

## THE HYPOPHYSIS CEREBRI AND ITS MORPHOLOGICAL INFLUENCE.\*

DR. F. PARK LEWIS, Buffalo, N. Y.

It is the purpose of this paper to point out a little glimmering light which may ultimately become an illuminating physiological and pathological fact. The demonstrations are not yet sufficiently clear to serve as a basis on which to predicate such a conclusion, but physiological experimentation and clinical observations both point so strongly to the principle about to be formulated that there can be no question whatever as to the desirability of extending the inquiries in order that the range of its application may be more fully understood and its limitations determined. It is this: *That the hypophysis cerebri when normally functioning, exercises a controlling influence not only over the skeletal and muscular structures but over the nutrition and development as well of all of the tissues having an epiblastic and mesoblastic origin.*

If this conclusion is correct, its bearings must have a far-reaching significance. It will then follow that the aberrations of function of the pituitary body will find their expression not only in frank manifestations of acromegaly, and in the less commonly recognized forms of dispituitarism which have been observed, but in a wide range of atrophies and dystrophies which we have been obliged to relegate vaguely to congenital deficiencies or other equally indefinite causes. It will also be found, indeed it is already known, that between the advanced forms of hyperpituitary activity manifesting itself in the young subject in gigantism and in dispituitarism in retarded development, both physical and mental, in those cases in which the secretion of the gland is modified or vitiated there is the entire gamut of possibilities in which vital physical disturbances occur without there being, of necessity, any discoverable alteration either in the organ itself or in the bony cavity in which it rests.

Let me briefly enumerate the recognized conditions which are present when the inhibitory control—whether it rests in the posterior portion of the gland, in the thyroid, in the parathyroids or elsewhere—is released, and the full force of this dominant organ is brought into play. They are not only skeletal changes, but the integument becomes thickened, the skin glands become more active, hair grows abnormally over the body, the sexual appetite may at first be increased and then lost, glycosuria, or polyuria, are present.

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These are vital, fundamental physical changes that could come only through an effect produced on the embryological tissues from which they originate. There are no known drugs that can cause all of these results. There are no known diseases, except those originating in the endocranial glands that can so influence the primordial cells.

The pituitary body is the final development of one of the first, and doubtless most important of the embryological tissues of the notochord. It is a small organ about the size of a shelled hazel nut and weighs only a little more than half a gramme. The anterior, the glandular portion which dominates the growth of structures, grows from the invagination of the buccopharyngeal epithelium. The posterior portion is an extension of the infundibulum and comes from the mid-brain, from the floor of the third ventricle. Vestigia of the buccal ectoderma sometimes persist and are known as the pharyngeal hypophysis. In the dural lining of the sella neuroglial elements are found which are called parahypophysis. Both, it is thought, may, in the event of the major structures being destroyed, take on their functions. "Curiously enough," as Cushing observes, "the anterior lobe of buccal origin receives its vascular supply from a number of small arterioles which pass down the infundibular stalk, whereas the posterior, or infundibular lobe, is nourished by a single artery which enters from below and behind."

Now the effect of the active principle which has been obtained only from the pars posterior on plain muscle fibre is definite and specific. Like the extract of the suprarenals it produces a great rise of the blood pressure, with a contraction of the vessels and increase in force of the heart beats. "Moreover," according to Schafer, "while adrenalin either produces no action on the coronary vessels, or in some cases causes them to dilate, the autocoid of the pituitary constricts them as it does most other systemic arterioles." It has furthermore been shown that the extracts of the posterior lobe also contain a substance which stimulates the flow of cerebro-spinal fluid.

The only analogy which we possess to these conditions is the effect produced on the chromosomes in the ovum by the addition of the ferment introduced by the sperm. In order that we may understand, even to the limited degree to which it is known, the normal and the perverted action of the hypophysis, we must know that of the other glands of the group; for rarely, if ever, is the function of one of them increased or suspended without the others being modified at the same time. As thyroid hypertrophy and over-activity produces the syndrome known as tachycardia exophthal-

mica, with proptosis and the other well recognized symptoms, so does a deficient secretion give rise to degenerative changes no less characteristic, while in the former the rapidity of the bodily metabolism is greatly increased, the heart action quickened, and the nutritive changes so hastened that there is a consequent loss of weight, perspiration is easily induced, and a tendency exists to the production of glycosuria. A thyroid insufficiency is shown by the opposite of each of these signs; the bodily temperature is reduced and is usually subnormal, the circulation is poor, the pulse rate reduced, there is greatly increased sugar tolerance, the skin is dry, rough, eczematous. With this comes obesity, an expressionless face, carious teeth, gingivitis, or actual pyorrhea. In children the sexual development is delayed,—immature sexual organs only being present in many cases,—the stature remains stunted, and there is a faulty mental development. The effect of an atrophy of the thyroid in young children is most marked. "The muscles are limp and weak. Deaf-mutism is common. The highest functions of the nervous system remain undeveloped, the child becoming idiotic. This seems to be due to an arrest of development of the cortex cerebri." (Schafer.)

All of this is important because on removal of the thyroid the pituitary undergoes enlargement and gives every indication of increased secretion. When the thyroid secretion is excessive there is an increased elimination of calcium from the body, and *per contra* with a thyroid deficiency there is a retention of these salts, resulting in atheromatous formations in the walls of the arteries and in calcareous degenerations elsewhere. As the activity of the thyroid decreases with advancing years it is not unlikely that the development of cataract may be hastened thereby. With these facts in view the statement first predicated may be carried a step further by saying:

That any interference, mechanical or otherwise, with the normal functioning of the hypophysis will exercise a controlling influence on the metabolism, the growth and development in the young subject, and on the nutrition and normality in the mature of all of the structures within the sphere of its activities.

We cannot, therefore, ignore in this connection the action of the other ductless glands. Gigantism is produced, not only by overaction of the pituitary, but, as Bramwell has shown, it is associated also with sexual development, and increased stature is a result of castration before puberty. With dispituitarism comes atrophy of the ovaries and testes so definitely that the relationship is incontestible. The diminutive stature of cretinism shows that the thyroids

and parathyroids have also an influence on elemental cellular structure, while in hypopituitarism the subnormal temperature, the slow pulse, the low blood pressure, the sluggish mentality give a clinical picture closely resembling the myxedema with thyroid insufficiency.

We have, then, in the series of ductless glands interacting ferments controlling cellular activities which are seemingly as potent as those which are developed in the elemental cell. There is no structure which escapes. With the enlargement of the bones of the face, with the modifications of the skin, and with the change in nerve structure, the fibrous tissues are at the same time involved. And when activity of any of these glands is disturbed, and the balance of function is lost resulting metamorphic changes may be expected, although they may manifest themselves only in the smallest degree. Morphogenetic substances and hormones act in very minute doses; they are substances which appear to act after the fashion of a nervous excitation or of a diastatic action; they bring no energy to the tissues or organs which they influence, but they only liberate pre-existing energy; they regulate anabolism and katabolism, construction and disintegration of the tissues.

It has already been shown that the action of the pituitary is to contract the arteries. The pathology of retinitis pigmentosa is that of a slow atrophic process with invasion by the pigment epithelium of the atrophic retina. In some cases the vessels are so reduced in size that they appear as white lines, and in others very dark lines can be discerned down the center of the pale path. Now when this is associated with those forms of physical development which would indicate an over-action of the anterior portion of the hypophysis, and a reduction of the action of the posterior portion, the condition which we would expect to find is thus described by Cobb. He says: "With one part of the gland functioning adequately, and the other deficient, the clinical picture might correspond to what is expected when the particular part of the gland is abnormal. Supposing the anterior part of the gland to be normal and the posterior deficient, we should expect a fully grown individual, but with excessive deposits of fat, slow circulation, sluggish mentality and the other features of hypopituitarism, with the exception of stunted skeletal development."

I have the good fortune of being able to present precisely such a picture in a lad twelve years old, who is five feet four inches in height. He weighs one hundred and twenty pounds. The clothes which he requires are those of a youth of eighteen years. He has a smooth skin, sexual organs quite undeveloped, he has a drooping

mouth, which is usually open, a slow pulse, a well developed sella with a pituitary apparently of normal size, a developing retinitis pigmentosa, markedly atrophic arteries, with the characteristic narrowing of the field.

And if the contention is correct, so forcefully urged by Jones, that the excessive or deficient action of the pituitary may modify the development of the eye structures, we should expect to find in advanced forms of hyperpituitarism changes in the nutrition of the globe. Unfortunately I do not find in a very large number of cases examined these changes have been noted. Even so careful an observer as Cushing merely notes in certain of his cases "that such a degree of visual acuity was secured when corrected," without mentioning the character of the correction employed.

It has been my good fortune to follow with very close attention a case of acromegaly since the year 1902. The characteristics are pathognomonic. The bitemporal hemianopsia follows an almost directly vertical line through the macula on one side and invading the macula on the other. When first observed there was an axial myopia of 10 diopters in each eye. This has progressively increased until it has reached 15 diopters but under glandular feeding all of the symptoms, except the limited field and the increased myopia, have been markedly relieved. The especial interest in this case is the length of time it has been under observation, the typical syndrome which it presents, the verification of hypophyseal hypertrophy by the Roentgenogram and the conclusion to which the demonstrable changes give warrant.

Miss M., who subsequently married, came under the observation of the writer in 1903. There was no suspicion at that time of there being anything other than the rather high degree of myopia, so that the general physical observations, which are not usually made by an ophthalmologist, were not recorded. There was nothing sufficiently characteristic in the facies to suggest the presence of the beginning of a serious organic disease, although a narrowing of the temporal fields was already present.

The patient who presented herself was rather a slight woman, 34 years of age, and about five feet six inches in height. Earlier pictures show very little of the coarseness of expression in the face which subsequently developed. She has light brown hair of moderately heavy texture, rather full, somewhat protuberant eyes, and a clear skin with a pink flush in the cheeks. She had worn glasses for the correction of her myopia since she was a little girl. At that

time she was having some discomfort in using her eyes, with an occasional sense of blurring. Her refraction under careful test was:

R—10 Dsph—50 Dcyl ax  $150^{\circ}$  v=20/30

L—10 Dsph—50 Dcyl ax  $180^{\circ}$  v=20/30

There was a choroidal atrophy around the disc with some pigmentary degenerative changes and a general fullness of the choroidal vessels without any marked staphyloma posticum.

Two years later, in 1905, the blurring was more frequent. Headaches had developed. The pain in the head began with scintillating motion on the temporal side; the pain usually being on the opposite side of the blurring eye. Vision was still 20/30 in each eye, with a slight change in the angle of the astigmatism, but as yet no increase in the myopia. About this time a change in the facial expression must have begun, although it was so gradual that no definite date can be fixed. The following year, 1906, still no refractive change, but vision had become reduced in the right eye to 20/40 and in the left to 20/30. No further changes in the eye ground.

In 1907 a slight increase in the myopia is recorded. Vision has been reduced to 20/30, with difficulty in each eye. The temporal fields are still narrowing. By 1911 the myopia has increased in each eye to 11.50 D. Vision reduced in the right to 20/40, in the left to 20/50.

The next year the bitemporal hemianopsia has markedly increased. In the left eye vision is 20/100. The macula has been invaded, only by looking to one side of an object can it be seen. At about this time an enlargement of the jaw is noticed. It begins to develop a prognathous form. She is conscious that the bite is different from formerly. The nose becomes broad and prominent, and a peculiar symptom develops, which may prove to be of importance in the subsequent study of this disease, and which the writer has not discovered in any of the observations connected with it. It is the opposite of the Stellwag sign in Morbus Basedowii. In place of the upper lid being retracted, showing a white scleral line and imperfectly following the eyeball in its downward excursion, the *lower lids droop showing a wide scleral line from below up*. There is still a proptosis, but not of a sufficiently marked character to attract notice, but the lower lids seem to sag down as though the nerve control were diminished. At about this period glandular feeding was begun. The face had assumed a somewhat myxedematous character and the treatment given was largely the substance of the thyroid, and the thymus gland of the corpus luteum. Once or twice the substance of the pituitary was given carefully and experimentally but with an aggravation of the symptoms.

By 1914 there was an increase of the myopia, also a distinct increase in the visual acuity. The refractive values were as follows:

R—13.00 D—1.50 Dcyl ax 105 v=20/30

L—14.00 D—1.50 Dcyl ax 75 v=20/30

The visual fields on each side were limited by the macula, marked staphyloma posticum, with a large crescent on the nasal side of each disc, but the headaches had wholly disappeared. The sense of blurring was also gone, and with definite bitemporal hemianopsia large objects could be discovered when moved through the obscured areas.

In March, 1917, fourteen years after the first observation, the subject, now a woman of 48 years of age, has a slight enlargement of the right lobe of the thyroid. Menstruation ceased at about the age of 37, but for a long time there was much irregularity in the menstrual functions. She has rather an excessive growth of hair on the face. All of the acromegalic symptoms, except that of height, are pronounced. The skin is clear, and at times she is subject to excessive perspiration which rolls off her face. Attacks of dizziness, to which she has been subject, have disappeared. Urinalysis shows nothing abnormal. Polyuria is present; sometimes she is obliged two or three times in the night to pass water. She likes sweets, but not excessively. Her digestion is good, her rheumatism is much better than formerly. Her fingers are square and chubbied. The field of vision taken on the tangent screen shows typical hemianopsia, almost directly vertical, reaching to the macula in the right eye and including the macula to the extent of 2 m. m. in the left.

From what has been written we might expect the symptoms produced by over-action of the anterior portion of the hypophysis might be corrected by the exhibition of the substance of the thyroid, and a sufficiently large number of cases are now on record in which enlargement of the restricted visual field, improvement in visual acuity and general physical betterment have been noted. Particularly striking are the cases reported by De Schweinitz (*Archives of Ophthalmology*, March, 1917). In addition to the substance of the thyroid that of the thymus has been of value. As hyperpituitarism causes a lengthening, a thickening, and a strengthening of the bones, *per contra* the hypofunction of the thymus renders the bones shorter, thinner and more fragile. As increased pituitarism is associated with, if not the direct cause of the atrophy of the testes and ovaries and the organism is deprived of the internal secretion of these glands, the employment of their substance in the absence of any

active principle obtained from them is especially justifiable. But the use of any of these materials cause at times profound effects and they should be used with judgment and caution. The initial dose should be small, and Cobb is undoubtedly correct in saying that these substances, especially that of the thyroid, are often given in doses that are too large.

In a paper presented before the New York Stomatological Society in 1902, and in another read before the American Society of Orthodontists in 1903, on the "Conformation of the Face in Relation to the Development of the Eye," the writer urged the importance of broadening the narrow jaw and removing lymphoid obstruction in the pharynx, in order that the lymph and nerve channels should be unimpeded, thereby preventing abnormalities in the area of distribution with the resultant atrophies, neuralgias and other trophic disturbances of the part involved. It was then urged that the marked benefit that follows adenectomies and the opening of obstructed nasal passages was not wholly dependent upon a freer admission of oxygen,—necessary as this is, because there may be occlusion of the nose, without any such group of symptoms as adenoids presents. The relief comes from the removal of the pressure on the nasopharyngeal vessels connecting with the hypophysis, the interference with the function of which causes an abnormal hebetude. Quite recently orthodontists are recognizing the importance of their work in this respect in the effect of the relaxation of constricted tissues upon physical growth.

There are two other ways at least in which the cavity of the endocrinal glands may be modified. The first is by excessive emotion,—and there are many such cases in which this is the exciting cause. The second has been urged by Mr. Lane in his work on the "Colon," and is toxic absorption.

Dr. Zentmeier, in his address before the Section on Ophthalmology of the American Medical Association in June last, found authority for ascribing to the disturbed action of the endocrinal glands hereditary optic nerve atrophy, optic atrophy with hyperthyroidism, an especial syndrome as described by Lamb, pigmentary degeneration of the retina as urged by Jones, retinal degenerative changes with osteitis deformans and amaurotic family idiocy.

Surely with such basic observations the subject is well worth the closest study until our knowledge of the relation of the ductless glands to organic eye changes is put on a more exact foundation.