Stigmata of Deficient Activity of the Adrenals as a Whole.—These having been described in full under the caption of Hypoadrenia in the second chapter, they will be only summarized in the present connection. They are briefly: muscular weakness, sensitiveness to cold and cold extremities, low blood-pressure and weak cardiac action and pulse, anorexia, constipation, emaciation, anemia, pallor, and mental torpor, slow intellection or even idiocy if the adrenal deficiency has started *in utero*. As these represent the stigmata of both the medulla and cortex, it becomes a question whether additional light might not be afforded by an analysis of the influence of deficient activity of the adrenal cortex alone.

Stigmata of Deficient Activity of the Adrenal Cortex.—The prevailing conception of the functions of this structure, as was shown in the first chapter, is that it produces some hormone "which influences, directly or indirectly, somatic and psychic development," experimental and clinical evidence having shown that this influence was exercised mainly upon development of the sexual glands, the body growth and the changes that occur at puberty. These, however, as we shall see, are phenomena due to overactivity of the cortex. When we come to deficiency of this structure, but little may be added to the list of stigmata awakened by deficient activity of the whole gland. Thus its complete removal causes death even if the medullary portion of the adrenals is left, according to Biedl; but other physiologists failed to observe a fatal issue owing doubtless to the presence in the experimental animals of accessory cortical structures well known to exist in the kidneys, ovaries, and other organs. Variot and Pironneau[35] attribute to aplasia of the adrenal cortex a case of senile dwarfism in a girl of 15 years, Gilford's progeria, in which, besides the defective body growth, there was almost universal absence of hair. The presence of osseous dystrophy, however, would point to insufficiency of the thymus, to which I have ascribed progeria.[36] Yet the universal alopecia, which included absence of eyebrows and lashes, suggests concomitant atrophy of the adrenal cortex

[35] Variot and Pironneau: Clinique Infantile, vol. viii, p. 705, 1910. Quoted by Rand: Boston Medical and Surgical Journal, July 16, 1914.
[36] Sajous: New York Medical Journal, March 20th and April 3, 1915.

in the case of Variot and Pironneau, as well as in one reported by Hastings Gilford,[37] in which generalized alopecia was also present, owing to the fact referred to below, that hirsuties is one of the leading stigmata of excessive activity of the adrenal cortex.

All we can add to the preceding list of adrenal stigmata of insufficiency therefore is deficient hair growth, this being controlled by the fact that, as shown below, overactivity of the cortex, such as that produced by tumors, or hypertrophy of this portion of the adrenals, gives rise to overgrowth of hair.

Stigmata of Excessive Activity of the Adrenal Cortex.—The clinical phenomena based upon tumors of the cortex can alone be taken as guide in this connection. These depend materially, as to their nature moreover, upon the age of the patient. Thus, a child of 5 years may, as a result of neoplasm in this location, promptly attain the dimensions and physical characteristics of an adult. Bulloch and Sequeira[38] observed a case in a girl of 10 years, whose physical development was that of a woman of 40 years. She began to menstruate at the age of 10, the breasts were fully developed, and the hair about the pubis and axillæ likewise. There was besides, however, pronounced facial hirsuties. She weighed 99 pounds. The autopsy showed a large hypernephroma of the left adrenal. The authors found 11 similar cases in literature, almost all girls. Jump, Beates and Wayne Babcock[39] reported a case, in a girl of 7 years, in whom the abnormal development began, and a growth of hair was noticed first over the pubis, then in the armpits, then over the legs and trunk, and subsequently on the chin and upper lip. She grew rapidly and showed a surprising mental and physical development. Her voice became much deeper and she developed amazing muscular strength, the arms and legs being very muscular. The external genital organs were fully developed, the clitoris, however, being very large and penile in appearance. The uterus and adnexa were found to be infantile, however, in the course of the operation, a large hypernephroma involving the entire right kidney having developed.

[37] Gilford: Practitioner, August, 1914.
[38] Bulloch and Sequeira: Trans. of Path. Soc. of London, vol. lvi, p. 189, 1905.
[39] Jump, Beates and Babcock: Amer. Jour. Med. Sciences, April, 1914.

The child died three hours after the operative procedure. Of the 17 cases found by the authors in literature, besides their own, all had died before their sixteenth year.

In the male sex the abdominal growth is manifested especially in the direction of marked muscular development and obesity. Guthrie[40] attributes the infant Hercules or Samsons of shows, mythology, and art to examples of this type of disease, just as acromegaly has served as type for Punichinello.

When the cortical tumor occurs later in life, hirsuties is the main phenomenon: the formation of long hairs on the cheeks and chin, the chest, back and limbs of young girls, with perhaps obesity. There is a tendency toward male characteristics, as in the case reported by Jump, Beates and Babcock in a child, the voice becoming deeper, the menses ceasing, and the organs of generation showing progressive atrophy in some. This transformation thus leads to hermaphrodism. Apert[41] refers to 14 cases, in 10 of which the male organs were sufficiently developed to cause them to live as men. The scrotum was empty, and at autopsy the deeper organs were found to possess the female attributes. In the remaining 4 the clitoris was penis-like and the female organs were atrophied. In all of the 10 marked cases either the adrenal cortex was greatly enlarged or large accessory adrenals were present. Auvray and de Pfeffel[42] have also reported a case of hermaphrodism with enormous hypertrophy of the adrenals. According to Glynn[43] hypernephromata are associated with sex abnormalities almost invariably in children and usually in adult females before the menopause.

Summarizing all these facts, the stigmata of *adrenal deficient activity* are as follows:—

1. Muscular weakness and emaciation.

2. Weak heart action and pulse, low blood-pressure, and constipation due to deficient peristalsis, the result in turn of torpor of the intestinal muscular layer.

3. Sensitiveness to cold and cold extremities due to inadequate oxidation and recession of the blood-mass into the splanchnic area.

[40] Guthrie: British Med. Jour., Sept. 21, 1907.
[41] Apert: *Loc. cit.*
[42] Auvray and de Pfeffel: Société de Chir., May 31, 1911. Quoted by Apert.
[43] Glynn: Quarterly Jour. of Medicine, Jan., 1912.

4. Defective hair growth and pallor owing to inadequate circulation and oxidation in the cutaneous tissues.

5. Mental torpor, slow intellection, or even idiocy where adrenal deficiency is initiated *in utero*.

The presence of these stigmata seem plainly suggestive in the disease treated below, with which, as far as I know, deficiency of the adrenals has not so far been connected by other observers.

AMAUROTIC FAMILY IDIOCY.

This disease, first described by Warren Tay in 1881, has been attributed, by most authors, to some obscure congenital defect. It is uniformly fatal.

Any time between the fifth and tenth month, a normal infant, born at term, will more or less suddenly cease to grow physically and mentally, the physical phenomena consisting mainly in increasing weakness and blindness. The little patient can no longer hold up its head, sit or grasp; and its myasthenia soon becomes so marked that virtual paralysis is suggested. Marked pallor supervenes, due doubtless to atony of the vascular muscles. These phenomena present some kinship with the profound myasthenia of Addison's disease, a fact which suggests failure of the adrenals and of its functional corollary, the chromaffin elements of the sympathetic system, as a feature of the morbid process. The infant also presents evidences of diminished vision: it fails increasingly to notice its mother or nurse, and also objects which, before, attracted its attention. Examination of the fundus, at this time, reveals a picture which has been considered pathognomonic. While atrophy of the optic nerve may be more or less marked, the region of the macula lutea is dark red, and surrounded by a whitish-gray or pearl halo, through which the retinal vessels may be readily seen. Strabismus, nystagmus, and irregularities of the pupils and dysphagia further indicate profound involvement of the muscular system. This is shown also by the profound myasthenia previously mentioned, the child losing increasingly the use of all muscles. What mental development—which may have been quite normal previously—the infant may have shown gradually recedes, the first signs being loss of interest, the torpor in

responding to things which before attracted its attention, and indifference concerning its food.

Another suggestive feature in the pathogenesis of this disease is one commonly met in the cerebral palsies of children, viz., periodical convulsions. If the prevailing view that a toxemia underlies the disease is justified, another link with the adrenals asserts itself. In 1891, for example, Abelous and Langlois were led experimentally to conclude that "the adrenals possess the function of neutralizing or destroying toxic substances evolved during muscular labor." Since then, the investigations of Charrin, Oppenheim, of Paris, and others, including myself, have shown that this antitoxic function is exercised in many directions and that poisons of exogenous origin, toxins, inorganic toxics, and drugs, are all neutralized as well as those of muscular origin identified by Langlois as "fatigue poisons" referred to above.

While a toxic of some sort has been incriminated by practically all authors as the cause of amaurotic family idiocy, its nature has not, so far, been identified. Extreme adrenal insufficiency, by permitting the accumulation of certain (probably myogenic) wastes in the blood, seems to afford an explanation. Not only does it correspond clinically in many particulars with the disease in question, but it explains also why the infant is so prone to periodical convulsions. These, under such conditions, occur when the accumulation of poisons reaches a certain limit, the convulsive paroxysm being a protective reaction which brings into abnormal activity all the antitoxic functions of the body, including those exercised by the ductless glands, which, from my viewpoint, and with the digestive glands, as shown later in the present work, form the foundation of the immunizing mechanism in so far as its chemical attributes are concerned. Examination of the adrenals in the autopsies of these cases has unfortunately been superficial. Even under these conditions lesions in these organs have been discerned. Thus, F. Petersen[44] describes his findings in a characteristic case in the following words: "The left suprarenal, pale-yellow color; firm, small cavity in center. Right suprarenal, same."

The genesis of the disease, with deficiency of the adrenals as chief factor of the process, may, quite in keeping with the prevailing view, be traced to a toxemia which the adrenals and other ductless glands are unable to counteract. To refuse these organs immunizing properties, nowadays, is unwarranted. As stated recently by Albahary[45] before the Paris Society of Biology, "As regards neutralizing secretions that the organism can oppose the action of a toxin in general, we know today that this rôle belongs mainly to the ductless glands." This fact established, a toxemia from any cause capable of exhausting these organs or causing hemorrhagic or other organic lesions in them (we have seen in the first chapter that such occur frequently) may thus initiate the disease.

Church,[46] however, states that "none of the alleged toxic factors can be accepted as competent in all instances. As many as 4 cases have been observed in a single family." This is precisely where the prevailing interpretation of the disease is weak: a direct toxemia fails totally to explain one of its characteristic features: that of being a familial disease. This feature is met, however, by the fact that precisely as is the case with other organs, functional debility of any or all ductless glands and their predilection to certain disorders or vulnerability to organic lesions may be transmitted to offspring. An infection capable through its toxins of causing inhibitory lesions in such vulnerable organs—and this may apply as well to any of the ductless glands or to all of them in the same subject—may thus impair sufficiently the nutrition not only of the central nervous system, causing degenerative changes and chromatolysis, but also that of the muscular system at large, the cardiovascular system, etc. That other glands may be involved in the morbid process is suggested by the fact that McKee found lesions in the thymus gland, while Gordon noted enlargement of the thyroid—probably degenerative—in one case and atrophy of the same organ in another. One thing is certain, however: the clinical stigmata coincide with those of adrenal deficiency, and it is probably in these organs that, macroscopically or microscopically, the main causative lesions are to be found.

[44] Petersen: Journal of Mental and Nerv. Dis., July, 1908.

[45] Albahary: C.-r. de la Société de Biologie T., vol. lxxiv, No. 4, p. 175, Jan. 31, 1913.

[46] Church: "Nervous and Mental Dis.," by Church and Peterson, p. 250, 1908.

On the whole, available data seem to me to suggest that *amaurotic family idiocy is due primarily to a toxemia, including such as may be caused by a disease toxin, which, by provoking organic lesions in the ductless glands (particularly the most vulnerable of these, the adrenals) when these are congenitally debilitated or vulnerable, so weakens their functions as to inhibit increasingly their power to sustain metabolism and nutrition of the central nervous system, the muscular and cardiovascular systems.*

TREATMENT.—As now interpreted, amaurotic family idiocy is hopeless. That *early recognition of the disease* might check the lethal trend, if the pathogenesis just described proves true, is possible, unless actual destruction of the various ductless glands involved be complete. That such cannot be the case in most instances is self-evident when we recall that a small portion of parenchyma—one-eleventh in the case of the adrenals—will carry on vital functions, and that, moreover, this segment or fraction of organ will become hypertrophied under functional stress. Again, we must bear in mind the presence of the accessory organs some of which may have escaped organic lesions to a degree sufficient to enable them to recover their functions, at least in part.

Not only in so far as the disease in question is concerned, but to prevent the development of any of the forms of idiocy described, any infant who is subjected to any of the infections, particularly diphtheria, meningitis, tonsillitis with rheumatic complications, measles, and scarlet fever, should be closely watched long after convalescence. Unfortunately a condition capable of suggesting the possible development of the disease is usually absent, the process having even progressed *in utero* to such a degree in some instances that the infant is born blind.

As to the measures indicated in the light of the pathogenesis submitted above, they are as much as possible to supply the organic preparation which the stigmata present suggest. If the little patient be still a suckling, the remedy may be administered to the mother, adrenal gland being given in 2-grain doses three times daily and gradually increased to 5 grains. To arrest the degenerative process in the infant, intramuscular injections of infundibular extract, which acts much as does the adrenal

principle, may be tried. Pituitrin or "vaporole," an imported preparation, may be employed, diluted in saline solution, and injected into the gluteal muscles after the surface has been carefully asepticized. The dose should be small and adjusted to the age of the infant, any increase being carried out tentatively. Small doses of thymus and thyroid are also indicated to restore the metabolic equipoise in the nerve-cells or facilitate their regeneration.

The diet is an important feature in these cases. It is, in fact, possible that in some instances the maternal milk is found deficient in those agents which, as we shall see, are of primary importance in the development, physical and mental, of the child. When the possibility of this exists the diet of the infant should be reinforced with *fresh-drawn* cows' or goats' milk.

DYSTROPHIA ADIPOSO-GENITALIS.

(Fröhlich's Disease, Adipositas Cerebralis.)

Although the mental symptoms observed in some cases of disease of the pituitary are usually psychasthenic states of a melancholic type, attended, at times, with delusions of persecution, attacks of depression and exaltation, convulsions, etc., cases are occasionally witnessed in which the mental condition is such as to suggest high grade of imbecility in which mental apathy, dullness, and delusions are merged in with the more active symptoms, as observed in a personal case. In another instance, also a case of dystrophia adiposo-genitalis, the patient was irresponsible, childish, and showed a tendency to pilfering. He was unable to acquire knowledge beyond that taught in an elementary school, though showing a marked predilection for music.

Dystrophia adiposo-genitalis, which is a manifestation of deficient activity of the pituitary occurring as the result of an injury, local organic processes such as tumors, etc., is characterized by a marked tendency to obesity, especially about the face (the "moon face" type), the breast, abdomen, and thighs, with sometimes fat pads over the clavicles and under the arms. There is also arrest of development of the genital organs; these remain infantile or atrophy, women ceasing to menstruate when hypopituitarism develops after puberty. The male body assumes a feminine type, especially about the hips. The skin is smooth,

though very dry, but sometimes rough. There is absence or scantiness of hair about the pubes and axillæ and trophic disturbances of the nails, the hand being pudgy and the fingers tapering. Symptoms of tumor of the pituitary are usually observed, headache, hemianopsia, blindness, etc.. but in the two cases referred to above pressure signs were altogether absent. The temperature is generally subnormal, 96° to 98° F., and the pulse weak. The blood-pressure is also low in some cases. The development of the bones and ossification of the epiphyses may be retarded and the stature deficient if the case is traceable to the first years of life. If the hypothyroidia be the result of a temporary tumor or of a period of hypertrophy of the gland from any cause capable of increasing for a time its functional activity, the patient may be of normal stature for his age or even exceed it. Under these conditions the acromegalic facies is sometimes clearly discernible. I have seen 2 cases in which it had existed many years, the disorder in the pituitary having doubtless ceased permanently.

In view of the functions I attribute to the pituitary body these symptoms of hypothyroidia are not due to deficiency of a secretion of the organ, but to inadequate activity of the thyroid, adrenals, and thymus, and the resulting vascular dilatation and circulatory torpor in these organs the functions of which the posterior or neural lobe of the pituitary co-ordinates as sympathetic center. Hypopituitarism thus becomes the expression of pluriglandular deficiency, but mild in type, as a rule, death in such cases being due to the lesions caused by the growth in the neighboring cerebral structures. The glandular stigmata in a case of imbecility due to hypopituitarism are as follows:—

1. Subnormal temperature; low blood-pressure; pigmentation (symptoms of deficient activity of the adrenal medulla). Muscular weakness and scanty hair growth; also in a preadolescent case, undeveloped or infantile genital organs (symptoms of deficient activity of the adrenal cortex).

2. Adiposis; smoothness, but in some cases roughness and dryness of skin (symptoms of deficient activity of the thyroid).

3. Undersized growth owing to deficient skeletal development and imperfect ossification of the epiphyses (symptoms in a preadolescent case of deficient activity of the thymus).

TREATMENT.—The medical treatment of these cases can only serve to compensate for the defective activity of the various ductless glands which, from my viewpoint, control the circulation in these organs. In the vast majority of cases the functional activity of the pituitary is compromised by a tumor which, unless removed, compresses and destroys the surrounding tissues and, as previously stated, ultimately causes death. When, therefore, symptoms of pressure appear, such as intense "bursting" headache, visual disorders (due to compression of the optic thalamus), etc., surgical measures are necessary to insure decompression.

At times, however, we witness instances such as the two patients referred to above, in which the pituitary lesion was temporary, though sufficient, when active, to have left permanent nutritional abnormalities such as those recited. In such patients the combined use of the desiccated powders of thyroid 1 grain, pituitary body 3 grains, and thymus gland 2 grains, three times daily for an adolescent, proves very helpful. Pituitary gland alone in large doses—from 3 to 10 grains three times a day—is sometimes sufficient. As I have repeatedly urged, the action of this agent does not prove that it represents that of a secretion, but that the powdered gland contains phosphorus in organic combination owing to the wealth of nerve-cells in the neural lobe—which represents in assimilable form the nucleins produced by the thymus—and also adrenal substance, as shown by the chromaffin test. Watanabe and Crawford[47] also found recently that "pituitary extracts prepared by certain methods give color reactions similar to those given by suprarenal extracts." The activity of pituitary is enhanced, however, when thyroid gland in small doses is administered simultaneously.

THE BACKWARD CHILD.

The great number of these more or less mentally weak children is fortunately beginning to attract serious attention. Particularly is this the case since the investigations of the Russell Sage Foundation in thirty-one American cities have shown that over 20 per cent. of the children in their schools belonged

[47] Watanabe and Crawford: Jour. of Pharmacol. and Exper. Therap., Jan., 1916.

to the "retarded" class, this proportion leaving out of all consideration the 17 per cent. of subjects in whom the retardation was due to late entrance. In other words, approximately one-fifth of all the children in the public schools of the United States are more or less feeble-minded.

DIAGNOSIS AND PATHOGENESIS.—As Barr has well said, "The backward child is not a mental defective but a mental invalid, so to speak, possessed of all his powers, and has the same chance of attaining mental vigor that any sickly child has of being brought to normal health through proper treatment." Thanks to the Binet and Simon method, backward children are now being duly identified, and saved the brutalities which formerly were meted out to them when their defective work and slow progress at school were attributed to laziness, arbitrariness, and stupidity.

The medical diagnosis of these cases requires a careful scrutiny of the many factors which may prevent development of the mind. The stigmata of the various ductless glands described under the preceding headings must be carefully sought. Yet, to attribute all cases of retarded mentality to deficient activity of these organs would be to err as gravely as to ignore them altogether. The nasopharyngeal cavity should be carefully examined for adenoids and hypertrophied tonsils. Not only do they interfere with respiration, both as to intake of oxygen and output of carbon dioxide, but they also compromise the hearing and thus interfere with one of the most important avenues through which the brain receives impressions. Diseased tonsils are detrimental also in that they are frequently the seat of bacterial colonies which, through the toxemia engendered, provoke a protective reaction which, owing to the excess of antibodies produced, exhausts the child (sometimes keeping up a persistent hemolysis with marked anemia, and even chlorosis) and interferes with its physical and, therefore, mental development. Excessive myopia, errors of refraction, any form of markedly defective vision, in fact, is also conducive to mental starvation in exogenous stimuli so necessary to the psychic development of the organ of mind. To remedy adequately these morbid conditions is imperatively necessary; in their presence organotherapy will prove useless.

TREATMENT.—Before medical treatment is instituted several factors must be taken into account. That insufficient food is a prominent causal feature of backwardness, encountered with special frequency in our public schools, is well known. The functional relationship between the thymus and the brain, maintained through the continuous supply by the former of nucleins which constitute the essential dynamic agent of the cortical cell, accounts for this phenomenon. Organotherapy without an increase of nutritious food in half-starved children is not productive of good, but in some of harm where thyroid is made the sheet anchor of the treatment. It is precisely in such cases that the untoward effects of thyroid treatment and osseous deformities resulting therefrom, especially genu varum, are most frequently observed.

Environment is another factor having considerable influence over the result to be expected from organotherapy. The latter may endow the brain with the potentiality for development, and the neurons reach the maximum state of physical perfection of which they are capable; but if exogenous impressions to develop the psychic functions of the brain are missing, the organ lies dormant and little if any progress is made. In every instance, this phase of the child's every-day life should be carefully scrutinized, and corrected if need be. The company of other children, the schoolroom, where the patient is old enough, and parental efforts to extend the vocabulary and develop understanding, are potent adjuvants when available. Under such conditions marked improvement is often obtained when organotherapy is resorted to to compensate for the deficient hormones in the child's organism.

All the organs of special sense, the child's environment, nutrition and general state of health, especially as regards anemia, tuberculosis, and hereditary syphilis having been fathomed, the condition of the ductless glands must be inquired into, by seeking for the various stigmata described under the preceding headings. Once memorized these signs are readily discerned and the underlying cause of the backwardness, if of glandular origin, is soon established. It is well to bear in mind, however, in many instances the signs of deficiency of any one gland are not easily identified, and that symptom-complex of several glands may