewise rich in phosphorus.

The vascular phenomena, referred to above, and others they entail, are due, as stated in my definition, to this excessive oxidation and breaking down of all organic phosphorus, including that of vascular and nerve cells, and particularly Ludwig and Cyon's depressor nerve, which, as is well known, causes general vasodilation and a fall of the blood-pressure. Cyon found, moreover,

[10] Rendu: Lyon médical, March 11, 1900.



VASCULAR SUPPLY OF THE THYROID GLAND.

that thyroid extracts excite the depressor nerve, an effect which the action of thyroid on the phosphorus of all cells explains.

The vascular dilatation may affect all the arteries of the body and be sufficiently marked to cause pulsation of all the large arterial trunks, most marked at the carotids and transmitted to the capillary system. It explains many, now obscure, phenomena that attend the disease. The tendency to hæmorrhages in the mucous membranes and skin is doubtless due to the fact that the dilated arterioles admit blood into the capillaries in excess of the volume the venules can readily carry off. Hence, the flushing of the skin, the hæmorrhagic areas in the mucous membranes, the epistaxis, the coffee-ground emesis, the subcutaneous extravasations of blood which, as in Popoff's case,[11] may attain huge dimensions, the telangiectasis, and, indeed, the gangrene occasionally witnessed. To the vasodilation may also be ascribed the œdemas often observed in the eyelids and legs, the fugitive swellings of the face, neck, arms, and joints, none of which are, of course, beneficially influenced by thyroid treatment. A distinct "whirr" may be heard in some cases over large vessels, as a result of the unusual volume of blood circulating through them.

The thyroid is, as a rule, only moderately enlarged, and its greatly dilated vessels likewise give rise to a distinct whirr under auscultation, while palpation elicits a thrill. During the first stage the goiter is relatively soft, and yields under pressure.

Exophthalmos, commonly the first sign (sometimes unilateral), belongs, when not merely apparent, *i.e.*, due to retraction of the eye-lids, to the same vasodilation of depressor origin, the vessels behind the eye-ball, especially of the retro-bulbar venous plexus, becoming greatly engorged. Here also we have dilatation of the arterioles, which admits an excess of blood into the tissues drained by this venous plexus. At first the exophthalmos fluctuates with the vascular dilatation, and may even be caused to disappear temporarily by pushing gently on the eye-balls. Later, no recession occurs owing to the local deposition of fat and connective tissue.

Stellwag's sign (in reality Dalrymple's,[12] who described it twenty years earlier), retraction of the lids, also finds its explanation in this vascular dilatation: the palpebral muscle

[11] Popoff: Neurol. Centralblatt, April 15, 1900.
[12] Dalrymple: London Lancet, May 26, 1849.

receiving an excess of arterial blood, it is unduly spastic, in keeping with other muscles of the body. This applies also to Graefe's sign: lagging of the upper lid when the eye-ball moves downward; its muscle being spastic, it cannot carry on its movements physiologically, that is to say, synchronously with those of the eye-ball. This spastic state may, in fact, be discerned by means of L. Napoleon Boston's sign[13]: . The head being firmly braced, the patient is directed to follow as high as possible with his eyes the operator's hand, raised upward, starting from the level of the patient's chin about three feet away from his face, then brought down again. The upper lid will be noticed to follow the pupil downward a short distance, then to stop, when what the author terms a "spasm" occurs before it resumes its downward course. The dependence of both Stellwag's and von Graefe's signs upon so fluctuating a factor as the circulation is shown by the fact that they may vary from day to day and that they are not constant.

The tachycardia, one of the cardinal signs of the disease, in the light of these facts, is an expression of the febrile process, but only in part, for it persists even when the temperature is practically normal. The erethism of the central nervous system and of the nerves themselves, including the accelerator nerve, provoked by excessive oxidation in them, being taken into account, however, the abnormal pulse-rate finds its normal explanation even without the presence of a febrile state. Especially must this be the case in view of the fact that the myocardium itself is rendered hyperexcitable by the blood overladen with thyroiodase and adrenoxidase it receives. The cardiac symptoms of the disease, extreme irritability, distressing violent palpitations, with loud valvular sounds, especially marked at night, and even endocarditis, betoken the presence of such a condition of the entire cardiac mechanism. In children, in whom the disease develops rapidly, as a rule, the cardiac signs are often the first to appear.

The respiratory phenomena are closely allied to the cardiac, in that the respiratory muscles, including the diaphragm, are also rendered supersensitive by the excessive oxidation to which they are subjected by the blood, and the irritability of the nerves:

[13] Boston: New York Medical Journal, August 17, 1907.

the phrenic, the respiratory nerve of Bell, the vagus, etc., they receive. The chest muscles being cramped, their excursions are restricted, and the air intake is corresponding y reduced. That the bronchial muscles are likewise contracted, abnormal y reducing the caliber of the air channels, is probable. These two sources of diminished respiratory capacity suffice, it seems to me, to explain the sensations of suffocation or dyspnœa so often observed in these cases. As is the case with the tachycardia, this dyspnœa is subject to crises, during which the respirations become extremely rapid, sixty a minute, sometimes, as observed in two cases by Sharp.[14] This observer noted that "opium had a marvelous action in slowing the respirations." As shown in the second volume, page 1272 of this work, opium, from my viewpoint, produces its effects by causing constriction of the arterioles—thus opposing precisely the muscular hyperæmia to which I ascribe the abnormal effects.

The alimentary canal is morbidly influenced by the same process, congestion and irritability of the gastric mucosa and muscular coat predisposing to emesis. A similar condition of the intestine is the underlying cause of diarrhœa. The liver, spleen, and lymph-glands are often found enlarged. The hyperæmia of all organs moreover gives rise to a general *malaise* or sensation of discomfort, the sensory terminals of all nerves being rendered irritable.

Various complications may occur, most distressing of which is ulceration of the cornea and loss of vision, through loss of protection of the lids and imperfect lachrymation and lubrication of the ocular surface.

Some cases of exophthalmic goiter recover spontaneously, though very gradually; others suddenly enter into a rapid downward course, which W. G. Thompson has compared to malignant endocarditis, for which disease it is frequently taken. A very rapid, tumultuous, and irregular heart action; hyperpyrexia; dyspnœa with labored breathing; vomiting; diarrhœa; hæmorrhages and ecchymoses; marked congestion and enlargement of the liver; delirium; stupor, and coma. In most cases, however, the typical symptoms of hyperthyroidia are replaced by a period of apparent quiescence—the transition stage—and then lapse

[14] Sharp: London Lancet, June 27, 1903.