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DYSPITUITARISM

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HISTORICAL

Vesalius was the first to describe the pituitary, and in his "De Corporis Humani Fabrica" he named it the "glans pituitam excipiens"; he believed that this gland secreted the nasal mucus (*Pituita*, phlegm). However, Galen many years before him knew of this gland, and judging from its well protected location, thought it was of great importance to the human economy. In 1778, Soemmering described it more fully and called it the "hypophysis cerebri." Both Vesalius and Soemmering were of the opinion that the pituitary is a gland; but as they could not find any duct, they considered it a part of the nervous system. Wepfer, Bonnet (1679) and Morgagni found colloid cysts in the pituitary, and Greding (1771) and Melcrave observed and described enlargements of the pituitary. Wenzel claimed that diseases of the pituitary may cause epilepsy; and in the light of present knowledge this is true; for many cases suffering from dyspituitarism have manifested epileptiform seizures.

In 1838, Rathke¹ discovered the dual origin of this gland from the floor of the third ventricle and from a diverticulum of the pharynx (Rathke's pouch). In 1840, Mohr demonstrated the relation of adiposity to tumors of the hypophysis. In 1860, Liégeois,² studying the anatomy of this organ, added it to the list of the ductless glands. Marie³ and Marinesco reported two cases of acromegaly in 1886, and although they were mistaken, in that they thought this disease was due to hyposecretion of this gland, they were the first to draw attention to the relationship between this disease and changes in the hypophysis. About this time Launois described gigantism, and thought that some of these cases may be due to diseases of the pituitary; but it was Cunningham, who, in 1891, had proved that gigantism and acromegaly are the same disease, the only difference being that gigantism was the result of

1. Rathke, H.: Ueber die entstehung der Glandula pituitaria, Arch. f. Anat. Physiol. u. wissenschaft. Med., 1838, No. 5, 482.

2. Liégeois: Anatomie et Physiologie des glandes vasculaires sanguines, Paris, 1860.

3. Marie, P.: Sur deux cas, d'acromegalie, Rev. de méd., 1886, vi, 297.

pituitary disease in cases where the epiphyseal centers had not yet ossified, and acromegaly in cases where ossification had taken place. In 1899 Oppenheim⁴ recognized the importance of x-ray examinations of the sellar region as an aid in diagnosis of tumors of the pituitary. Although Pechkranz correlated adiposity with abnormal skeletal changes, with anomalies of the hypophysis, and although Babinski⁵ reported a case of tumor of the pituitary without acromegaly in 1900, Fröhlich⁶ is usually given the credit of describing this type of dyspituitarism, in spite of the fact that his communication did not appear until 1901. To Cushing⁷ (1909) is due the credit of putting our knowledge of the secretion of the pituitary on a scientific basis; it is he who pointed out and clearly stated the functions of the individual lobes and showed that clinically we may have many different types, depending on whether one or both lobes are hypo- or hypersecreting. In 1912, Burnier⁸ collected a group of cases in which dwarfism is associated with hypophyseal symptoms; he refers to them as cases of "Hypophyseal Nanism."

Sir Victor Horsley was the first to publish a personal note regarding the experimental removal of the gland; however, the first actual contribution was made by Marinesco (1892); he concluded that the loss of the whole gland was compatible with life for a long time. The first studies which include any suggestive observations on the symptomatology of a pituitarism were published in 1892, and in 1894 by Vassale and Sacchi; among others who experimented were Cyon, Caselli, Friedmann, Maas and von Eiselsberg.⁹ The most important contribution was made in 1908 by Paulesco¹⁰ of Bucharest; he found that removal of the anterior lobe is equivalent to removal of the entire gland (i. e., death in

4. Oppenheim: Discussion, Arch. f. Psychiat., 1901, xxxiv, 303.

5. Babinski, J.: Tumeurs du corps pituitaire sans acromégalie et avec arrêt de développement des organes génitaux, Rev. neurol., 1900, viii, 531.

6. Fröhlich, A.: Ein Fall von Tumor der Hypophysis Cerebri ohne Akromegalie, Wien. klin. Rundschau., 1901, xv, 883.

7. Crow, S. J., Cushing, H., and Homans J.: Experimental Hypophysectomy, Bull. Johns Hopkins Hosp., 1910, xxi, 127; Effects of Hypophyseal Transplantation, Quart. Jour. Exper. Physiol., 1909, ii, 389; Cushing, H.: Sexual Infantilism with Optic Atrophy in Cases of Tumor Affecting the Hypophysis Cerebri, Jour. Nerv. and Ment. Dis., 1906, xxxvi, 704; The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism, Jour. Am. Med. Assn., 1909, liii, 249; Partial Hypophysectomy for Acromegaly, Ann. Surg., 1909, i, 1002; The Functions of the Pituitary Body, Am. Jour. Med. Sc., 1910, xxxix, 473; 1913, cxlv, 313; Diseases of the Pituitary, 1912; Cushing H., and Goetsch, E.: Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and Its Presence in the Cerebrospinal Fluid, Am. Jour. Physiol., 1910, xxvii, 60.

8. Burnier: Hypophyseal Nanism, Ann. Ophthal., January, 1912.

9. Eiselsberg, F. v.: Discussion Wien klin. Wehnschr., 1909, xxii, 287; Operations on the Hypophysis, Tr. Am. Surg. Assn., 1910, xxviii, 55; Am. Surg., 1910, lii, 1; Arch. Chir., 1912.

10. Paulesco, N. C.: L'hypophyse du cerveau, Paris, 1908, Vigot Frere.

twenty-four hours); that loss of the posterior lobe led to no appreciable disturbances, and that separation of the stalk from the base of the brain amounted to a complete or nearly complete removal, as the case might be. In the same year (1908) appeared the notable work of Herring¹¹ on the anatomy and the histology of the pituitary.

The first operations on the hypophysis were by Horsley;¹² the operative procedure in attacking the hypophysis has been studied on cadavers by Lowe and Koenig, Jr., but has been cleared essentially by Schloffer,¹³ who also operated on the first patient on the continent in March, 1907.

ANATOMY OF THE PITUITARY

The pituitary body is found in all vertebrates; the development of this gland begins very early in embryonic life. The pituitary is a small reddish-gray, vascular mass of an oval form, situated in the sella turcica, where it is retained by a process of dura mater; this process covers the sella turcica and has a small hole in its center through which the infundibulum passes. The pituitary has a dual origin, the cerebral part develops from a hollow protrusion which comes down from the floor of the third ventricle; the ectodermic portion originates from a diverticulum of the pharynx (Rathke's pouch) which passes upward and unites with the cerebral portion to form the adult gland. As development goes on the anterior or lower part of the closed sac becomes thickened, forming the anterior part of the pituitary body. A more or less definite cleft separates this portion from the posterior lobe, which is composed of the cerebral portion and of the upper portion of the primitive closed sac; these two parts become closely adherent and remain functionally associated; thus the neural part becomes surrounded by an intimate epithelial investment possessing a different histological picture from that which characterizes the anterior lobe, though the two are of ectodermic origin. The epithelial investment of the posterior lobe, together with its upward extension on the outer walls of the infundibular stalk, is designated the pars intermedia. During fetal life the posterior lobe contains a cavity which communicates through the infundibulum with the cavity of the third ventricle; in the adult it becomes firmer and more solid, and the cavity is replaced by lymph-channels, surrounded by cells; these lymph-channels empty directly into the cavity of the third ventricle.

11. Herring, P. T.: The Histological Appearance of the Mammalian Pituitary Body, *Quart. Jour. Exper. Physiol.*, 1908, i, 121; The Development of the Mammalian Pituitary and Its Morphological Significance, *Ibid.*, p. 161; A Contribution to the Comparative Physiology of the Pituitary Body, *Ibid.*, p. 261.

12. Horsley, V.: On the Technic of Operations on the Central Nervous System, *Brit. Med. Jour.*, 1906, ii, 411.

13. Schloffer, H.: Zur frage der Operationen an der Hypophysis, *Beitr. z. klin. Chir.*, 1906, i, 767.

In the cat the posterior lobe retains throughout life its original cavity in free communication with the third ventricle of the brain; the parts which are derived from the buccal epithelium form an almost complete investment for the nervous portion, and the original lumen of the epithelial pouch also persists throughout life in the form of a well-marked cleft.

The pituitary of the monkey more closely resembles that of man, and is a type in which greater fusion of the original elements from which it has developed has taken place. The posterior lobe is solid throughout. Its investment by the epithelial portion is not so complete as it is in the cat, and only a small cleft remains as the representative of the original buccal pouch.

The pituitary in man is therefore composed of a large anterior lobe (*pars anterior*), composed entirely of epithelial tissue; of a posterior lobe (*pars nervosa*) which is of neural origin, and of an intermediate portion (*pars intermedia*), which, though of neural origin, becomes invested by and intimately fused with a portion of the epithelial sac.

The anterior lobe consists of large granular cells and numerous blood-vessels; the protoplasm of some of these cells being receptive to eosin, some to hematoxylin and some barely staining at all; it is a gland producing an internal secretion, which is poured directly into the blood. The *pars intermedia* is composed largely of neutrophilic elements. The posterior lobe is made up of two structures; of these the part developed from the brain and consisting of neuroglia and ependyma cells and fibers acts as a framework; it is more or less surrounded and invaded by epithelium which probably furnishes its active part; the secretion passes into the lymph-vessels and is destined to enter the ventricles of the brain.

The *pars anterior* is very vascular,¹⁴ and the *pars nervosa* is poor in blood-vessels. The anterior lobe receives its blood-supply from about eighteen or twenty small arteries which converge toward the stalk from the various components of the circle of Willis; these vessels immediately break up into numerous large sinusoidal spaces, in apposition with the cells, and are lined only by endothelium; hence there are no veins or arteries proper in the anterior lobe.

The *pars intermedia* derives its supply from the vessels of the stalk, from the adjacent brain and from the posterior lobe. The posterior lobe receives its arterial supply from a small artery formed by the union of symmetrical branches from each internal carotid.

According to Creutzfeldt,¹⁵ the hypophysis in the new-born is cylindrical, and its dimensions are, sagittal diameter 5 mm., frontal 9 to 11 mm., vertical 2 mm., and its weight is 90 to 150 mg.; at 10 years it

14. Dandy, W. E., and Goetsch, E.: The Blood-Supply of the Pituitary Body, *Am. Jour. Anat.*, 1911, ii, 137.

assumes a more oval form, mostly due to growth of anterior lobe; it continues to grow to 30 years, is stationary until 40 to 50 years, and then begins to decline. In adults it has an oval form and is larger in women than in men; its weight is 550 to 800 mg.; the sagittal diameter is 6 to 10.5 mm., the frontal 10 to 14.5 mm., and the vertical 5.9 to 9.75 mm.

Erdheim and Stumme¹⁶ examined 150 glands of pregnant women; they noted a color change from gray-red to white, and an increase in size and weight of the structure (900 to 1,800 mg.).

EXPERIMENTAL DATA

The researches of Goetch, Cushing, Jacobson,¹⁷ Crowe and Homans,⁷ and Weed, Cushing and Jacobson,¹⁸ have put our knowledge of the physiology of the pituitary on a firm foundation. On the whole, they were able to confirm the findings of Paulesco. They discovered that total removal of the gland in adult dogs causes death in two or three days, with symptoms of cachexia hypophysipriva; in puppies death does not follow for ten days (three to twenty). The symptoms of cachexia usually do not appear for twenty-four to forty-eight hours after the removal of the gland; a marked diminution of urinary output, even to anuria and a transient glycosuria may occur immediately after operation in adult dogs; and in puppies a post-operative polyuria has been often observed, contrasting with the opposite condition seen in the adult dogs. The symptoms of cachexia are unsteadiness of gait and lowered body temperature; an awkward arching of the back, with incurvature of the tail is characteristic; later there is still further fall of temperature, slow respiration, slow pulse, irregular muscular contraction, tremors, lethargy, anesthesia, coma and death; the temperature just before death may fall 20 C. Grafts in cases of total removal cause a distinct prolongation of life through this means.

The effects of posterior lobe removal are inconclusive; some of the dogs had convulsive attacks with maniacal excitement and persistent erotomania.

The results of partial removal of the anterior lobe are the same if the posterior lobe is removed also. In puppies such removal leads to

15. Creutzfeldt, H. G.: Ein Beitrag zur normalen und pathologischen Anatomie der Hypophysis Cerebri des Menschen, *Jahrb. d. Hanb. Staatskrankenanst.*, 1909, xiii, 273; Drie Falle von Tumor hypophysen ohne Akromegalie, *Ibid.*, 351.

16. Erdheim, J., and Stumme, E.: Ueber die Schwangerschaftsveränderung der Hypophyse, *Beitr. z. path. Anat. v. z. allg. Path.*, 1909, lvi, 1.

17. Goetsch, E., Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, *Bull. Johns Hopkins Hosp.*, 1911, xxii, 165.

18. Weed, L. A., Cushing, H., and Jacobson, C.: Further Studies on the Role of the Hypophysis in the Metabolism of Carbohydrates, *Bull. Johns Hopkins Hosp.*, 1913, xxiv, 33.

infantilism; the animals remain undersized and the secondary sexual characteristics do not develop; there is also a tendency to hypotrichosis and to subnormal temperature. In adult dogs partial removal causes adiposity, sexual degeneration, subnormal temperature, hypotrichosis, polyuria and somnolence or restless playfulness.

Total removal of the anterior lobe causes death in sixty-eight hours with symptoms of cachexia; the consequences of stalk separation are equivalent to a total or nearly total hypophysectomy.

They also found that repeated injections of the entire gland cause a rapid loss of weight in puppies and in adult dogs; in cases of anterior lobe insufficiency injections of anterior lobe extract cause a thermic response (2 to 4 C.).

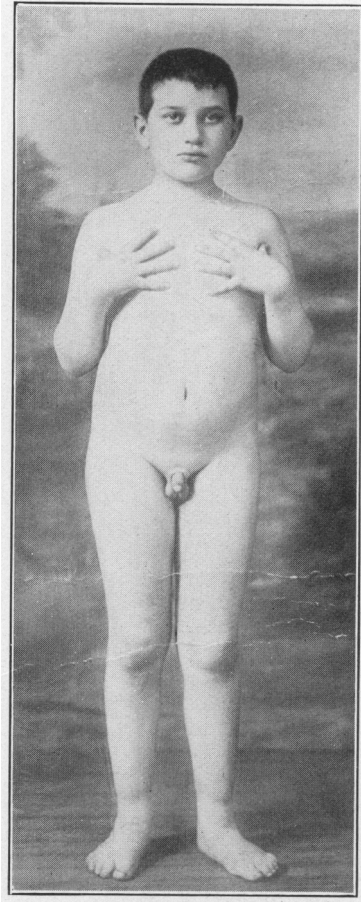
The occasional appearance of glycosuria after hypophysectomy had led these observers to further study along this line. They noticed that removal of the posterior lobe and part of the anterior lobe causes a primary fall and a subsequent rise above the normal in the assimilation limit for sugars; that removal of part of the anterior lobe, however, produces little or no alteration in the carbohydrate assimilation limit; the removal of posterior lobe alone causes no primary glycosuria, unless there is considerable traumatism of the stalk, but there is an increased sugar tolerance; this increased tolerance can be brought down to normal by giving posterior lobe extract, 1/20 gm. subcutaneously, 1/80 gm. intravenously; or 2/5 gm. by mouth. In man the normal limit for glucose by mouth is 150 gm., and for levulose 100 gm. It will be seen that in cases of posterior lobe insufficiency there is an increased sugar tolerance; such patients can take as much as 400 gm. of glucose without appearance of glycosuria.

To summarize, we may say that total removal of the gland, or total removal of the anterior lobe, causes death in two or three days, with symptoms of cachexia. Anterior lobe insufficiency in puppies caused adiposity, skeletal infantilism and failure in appearance of the secondary sexual characteristics; in adult dogs anterior lobe insufficiency causes adiposity and sexual degeneration. The symptoms of posterior lobe insufficiency are increased sugar tolerance, subnormal temperature, hypotrichosis, dry skin, low blood-pressure, adiposity and large appetite.

RELATION OF DIABETES INSIPIDUS TO DYSPIUITARISM

It has long been recognized that polyuria with the appearance of dextrose in the urine is a not infrequent accompaniment of acromegaly; but it is only within the last year that both experimental and clinical evidence has accumulated to prove that diabetes insipidus is probably due to disturbed secretion of the pituitary.

In 1674 Thomas Willis first recognized a distinction between two forms of diabetes, a saccharine and a non-saccharine. Claude Bernard discovered his so-called diabetic center in 1849; this point is situated in the floor of the fourth ventricle, between the centers of the pneumogastric and the auditory nerves; puncture at a point a little lower, causes simple polyuria, while puncture at a point a little higher in the frontal direction causes albuminuria.



Author's patient with hypopituitarism.

Cushing found that after certain experimental manipulations of the canine hypophysis, a postoperative polyuria was of frequent occurrence; in adults oliguria rather than diuresis follows a total extirpation; in younger animals there was diuresis. On the other hand, in a series of partial extirpations, postoperative polyuria was almost always observed. Experiments support the view that the clean-cut posterior lobe removals elicit polyuria with the greatest regularity. Schäfer found that posterior

lobe substance given by mouth increases the urinary output; the experimental polyurias have therefore been brought about either by a direct hypophyseal insult, by the injection of extracts, or by glandular implantations. An hypophyseal diuresis may also be elicited by nerve stimulation.

A review of the clinical histories included in many of the past articles on diabetes insipidus makes it clear that a large per cent. have shown symptoms found in lesions involving the base of the brain; a gummatous meningitis affecting the structures in the middle cerebral fossa being a particularly common accompaniment of the disorder. Fuchter and Frank have emphasized the surprising frequency with which primary optic atrophy, often with bitemporal hemianopsias which accompany the encephalitic polyurias, are classified as diabetes insipidus. Kohler in seven of his twenty-two cases of diabetes insipidus found an affection of the infundibulum; Oppenheim in thirty-six patients with basilar luetic meningitis observed polyuria in twelve; Kruse in thirty-four cases of bitemporal hemianopsia noticed diabetes insipidus in seven cases; Oppenheim in two cases of general cerebral symptoms with double temporal hemianopsia and diabetes insipidus found on autopsy a gumma in the region of the chiasma in one case, and a gummatous meningitis in the region of the chiasma in another; in 1882 Hagenbach found a tubercle in the infundibulum of a girl ($4\frac{1}{2}$ years old) who had suffered a good deal from thirst and polyuria; in 1903 Rosenhaupt reported a case of diabetes insipidus in which a sarcoma of the anterior lobe of the hypophysis was found; in 1913 Frank reported a case of diabetes insipidus, due to a metastatic carcinoma of the hypophysis, and Simmond reported a case due to a gunshot wound of the hypophyseal neighborhood. The evidence, both experimental and clinical, is therefore in favor of the view that diabetes insipidus is probably a manifestation of dyspituitarism.

THE NERVOUS CONTROL OF PITUITARY SECRETION

Recent studies by Dandy demonstrated the presence of non-medulated fibers coursing from the carotid plexus into both lobes of the pituitary body. This histological demonstration of a sympathetic nerve supply to the gland spoke in favor of a possible nervous influence over its secretion. This discovery led Weed, Jacobson and Cushing¹⁸ to study the nervous control of pituitary secretion, and to further studies on the rôle of the hypophysis in the metabolism of carbohydrates. They found, "provided there is a storage of glycogen available for discharge," that:

1. A piqûre of the hypophysis in the rabbit is comparable in its glycosuric response to piqûre of Bernard's so-called sugar center in the fourth ventricle.
2. Stimulation of superior cervical ganglion by faradization, or even by the manipulation necessary for its exposure, causes glycosuria in the rabbit, cat and dog.

3. Stimulation of the superior cervical ganglion, after exclusion of all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks, or spinal cord, leads to glycosuria.

4. Stimulation of the superior cervical ganglion, after separation of all synapses of the sympathetic system by administration of nicotin, causes glycosuria.

5. Direct faradic stimulation of the hypophysis itself, by a transphenoidal operation, gives glycosuria even after preliminary transection of the spinal cord and cervical sympathetic trunks.

6. If the posterior lobe of the hypophysis has previously been removed by operation the usual stimulation of the superior cervical ganglion fails to give glycosuria.

7. Direct faradic stimulation of the hypophysis provokes glycosuria, even after transection of the spinal cord above the splanchnics.

8. A Bernard piqure will likewise cause glycosuria even after transection of the spinal cord above the splanchnics.

They came to the conclusion that stimulation of the superior cervical ganglion causes a discharge into the blood-stream of the posterior lobe secretion; this substance is presumably carried through the vascular system to the glycogen storehouses of the body, where it inaugurates glycogenolysis.

PHYSIOLOGICAL ACTION OF PITUITARY EXTRACT

Schäfer¹⁹ and Oliver were the first to study the physiological action of pituitary extract; they experimented with the whole gland. They found that watery or salt extracts, even when boiled, raised the blood-pressure and constricted the peripheral blood-vessels. In 1898 Howell observed that the blood-pressure rise was due to posterior lobe extract only, and that when the blood-pressure was raised the pulse was slowed. In 1901 Magnus and Schäfer noticed that the pituitary extract was diuretic, and in 1906 Herring and Schäfer²⁰ observed that although posterior lobe extract constricts the arteries of the whole body, it dilates the arteries of the kidneys. Wiggers pointed out that the extract slows the heart and increases the amplitude of its contractions; he also observed that it inhibits the flow of pancreatic juice and is mydriatic. Other writers^{21, 22} have discovered that pituitary extract causes contraction of uterine, vesical and intestinal muscles, and that it promotes the secretion of milk. Cushing pointed out that in puppies suffering from hypopituitarism, injections of anterior lobe stimulate growth and cause

19. Schäfer, E. A.: Die Functionen des Gehirnanhangs, Berner Universitätschriften, 1911, part B; Schäfer, E. A., and Vincent, S.: The Physiological Effects of Extracts of the Pituitary Body, *Jour. Physiol.*, 1899-1900, xxv, 87.

20. Schäfer and Herring, P. T.: The Action of the Pituitary Extract Upon the Kidney, *Phil. Tr.*, London, 1906, cxcix, 1.

21. Bell, W. B.: The Pituitary Body and the Therapeutic Value of the Infundibular Shock, Uterine Atony and Intestinal Paresis, *Brit. Med. Jour.*, 1909, ii, 1609.

22. Biedl, A.: *Innere Sekretion*, Berlin, 1910.

a thermic rise (2 to 4 C.), and that injections of posterior lobe lead to emaciation and reduced sugar tolerance.

CLINICAL MANIFESTATIONS OF DYSPIUITARISM

In man the clinical manifestations are nearly the same as those found by Cushing in dogs; the symptoms resolve themselves into those due to, (1) hypo- or hypersecretion or perversion of secretion of the gland itself; (2) those due to increased cerebral pressure; (3) those due to the local pressure of the tumor, and (4) those due to the involvement of the other ductless glands.

Deficiency of anterior lobe in children leads to infantilism; there is inhibition of skeletal development. Hypersecretion of the anterior lobe leads to gigantism in cases in which the epiphyseal centers had not yet ossified, and to acromegaly in adults; that gigantism and acromegaly are closely related is evident from the observations of Sternberg;²³ he found that 20 per cent. acromegals are over 5 feet 10 inches in height, and that 40 per cent. of all giants have some signs of acromegaly. In hyperpituitarism there is hypertrophic alteration of the skin, and increase in size of the hair follicles; there is also hypertrophy of the papillae and activation of the secretory glands; so that the skin becomes greasy and moist; hypertrichosis is marked. Deficiency of posterior lobe is usually associated with adiposity and increased sugar tolerance; the temperature is usually subnormal, and the subjective chilliness and drowsiness indicate diminished metabolism. The skin is usually smooth; may even suggest edema, but does not pit; hair on the scalp may be abundant, but axillary and pubic hair may be entirely wanting; the nails are often small and do not show the crescent at their base; constipation is often obstinate and usually improves on glandular therapy; psychic disturbances are frequent and are usually due to involvement of frontal and temporal lobes. The symptoms of cerebral involvement are, change in disposition, enfeeblement of memory, disorientation and ". . . notable always is the utter lack of appreciation of, and complete indifference to, the existing condition." In hyperpituitarism, temperamental changes, wakefulness, lack of concentration and irritability are more common; in hypopituitarism mild psychoses to extreme mental derangements with epilepsy are not infrequent.

SYMPTOMS OF INCREASED CEREBRAL PRESSURE

These are too well known to need any detailed mention here; they are, in general, headache, general convulsions, double optic neuritis and optic atrophy, change of disposition and of mental power, vomiting, vertigo, changes in the pulse-rate and attacks of syncope; the general

23. Sternberg, M.: *Beitrage zur Kenntniss der Akromegalie*, Ztschr. f. klin. Med., 1895, xxvii, 86.

symptoms occur irrespective of the location of the tumor and depend on its rapidity of growth, its vascularity and its pathological character. They vary in severity from time to time. When a tumor is growing rapidly they are very severe; if it remains stationary, they may almost disappear. Headache is the most important and constant symptom of brain tumor; it varies in intensity, but is usually severe; general convulsions are the next most frequent symptom of brain tumor; they are particularly liable to occur as an early symptom in children; vomiting is also more frequently observed in children than in adults; it usually occurs without special relation to the time of meals.

NEIGHBORHOOD SYMPTOMS

One of the most important local symptoms is primary optic atrophy; later there is a superimposed optic neuritis due to the growth reaching a large state. There is some distortion in the visual fields in almost all cases; bilateral defects are almost twice as common as homonymous lesions; mere tendencies toward temporal defects must be carefully looked for; particularly defects limited to color peripheries. The primary defect usually first involves the color boundaries alone, in one upper temporal quadrant; this is followed by a more or less complete temporal hemiachromatopsia; in all cases the color fields become involved first, the form fields later; the macular area is often spared for a long time, but finally becomes implicated; rarely are the two eyes affected to the same degree. Abnormal pupillary conditions are often present; a definite hemiopic pupillary response and a negative oculomotor reaction to the prism deflection of an image in the blind half of the retina may be expected when only half blindness is complete. Oculomotor implication is often present, as are also double vision, palsies and nystagmus.

Other nerves may be involved; the individual may have anosmia, trifacial neuralgia and spasticity due to pressure on the central peduncles. Uncinate seizures are surprisingly common and the frontal lobe is not infrequently involved.

He may also have local signs in the nasopharynx, as troublesome epistaxis, intermittent discharge of mucus into the pharynx and in a few a tumor can be seen and felt in the retropharynx.

Among the most important of the local symptoms is deformation of the sella turcica; extreme hypersecretion and hyposcretion may exist with but little if any alteration in the shadow cast by the bony encasement of the gland; the sella may be well preserved, even though the tumor may be enormous and has been of long duration. There are three types of sella deformation; (1) those associated with thickening of the clinoids and dorsum epiphii; (2) those with thinning from pressure absorption of these parts, and (3) those with more or less destruction of

all outlines. Equally important are the abnormally small sellae, which accompany the primary glandular hypoplasias of the young.

SYMPTOMS REFERABLE TO OTHER DUCTLESS GLANDS

Although our knowledge of the internal secretions is incomplete and confused, much progress has been made in this branch of medical science in the last decade. One fact has been clearly brought out, and that is that the physiological connection of all the ductless glands is an intimate one, and that in pathological conditions of one of them all the other glands are affected.^{24, 25, 26, 27, 28} The influence of one gland on another may be compensatory or inhibitory. The existence of a relationship between the thyroid and the hypophysis is perhaps the most satisfactorily demonstrated of all the possible interrelations of endosecretory organs. Rogowitch has found that after thyroidectomy the pituitary hypertrophies. In Basedow's disease sex functions are often affected; in myxedema there is sex depression. Parchow and Goldstein have concluded that there exists a distinct antagonism between the thyroid and the ovaries. Charrin and Jardy,²⁹ however, came to the opposite conclusion. Cooper had observed hypertrophy of the thymus in Basedow's disease. In Switzerland the offspring of goitrous mothers have both thymus and thyroids enlarged; thyroidectomy raises the assimilation limit for dextrose, showing the influence of the thyroid on the pancreas. A theory that the adrenals are related to the sex functions was proposed by Meckel (1806); in certain aborted fetuses he had noted that both the adrenals and the gonads were lacking; in animals in which sexuality is marked, the adrenals are notably large; in birds and in amphibia the gonads and the adrenals are closely associated in position. Bullock³⁰ and Sequeira have been able to find in the clinical literature twelve cases of children showing sexual precocity, who at autopsy were found to have enlarged adrenals; ten of these were females from 2 to 11 years of age. Pansini and Boneanti noticed hypertrophy of the thymus in Addison's disease. Erdheim and Stumme¹⁶ found hypertrophy of the pituitary in pregnancy; the pituitary is normally held in check by secretions of the gonads.

24. Hopkins, R. G.: The Interrelation of the Organs of Internal Secretion, *Am. Jour. Med. Sc.*, 1911, cxli, 374.

25. Kidd, L. J.: The Pineal Body, *Med. Chronicle*, 1912, lvii, 154.

26. Sajous: *The Internal Secretions*, 1912.

27. Tandler, M.: Ueber den Einfluss der innersekretion Anteile der Geschlechtsdrüsen auf die äussere Erscheinung des Menschen, *Wien. klin. Wchnschr.*, 1910, xxiii, 459-467.

28. Vincent, S.: *Internal Secretions and the Ductless Glands*, London, 1912.

29. Charrin and Jardy: *Comp. rend. Acad. d. sc. Paris*, 1906, cxlii, 1442.

30. Bullock, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, *Tr. Path. Soc. London*, 1905, lvi, 189.

Enough has been stated to substantiate the statement that every disturbance of a ductless gland is really a polyglandular disturbance, and that some of the symptoms present in disturbances of any one of the glands are probably due to the secondary involvement of the other glands.

In studying the table, it will be evident that the presence of any of the following symptoms in any case should arouse our suspicion of a disturbance in the ductless gland system. The symptoms are as follows: Dwarfism or skeletal overgrowth, adiposity or emaciation, sexual precociousness or impotence, hypertrichosis or hypotrichosis, genital hyperplasia or atrophy, mental precociousness or dulness, high or low blood-pressure, glycosuria or increased carbohydrate tolerance, asthenia, pigmentation of the skin and subnormal temperature. This table also shows that, although the same symptom may be present in disturbances of different glands, yet there are symptom-complexes which are pathognomonic and strongly point to the involvement of a particular gland.

The following symptoms present in dyspituitarism are referable to secondary involvement of the other ductless glands: Imperfectly acquired secondary sexual characteristics in cases in which the lesion antedates puberty, and of resultant amenorrhea or impotence with retrogressive sexual changes, when the malady develops after the acquirement of adolescence; pigmentation of the skin, asthenia, low blood-pressure and hypoglycemia point to adrenal involvement.

PATHOLOGY

Disturbances of the pituitary may be primary or secondary, functional or organic. The primary organic disturbances may be due to hyperplasia of the gland, to tumors of the gland or to tumors arising in the neighborhood of the pituitary, and which compress it and alter its secretion; such tumors usually do not cause acromegaly; any tumor of the brain or anything which prevents the secretion of this gland (e. g., hydrocephalus) from entering the third ventricle, may cause symptoms of dyspituitarism.

In 29 cases that were operated or came to autopsy, Cushing found that 23 were due to homoplastic epithelial growths and 6 were heteroplastic; of these, 1 originated from a developmental rest, 2 were teratomas, 2 infundibular cysts and 1 endothelioma. Of 60 cases of acromegaly which came to autopsy, collected by Creutzfeldt,¹⁵ 8.3 per cent. were without any hypophyseal changes; 25 per cent. were sarcoma; 20 per cent. hyperplasias; 13.3 per cent. struma; 20 per cent. adenoma; 1.6 per cent. glioma; 6.6 per cent. no definite diagnosis made. In 55 cases of tumor of the hypophysis, without acromegaly, he found sarcoma in 27.27 per cent.; hyperplasia in 9.09 per cent.; struma in 5.45 per cent.; ade-

noma in 18.18 per cent.; *Platten epitheltumoren*, 34.54 per cent.; teratoma, 1.8 per cent.; lipoma, 1.8 per cent., and metastatic, 1.8 per cent.

CLINICAL TYPES

One of the earliest types to be recognized is acromegaly.³ This type is too well known to need any detailed description. Closely associated with this type are the cases of gigantism;³¹ they are both due to hypersecretion of the anterior lobe; gigantism occurs in cases in which the epiphyseal centers had not yet ossified; whereas, acromegaly usually occurs in adults; still cases of acromegaly have been reported in children by Antonini and Marzocchi, de Cyon,³² Rake, Salle and others. The most notable symptoms of acromegaly are skeletal overgrowth, *main en large*, phalangeal alteration, mandibular prognathism, spacing of teeth, rounding of shoulders, sternoclavicular enlargement, peculiar cranial configuration and hypertrichosis.

TYPE FRÖHLICH

To this type⁶ belong those cases which have neighborhood symptoms of tumor of the hypophysis, without any evidences of acromegaly; these cases have a peculiar adiposity; with a feminine type of distribution of the fat when it occurs in males; there is aplasia of the genitals, hypotrichosis, subnormal temperature, undersized stature, psychoses of varying nature and increased carbohydrate tolerance. These cases are due to hyposecretion of the posterior lobe. Such cases in children have been reported by Fröhlich, Babinski, Hochwart, Uhlthoff, Cagnetto,³³ Erdheim, Israel, Woolcombe, Creutzfeldt, Cushing and others.

TYPES BURNIER

In 1912 Burnier⁸ collected a group of cases from the literature and added one of his own cases, which in addition to local signs of hypophyseal tumor and signs of posterior lobe insufficiency, showed marked dwarfism. These cases are due to hyposecretion of both lobes. The most important symptoms of this type are optic nerve atrophy (almost invariably present), adiposity, dwarfism and atrophy of external and internal genitals. Such cases have been recorded by Burnier, Kon, Benda, Hutchinson, Heuter, Bartels, Nazair, Zöllner, Mixter and Quackenboss and others.

TYPE CUSHING

It is Cushing who pointed out that a pituitary may be hypersecreting at one time and hyposecreting at another; and that in fact all cases of

31. Launois, P. E., and Roy, P.: *Etude biologique sur les géante*, Paris, 1904.

32. Cyon: *Prog. méd.*, 1898.

33. Cagnetto: *Virchow's Arch. f. path. Anat.*, 1904.

hyperpituitarism show evidences of hypopituitarism as the disease progresses. It is he also who made the observation that one lobe may be hypersecreting and the other lobe hyposecreting at the same time; and thus we may have a variety of mixed types. He especially called attention to cases of skeletal overgrowth associated with adiposity and sexual infantilism without acromegaly.

DIAGNOSIS

Diagnosis of acromegaly and gigantism is simple; the Roentgen rays, however, are of great aid. They may show an enlarged sella turcica, or they may show enlargement, broadening and tufting of the phalanges. In posterior lobe insufficiency, the estimation of the sugar tolerance is of importance. We must always suspect posterior lobe insufficiency in individuals who can take more than 150 gm. glucose and 100 gm. levulose by mouth without glycosuria. In some cases of anterior lobe hyposecretion there is a thermic response when they receive an injection of anterior lobe extract. The symptom-complex of skeletal overgrowth or dwarfism, adiposity, genital atrophy, optic nerve atrophy, deformation of sella and increased carbohydrate tolerance are absolutely pathognomonic of dyspituitarism.

TREATMENT

Treatment may be medical, surgical or both; surgical intervention is indicated to relieve general central pressure; to relieve neighborhood symptoms and to implant pituitary gland in cases of hyposecretion. To relieve general cerebral pressure symptoms a subtemporal decompression is indicated; for the neighborhood symptoms, fragmentary extirpation of the tumor or removal of the sellar floor and opening of the capsule are the operations of choice in the absence of pressure symptoms, but when headaches are very severe a sellar decompression should be advised. The medical treatment consists in the application of radium after operation and the administration of whole gland extract by mouth or hypodermically, the dose varying in each case, depending on the amount of posterior lobe insufficiency.

Alex. K., 12 years old, was brought to the Vanderbilt clinic (Pediatric section), by his mother, April 27, 1912. The mother's chief concern was that her son's genitals were very much undeveloped; she also stated that he suffered a great deal from headaches, vertigo, double vision and vomiting, and that he always felt cold.

Family history was negative. A brother of the patient, who had also been treated at the clinic two years previously, was a Mongolian idiot and had died of pneumonia. The birth of the patient was normal; he was breast fed for nine months; he had pneumonia at 5 months and measles at 1 year; suppurative adenitis at 2 years; no other acute illness; for the last two or three years the patient had been complaining of headaches, double vision, vertigo and vomiting; the vomiting was regardless of the nature of food or time of feeding. He was always cold and suffered a good deal from constipation.

Physical examination revealed a very well nourished boy; weight 93½ pounds (normal weight for boy of 12 years is 81 pounds); height 53 inches (that is 4 inches undersized for his age); facies was somewhat peculiar and the expression anxious; slight exophthalmos was present; no enlargement of the thyroid could be made out; chest and abdomen negative; the adiposity was of a feminine type of distribution; the fat folds over the hips, knees and feet were quite marked; the genitals were hypoplastic; there were no axillary nor pubic hair; the fingers were of a peculiar tapering kind; there was a fine tremor of the fingers present; the pulse was 84 to the minute; temperature 97.8 F.; examination of the eyes revealed a bitemporal hemianopsia; mentality was normal; Roentgen ray examination of the hands showed nothing abnormal; that of the head showed slight enlargement of the sella turcica.

May 14, 1912, the patient was given 250 gm. of glucose on an empty stomach, and all subsequent specimens of urine were collected; none showed any sugar; this was repeated three times with the same result; levulose the patient could not tolerate in any form; it was invariably vomited. The patient was given 10 grains of pituitary extract (whole gland) three times a day. The urine was constantly examined while the patient was under treatment and no glycosuria appeared; the temperature, which was subnormal before treatment; never ranged lower than 99 F. after treatment was instituted; the constipation was also much relieved; the pulse ranged from 85 to 100. Under treatment the patient lost 10 pounds in two months; treatment had no effect on the headaches, vertigo or vomiting; a sellar decompression was suggested, but was refused and the patient stopped coming to the clinic.

The presence of genital hypoplasia, hypotrichosis, adiposis, skeletal undergrowth, with symptoms of cerebral pressure and an enlarged sella turcica, led us to conclude that we were dealing with a case of hyposecretion of both lobes (type Fröhlich), probably due to a tumorous growth. The presence of slight exophthalmos, tachycardia and tremor suggest the presence of hyperthyroidism, which is secondary and probably of a compensatory nature, as the thyroid and the pituitary are synergic.

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