abscess should be done with due care, and the cavity washed out to remove all pus, rather than cleared with the curette or with the finger, which may provoke dangerous hemorrhage, as in a case observed by Bonney.

CHAPTER VI.

THE THYROID, THYMUS, PITUITARY, AND ADRENALS IN MENTAL DEFICIENCY.

IDIOCY AND MENTAL BACKWARDNESS IN CHILDREN.

In treating this general subject, it will be necessary to refer briefly to a function of the adrenals which I first pointed out in 1903 and describe elsewhere in this work. I shall urge that the nerve-cell, *i.e.*, the neuron, should be regarded as an organ through which circulates, as elsewhere in the body, the albuminous constituent of the hemoglobin which I have identified as the adrenal secretion converted in the lungs into an oxidizing substance (adrenoxidase). This will be shown to react throughout the cell, with its phosphorus-laden myelin (supplied in turn with its nucleins by the thymus, as we shall see), the reaction leading to the production of nerve-energy. This energy, in turn, being the *sine qua non* of the functional activity of the neuron in so far as its efficiency as the organ of mind in the cortex is concerned, all conditions capable of interfering with the development of this energy through deficient activity of the ductless glands, or with the structure or functional efficiency of the neuron, will be introduced as so many factors capable of engendering mental deficiency.

The ductless glands being thus regarded prominent factors in the development of the brain and the maintenance of its psychic functions, it follows that toxemias, whether occurring *in utero* or after birth, especially those caused by certain infectious diseases of childhood, should, by provoking organic lesions, such as interstitial hemorrhage and its resulting fibrosis and atrophy, or by exhausting the organs, render them incapable of carrying on that nutritional function of the brain-cells and thus engender a corresponding degree of mental deficiency.

These two essential factors, added to those that have previously been established by the labors of others, seem to me to place the whole field of idiocy upon a more rational plane than

it has occupied heretofore. To make this clear, the pathogenesis of each form of idiocy treated will be considered in its relationship with the ductless glands. We shall see that this course will elucidate many mooted points and make it possible to identify clearly the stigmata of each gland involved in the morbid process as a causal agent, and therefore to point to the organic product or products indicated in each of the types of idiocy considered.

THE THYROID APPARATUS IN MENTAL DEFICIENCY.

Cretinism, or infantile myxedema, was treated in full in the preceding chapter. This type of defective may be said to represent the characteristic form of thyroid idiocy, since, in *bona fide* cases that have not progressed too far, the disease yields to thyroid gland. Under the headings of Hypothyroidia and Myxedematous Infantilism we also reviewed larval and aberrant types of deficiency in which the thyroid apparatus plays the essential part. These disorders belong also to the class in which the thyroid gland is functionally deficient, the other ductless glands being also inadequate, but less so and only as a result of the primary thyroid deficiency, precisely as is the case in cretinism. There are types of idiocy, however, in which thyroid deficiency is either a concomitant or a result of deficient activity of other organs, and in which it is important to identify the stigmata which point to participation of both the thyroid and parathyroids in the morbid process. These thyroid stigmata will now be rehearsed in outline, however, to facilitate their recognition and the manner in which those other ductless glands merge with those illustrated.

Stigmata of Deficient Thyroid Activity.—As we have seen in the preceding chapter, hypothyroidia is the symptom-complex of thyroid deficiency. It seldom appears before the first year, especially in breast-fed infants, because they receive, through the maternal milk, enough thyroid secretion to compensate for any deficiency that their own gland may have acquired *in utero* or in the course of delivery. The earlier signs of hypothyroidia in infants are, in most instances, an unusual thickness of the neck, which may then lose its regular outline by swellings or pads due to localized myxedematous infiltrations. These pads may also be met in older children and adults. They frequently extend to the supraclavicular spaces and sometimes the axillæ. Obesity is suggestive when the skin is "pasty" or wax-like and dense,—a characteristic of myxedematous infiltration. The lips may be thickened and the lids and circumorbital tissues likewise, the eyes sometimes appearing unusually small. There is more or less delay, according to the severity of the case, in learning to speak and walk. The skin if thickened may become dry and scaly and the hair dry, coarse, and brittle, but only in cases in which the hyperthyroidia is marked. The nose may also remain squatty in such cases, and the child appear aged, *i.e.*, yellowish and wrinkled. The hearing and eyesight may be defective and the voice husky. The teeth are, as a rule, irregular and tend to decay early. The nails are short, thin, streaked, and brittle, and the hands broad and spade-like. The temperature is often subnormal and the extremities cold. The legs are unusually short and more or less bowed, while the general musculature is weak,—a fact which accounts for the constipation. Menstruation is frequently scant; in some cases, however, it is prolonged beyond the normal limits. In such cases metrorrhagia, epistaxis, and bleeding at the gums may also be witnessed.

Can all these symptoms be attributed to the thyroid only? While all of them may be observed in hypothyroidia, several bear the imprint of stigmata belonging to other ductless glands. Thus, as we shall see under their corresponding headings in the present chapter, the osseous deformities belong to the sphere of the thymus, while the muscular disorders, which include the intestinal, menstrual, and vascular atony, belong to that of the adrenals. As previously stated, however, they are secondary to the thyroid insufficiency, the secretion of this organ being a factor, as hormone, of the functional efficiency of the other glands, particularly in so far as their effects in tissues at large are concerned.

The stigmata of other ductless glands being isolated, we have left as belonging strictly to the domain of the thyroid:—

1. The subnormal temperature, cold extremities due to defective oxidation and metabolism, the thyroid collaborating actively with the adrenals and thymus (before puberty only as to the latter gland) in sustaining this process.

2. The myxedematous or doughy, dry skin, forming at times in cervical or axillary pads; due to plasmatic infiltration and circulatory torpor; also in very marked cases, the scaly skin and dry, brittle hair and nails, due to deficient nutrition of these structures.

3. The mental deficiency where true thyroid stigmata are discernible, complete development of the brain requiring perfect co-ordination of the thyroid, adrenal and thymic functions.

The importance of a clear identification of these specific signs will appear when the treatment of the various forms of idiocy other than cretinism, already reviewed, will be considered.

We shall now proceed to consider types of idiocy in which other ductless glands play the leading rôle. Prominent among these is the thymus. As this organ has not been considered so far, its physiological functions will first receive attention.

THE FUNCTIONS OF THE THYMUS.

While the thymus is a temporary organ in so far as its maximum activity is concerned, modern observations have demonstrated that its functions sometimes persist, though to a greatly diminished degree, to old age. It was at one time believed that its weight increased to the end of the second year, remaining thus until puberty. Hammar, of Upsala, showed, however, that if care were taken to study the organ in absolutely healthy subjects such as victims of accidents, suicides, etc., it would be found to increase in size from birth to puberty. At this time it averages in weight 25 grams. This represents a considerable increase, the average weight of the organ at birth being approximately one-fourth of this—5 grams (Testut), 6.7 grams (Thursfield), 13 grams (Friedleben). Bovaird and Nicoll,[1] in an examination of 495 consecutive cases, found, moreover, that while no decrease in weight occurred during the first five years, the organ could persist or continue to grow in the infantile state, the increase in size being thus a pathological condition. It is only, according to Hammar, when the thymus reaches 25 grams at puberty that it begins to diminish in size—rapidly from 15 to 25 years (5 grams), then slowly to 50 or 65 years, when it may weigh but 0.73 gram. In the aged it

[1] Bovaird and Nicoll: Archives of Pediatrics, Sept., 1906.

is represented by a small mass of adipose tissue in the anterior mediastinum—Waldeyer's retrosternal adipose body. It usually contains fibrous tissue and small patches or remnants of the thymic parenchyma, thus suggesting the possibility of continued function late in life. The discrepancies in the weights given by the various observers may be accounted for, to a certain extent, by the fact that what has been termed "accidental" involution of the organ may be produced rapidly at any time through starvation, illness, especially wasting diseases, exhaustion, etc. Such wide fluctuations, in fact, are not witnessed in any other organ, and have an important clinical bearing.

There is thus ground for the belief, sustained by considerable clinical evidence, that the functions of the thymus may not cease completely at puberty, and in fact persist, though perhaps to a very limited extent, to advanced age.

As to the function of the thymus gland, a general survey of the literature of the subject, experimental and clinical, evokes as leading clue some important relation with metabolism as regards the rôle of phosphorus in the process.

A suggestive feature in this connection is the influence of deficient thymic activity on the osseous system. Disorders of the thymus in which its functions are deficient or inhibited, growth, particularly that of the bones, is stunted. There are discrepancies in the reports of experimenters concerning the effects of removal of the organ; but if this is done completely and care be taken to avoid certain animals, rats for instance, in which supplementary ductless glands are frequently found, and the thymectomy is performed as soon as possible after birth, the results are sufficiently uniform to warrant their acceptance as sound factors in our inquiry. This has been emphasized by the recent labors of Basch (1906), Klose and Vogt (1910), Morel (1911), Matti (1912), and Lampé (1913). In dogs, bone deformities appear about the fourth month; the front paws curve inward and appear too short, while the back paws, also curved inward, appear too long. The cranium is large, flat, and short. Toward the fifth month the animal becomes somnolent, depressed, loses weight, and becomes cachectic, the morbid process progressing until, between twelve and eighteen months later, coma and death supervene.

The syndrome, in so far as the effects on the osseous system are concerned, recalls plainly that of rickets. The bones become soft and pliable, sufficiently so in some instances to cause them to yield, provoking various deformities, while the ligaments are elongated. The bones may be cut readily with scissors, in fact, until the cachectic period supervenes; flexibility then gives way to fragility and friability, the bones becoming very brittle. The bony tissue, we know, is deficient in lime salts. Osteomalacia is also characterized by softening of the bones in adults and occurs most frequently in nursing women.

These phenomena indicate clearly that thymectomy, rickets, osteomalacia, and other osseous disorders are all due to some impairment in the use of lime by the bones. Indeed, while we know that in the diseases mentioned there is a reduction of calcium in the osseous system at large, Bracci (1905) found that thymectomy caused a similar condition in the latter and in all tissues. Yet we are brought to realize that the morbid process must be due to *deficient use* of calcium by the structures, for Basch found that thymectomized animals excreted calcium in considerable excess. That this is all due to the absence of thymic influence was well shown by Sommer and Floecken in 1908, who found that the successful implantation of thymus in thymectomized animals caused resumption of skeletal growth.

Inadequate assimilation of calcium by the bones being self-evident, we are normally brought, knowing the cardinal rôle of calcium phosphate in the composition of bone, to look upon defective formation of this salt as the key to the morbid process. What is the nature of the relationship between the element linked to calcium, *i.e.*, phosphorus, and thymectomy? It is in this connection that light begins to appear.

A striking feature of thymic chemistry is the wealth of the parenchyma in nucleinates, its lymphoid cells, according to Chittenden,[2] containing a nucleoproteid rich in phosphorus, *i.e.*, 3.5 per cent. Hinskamp[3] also found that nucleohiston, which contains 3.7 per cent. of phosphorus, was the most abundant proteid in the thymus.

This wealth in phosphorus recalls another clinical phenomenon connected with the functions of the thymus, viz., the all-important influence which this organ seems to possess in the production of idiocy. At Bicêtre Hospital, according to Morel,[4] 75 per cent. of 408 non-myxedematous idiotic children, ranging from 1 to 5 years old, examined *post mortem* from 1890 to 1903, showed absence of the thymus. At the request of Bourneville, Katz[5] performed autopsies in 61 mentally normal children, in age from 1 month to 13 years, who had died of various diseases. In all of these the thymus was present conversely in 28 mentally weak children examined *post mortem* by Bourneville, the thymus was absent.

[2] Chittenden: Boston Med. and Surg. Journal, Aug. 20, 1896.
[3] Hinskamp: Zeitschr. für physiol. Chemie, 1901.

These observations correspond with the results of complete thymectomy. Basch, Klose and Vogt, Morel and others observed mental disorders in puppies the fifth or sixth month after removal of the organ. The animals appeared idiotic and crushed, slow in hearing the voice or in understanding threatening gestures, or in recognizing their sleeping place or even their food. They showed great voracity, ate anything—cork, wood, cotton, etc.—and even gnawed their own tissues, their paws, penis, etc. All discerning power denoting intelligence seemed in abeyance. Concomitantly, both in idiotic children and lower animals, owing to absence of thymus, bony deformities such as those previously mentioned were frequently observed. That phosphorus in a fundamental constituent of brain-cells, as well as of osseous tissue, need hardly be emphasized.

We are thus dealing with an organ which, while itself capable of supplying nucleins rich in phosphorus, is clearly connected pathogenically when its functions are inhibited with disorders due to lack of phosphorus, such as rickets, retarded growth, idiocy, etc. The conclusion that the nucleins represent the connecting link between the gland and the tissues is self-evident.

Infantile marasmus has also been attributed to impaired activity of the thymus. In 18 cases of this disorder reported by Ruhräh[6] this organ was the only one which showed lesions. R. L. Thompson[7] also found marked thymic atrophy in 20 cases

[4] Morel: Paris médical, Jan. 17, 1914.
[5] Katz: Le Progrès médical, June 23, 1900.
[6] Ruhräh: British Medical Journal, Aug. 29, 1893.
[7] Thompson: American Jour. of the Med. Sciences, Oct., 1907.

of marasmus in infants under 1 year old. Atrophy of the thymus is regarded by Dudgeon[8] as the most characteristic feature of the disease, a view concurred in by Rohrer, Bovaird, Nicoll, Warthin, Rachford, and others. Friedleben urged, as far back as 1858, in fact that "the size and condition of the thymus is an index to the state of nutrition of the body." From my viewpoint, however, this is a result of the marasmic state rather than a cause, since we know that starvation causes atrophy or contraction rather than enlargement of the gland. The rapidity with which some cases of marasmus recover when given proper diet, the breast, etc., also shows that the functions of the organ cannot have occurred by organic degeneration.

As to the manner in which the thymic nucleins are furnished to the tissues, the older view that the thymus supplies the body a true internal secretion is no longer believed, all the methods used in the study of other glands such as the thyroid, the adrenals, etc., having failed to sustain it. The slight effect on the blood-pressure noted does not militate against this view; nor do even the beneficial effects obtained in various disorders due to deficiency or absence of thymic activity, from the expressed juice, extracts, or other preparations of the organ, since they all contain the characteristic nucleins. The bulk of evidence available points to another mode of transmission viz., *through the agency of lymphocytes which develop in the thymus.* What evidence have we to this effect?

The thymus is composed, as is well known, of lobules varying in size from that of millet seed to that of a small pea. Each lobule in turn is subdivided into small follicles (varying from 1 to 2 mm.) which constitute the functional structure of the gland. An important feature in the present connection is that each follicle is composed of two portions, the medullary and cortical. In the former, mainly composed of coarse reticulum, the cells, including the Hassall corpuscles, are relatively few. The important portion of the follicle in the present connection is its external or cortical portion.

The bulk of evidence at the present time (1916) favors the view of Stöhr, Weidenreich[9] and others, that the cortical portion of the thymic follicle is of epithelial origin and the source of lymphocytes, *i.e.*, small leucocytes containing a round nucleus which fills them almost completely. The earliest evidence that these cells are formed in the organ appears in the course of the third fetal month, when there appear numerous readily stained nuclei in the small thymic cells. The histological studies of Flemming, Prenant, and others have shown that these small cells multiply by karyokinesis in the most peripheral part of the cortical portion and ultimately become lymphocytes. In certain lower forms—Teleostei, for instance—the process of development of these cells may readily be traced, as shown by Maximow in 1912 and Fulci in 1913.[10] The thymus contains other cellular elements, but, as recently emphasized by Dustin,[11] these structures, the myoid, epithelioid, and granular cells, and also the Hassall corpuscles, are non-typical, inconstant, and auxiliary as to function. The only cellular elements which are constantly present in the thymus are the characteristic small "thymic cells" which become the lymphocytes.

Modern researches are believed, by most writers, to show that the older view of Kölliker based on histological studies, and more recently revamped by Beard, to the effect that the thymus was the original source of lymphocytes and leucocytes which, according to these investigators, arose from the thymic epithelial cells, was erroneous. In the light of my own views the only flaw in the teaching of Kölliker and Beard is that they attributed to the thymus the power of generating *all* leucocytes.

The evidence submitted and much that could be added warrant only the conclusion that the thymus contributes lymphocytes to the general asset. This is shown by the fact that, in conditions in which lymphocytosis of thymic origin is met by thymectomy, all lymphocytes do not disappear from the blood, the proportion of these cells falling to normal. Or the percentage may decline to a certain figure; in a case reported by Schumacher and Roth,[12] for example, the lymphocytosis of a case of Graves's disease went down gradually after the operation

[8] Dudgeon: Jour. of Path. and Bact., vol. x, p. 173, 1905.
[9] Weidenreich: Münchener med. Wochenschrift, Nov. 26, 1912.
[10] Fulci: Deutsche med. Wochenschrift, Sept. 11, 1913.
[11] Dustin: Annales et bulletins de la Société Royale des Sciences médicales et naturelles de Bruxelles, vol. lxxii, No. 5, 1914.
[12] Schumacher and Roth: Mitteilungen aus de Grenzgebeiten der Med. und Chir., xxv, 4, 746, 1912.

from 46 to 34 per cent., but remained there. In another case, one of the thymic hypertrophy mentioned by Klose, Lampé and Liesegang,[13] the decline was from 68 to 73 per cent, after removal of the organ. The two latter investigators found, moreover, that diminution of the number of lymphocytes occurred after thymectomy in normal animals, thus showing clearly that the thymus contributed its typical cells to the circulation.

My belief that *the thymic lymphocytes are specific as to function* is based on many facts. Modern investigations are showing increasingly that the former belief that the human thymus was a lymphoid organ, *i.e.*, one similar in structure to the lymph-glands, was unwarranted, and that it is an epithelial organ. We are thus brought to realize that the thymic lymphocytes, which might thus be termed "thymocytes," are produced, in a special manner, *i.e.*, as previously stated, by epithelial cells. Chemically, as shown by Herlitzka and Borrino,[14] the thymic nucleohistons differ from similar bodies of other organs; they possess no glycolytic power and are unable to destroy glycogen. Bang,[15] moreover, found that the small thymic cells which develop into the so-called lymphocytes have a different reaction from those derived from other structures, the spleen, bone-marrow, and bones. "That the thymus-cells are not identical with those of the lymph-glands," writes Biedl,[16] "is proved by the fact that the amount of the nucleinates, the substances which are characteristic of the nuclear structure of the true glands, is *at least five times as large* in the thymus- as in the lymph- glands."

Apart from that of producing lymph-corpuscles which in the blood become lymphocytes—those which the thymocytes supplement during development—the functions of the thymus, as illustrated by experimental thymectomy, bear no resemblance to those attributed to lymph-glands. The influence of the thymus, as illustrated by this operation in animals, on the development of the osseous system, the mind, etc., previously described, has no counterpart in the functions of the lymph-glands. The latter, acting as filters of the lymph which passes through them, to rid it of bacteria, cell detritus, tumor-cells, etc., serve to destroy

[13] Klose, Lampé and Liesegang: Beiträge zu klin. Chir., lxxvii, No. 3, 1913.
[14] Herlitzka and Borrino: Archives Italiennes de Biologie, June 10, 1903.
[15] Bang: Hofmeister's Beiträge zu chem. Physiol. und Pathol., 4 and 5, 1904.
[16] Biedl: Internal Secretory Organs, p. 112, 1913.

these harmful substances—though often destroyed themselves in the course of their protective rôle, as in syphilitic bubo, bubonic plague, tuberculous adenitis, etc. All these processes have nothing in common with those witnessed in the thymus. The clinic confirms physiological teachings that bone deformities, rickets, idiocy, and other disorders due to thymic inadequacy are in no way connected pathogenically with, or resembling, disorders of the lymphatic glands.

Suggesting also that the thymic lymphocytes carry on an autonomous or specific function is the adaptation of its *main* activity to a temporary period, *i.e.*, that during which the body is developed, when it requires an excess of nucleins. Hence the extraordinary wealth of the thymus in nucleinates. As is well known, the phosphorus-laden nuclear materials are essential in the composition of the nucleus of every cell, the dynamic initiator as it were—with the oxygen carried also by a blood-cell to all tissues—of all processes considered particularly vital. Indeed, we are dealing here with a fundamental process concerning not only vital phenomena, but also, in my opinion, heredity. As emphasized by Kossel[17] it is the nuclein, the chromogenic portion of the nucleus, which initiates cell division and, according to present knowledge, hereditary characteristics.

Additional evidence of the constructive power of the thymic cells in their influence on bone growth is afforded by the fact that while thymectomy soon after birth is followed by defective growth and deformities, thymus, administered early, restores normal development. Indeed Gudernatsch[18] found that this substance fed to tadpoles prolonged their early growth markedly, the animals becoming unduly large, though metamorphosis, evolution of limbs, etc., was delayed. R. Webb Wilcox[19] obtained a gain in height of 9¼ inches in an undersized boy, also by the use of thymus-gland. The delay in the development of the brain, illustrated by the idiocy of thymectomized animals and of children with small or no thymus-gland, indicates its constructive influence in this organ. The genital organs are influenced in the same way. Thymectomy causes loss of sexual instinct and sterility and defective development of organs of reproduction;

[17] Kossel: Münchener med. Wochenschrift, B. lviii, 65, 1911.
[18] Gudernatsch: Zentralbl. für Physiologie, xxvi, p. 323, 1912.
[19] Wilcox: Boston Medical and Surg. Journ., Aug. 13, 1908.