marked asthenia, emaciation, hypothermia, etc., and the presence of a tumor and hyperæsthesia on one side only, offer a better chance of success, since they indicate that the other adrenal will probably be able to subserve alone the needs of the organism. The chief difficulty encountered in the course of the operation is a marked tendency to hæmorrhage owing to the friability of the morbid tissues.

CHAPTER III.

THE THYROPARATHYROID APPARATUS IN GENERAL OXIDATION AND IMMUNITY.

We can no longer speak of the thyroid gland as a functional entity. The two external parathyroid glandules, discovered in 1880 by a Swedish physician, Sandström, and the two internal parathyroid glandules, discovered by Nicolas,[1] of Nancy, in 1893, and independently by Kohn,[2] of Prague, in 1895, introduced a new era in our conception of this organ. Foreign investigators, therefore, tend increasingly to adopt the term "thyroparathyroid apparatus" owing mainly to the anatomical relationship between the glandules and the thyroid vessels, with which their own circulation is directly connected. We shall see, however, that many physiological facts, the first of which were pointed out by Gley, of Paris, in 1892, and clinical observations warrant the use of this compound term.

PREVAILING VIEWS AS TO THE FUNCTIONS OF THE THYROID AND PARATHYROIDS.

In 1859, Shiff, of Geneva, found experimentally that removal of the thyroid gland in the dog caused violent nervous disorders and death. Two surgeons of the same city, the brothers J. L. and A. Reverdin, then pointed out (1882) that in certain goitrous subjects, and after the complete removal of goiter in otherwise normal subjects, there also appeared marked trophic and nervous disturbances. This was confirmed the following year by another Swiss surgeon, Kocher. The principal postoperative phenomena noted were: marked weakness and fatigue, a sensation of cold, pallor, muscular stiffness, and pains; œdematous thickening and pallor, hardness and dryness of the skin, the normal folds being more or less effaced, and loss of hair. The main nervous and mental phenomena were: tetany, sometimes attaining the violence of true tetanus and passing into

[1] Nicolas: Bull. de la Soc. des Sci. de Nancy, vol. v, p. 13, May 3, 1893.
[2] Kohn: Archiv f. mikrosk. Anat., Bd. xliv, S. 366, 1895.

clonic convulsions. The intelligence was also diminished, with slow intellection and enunciation as characteristic features. Paroxysms of suffocation, vertigo, syncope occurred, followed by death within a period varying from four to nine days in the vast majority of cases, the fatal ending being sometimes delayed two or three weeks beyond this period.

The brothers Reverdin termed this condition *postoperative myxœdema,* while Kocher called it *cachexia strumipriva.* The term *myxœdema* had already been attributed (1877) by Ord to the, now familiar, disease of which thyroid insufficiency is the predominating pathogenic factor, and which Sir William Gull had, in 1873, called "a cretinoid change."

The same phenomena were observed in the monkey by Horsley, in 1885. This observer and many others also found that the symptoms were most severe in carnivorous animals; somewhat less so in man and in the monkey; still less so in ruminants and undulates, and that they failed to occur in birds and rodents. But these experimental dissimilarities were to a great extent obliterated by the subsequent experiments of Gley, de Quervain, Hofmeister, Edmunds, and others, which showed that the variations depended mainly upon the anatomical relationship of the parathyroids and the thyroid. Thus Gley, of Paris, found, in 1892, that in the rabbit two of the four parathyroids were situated below the thyroid and were, therefore, not removed with the thyroid; while in the dog, all four parathyroids are so imbedded in the latter that it is only with great care that they can be left *in situ.*

Gley discovered another important fact: he showed that, while removal of the thyroid alone does not necessarily cause death, it was the removal of the four parathyroids which caused the nervous phenomena and the fatal ending. These observations have been sustained by many investigators, who have gradually accounted for many phenomena attributable to each organ, as will be shown in the following pages.

Removal of the thyroid only, produces morbid phenomena the severity of which depends upon the age of the animal; the younger the animal, the greater are the morbid effects witnessed, though life itself is not necessarily endangered. The animal fails to grow. The bones and epiphysial cartilages fail to develop, the skull alone escaping; the abdomen projects and becomes larger, though relatively flabby. The testicles remain small and may fail to descend; the ovaries are also, as a rule, atrophied.

Sterility due to the non-formation of semen has been noted. Pregnant rabbits abort; hens produce very small eggs or none at all. The animal is apathetic, indifferent, dirty, awkward and apparently devoid of intelligence, and quite recalls the human cretin. The skin is rough, coarse, and squamous, being, in some, considerably creased, as in the aged, and, in others, swollen, hard, and resistant, as in myxœdema. The hair becomes coarse and shaggy, losing all luster, and tends to grow irregularly and fall. The temperature, normal at first, steadily decreases until death, the respiratory exchanges and oxidation being diminished, the nitrogen excretion likewise showing, clearly, inhibited metabolism. Anæmia, with reduction of the red corpuscles, is marked. Paralysis and convulsions may appear, but, as a rule, the animal dies cachectic after a prolonged period, the development of the trophic disorders being slow—two or three months in the most rapid cases—*i.e.,* the youngest, according to Jeandelize.

As observed by Charrin, and as will be shown later in this chapter, removal of the thyroid reduces the resistance to infections, and also, according to Lindemann, to intoxications. In man the postoperative phenomena, *i.e.,* cachexia strumipriva, rarely appears before three or four months and occasionally after a year. The same vulnerability to infections is also prominent and the sufferers are often carried away by an intercurrent infection, especially tuberculosis and pneumonia.

In full-grown subjects no marked physical changes occur, but nutrition is nevertheless impaired, emaciation, anæmia, coarseness of the skin, falling of hair, hypothermia, and other manifestations of myxœdema manifesting themselves. These phenomena are aggravated by pregnancy and lactation, repeated pregnancy and prolonged lactation having in fact been found by Morvan to favor the development of myxœdema irrespective of thyroidectomy.

On the whole, removal of the thyroid gland alone gives rise in the young: 1, to arrested growth especially marked in the

skeletal bones and sexual organs; 2, to myxœdematous thickening of the skin; and 3, to a low grade of intelligence with general apathy—as main morbid phenomena, constituting the syndromes recognized under the term cretinism; while in the full grown it causes the condition known as myxœdema.

Removal of the Parathyroids Only.—Removal of the thyroid and parathyroids causes early death, while removal of the thyroid alone, we have just seen, is followed by a prolonged postoperative life. It is to the removal of these diminutive organs, in fact, that all the nervous phenomena must be ascribed. Even when the thyroid is left *in situ*, and the four parathyroids are removed, we witness a typical syndrome: The predominant feature of the syndrome is the tendency to spasm and convulsions which may range from tetany to violent tetanic or epileptic paroxysms, with foaming at the mouth, during which the subject may die, owing to spastic immobilization of the thoracic muscles. Fibrillary tremors, tetanic and choreic movements, sufficiently violent in some cases to throw the patient to the floor are also observed. As in strychnine poisoning, the least contact evokes contractures and convulsions. Marked dyspnœa, the dominant symptom in rabbits, and paroxysms of suffocation occur both during and after the latter. The respirations are greatly accelerated, 100 to 200 times a minute in animals. Although the temperature rises during the convulsive paroxysms, it goes down considerably during the intervals, both the external and internal temperature being 4° C. or more below normal and gradually receding as death approaches. Oxygenation is deficient; the blood contains less oxygen; the red corpuscles are reduced, though the polynuclear leucocytes are increased; cyanosis is clearly shown in the rooster's comb and in the monkey. The pulse, slowed during the intervals, becomes extremely rapid and tumultuous during the convulsions. Involvement of the alimentary canal is shown by ptyalism, fœtid breath, anorexia, the animal being also liable to spasm of the masseters when he attempts to take food, marked thirst, bilious and mucous vomiting, fœtid diarrhœal and bloody stools. Although the animal appears weak, somnolent, and indifferent to its surroundings, as a rule, it is sometimes terror-stricken and agitated, and seems to suffer. Pruritus is an evident

symptom. The urine is greatly reduced and abnormally toxic, especially during the convulsive and dyspnœic paroxysms; it is also markedly spasmogenic when injected into another animal. Albumin and glucose are often present; indican likewise; the chlorides and the potassium salts are present in excess; the pigments and biliary salts likewise, though their ratio tends gradually to lessen. Urea and phosphates are diminished.

These morbid effects usually begin about twenty-four hours after removal of all the parathyroids. In dogs, a single parathyroid of the four suffices in most instances to carry on their functions, but even two of them will fail to do so in some animals, removal of the other pair being followed by tetany. Death usually occurs in from three to five days after removal of all four organs; though, rarely, it does not occur until much later, forty-five days in some instances. The possibility of supplementary organs is, of course, not to be overlooked under such circumstances. As many as six parathyroids have been found at autopsies. Auerbach[3] recently found five in an infant, but only two in 5, and but one in 8. These 13 children all showed a tendency to spasm.

Dual Function Theory.—Gley having shown the vast importance of the parathyroids, he concluded that their purpose was to supplement the function of the thyroid. The fact that the parathyroids became atrophied on removal of the latter seemed fully to sustain this view. Additional proof was seemingly afforded by the continuation of life for some time after the same procedure, the parathyroids being thus shown capable of carrying on the functions of the thyroid independently.

Contrary to this conclusion, however, was the fact, noted by Moussu and verified by Gley and also Nicolas, that the parathyroids, which became hypertrophied after removal of the thyroid, never assumed the histological structure of the latter, but retained their own. Moreover, as emphasized by Moussu, in 1893, experimental evidence pointed to the presence of two functions. This view was sustained by the discovery of two investigators, Nicolas and Kohn, working independently, of the two additional parathyroids, two only having been described by Landström, as previously stated. These two glands sufficed to

[3] Auerbach: Jahrbuch für Kinderheilkunde, B. lxxxiii, Suppl., 1911.

maintain life after the thyroid and parathyroid had been removed. Vassale and Generali now obtained in the dog the complete effects of removal of the whole thyroid apparatus by extirpating only the four parathyroids, a result confirmed in the rabbit by Rouxeau. Moussu then showed that extirpation of the thyroid alone was practically harmless in adult animals, but that in very young animals it was followed by experimental cretinism, while removal of the parathyroids gave rise to the nervous phenomena described in all animals, excepting, perhaps, the ox and horse.

On the whole, the prevailing view is that the parathyroids are functionally independent of the thyroid. We shall see, however, that many facts militate against this conclusion.

Effects of the Internal Secretion of the Thyroid.—Various theories as to the manner in which the thyroid carries on its functions have been vouchsafed, but all have succumbed to the view that the organ secretes some substance which finds its way into the blood, *i.e.*, that it produces an internal secretion. This was suggested a century ago by the experimental work of King, of London, who found that the colloid substance of the gland passed into the lymphatics, an observation confirmed by Hurthle, Baber, Sir Victor Horsley, and others.

That the organ is a secreting one is shown by the fact that it can be transplanted or grafted from its normal site to other parts of the body. Grafting was first successfully performed by Schiff, and repeated by many other investigators, including von Eiselberg, but notably by Christiani, of Geneva. Very uncertain at first, the method was, however, so perfected by the latter experiments that success now attends every operation. It consists in inserting not a whole lobe, as had been previously practised, but small fragments. After a time there is produced *in situ* a nest, as it were, of typical thyroid tissue capable of carrying on the functions of the original gland. Moreover, this tissue seems capable of doing by means of its secretion what the thyroid tissue proper cannot do, viz., to protect the animal against tetany. Louis Morel[3a] recommends intraperitoneal, intrasplenic and intraosseous grafts as the most satisfactory.

Again, extracts of the gland, the gland itself, in its raw

[3a] Louis Morel: Archives génér. de chirurgie, May, 1912.

state or desiccated, antagonize the morbid effects of thyroidectomy. This was first shown by Vassale, who found that the intravenous injection of aqueous extract of thyroid controlled temporarily these phenomena. This experiment was the starting point of Murray's memorable introduction of the use of thyroid preparations in myxœdema in all its forms. In toxic doses, thyroid extract was found by Ewald, Fenwick, Haskovec, and many others to cause: rapid emaciation, marked vasodilation, a rapid pulse, diuresis, acceleration of the lymphatic circulation, hypothermia, polypnœa, polyphagia, polydipsia, glycosuria, excessive excretion of nitrogenous wastes, soon followed by extreme depression, anorexia, vomiting, loss of reflexes, paralyses, convulsions, and death—all phenomena which may be evoked in man by injudicious thyroid medication.

A feature worth retaining, in view of conclusions to be submitted later, is that many observers, including Treupel, Ord, and Ver Ecke, have laid stress upon the correlation of the thyroid functions with general nutrition. Not only is there increased elimination of nitrogenous and other tissue wastes, but, as emphasized by Magnus-Lévy, the respiratory exchanges, including, of course, the intake of oxygen, are greatly increased. Moreover, Vassale and Generali[4] advanced the view, quite compatible with all these biochemical observations and with the known effects of the thyroid extracts in cretinism and myxœdema, that the thyroid secretion served to activate metabolic processes, both in the cutaneous tissues and in the organism at large.

Effects of the Internal Secretion of the Parathyroids.—Removal of these organs being followed by spasm and convulsions, the normal conclusion at once suggested itself that their purpose was to destroy spasmogenic poisons produced within the body. Indeed, the blood of dogs subjected to parathyroidectomy was found by Rogowitsch and others to be toxic and to cause convulsions in normal animals, while Laulanié and others found the urine also toxic. The liver, according to Morel and Rathery,[5] shows acidosis degeneration, while Morel[5a] and Werelius[5b] found

[4] Vassale and Generali: Arch. ital. de biol., vol. xxxii, p. 154, 1900.
[5] Morel and Rathery: Jour. de physiol. et de path. gén., Sept., 1912.
[5a] Morel: La gynécologie, April, 1912.
[5b] Werelius: Surgery, Gynecol. and Obst., Feb., 1913.

that parathyroidectomy enhances the liability of pregnant animals to autotoxic convulsions.

The injection of parathyroid extract was found to antagonize the convulsive disorders caused by the extirpation of all parathyroids by Moussu and other observers, but the beneficial effects lasted a short time only, the animals dying nevertheless. As shown by Vassale, the same beneficial effects are obtained by the injection of thyroid extract. Transfusion of a normal dog's blood to that of one deprived of its thyroid and parathyroids was also shown by Fano and Zanda to palliate considerably the convulsive phenomena. Still, the fact that parathyroid extract arrests the latter temporarily has generally been accepted as proof that the parathyroids contribute independently of the thyroid some antitoxic substance to the blood.

Of experimental and clinical interest in this connection, however, are the observations of Macallum and Voegtlin,[5c] and Macallum,[5d] that calcium salts given by the mouth or hypodermically inhibit the tetany due to removal of the parathyroids, both in man and in lower animals, apparently restoring them completely. This suggests that it is by influencing in some way calcium metabolism that the parathyroid secretion produces its antitoxic effects.

OBSCURE FEATURES OF THE THYROPARATHYROID PROBLEM.

As the foregoing review of the status of the question indicates, much valuable work has been contributed toward its elucidation. Yet if we ask what the functions of the thyroid and parathyroids are in the economy, it must be admitted that none of the data or conclusions available answer the question. Growth and mental development are prevented by arrest, either through organic inhibition of the functions of the thyroid or through removal of this organ. What function does it carry on that enables it to influence so fundamentally the welfare of the entire organism? Vassale's view that the thyroid secretion serves to hasten tissue metabolism is a self-evident conclusion sustained by the symptomatology of and the use of thyroid preparations in myxœdema and cretinism, but it does not tell

[5c] Macallum and Voegtlin: Johns Hopkins Hosp. Bull., Mar., 1908.
[5d] Macallum: Jour. of the Am. Med. Association, Aug. 3, 1912.

us *how* it fulfills this function, *i.e.*, what its secretion does to incite and sustain it.

In the preceding chapter, I filled the corresponding gap in respect to the adrenals by tracing the adrenal secretion to the pulmonary alveoli, and showed that it was converted into adrenoxidase in this location, and that it served, through the intermediary of the red corpuscles, to sustain oxidation, metabolism, and nutrition. What is the corresponding itinerary of the thyroid secretion? Accepting the prevailing and irrefutable view that the latter does sustain metabolism, what is the functional relationship between the thyroid and the adrenals? Again, we find that removal of the thyroid, as does that of the adrenals, predisposes greatly to infection. In virtue of what property does the thyroid secretion contribute to the protection of the body against infectious diseases? These and many other questions have not as yet been answered.

The field of the parathyroids is at least as replete with obscure factors. The same lack of knowledge concerning the itinerary of their secretion, its relationship with the blood, and the actual rôle it fulfills prevails. The salient postoperative effects being convulsive disorders of various types, we are again brought to the necessity of attributing to these organs a very active participation in the autoprotective resources of the body, the poisons antagonized being no longer toxins, but, apparently at least, toxic products of metabolism, *i.e.*, spasmogenic intermediate wastes. Here, again, we find ourselves confronted with an active sway over metabolism or, better perhaps, catabolism. Indeed, the importance of this attribute is of major importance in the practical field. As Parhon and Golstein[6] write: "Certain pathological states, such as pregnancy, parturition, lactation, certain disorders of the female genital apparatus, certain diseases of the thyroid, can facilitate the appearance of tetany, which under these conditions is probably of parathyroid origin." As to the present status of the question, the same authors conclude (1909) "that the intimate mechanism of the production of parathyroid tetany—as well as other forms of tetany—has not as yet been elucidated. The data we possess for the time being

[6] Parhon and Golstein: "Les Sécrétions Internes," p. 209, Paris, 1909.

cannot but indicate the path that researches still necessary should follow to solve the question."

THE THYROPARATHYROID SECRETION AS AN OXIDATION ACTIVATOR THROUGH ITS ACTION ON CELLULAR PHOSPHORUS.

Verworn,[7] referring to Max Schultze's observation that the phosphogenic cells of lightning bugs absorb oxygen actively, quotes approvingly Pflüger's statement concerning this process: "Here, in the wonderful spectacle of animal phosphorescence, nature has given us an example that shows where the taper burns that we call life." If, on the other hand, we recall Hutchison's[8] remark: "Briefly then, it may be said that the effect of the administration of the thyroid is to increase oxidation in the body; it makes tissues, as it were, more inflammable, so that they burn away more rapidly" and also the fact that iodine when brought into contact with phosphorus causes ignition of the latter, the meaning of the above heading will be apprehended. Briefly, from my viewpoint, *the iodine in organic combination which the thyroparathyroid secretion contains renders the phosphorus of all tissue cells, and particularly their nuclei, more prone to undergo oxidation by the adrenoxidase of the blood.* Hence the great influence of the thyroid gland on oxidation, on the vital process itself, on development, physical and mental, as is well shown by the results of thyroid preparations in cretinism and other kindred disorders.

In the earlier editions of the present work, I advanced the view that it was in part through the adrenals that the thyroid secretion produced its effects, and that, conversely, "cachexia strumipriva," *i.e.*, the myxœdema which follows removal of the thyroid, was "partly a consequence of adrenal insufficiency." This view, which makes oxidation the common aim of two sets of organs, suggests itself when the effects of extirpation of the thyroid are compared with those following removal of the adrenals. Both postoperative syndromes include central and peripheral hypothermia, lowering of the blood-pressure, dyspnœa, cyanosis, accelerated respiration, weakness and increased rapidity

[7] Verworn: "General Physiology," Amer. ed., p. 255, 1899.
[8] Hutchison: Brit. Med. Jour., July 16, 1898.

of the heartbeat and pulse, muscular weakness, mental torpor, melancholia, muscular rigidity, convulsions, coma, and death; even bronzing is sometimes witnessed in the advanced stages of myxœdema. Conversely, the effects of thyroid preparations strikingly recall those awakened by the adrenal secretion. Beebe,[9] for example, while acknowledging that it is not known "on what tissue or set of tissues the thyroid secretion acts," states: "We know that it is connected in some way with the function of oxidation in the body. By the administration of thyroid to a cretin or a patient with myxœdema, it is possible to increase the absorption of oxygen from 20 to 75 per cent. There is a corresponding increase in the amount of heat given off from the body. The removal of the thyroid in an animal will cause diminution in the absorption of oxygen, which may be again increased by thyroid feeding. Administration of thyroid to a normal animal will cause an increase of from 10 to 40 per cent. in the oxygen demand."

All this naturally suggests a mutual stimulation between the thyroparathyroid apparatus and the adrenals. In 1903, I advanced the view that the thyroid secretion directly or indirectly increased the adrenal secretory functions.

Experimenters who have taken up the question have also been led independently to the conclusions I had previously reached.[10] That experimental thyroidectomy should produce no histological changes in the adrenals, as was observed by Hofmeister,[11] Bensen,[12] Bruckner,[13] and others, is self-evident, unless the adrenals be endowed with compensative functions, which has never been demonstrated. But it is when hyperactivity of the thyroid is used as the basis of the inquiry that such a functional relationship between the two sets of organs shows itself. While, for example, normal blood has no mydriatic power, injections of thyroid extract confer this property of the adrenal secretion upon it, owing, according to Kraus and Friedenthal[14] and Caro,[15] to stimulation of the adrenals. Kostlivy[16] also

[9] Beebe: Jour. of the Amer. Med. Assoc., Mar. 4, 1911.
[10] Sajous: "Internal Secretions and the Principles of Medicine," vol i, 1st ed., p. 152, 1903.
[11] Hofmeister: Beiträge z. klin. Chir., Bd. xi, S. 463, 1894.
[12] Bensen: Virchow's Archiv, Bd. clxx, S. 229, 1902.
[13] Bruckner: Comptes-rendus de la Soc. de biol., vol. lxiv, p. 1123, 1908.
[14] Kraus and Friedenthal: Berlin klin. Woch., Bd. xlv, S. 1710, 1908.
[15] Caro: Med. Klinik, Berlin, Bd. vi, S. 136, 1900.
[16] Kostlivy: Mitt. a. d. Grenzgeb. d. Med. u. Chir., Bd. xxi, Nu. 4, 1910,