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Harvey Cushing's interest in the pituitary gland resulted in more than 360 publications over a period of 30 years. The title of one of these, 'Is the pituitary gland the maintenance of life?', indicates how little was known about this structure in 1909. During the years that followed, Dr. Cushing played a significant role in the elucidation of pituitary function by closely examining clinical examples of pituitary malfunction. He established the surgical treatment of the pituitary adenomas and crystallized the concepts of hypophysectomy and hyperpituitarism.

Cushing's interest in patients with pituitary disorders was not limited to their scientific aspects.

"Cushing was always fascinated by the circus, particularly by the sideshows where he obtained stories of the giants, fat women, and dwarfs, and any other freak that might happen to be on display. In this way he made friends with many circus personalities and over the years managed to keep in touch with several well-known giants and dwarfs. Mr. Arthur Keith, the distinguished curator of the Hunterian Museum, commented some years ago, on Cushing's interest in the removal of the top of the skull of the famous Irish giant whose skeleton had long been on display in the Museum in order to accentuate the condition of the sela turcica where the pituitary body would have been. Sure enough, the sela was greatly enlarged and there was evidence that there had been a sizeable intracranial extension of the pituitary tumor."

But H.C. was as much interested in dwarfs as in giants, and many of his friends and patients agreed that during the hot summer of 1929 after the family went to Little Bear's Head he surreptitiously filled the house with dwarfs on whom an attempt was being made to test the efficacy of some growth hormones recently purified by Herbert Evans."

One of the circus patients "...was the subject of a letter which H.C. felt impelled to send to Time magazine after she had been made the object of ridicule in a previous issue. The letter, which Time published under the caption 'Skin Deep', ran as follows:

"Sir... May I accordingly tell you something of the woman whose picture you published or p. 17 of Time, May 2, 1927 under the caption 'Ugly'? This unfortunate woman who sits in the side show of Ringling Brothers Between Pat Lady and Armless Wonder and 'afflicts white hair, woolen mitens and high laced shoes' has a story which is far from mirth provoking. Could it have been written up for you by O. Henry, it would have provoked tears rather than laughter. The facts are as follows: She is, as you say, a peasant of Kent and four times a mother. The father of these four children, a truck gardener, died three years ago and left her their sole support. She, previously a vigorous and good looking young woman, has become the victim of a disease known as acromegaly. This cruel and deforming malady not only completely transforms the outward appearance of those whom it afflicts but is attended with great suffering and often with loss of vision."

"One of Mr. Ringling's agents prevailed upon her to travel with the circus and to pose as the 'ugliest woman in the world' as a means of livelihood. Mr. Ringling is kind to his people and he is well cared for. But she suffers from intractable headaches, has become nearly blind, and permits herself to be laughed at and heckled by an uncaring people in order to provide the wherewithal to educate her four children. Beauty is but skin deep. Being a physician, I do not like to feel that Time can be frivolous over the tragedies of disease."

Because of Cushing's interest in chromophobe and acidophiles adenomas of the anterior hypophysis, many patients with these tumors were referred to him. Of the 203 patients with verified brain tumors seen in his clinic, 380 had pituitary adenomas."

"Among his pituitary patients Cushing over the years had a special group with a condition which had been somewhat vaguely labelled 'polycystic syndrome'. They were seldom subjected to operation because, unlike other pituitary cases, they did not exhibit visual difficulty or signs of increased intracranial pressure; and since none had come to autopsy he had had no opportunity of definitely establishing the fact that their difficulties were of pituitary origin..."

Until 1930 Cushing had never seen a basophilic tumor of the pituitary but he had often suspected that such might occur."

...It is a matter of some interest that at the time of Cushing's original paper on basophilic no one of his own cases had yet come to autopsy. Three patients, however, who died after the paper was published all proved at autopsy to have basophilic adenomas.

"...Cushing first described his deductions concerning the basophil tumors before the New York Neurological Society on 5 January 1930. He presented the same material again at the Harvard Medical Society on the 30th, and on 24 February he made it the subject of an Alpha Omega Alpha Lecture in New Haven... These first three accounts of basophilic adenomas were merely cursory raisers, for his official presentation was given before the Johns Hopkins Medical Society on 29 February, and the full text appeared in the March number of the Johns Hopkins Hospital Bulletin."

During the century prior to 1930, basophil adenomas had been described (as unimportant curiosities), experiments had shown that relationships existed between the pituitary gland and the adrenal cortex, and the clinical changes associated with adrenocortical hyperfunction had been recognized. Dr. Cushing's observations substantiated and correlated these findings.

"Ideas about the underlying pathological lesions have changed since 1930, but because of the classical descriptions by Cushing, the clinical picture presented by these patients has become widely known as Cushing's syndrome."

"For those who believe that the originality of most men reaches its peak before the age of forty and that it would be a good thing if most of us were chrysemorphic at sixty, it is a fact of some significance that one of Cushing's most original single contributions to clinical medicine was made in his sixty-third year as he was about to retire."

References:


THE BASOPHIL ADENOMAS OF THE PITUITARY BODY AND THEIR CLINICAL MANIFESTATIONS (PITUITARY BASOPHILISM)*

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Introduction. In a long since superseded monograph on the pituitary body and its disorders, published in 1918, a section was devoted to a group of cases which show this peculiar and sandy polyglandular syndromes. It was stated at the time that the term "polyglandular syndromes" implied nothing more than that secondary functional alterations occurred in the glandular system whenever the activity of one of the glands becomes primarily affected; and further, that the term, as such, was restricted to those cases in which it was difficult to tell where the initial fault lay.

That a primary derangement of the pituitary gland, whether occurring spontaneously or experimentally induced, was particularly prone to cause widespread changes in other endocrine organs was appreciated even at that early day, and it was strongly suspected that this center was capable of such well protected structure in all probability represents the master gland of the endocrine system. The multiglandular 1st (of this group) is, as far as the evidence go, the hypothalamic and adrenal cortex, were already known, and the non-striking endocrine picture and adrenal cortex are the best known.

The usual method of progression has been somewhat as follows. A peculiar clinical syndrome has been first described by someone with a clarity sufficient to make it reasonably recognizable by others. This syndrome in course of time has been found to be associated either with a destructive lesion or with a tumefaction primarily involving one or another of the organs in question. These tumefactions have proved in the majority of cases to be adenomas of the anterior pituitary gland, and it was finally recognized (first in the case of the thyroid) that adenomas of this group are functionally active structures that produce hypertrophic effects. It then gradually came to be realized that the term "basophil" did not necessarily bulkly, as with the anterior pituitary gland. In fact, not even the protrusion produced by minute, symmetrically predictable changes. So it is the degree of secretory activity of the adenoma which best indicates the character of its functioning activity, which reflects the endocrine activity is present in all hypoderal zones.

The pituitary adenomas. The anterior-pituitary body, as distinct from the neurohypophysis, is a compact cellular element of three recognizable kinds, divided by histologists, on the basis of their staining reactions, into two principal types: (1) those having a non-granular cytoplasm, and (2) those with a cytoplasm which is distinctly granular. Cells of the former type are known as neurophil (chromophobe) elements and of the latter-the granular type-as chromophil elements of which there are two sorts: (a) those which show an affinity for acid dyes (acidophil cells) and (b) those with an affinity for basic dyes (basophil or cytoplasmic) cells. Each of these differentiation is further divided by the staining of its own peculiar adenomatous formations.

Whether these three types of cells are fixed in character or whether all types are capable of differentiation, stages in activity of the same original cell is a matter of dispute. The most recent advocate of the view that the cell may change from a basophil into a chromophil, or from a chromophil into a cytoplasmic cell, and so on, is the cell in which the process of differentiation acquires a granular cytoplasm that is primarily acidophilic (eosinophilic). When the differentiated granular cytoplasm comes to be discharged, the cell becomes either a basophil (basophil) or a chromophil (chromophile) cell as the case may vary in becoming basophil (cytoplasmic).
the fact that each of these varieties of cells is capable of forming adenomata whose elements appear to be of fixed rather than of a changing type is highly peculiar. What is more, one would naturally expect that adenomata composed of the non-granular mother-cells (Hauptstelle: celluloid, principal cell) would be more likely to show evidences of cell division than would adenomata composed of elements in the more advanced stages of the acromegaly. But just the opposite occurs; the elements composing the common chromophobe adenomatous if ever show cell division, whereas those of a chromophobe adenoma, whether acromegalic or basophilic, are frequently multinuclear (cf. Figs. 8b, 10, 23) and show numerous mitotic figures.

Meanwhile, experimental pathology has provided us with some fairly definite facts concerning the function not only of the anterior pituitary considered as a whole, but, in turn, of its different cellular constituents. When its frequent association with a pituitary tumor came to be recognized, it was at first supposed that acromegaly was an expression of glandular deficiency and theoretically should be reproducible by experimental extirpation of the gland. This, however, in the majority of cases led to early death, at least of adult animals (chiefly dogs), whereas younger animals when hypophysectomized, though they might recover for long periods, ceased to grow and remained sexually infantile.

It had already been observed that tumors, grossly indistinguishable in their shape and size from those associated with hypophyseal malignancy, were of far greater frequency and provoked a syndrome, so far as its endocrinological manifestations were concerned, of a wholly different character. Individuals affected by these tumors when of adult age, instead of a tendency to overgrowth, showed, on the contrary a tendency to become adipose, to

without particular change in form, as in gastric secretion; they may wholly destroy their ripened cytoplasm, as in mammary secretion, or the entire cell may be cast off, as in sebaceous secretion—and this apparently is what takes place more particularly in the neurohypophysis from whose epithelial envelope (pars intermedia) degenerating cells are cast off which migrate through the pars nervosa where they become transformed into the hypothalamic bodies that presumably represent the secretory principle of this part of the gland.

It would seem that the only possible way this question of utopia or unchangeableness of the elements composing pituitary adenoma could be conclusively answered would be by culturing the cells of the different types to determine whether they breed true to their original type or whether they form a neurohypophysis.
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the growth-provoking and sex-maturing principle—the former almost certainly elaborated by the acidophil and the latter presumably by the basophil elements of the pituitary gland—may be chemically separable hormones. Hence the former working conception of hyperpituitarism versus hypopituitarism as an indication of the entire function of the hypophysis is erroneous or non-gonadism; and, on the other hand, the hormone under-secretory leading to anovulatory or amenorrhea or gigantism, and is unable to replace by hyperpituitary versus hypopituitary states due to excessive or insufficient secretion not only of the acidophil elements concerned with growth but also of the basophil elements chiefly concerned, presumably, with the ovulatory mechanism.

In an attempt to interpret in terms of human pathology the highly informer later-day disclosures of experimental biologists, we may properly review, with necessary brevity, the development of the idea that the adenoma which affect the organs of internal secretion are not mere static conglomeration of cells but represent lesions possessing an incredible degree of physiological activity, those which have most recently attracted attention being the tiny adenomas of the parathyroid glands and those of the pancreatic islets.

The common tumors of the anterior pituitary—first looked upon merely as a local expression of adenomatous overgrowth, and subsequently as sarcomas or "stromas" of the gland—were first clearly differentiated by Benda in 1900 as vari-

cies of adenomas; and we have slowly come to understand with some degree of definiteness the clinical pictures produced by those whose cells possess a granular and acinar cytoplasm and those with a non-granular or chromophobe cytoplasm. The former, even when small that they may easily escape postmortem detection, are productive of unmistakable acromegaly or gigantism or a combination of the two. The more common chromophobe adenoma of the other hand, usually attain a size sufficient to distort the vision before they give appreciable clinical symptoms, and it is quite probable that the cells which comprise them possess no secretory activity—which produce no hormone. Nevertheless, not only their own peculiar constitutional disorder, this being a deprivation syndrome,4 brought about in all probability through compression of the residual acidophil and basophil elements which no longer are able to produce their peculiar secretory product (Fig. 3).

In general terms at least approximates the truth. It must, however, be admitted that there are certain borderline syndromes in which a primary pathologic overgrowth appears to have been succeeded by a hypopituitary state—a condition which for lack of a better term has been called "adrenocortical," the adenoma in these states proving to be of a mixed cellular type. Though the cells of these mixed adenomas are predominantly chromophobic, a few of them show a peripheral disposition of acidophil granules suggesting the functional regression of previously mature acidophil elements; and since these cells resemble the hyperplastic ("Hans scopolium") stage of development as described by Colins, the observation might be construed as an argument favoring his views. In other words, the supposed functional immutability of the cells of an anterior pituitary adenoma is proved to be a misconception; but this need not particularly concern us here.

Two examples of a thir type of anterior pituitary adenoma, composed of basophil elements, were first described twenty years ago by Ebeling,5 and the cases here being looked upon as curiosities of morphological anatomy rather than as findings of any conceivable clinical significance. In one instance a small basophil adenoma, 1.5 mm. in diameter, was found in a woman forty years of age, previously the victim of Baslow's disease. The other example was found in a 45-year-old aortic aneurysm whose relatively small pituitary body was chiefly occupied by a fair-sized eosinophil adenoma; the minute basophil adenoma measuring only 1 mm. in diameter, having been regarded as an accessory finding.6

PREVIOUS EXAMPLES OF BASOPHIL HYPERPLASIA

After this explanatory digression, let us return to a consideration of the peculiar polyglandular syndrome to which allusion was made in the introductory paragraph. The original example of the syndrome around which the present discussion hinges was described in my monograph (Case XVII, page 97) as having shown a syndrome of polyendocrine hyperplasia and increased in secondary sexual character-

neural development of secondary sexual characters. Whether these symptoms were chiefly attributable to disorder of pituitary, adrenal, pituitary, or ovarian influence remains uncertain. Case J. L. H. T. (J. L. H. T. Surv. No. 4760) Manse J. G., 11, unmarried Russian Jewess, aged 35, referred by Dr.
Stemon of New York, was admitted to the Johns Hopkins Hospital on December 29, 1910.

Clinical History. One of a numerous and healthy family, though slight and undetermined, she was well until 18 years of age, having escaped the customary children's ailments. Her menarche which started at the age of 14 were regular for two years and then suddenly ceased. She began to grow short and in the two years prior to admission her weight had increased from 112 to 137 pounds. She suffered greatly from headaches, nausea and vomiting sometimes accompanying the more severe attacks. She complained also of aching pains in the eyes which laterly had become prominent and there had been occasional periods of seeing double.

Other noteworthy symptoms were insomnia, timidity, extreme drowsiness of the skin, frequent sore throats, shortness of breath, palpitation, puritic outbreaks, recurring sore throats, and marked constipation accompanied by bleeding piles. A definite growth of hair had appeared on the face with thinning of hair on the scalp. She had become increasingly round-shouldered. Muscle weakness had become extreme and there was constant complaint of backache and epigastric pain.

Physical examination. This showed an asthenic, kyphotic young woman 4 feet, 9 inches in height (145 cm.), of extraordinary appearance (Fig. 4). Her round face was dumpy and eunuchoid and there was an abnormal growth of hair, particularly noticeable on the sides of the forehead, upper lip and chin. The mucous membranes were of bright color despite her history of frequent bleeding. Her abdominal body had the appearance of a full-term pregnancy. The breasts were hypertrophic and pendulous and there were pads of fat over the supra- and inferior pubic regions. The cystic appearance of the skin was particularly apparent over the body and lower extremities (Fig. 8), which were spotted by subcutaneous ecchymoses. Numerous purple, purplish striae were present over the stretched skin of the lower abdomen, hips, and also over shoulders, breasts and hips; and a few hairlines were present over the hips and supraumbilical regions. The skin everywhere was rough and dry, and showed considerable pigmentation, particularly around the eyelids, groins and regions of the breasts. The precordial pain and painful adiposity affecting face, neck and trunk was in marked contrast to her comparatively spare extremities.

From a neurological aspect nothing was notable other than what at the time were taken to be signs of intracranial pressure—namely, headaches and over stretching, nausea, dizziness, numbness of the eyelids and congestion of the optic discs—later, when would appear to be due to depression of intracranial air. The cranial a-ray showed what was, for the day was regarded as a normal section (Fig. 1). The epiphsyseal lines (adult end-phalanges) were still methodologically visible. Not only did the skin bruise easily but spontaneous ecchymoses frequently appeared. Lateral punctures, taking of ear, etc., caused subcutaneous extravasations. Blood examination showed 8,000,000 erythrocytes and 15,000 leucocytes (polymorphonuclears 77 per cent), with a haemoglobin of 85 per cent. The systolic blood pressure was consistently high, averaging 200 mm. Hg.

There were no clear therapeutic indications and she was discharged. She returned to the hospital again in July, 1911, at which time, owing to the assumption that her condition was due to intracranial pressure, an operation for decompression was performed, a wet bean being introduced without subsequent perforation at the site of the defect. She also at this time complained of great left backache and pain in the left side that an exploration of the kidney and adrenal gland was under contemplation.

It was at this stage of the story that the case was first reported. Its most striking feature was the rapidity with which quantities of peculiar distribution in an amenorrheic young woman. At the time, Dercum's adiposis dolorosa (usually a menopausal disorder) Bartel's and Plochit's adrenocortical dystrophy (commonly associated with hypophysial-duct tumors) and the adenosia cerebelli (Acher and Zeidler due to hypothyroidism) were but vague terms; and the possibility of the relationship of the patient to the reproductive function was even suspected.

In commenting on the case at the time, it was pointed out that a somewhat similar polyglandular syndrome had previously been recorded not only in association with pimelomas but with adenomatous or hypertrophic adrenal tumors. A chance remark that we might be on the way toward the recognition of the consequences of hyperadrenalism may possibly have inclined some of those who had previously reported similar cases, to believe that this was the cause of the trouble in all probability in the adrenal gland. To this I shall return.

The case of Missie G., further: Because of her continued complaints with an increase of weight up to 151 pounds, Dr. Stenton's recommendation she again came under observation for a period of two months from May to July, 1918, at the Brigham Hospital in Boston.

Her symptoms and general condition at this time were found to be essentially unaltered. Though there was no protrusion at the site of the old decompression, the optic discs were still hyperemic and congested, with hazy margins, while the fields of vision were contracted and the acuity considerably reduced. Her blood-pressure fluctuated around 120/100, on one occasion reaching 10/140. She was still somewhat polyphemetic, the erythrocytes slightly exceeding five million, the highest count having been 5,410,000 with a haemoglobin estimation of 165 per cent. Several differential blood counts were essentially within normal limits.

One of these cases was studied by my medical colleague, Dr. Christian. On the basis of a defective secretion of phalangeal epiphysitis and the presence of a slight transitory change in the skin with occasional hyperalgesia, he felt that a vascular type of neoplasia was the probable cause of her hypertension. She was again discharged from the hospital.

On November 15, 1918, after an interval of nine years, she was for the second time admitted to the Brigham Hospital. It was then learned that she married, after complete cessation for ten years, had late in 1913 again become irregularly re-established; that is, in 1917 she had had an exploratory operation for a stone in the left kidney, but was uncertain whether a calculus had been removed.

The blood-pressure at this time averaged in the neighborhood of 105/60; the blood-count showed 3,400,000 erythrocytes, the haemoglobin in minus nine. Her general appearance was much as before, though she had lost some weight. The cranial roentgenograms taken at this time show (as subsequently verified) an unmistakable diffuse calcification of the bone. The hypophyses were made, no trace of bone or other abnormality being disclosed. There was no evidence of advancing neoplasma and on the whole the symptoms seen no worse than in 1918. She accordingly was discharged once more without further light having been thrown on the nature of her disorder. From correspondence it may be observed that she is present (1925) is reasonably good health though some of the symptoms of her malady still persist.

In the intervening years, other cases of the same or a highly similar disorder have been carefully studied at the Brigham Hospital. The patients were all comparatively young women, who, in association with a more or less abrupt

anomalous, had become rapidly obese with a peculiar tense and more or less painful adiposity chiefly affecting head, neck and trunk. They were all plectic in appearance, all had become abnormal in hirsutism, all but one showed purely cutaneous stigmata. Vascular hyperesthesia with a high blood count and low eosinophil percentage was usually present, and all complained of aches and pains and general enfeebledness. In some of the cases the acuteness of the condition appeared to subside, and only one, so far as known, succumbed to her malady.

Meanwhile, soon after the case of Missie G. had been reported in 1918, descriptions of polyglandular syndromes closely resembling her began to appear in the literature; and in a few instances, owing to the fatal outcome of the disorder, a systematic study of the organs was made possible. Much of these cases, as is shown to my attention may be given in the chronologic order in which they appeared in print. The first of them was recorded in 1923 by Dr. H. G. Turner of London.
Renal function was unimpaired. The eyes were normal, except for a polar cataract visible in both of them. Blood urea (non-protein nitrogen) was 14 mg.%; fasting blood sugar, highest estimate 150 mg.%, No ketosis was observed. Only on days of fasting was it possible to make the patient sugar-free even on an anti-diabetic diet with greatly reduced calories the urine still showed sugar. Insulin was not used.

Course of disease. There was considerable variation from day to day, not only in the hypertension, but in the albuminuria and in the percentage of sugar in the blood. The patient complained of headaches, of pains in the ears, and became dull and sleepy. On one occasion, he had subjective dimness of sight, marked dizziness, and vomiting, the blood-pressure registering 180/160 with a rapid pulse. The abdominal swellings grew more pronounced and finally reached all the way up to the axillae on both sides. Edema increased from time to time on the legs and arms; his left hand became edematous. On August 1st, the patient became dyspneic and cyanosed and died that evening.

Autopsy: August 2nd. The extremities were lean compared with the trunk. There were striae distensae on the abdomen, running longitudinally to the sternum and even to the axillae. The skin was without oedema, apart from that on the left hand and back of hand. The growth of the hair was normal, except for some scanty, broncho-pneumonia was found, and a marked hyper trophy of the left side of the heart and atheroma of the aorta and common iliac arteries. The pancreas was exceedingly large. The kidneys were slightly granular.

The thyroid gland was small (each lobe measuring 2 by 1.5 cm.) and firm. The right lobe was normal, but the left was hyperplastic, weighing 175 g.; the tissues on section appeared normal, but the medullary portion was edematous and of a brownish-green color. The papillary gland, on removal of the brain, was found to be replaced by a soft, tan-colored growth of reddish color, which measured 3 by 2 by 0.5 cm. The brain itself was edematous, the ventricles moderately dilated.

Macroscopic examination. The thyroid gland showed changes of those found in a chronic struma, the epithelial lining of the follicles being low cuboidal, with no proliferation and no increase of connective tissue. The papillary gland had a normal structure without oedematous cell proliferation. Toward its center, there was some edema and congestion of the vessels without cell degeneration. The hyperplasia was evenly distributed between cortex and medulla. The structures were indefinite in contrasted with indistinct arrangement of cell columns. The kidneys showed no definite changes, though casts were found in the tubes.

Hypoplasia: The primary change consists of a coarse network of rather delicate connective tissue, containing thin-walled, empty blood vessels. Although there are post-mortem changes, one is of the impression that the network of connective tissue is due to hyperplasia of the medullary portion. The outer portion of the gland is somewhat extended, and a number of varying sizes and shapes with a dark nucleus. Occasionally seen are loose groups of nuclei, a few mitoses. These cells form, as a rule, a quite dense layer and irregularity-shaped vacuoles which are filled with granular material consisting of secretory and degenerative cells. Thus, the tumor tissue appears papillomatous in structure. The connective tissue, which is increased in amount in the periphery of the tumor, is also infiltrated with tumor cells. There is no evidence of sarcoma. The endothelium of the vessels appears normal.


In his interesting discussion of the two cases, the author naturally described the polycystic disorder in the first of them to the adrenal tumor. In the second case, he laid chief emphasis (as did Dr. Pach's in Case 6) upon the unilateral adrenal hyperplasia. He however described the delayed puberty, retarded ossification and the adiposity as a pellagra affect as an example of dys trophy adiposa-genitalis [sic].

COLLATION OF SYMPTOMATIC AND PATHOLOGICAL DATA

The twelve patients whose case histories have been presented, as will have been noted, were all related to young adults. Their average age at the onset of the malady, so far as can be estimated (Case 20 being eliminated for want of information) has been 16 years. The youngest was six (Case 3) and the oldest 21 (Case 11).

In stature, the female patients appear all to have been definitely undernourished. Where heights were given, the tallest (Case 9) was 5'9" and the shortest (Case 1), 4'10". Of the male patients, on the other hand, were tall: Case 6, 5'10"; Case 10, 5'11"; Case 11, 5'8". The average duration of the disease from onset to death in the cases where definitely stated (Case 6 again eliminated) has been slightly over five years, the extremes being three (Case 9) and seven (Case 8).

The following features are characteristic of all cases: (1) A rapidly acquired, peculiarly disposed and usually painful adiposity (in one instance representing 40 per cent gain in weight) confined to face, neck and trunk, the extremities being spared; (2) A tendency to become round-shouldered (hypostatic) even to the point of metastasis of height; (3) a more severe case of anemia and associated with probable spinal pains; (4) A mental dysphoria shown by early enuresis in the female and ultimately functional impotence in the male; (4) An alteration in normal hrstotypes shown by a tendency to hypertrichosis of face and trunk in all the females as well as the pseudosexual males (Cases
9 and 18) and possibly the reverse in the adult male; (6) a dusky or petechial appearance of the skin with purpuric lesions (arterial); (6) Vascular hemorrhage, present in all cases except Cases 4, 7, and 10, which was made of blood pressure; it varied from the highest recorded in Case 6 of 320/170 to the lowest in Case 11 of 117/100 (19). A tendency to exanthem is noted, a count exceeding five million having been present in five of the nine cases in which blood counts were reported; (8) Variable degree of abdominal pain, fatigue, and mental confusion.

Other features less consistently recorded have been as follows: Anosmia (e.g., Cases 1, 12); Purpura-like eczema, whether from bruising or occurring spontaneously (Cases 1, 3, 5, 6, 11); Alopecia in women, associated with slight exophthalmos (Cases 1, 3, 5, 6, 11), with transient diplopia (Cases 6, 7, 11), with suggestive papilledema (Cases 1, 6, 11), with dimness of vision (Cases 8, 9, 14), with subcutaneous ecchymosis and red haemorrhage (Case 8); Extreme degree of hyperalgesia in skin (e.g., Cases 1, 4, 5, 6, 10, 12); Polyphagia, polydipsia, and polyuria (e.g., Cases 11, 12); Edema of the lower extremities was noted in several cases and in Case 12, of the hand; A susceptibility to pulmonary infections (Cases 5, 6, 7, 8, 9, 10); Albuminuria of slight degree was noted in several cases and was found in six patients, Cases 5, 6, 8, 9, 10, 12; A sense of suffocation and difficulty in swallowing, occasionally noted (Cases 3, 4, 5); Anemia was not uncommon; An increase in non-protein nitrogen and of cholesterol in the blood was recorded in the only patient Cases 8, 11 and possibly 16 (Case 11); what was described as an adenomatous-like structure in a fibrous area of the anterior pituitary was noted in Cases 4 and 6; and the gland was said to be "normal." The thyroid was described as slightly enlarged (colloid); in Cases 7, 10, 11, as small in Case 7; and atrophy of the thyroid was noted in Case 10. The suprarenal glands in Cases 3 and 5 showed a cortical hyperplasia; in Case 11, a small amount of fatty degeneration was found. If Cases 9, 10, 11, and 12, no abnormality was noted. The ovaries and uteri were said to be small in Case 3; in Case 5, the ovary was said to be small but normal; and in Case 7, the size and condition of the ovary were reported.

In Case 8, it showed hyperostosis with signs of increased functional activity. The uterus in Cases 9 and 10 showed atrophy of the stroma, and in the latter case, generalized atrophy. The pituitary gland was normal in Cases 3, 4, 5, 7, 8, 10, 11, 12.

DISCUSSION AND RECAPITULATION

In assessing this obscure polyglandular syndrome to a pituitary rather than to an anterior source, I am aware that much might be said in favour of the latter in the absence of origin. Indeed, it was my original belief in the case, first of all, that her malady was in all probability associated with an adrenal tumor. What light the contemporary literature must it is a remarkable fact that the pituitary gland is strongly in favour of such an interpretation, containing, as it did, numerous examples of precocious sexual development in animals or children of the masculinization of women who were found to have large suprarenal tumors. A striking example was that reported in 1916 by Launois, Pinard, and Gallais.11 in the case of a 3-year-old woman who showed phlebitis, a tendency to the purplish disc coloration of the skin with an abundance of purpuric lesions over the trunk. A suprarenal tumor of cortical type with metanephalic cortex to liver and lungs was found at autopsy in association with such an abnormality; though the sella turcica was said to have been normal, macroscopic necrosis was present in the case of a patient 3. It may be noted that in the upper limit of normal for her age, this being 14.4 mm. according to Erdheim and Stumm at the age of 12.

About this same time, twenty years ago, I had the opportunity to see with Dr. J. and Department's interesting example of a case with multiple pituitary tumors, which have since been removed by the pituitary sinus tract. The case was marked by the presence of an adenoma tumor that was subsequently removed by Sir Percy Sargent with prompt restoration of the patient's normal female sexual appearance and functions. This woman had a lean, manhood habitus quite unlike the hyperplastic and adriosis seen elsewhere and described, and the case may possibly have unduly coloured my impressions of the hyperadrenalism of which, to be sure, several differing types have been described. Primary adrenal tumors, however, may cause striking constitutional transformations, but there nevertheless is justification in again emphasizing the fact that all known primary pituitary disorders inevitably cause marked secondary changes in the adrenal cortex, a pathological observation which is amply supported by what appears after experiments. In Case 3, a small amount of fatty degeneration was found. If Cases 9, 10, 11, and 12, no abnormality was noted. The ovaries and uterus were said to be small in Case 3; in Case 5, the ovary was said to be small but normal; and in Case 7, the size and condition of the ovary were reported.

In Case 8, it showed hyperostosis with signs of increased functional activity. The uterus in Cases 9 and 10 showed atrophy of the stroma, and in the latter case, generalized atrophy. The pituitary gland was normal in Cases 3, 4, 5, 7, 8, 10, 11, 12.

The disorders under discussion in all probability are much more common than one would have thought from the present cases, because of the absence of a complete history or the presence of a complete history, and because of the absence of a complete history of the patient's past history. One of the patients was examined more recently, and in the present form may still be so considered. However, one encounters on every hand persons with unexplained cases of polyglandular acromegaly which have been given to the medical profession, and these, when carefully studied, will be found to show a complete similarity to the case described by the patient. The disorder of the gonadotrophic axis, as well as that of the pituitary axis, may possibly have unduly coloured my impressions of the hyperadrenalism of which, to be sure, several differing types have been described. Primary adrenal tumors, however, may cause striking constitutional transformations, but there are nevertheless is justification in again emphasizing the fact that all known primary pituitary disorders inevitably cause marked secondary changes in the adrenal cortex, a pathological observation which is amply supported by what appears after experiments. In Case 3, a small amount of fatty degeneration was found. If Cases 9, 10, 11, and 12, no abnormality was noted. The ovaries and uterus were said to be small in Case 3; in Case 5, the ovary was said to be small but normal; and in Case 7, the size and condition of the ovary were reported.

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However, I am quite aware that in ascribing the disorder to the pituitary element, even were their association with maturation and the ovulatory mechanism established beyond question, many questions arise which are at present unanswerable. For example: (1) If the sex-maturing principle, which during pregnancy appears to spill over into the urine, is excreted by the basophilic cells, should it not be found in (Case 11) in the urine of patients with basophilic adenomas? If the polyglandular disorder under consideration is actually due to the hyperadrenalism of which, to be sure, several differing types have been described, primary adrenal tumors, however, may cause striking constitutional transformations, but there are nevertheless is justification in again emphasizing the fact that all known primary pituitary disorders inevitably cause marked secondary changes in the adrenal cortex, a pathological observation which is amply supported by what appears after experiments. In Case 3, a small amount of fatty degeneration was found. If Cases 9, 10, 11, and 12, no abnormality was noted. The ovaries and uterus were said to be small in Case 3; in Case 5, the ovary was said to be small but normal; and in Case 7, the size and condition of the ovary were reported.

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