into those of hypothyroidia, the normal terminal morbid process of progressive exophthalmic goiter.

*Transition Stage.*—What appears to me to be entitled to this designation is a period in the course of the disease when there occurs apparently considerable improvement. The skin ceases to be abnormally moist, the heat flushes, the sensation of heat and the fever disappear, and the skin loses its suffused appearance, and may even become pale. The tremors and nervous irritability, and even the mental aberrations and emotionalism, are replaced by a gratifying placidity; the tachycardia greatly lessens, though reawakened by exertion. The emaciation tends also to disappear, and the patient, though weak, may even show a tendency to corpulence. On the whole, he appears to his surroundings greatly improved and even on a fair way to recovery.

If the goiter be examined with due care at this time, it will be found, at least in most instances, to have receded, and to have lost somewhat of its rounded shape. Its former softness still remains in some places, but in others nodular masses or bosses can readily be detected by passing a finger over the mass, and exerting slight pressure. The meaning of this is self-evident: the goiter is undergoing atrophy owing to the sclerotic areas with which it is now studded, and the transition stage is that period of the process during which the normal tissues, *i.e.*, what remains of them, are just able to sustain the metabolic equilibrium—although the latter is further compromised by the deficiency of cellular phosphorus following its excessive oxidation. The time finally arrives when the thyroid secretion produced is no longer sufficient and the case then enters into the:—

*Asthenic or Myxœdematous State.*—In this stage, reached, as previously stated, if cure or death does not occur early in the course of the disease, we witness the results of exhaustion of both the thyroid and the adrenals with fibrosis of the former. The recognition of this fact is important, for, while thyroid preparations are very harmful in the first stage, as many reported cases show, they may be useful when myxœdema has appeared. During the transition period the change is so rapid in some cases that certain symptoms of both exophthalmic goiter and myxœdema may occur together, the case lapsing ultimately into myxœdema. In textbooks its symptoms, unrecognized, are promiscuously



merged in with those of exophthalmic goiter. In a case witnessed by de Smet,[15] the transition followed premature labor, the goiter alone remaining of the first disease. The exophthalmus may also persist.

The myxœdematous phenomena include most of those reviewed under Myxœdema, *i.e.*, the manifestations of hypothyroidia and hypoadrenia, and, as previously shown, the symptoms of impaired oxidation and metabolism these conditions entail. They are, briefly: hypothermia, sensation of coldness, obesity with a non-pitting, rough, dry skin; suprascapular swellings or pads, loss and coarseness of hair, brittleness and ridging of the nails, predisposition to onychia; various cutaneous disorders, leucoderma, scleroderma, vitiligo, brown pigmentation, etc.; mental torpor, depression, and irritability. There is intense weakness, especially of the legs, with occasionally a tendency to tabes-like paralysis, hemiplegia, or muscular atrophy, which may begin during the sthenic stage. There is a tendency to greater heart weakness and dilatation than in ordinary cases of myxœdema, owing probably to exhaustion of the cardiac muscle during the sthenic stage. If the patient is not carried off by some intercurrent disease, cachexia supervenes with a tendency to fainting spells and heart-failure, the usual cause of death.

Enlarged Thymus as Complicating Factor.—The thymus sometimes assumes considerable importance in the pathogenesis, pathology, and prognosis of exophthalmic goiter, and may even assume the leading rôle. Both Halsted[16] and Kocher hold that these cases are exceptional, the former surgeon having met about 20 in a series of 500 cases treated by him; others—von Haberer, for example—deem them more frequent than is generally supposed. The fact remains, however, that the thymus has been found persistent in about 82 per cent. of the cases of exophthalmic goiter examined *post mortem* in subjects in whom death had been due to intercurrent diseases, and that out of 133 recorded patients who had died during or soon after an operation on the thyroid, ligation of arteries, lobectomy, etc., for exophthalmic goiter, Matti[17] found that 76.5 per cent. had an

[15] De Smet: Le bulletin médical, Oct. 24, 1906.
[16] Halsted: Johns Hopkins Med. Bull., Aug., 1914.
[17] Matti: Deut. Zeitsch. f. Chir., Bd. cxvi; Kocher: Festschrift, 1912.

unusually large thymus. According to Capelle the proportion is 95 per cent. Such cases are a source of great anxiety to the attending physician. Death may not only occur suddenly during any of the operative procedures on the thyroid, but several days after the operation or even when the patient is apparently convalescent.

Although Halsted states, and doubtless correctly, that the characteristic features which most of these cases present are great emaciation, dilatation of the heart, sweating, diarrhœa, relatively slight exophthalmus, not excessive tachycardia, small goiter, and frequently a peculiar grayish, bronze-hued skin, my own experience has been that it is difficult to identify these cases through this aggregate of phenomena. The clinical history of many personal and reported cases of exophthalmic goiter shows, in fact, that these symptoms may occur irrespective of any participation of the thymus in the morbid process. Yet the presence of this group of symptoms suggests pointedly thymic influence and the importance of establishing this feature of the pathogenesis on a firm basis, since the presence of a persistent thymus in a case of Graves's disease increases greatly its malignancy, and often calls for surgical intervention.

There are a few symptoms that stand apart from the typical Graves syndrome which facilitate materially the recognition of thymic influence. When the goiter is small and the possibility of pressure symptoms from this source is eliminable, dyspnœa on exertion with a sensation of pressure behind the manubrium is suggestive. It is this symptom which, suddenly aggravated, may end in death, after an operation on the thyroid. The patient may then of a sudden gasp for breath, become cyanotic and violently excited, then lapse into unconsciousness and promptly die. Dysphagia with a sensation of impediment, the patient referring to a "lump" also behind the manubrium, may likewise be complained of. The superficial veins of the chest or neck may appear abnormally dilated and prominent. An X-ray examination and dullness over the thymic area will probably indicate the presence of a persistent thymus, which, firmly wedged behind the hard and resistant manubrium, presses more or less upon the underlying blood-vessels and nerves. It is to this pressure that, from my viewpoint, these



symptoms should be ascribed, the anatomical relations being such as to account for them.

An important feature which I have never seen mentioned in this connection, is that the size of the thymus varies greatly with the quantity of food ingested. Thus, what has been considered as atrophy of the organ in infantile marasmus is in reality a contraction of the sponge-like organ, which may readily be produced by starvation. Again, any condition capable of raising the vascular tension may so congest the gland as to increase its volume materially. Hence the temporary aggravation of the dyspnœa, dysphagia, etc., under the influence of exercise, a copious meal, etc. Were all symptoms due to a thymic toxicosis they would be continuous, as are, in fact, some of those enumerated by Halsted,—marked emaciation, dilatation of the heart, sweating, etc.

How is this thymic toxicosis produced? This feature of the problem, which has remained obscure, finds a normal explanation through the interpretation of the functions of the thymus I urged in the present work in 1903. Briefly, as stated in the next chapter when describing the functions of this organ, it supplies, through the agency of its lymphocytes, the *excess of nucleins* which the body, particularly the osseous, nervous, and genital systems, requires during its development and growth —*i.e.*, during infancy, childhood, and adolescence, or later if need be, to construct and sustain the functions of the nuclei of its cells. In other words, as is well known, we are dealing with an organ of temporary usefulness, as far as its maximum activity goes, whose activity should virtually cease at a given time—*i.e.*, when the permanent purveyors of nuclein-producing lymphocytes, the bone-marrow and lymphatic glands, are able fully to carry on their functions. When, however, this permanent function is fully established, and a persistent, or even hyperplasic thymus continues abnormally its functions, we have two *sources of nucleins, one of which, the thymic, is in excess and, therefore, injurious.*

This brings us back to what I deem to be the common cause of exophthalmic goiter, viz., some toxic, of which there are at least several, capable of exciting excessively, and through their centers, the functions of the thyroid and adrenals, in a

predisposed or neurotic subject, as will be shown presently under Etiology. The poison here being an excess of nucleins, all tissues are abnormally supplied with these phosphorus-laden bodies. The thyroid and adrenals, which, we have seen, participate in tissue oxidation, being also inordinately stimulated, *excessive metabolism is induced in all tissues.* Hence the marked emaciation, the sweating, the diarrhœa (to facilitate the elimination of tissue-wastes), and the exhausted and therefore dilated heart. The tissues are, as it were, "worked to death," the symptom-complex being such as to make of these patients what Halsted has well termed "dreadful cases."

The experimental and clinical data available sustain the pathogenic relationship between the thymus and exophthalmic goiter. Thus, we have seen that lymphocytosis is a feature of these cases, as pointed out by Kocher; removal of the thymus causes a fall of these small mononuclear leucocytes from 40 per cent. to 25 per cent., then often to normal. The fact that, as shown by Garrè, it is the thymus which so aggravates the disease is demonstrated by the observations of Haberer, that the injection of the juice of thymus gland caused thyrotoxis, and of Bayer, that it brought on the lymphocytosis. Bircher, according to Gebele, has also produced typical exophthalmic goiter symptoms by means of intraperitoneal implantation of fresh hyperplasic thymus. On the whole, it is permissible to conclude that *a persistent and particularly a hyperplasic thymus may cause exophthalmic goiter, or aggravate this disease, by adding to the tissues at large, including the nervous system, an excess of nucleins which, acting as a toxic, excite in those tissues abnormally rapid metabolism. The thyroid and adrenals, themselves overstimulated directly, are, besides, rendered overactive owing to their participation in the defensive functions of the body. In both the transition and asthenic stages the thyroid and adrenals, when exhausted, undergo atrophy.*

I urged, as far back as 1903, that the adrenals should be looked upon as participants in the morbid process of Graves's disease; this applies also to the thymic form of this disorder. Thus, Matti[18] found that in all of 10 cases in which the patients had died during or soon after an operation on the thyroid and

[18] Matti: *Loc. cit.*



thymus was found enlarged *post mortem* the adrenals were noted to be exceptionally small.

Etiology.—In the first edition of this work (1903)[19] I traced the primary cause of exophthalmic goiter to the pituitary body (the neural lobe), through sympathetic nerve-paths. The following year Salmon[20] also concluded that the pituitary body was the seat of primary irritation, though his explanation of the process differed from mine. Briefly, from my viewpoint, the pituitary body contains the co-ordinating centers of the thyroid and adrenals, and when certain toxics capable of irritating this center, such as the toxic wastes of pregnancy and menopause, various toxins, endotoxins, autotoxins of intestinal origin, etc., occur in the blood during a prolonged period, both these organs are unduly excited, and, their secretions being produced in excessive quantities, the disease is awakened.

That exophthalmic goiter occurs in persons predisposed to it by supersensitiveness of the central nervous system, as in hysterical, epileptic, and other neurotic subjects, is suggested by the frequency with which such disorders proceed or occur with the disease. Robinson[21] and others have even gone so far as to consider it as a form of hysteria. Grandmaison,[22] in a study of 32 cases, found hysteria in 19. Abadie ascribes the disease to irritation of whichever center governs the sympathetic vasodilator branches of the thyroidal vessels. Dana[23] vouchsafed a similar opinion. Von Gräfe, Köber, Charcot, and many other authorities have directed attention to the sympathetic in this connection, while Virchow, Trousseau, von Recklinghausen, and others have found lesions (which, from my viewpoint, need not necessarily occur) of the cervical sympathetic, whose branches supply the thyroid. Now, it is through the sympathetic that Cyon traced nerve-paths from the pituitary (the posterior lobe of which is a sympathetic structure, rich in chromaffin substance) to the thyroid, and, as I show in the second volume (p. 982 *et seq.*), the pituitary contains, in all likelihood, the previously unidentified center of the sympathetic system.

[19] Sajous: "Internal Secretions," etc., 1st ed., p. 514, 1903, and p. 1861, 1907.
[20] Salmon: Clinique Moderne (or Clinical Med.), Aug. 3, 1904.
[21] Robinson: "Etude sur les syndrome de Graves-Basedow considéré comme manifestation de l'hystérie," Paris, 1899.
[22] Grandmaison: Médecine moderne, July 7, 1897.
[23] Dana: New York Medical Journal, June 14, 1902.

One of the most evident indications of the influence of the waste accumulation on the genesis of the disease is shown in pregnancy. Richardson[24] states that "in southern Italy it has long been the custom for the parent to measure the circumference of the daughter's neck before and after marriage, an increase in size being considered as an evidence of conception." Time has sanctioned this popular custom, various observers having shown that the thyroid becomes temporarily congested and enlarged under the influence of what Audebert[25] terms, in describing a case in which exophthalmic goiter developed during the seventh month: the "usual symptoms of hepatic toxæmia." While exophthalmic goiter occurs rarely, the fact remains that it is but the exaggerated expression of a physiological process. Thus, Lang,[26] in a series of 133 cases of pregnancy, found the thyroid enlarged in 108, the enlargement beginning about the fifth month. The thyroid ceased to increase in volume when thyroid gland was administered, and resumed its growth when the remedy was withdrawn.

That we are dealing with an antitoxic function having for its purpose the destruction of wastes of fœtal and maternal origin, is suggested by the fact that the thyroid gland has long been credited with such a function. We have seen that my view that it increased the opsonic power of the blood has been sustained. Reid Hunt[27] found, moreover, that when mice were fed on small amounts of thyroid they showed marked resistance to poisoning by acetonitrile. The relationship of the pituitary body with the toxæmia of pregnancy is also shown by the observations of Comte,[28] that during pregnancy the pituitary body is also markedly enlarged, a fact confirmed by Launois and Mulon.[29] In a more recent paper Launois[30] reaffirms his former conclusion, stating that the anterior lobe (which, from my viewpoint, receives the toxics that awaken the impulses transmitted by the posterior lobe to the thyroid and adrenals) is, during pregnancy, "in a state of marked hyperactivity."

[24] Richardson: "The Thyroid and Parathyroid Glands," p. 20, 1905.
[25] Audebert: Annales de gyn. et d'obstétrique, Sept., 1906.
[26] Lang: Zeitsch. f. Geburts. u. Gyn., Bd. xl, S. 34, 1889.
[27] Hunt: Jour. Amer. Med. Assoc., July 20, 1907.
[28] Comte: Thèse de Doctorat; Lausanne, 1898.
[29] Launois and Mulon: Ann. de Gynécol. et d'Obstét., 2d série, vol. i, p. 2, 1904.
[30] Launois: Thèse de la Faculté des Sciences de Paris, 1904.



Another feature which points to the pathogenic rôle of intoxication is that, as stated by Ord and Mackenzie: "In districts where ordinary goiter prevails, the exophthalmic form is also met with." Grasset observed a similar coincidence in France, and Carter[31] in England. The latter author states, moreover, that, while, in a certain valley in the West Riding, the inhabitants on one side of the river, who drink water from hills to the south, do not suffer from goiter, those on the other side of the river, who drink water from hills to the north, suffer a good deal from this growth. Moreover, it is from the latter, or goiter side, that cases of exophthalmic goiter are derived. This clearly suggests that the exophthalmic form is but a development of simple goiter. Indeed, referring to 3 cases of this "secondary" type, Dean D. Lewis[32] writes: "In all these cases a history of goiter of some years' standing could be elicited. Two of these goiters were of the diffuse, colloid type, and one of the mixed type, partly parenchymatous, partly colloid. So far as I was able to determine, these goiters do not differ, histologically, from the simple colloid or parenchymatous goiter, unassociated with Basedow's symptom-complex." Goiter being due, according to prevailing views, to a telluric poison, its exophthalmic form must likewise be due to such a poison.

The relations between bacterial toxins, endotoxins and autotoxins and the thyroid (with the latter organ considered as the source of one of the antitoxic constituents of the blood) also afford considerable evidence in this connection. Roger and Garnier[33] examined the thyroids of 33 cases which had died from scarlet fever, measles, diphtheria, small-pox, typhoid fever, cerebrospinal meningitis, and septic peritonitis, and found in all congestion and hypertrophy with increased secretion, and in two instances (variola and diphtheria) foci of parenchymatous hæmorrhage. Marine and Lenhart[34] also state that syphilis, typhoid fever, influenza, and articular rheumatism are frequently associated with or followed by thyroid hyperplasia. R. Abrahams[35] reported 3 cases which developed in the course of active syphilis.

[31] Carter: Edinburgh Medical Journal, Oct., 1899.
[32] Lewis: Surgery, Gynecology, and Obstetrics, Oct., 1906.
[33] Roger and Garnier: La presse médicale, April 19, 1899.
[34] Marine and Lenhart: Archives of Internal Medicine, Nov., 1909.
[35] Abrahams: Philadelphia Medical Journal, Feb. 9, 1901.

Closely associated with this class of causes is that described by W. H. Thomson,[36] *i.e.*, auto-intoxication from the alimentary canal due to imperfect gastro-intestinal digestion of nitrogenous foods. Treatment based on this view, in which meat was banished from the diet, and intestinal antiseptics were used, gave satisfactory results. While this view has been criticised, it is evident that, from my viewpoint, such poisons can, as well as any of the others referred to above, bring about the disease in predisposed subjects, by exciting the thyro-adrenal center, and thus cause an excessive production of thyroiodase and adrenoxidase. In a case reported by Aiken,[37] the disease began under ether anæsthesia and persisted six years.

Excessive and prolonged exertion has also been known to produce the disease. Overwork is a generally recognized factor. Dauscher[38] reported a case which came on after climbing rapidly a steep mountain. Harland observed 2 instances which had appeared suddenly in soldiers who had been in action in the Boer War. Potain[39] called attention to the fact that violent anger, which has formed the starting point of exophthalmic goiter, awakens symptoms quite similar to this disease, procidence of the eye-balls, trembling, violent palpitations, sweating, diarrhœa, psychical disturbances, etc. In all such cases wastes accumulate in the organism more rapidly than they can be hydrolyzed into eliminable products, and the disease is brought about precisely as in all the forms of toxæmia previously reviewed.

Fright and other violent emotions, which are relatively frequent causes of the disease, bring it on through a different, though kindred, process. Darwin and Sir Charles Bell, according to Carter,[40] describe a person in intense terror in the following words: "The heart beats quickly and violently, so that it palpitates or knocks against the ribs; there is trembling of all the muscles of the body; the eyes start forward, and the uncovered and protruding eye-balls are fixed on the object of terror; the skin breaks out into a cold and clammy sweat, and the face and neck are flushed or pallid; the intestines are affected." The resemblance of these phenomena to the symptoms of exophthalmic goiter is obvious. I refer, elsewhere in this volume, to the sympathetic center as the *sensorium commune*, in the sense that it bears the brunt of violent emotions, shocks, etc., as one of the most sensitive of all somatic centers. Now, as Carter correctly says, intense terror is "a condition in which the somatic nervous system is, for the time being, almost paralyzed." Traumatic shock, blows upon the head, etc., may produce the disease in a similar way, the violent concussion to which the sympathetic center is subjected, along with the other cerebral and basal centers, being the cause of the molecular disturbance. Delorme and Leniez,[41] for example, reported 2 cases in officers who had been thrown from their horses and had struck the pavement on their heads. There was in both cerebral concussion, followed two months later in the one, and one month later in the other, by exophthalmic goiter. They report a similar though less severe case in a soldier who had fallen from a roof, striking his head. Dyrenfurth[42] observed 3 cases due to accidents. The morbid effects of emotions, traumatic shock, etc., are attributable to a molecular disturbance of the sympathetic center,—which governs the caliber of the arterioles,—*i.e.*, the thyro-adrenal center.

We have seen that poisons, by exciting the sympathetic thyro-adrenal center, so exaggerate the functional activity of the thyroid and adrenals that the characteristic action of an excess of thyroid secretion on phosphorus oxidation manifests itself, viz., general vasodilation. With fright or any violent emotion capable of paralyzing the functions of the same center, we have general relaxation of all arterioles which the sympathetic center governs, the acute symptoms of fear being the expression of a temporary exacerbation of this vasodilation, *including those of the thyroid and adrenals*, and, therefore, an abnormal influx of arterial blood in these organs. This means for them, as shown by Claude Bernard in the salivary gland, a corresponding increase of functional activity. In the majority of such cases the resulting disturbances, though sometimes severe, are either recovered from as soon as the central molecular equilibrium is restored or,

[36] Thomson: Medical Record, Jan. 13, 1900.
[37] Aiken: Trans. Amer. Ophthal. Soc., 1897.
[38] Dauscher: Wiener med. Presse, Feb. 17, 1899.
[39] Potain: Revue intern. de méd. et de chir., Oct. 10, 1895.
[40] Carter: Edinburgh Medical Journal, Oct., 1899.
[41] Delorme and Leniez: Le bulletin médical, July 20, 1910.
[42] Dyrenfurth: Deutsche med. Woch., Nov. 21, 1912.

if this restoration does not occur, it may manifest itself by other disorders. If, however, heredity happens to predispose the victim of fright, shock, etc., to exophthalmic goiter, this disease is the one which develops; the circulation receiving an excess of thyroid secretion, the oxidation of cellular phosphorus becomes excessive, and the general vasodilation, the *deus ex machina* of the morbid process, is perpetuated.

The prevailing view that heredity influences greatly the development of the disease is based on a sound foundation. Among the examples may be cited the family referred to by Oesterreicher,[43] in which an hysterical woman's 10 children included 8 cases of exophthalmic goiter. One of these had 4 grandchildren, 3 of which suffered from the disease, while the fourth was hysterical. Hare[44] reported a case in a girl, whose great-grandmother and grandmother suffered from exophthalmic goiter, and whose great-aunt, aunt, and mother suffered from goiter, which increased with each pregnancy in the mother's case. Grober[45] reported 4 cases of exophthalmic goiter in the same family, a brother, two sisters, and a niece. R. G. Curtin[46] collected 40 cases of the disease in 15 families.

TREATMENT.—The great value of thyroid preparations in hypothyroidia suggests that they should prove harmful in the opposite condition, hyperthyroidia, and particularly in its most marked type, exophthalmic goiter. Indeed, many cases on record suggest that such is the case. But, in the light of the views submitted in the foregoing pages, the reason for these untoward effects is plain: they were due to the empirical use of these powerful agents and regardless of the stage of the disease and of dosage.

I have urged that exophthalmic goiter was divisible into three stages: the *erethic,* that during which there is excessive sensitization of the phosphorus of all tissues to oxidation and abnormally rapid cellular metabolism; the *transitional,* during which the overactive thyroid has undergone sufficient fibrosis to produce only such secretion as is needed by the body to carry on its functions, and the *myxœdematous,* during which advancing sclerosis of the gland is increasingly inhibiting its functions until these cease and death occurs. It is apparent that during the erethic stage the use of thyroid could but add fuel to the fire; that in the transitional it might prove useful to arrest the excessive activity of the thyroid, which is inducing sclerosis, by relieving it of part of its work, and finally that in the myxœdematous it should prove invaluable, as it does in myxœdema, as a life-saving measure. An even finer subdivision is necessary, however, one in which the primary cause of the disorder is taken into account, if satisfactory results are to be obtained. During the erethic stage, as a general rule, thyroid and iodine preparations are productive of serious harm. Thus, Lépine[47] reported a case in which the use of iodine in the course of a gynecological operation brought on symptoms of exophthalmic goiter, even though the patient had previously shown no evidences of this disorder. Kempner[48] noted, moreover, that the use of the iodides for arteriosclerosis and other disorders sometimes provoked symptoms of the disease. They enhance inordinately the oxidation of cellular phosphorus in all tissues and increase, thereby, the general vaso-dilation, which, as I have shown, underlies all the major phenomena of the disease. In certain *mild* cases that are clearly due to a toxæmia of ovarian, uterine, or intestinal origin, thyroid is valuable (I have seen it cause complete retrogression of the goiter) in small doses, *i.e.,* 1 grain (0.066 Gm.) of the desiccated gland during each meal, with abstention from meats to decrease the formation of toxic wastes; but where the symptom-complex of the disease is present in its entirety, the aim should be to promote constriction of the arteries, and particularly of the arterioles which control the volume of arterial blood admitted into the organs, including the thyroid itself, the post-orbital vessels, and the cardiac muscle. It is because of this action, in my opinion, that Huchard obtained good results from quinine in large doses and ergot recommended by Huchard, Paulesco, and others. The most efficient method of using these vasoconstrictors is to prescribe a gelatin-coated pill containing the *neutral* hydrobromide of quinine 5 grains and ergotin 1 grain, as suggested by Forchheimer, one

[43] Oesterreicher: Cited by Chamberlain: "Maladie de Basedow," p. 13, Paris, 1894.
[44] Hare: Intern. Medical Magazine, April, 1898.
[45] Grober: Medizinische Klinik, Aug. 16, 1908.
[46] Curtin: Trans. Amer. Climatol. Assoc., Sept., 1888.
[47] Lépine: Revue de médecine, Aug., 1912.
[48] Kempner: Centralbl. f. d. Grenzges. d. Med. u. Chir., July, 1914.