THE BASOPHIL ADENOMAS OF THE PITUITARY BODY AND THEIR CLINICAL MANIFESTATIONS (PITUITARY BASOPHILISM)\textsuperscript{1}*

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Introduction. In a long since superseded monograph on the pituitary body and its disorders, published in 1912, a section was devoted to a group of cases which showed peculiar and sundry polyglandular syndromes. It was stated at the time that the term “polyglandular syndrome” implied nothing more than that secondary functional alterations occur in the ductless-gland series whenever the activity of one of the glands becomes primarily affected; and further, that the term, as employed, 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 centrally placed and well protected structure in all probability represented the master-gland of the endocrine series. The multiglandular hyperplasias of acromegaly, so evident in the thyroid gland and adrenal cortex, were already known, and the no less striking atrophic alterations in these same glands brought about by the counter state of pituitary insufficiency were coming to be equally well recognized. But in spite of these hopeful signs, we were still groping blindly for an explanation of many other disorders, obviously of endocrine origin, like those associated with pineal, parathyroid or suprarenal tumors. Out of this obscurity, those associated with pineal, parathyroid or suprarenal tumors. Out of this obscurity, those seriously interested in the subject have, step by step, been feeling their way in spite of pitfalls and stumbling blocks innumerable.

The usual method of progression has been somewhat as follows. A peculiar clinical syndrome has first been described by someone with a clarity sufficient to make it easily 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 most cases to be of an adenomatous character and it was finally recognized (first in the case of the thyroid) that adenomata of this kind were functionally active structures that produced hypersecretory effects. It then gradually came to be realized that the tumor need not necessarily be bulky but, quite to the contrary, striking clinical effects might be produced by minute, symptomatically predictable adenomas. So it is the degree of secretory activity of an adenoma, which may be out of all proportion to its dimensions, that evokes the recognizable symptom-complex in all hypersecretory states.

The pituitary adenomas. The anterior-pituitary body, as distinct from the neuro-hypophysial, is a compact of cellular elements of three recognizable sorts, 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 neutrophil (chromophobe) elements and of the latter—the granular type—as chromophil elements of which there are two sorts: (a) those whose granules show an affinity for acid dyes (acidophil cells) and (b) those with an affinity for basic dyes (basophil or cyanophil cells). Each of these three cellular types—chromophobe, acidophil and basophil—is capable of producing its own peculiar adenomatous formations.

Whether these three types of cells are fixed in character or whether they represent different stages in activity of the same original cell is a matter of dispute. The most recent advocate of the unitarian view is Remy Collin of Nancy who, purely on anatomical grounds, presents\textsuperscript{2} a convincing argument to show (cf. Fig. 1) that the non-granular cell (cellule principale: mother-cell) represents the primitive stage of activity of an element which in the process of ripening acquires a granular cytoplasm that is primarily acidophilic (eosinophilic) but which may in turn become basophilic (cylanophilic). When the ripened granular cytoplasm comes to be discharged, little is left but the nucleus and membrane of the cell which may then either degenerate or, in a renewed cycle, once more pass through these same stages to be again discharged under proper stimulus.\textsuperscript{3} But if this is actually what takes place,

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\textsuperscript{3} Nothing of precisely this same sort, to be sure, occurs in other glands of internal secretion; but this need not unduly disturb us, for the pituitary body, whether taken from a morphological or functional aspect, is a tissue of surprises. It is now recognized by histologists that secretory cells discharge in three different ways. They may merely extrude their accumulated granules...
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 (Hauptzellen; cellules principales) would be more likely to show evidences of cell division than would adenomata composed of elements in the more advanced stages of secretory activity. But just the opposite occurs; the elements composing the common chromophobe adenomata rarely if ever show cell division, whereas those of a chromophil adenoma, whether acidophilic or basophilic, are frequently multinucleated (cf. Figs. 2b, 16, 23) and show numerous mitotic figures.4

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 situation and type from those associated with acromegaly, 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 lose their secondary sex-characters, and to become impotent, in company with recognizable atrophic changes in the sexual organs. When altogether comparable changes were seen occasionally to occur in animals (dogs) after incomplete experimental hypophysectomy, it became evident that the syndrome represented a deficiency state which was termed hypopituitarism; and this furnished an added reason to assume—what had already been conjectured—that acromegaly almost certainly represented the counter state of hyperpituitarism.5

The final experimental proof of the correctness of this assumption was delayed until Evans and Long,6 by daily parenteral injections of an alkaline anterior-lobe extract, succeeded in producing experimental overgrowth (gigantism) in the rat, an animal whose epiphyses do not close throughout

4 It would seem that the only possible way this question of fixity or changeableness of the elements composing pituitary adenomas could be conclusively answered would be by cultivating the cells of the different types to determine whether they breed true to their original form or whether their cytoplasm undergoes progressive alteration. Efforts in this direction have so far proved unconvincing owing largely to technical difficulties due to want of experience with the artificial growth of neoplastic tissues.

life; and subsequently in the dog, whose epiphyses like those of man normally do unite, Putnam, Benedict and Teel produced a condition of overgrowth comparable in all respects to that characterizing acromegaly.

But this is only half the story. There was evidently a complicating element in these experiments. If only a single pituitary principle (hormone) had been involved in experimental hyperpituitarism of this kind, one might well enough have expected increased growth to go hand in hand with increased activation of the reproductive functions. But quite to the contrary, while the injections unmistakably served to promote growth, they at the same time checked the normal ovulatory cycle of the animals. In consequence of this observation, Dr. Evans was led to suspect the presence of dual glandular hormones and he came to believe, indeed, that they were in some peculiar way opposed in their action.

At another time and place a review has been given of the steps leading to the disclosure that
the growth-provoking and sex-maturing principles—the former almost certainly elaborated by the acidophil and the latter presumably by the basophil elements of the lobe—are chemically separable hormones. Hence the former working conception of hyperpituitarism versus hypopituitarism as an indication on the one hand of secretory over-activity leading to acromegaly or gigantism, and on the other hand of secretory under-activity leading to a counterposed syndrome, wholly falls to the ground. Or, if not quite so bad as this, it at least must be replaced by hyperpituitary versus hypopituitaristate 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 ovolatory mechanism. In an attempt to interpret in terms of human pathology the highly informing later-day disclosures of experimental biologists, we may properly review, with necessary brevity, the development of the idea that the adenomas which affect the organs of internal secretion are not mere static conglomerations 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 acromegalic overgrowth, and subsequently as sarcomas or "strumas" of the gland—were first clearly differentiated by Benda in 1900 as various entities of adenoma; and we have slowly come to understand with some degree of definiteness the clinical pictures produced by those whose cells possess a granular and acidophilic cytoplasm and those with a non-granular or chromophobe cytoplasm. The former, even when so 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 adenomas, on the other hand, usually attain a size sufficient to distort the chiasm before they give appreciable clinical symptoms, and it is quite probable that the cells which comprise them possess no secretory activity—that is, produce no hormone. They nevertheless cause their own peculiar constitutional disorder, this being a deprivation syndrome 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).

This in general terms at least approximates the truth. It must, however, be admitted that there are certain borderline syndromes in which a primary wave of pathological overgrowth appears to have been succeeded by a hypopituitaristate—a condition which for lack of a better term has been called "fugitive acromegaly," the adenoma in these states proving to be of a mixed cellular type. Though the cells of these mixed adenomas are predominantly chromophobe, a few of them show a peripheral disposition of acidophil granules suggesting the functional retrogression of previously mature acidophil elements; and since these cells resemble the hypoacidophilic ("hypoeosinophilic") stage of development as described by Collin, 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 may prove to be a misconception; but this need not particularly concern us here.

Two examples of a third type of anterior-pituitary adenoma, composed of basophil elements, were first described twenty years ago by Erdheim, the tiny lesions having been looked upon as curiosities of morbid anatomy rather than as findings of any conceivable clinical significance. In one instance a small basophil adenoma, 1.5 mm.


7 The evidence of this is suggestive rather than conclusive. It is based on the facts: (1) that following castration, at least in the rat though not definitely in other species, there is an increase in the basophil elements; and (2) that the extracts of the pituitary glands of castrates of all species are more active than normal glands in their gonad-stimulating properties. P. E. Smith showed, moreover, that the central portion of the bovine anterior-pituitary which is particularly rich in basophil elements has a more pronounced effect in stimulating the thyroid to activity than the more eosinophilic cortical portion of the gland. The effect of these injections on the adrenal cortex and the genital system unfortunately was not noted.

8 Time has shown that hyperpituitarism and hypopituitarism are long words whose distinguishing syllable is easily misread and misprinted. And now that it becomes necessary or advisable to recognize two hypersecretory states, the terms pituitary acidophilia and pituitary basophilia are suggested as less unwieldy and more easily interpreted than acidophilic hyperpituitarism (for acromegaly) and basophilic hyperpituitarism (for the syndrome under discussion).
in diameter, was found in a woman forty years of age supposedly the victim of Basedow’s disease. The other example was found in a 43-year-old acromegalic 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.\textsuperscript{14}

\textsuperscript{14} It is quite conceivable that acidophil and basophil adenomata may not infrequently coexist in cases of acromegaly, but I know no other example than this in the literature. Such a coincidence might account for the differing syndromes shown by acromegalic patients some of whom exhibit disturbances which in the past we have been inclined to ascribe to the effects of secondary hyperplasia or adenoma-formation in the adrenal cortex.

**Presumptive Examples of Basophil Hyperpituitarism**

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 XLV, page 217) as having shown a syndrome of painful obesity, hypertrichosis and amenorrhoea with overdevelopment of secondary sexual characteristics. Whether these symptoms were chiefly attributable to disordered pituitary, adrenal, pineal or ovarian influences was uncertain.

**Case 1.** (J. H. H. Surgical No. 27140) Minnie G., an unmarried Russian Jewess, aged 28, referred by Dr.
Stetten 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 undersized, she was well until 16 years of age, having escaped the customary children's ailments.

Her menses which started at the age of 14 were regular for two years and then suddenly ceased. She began to grow stout 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 latterly had become prominent, and there had been occasional periods of seeing double.

Other noteworthy symptoms were insomnia, tinnitus, extreme dryness of the skin, frequent sore throats, shortness of breath, palpitation, purpuric outbreaks, recurring nose-bleeds, 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. Muscular weakness had become extreme and there was constant complaint of backache and epigastric pains.

Physical examination. This showed an undersized, kyphotic young woman 4 feet 9 inches in height (145 cm.), of most extraordinary appearance (Fig. 4). Her round face was dusky and cyanosed 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 colour despite her history of frequent bleedings. 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-clavicular and posterior cervical regions. The cyanotic appearance of the skin was particularly apparent over the body and lower extremities (Fig. 5) which were spotted by subcutaneous ecchymoses. Numerous purplish striae were present over the stretched skin of the lower abdomen and also over shoulders, breasts and hips; and a fine hirsuties was present over the back, hips and around the umbilicus. The peculiar tense 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, slight exophthalmos, diplopia, puffiness of the eyelids and congestion of the optic discs [due, as would now appear, to deposition of intraorbital fat]. The cranial x-ray showed what for the day was regarded as a normal sella turcica. The epiphyseal lines (radial and phalangeal) were still roentgenologically visible. Not only did the skin bruise easily but spontaneous ecchymoses frequently appeared. Lumbar puncture, pricking of ear, etc., caused subcutaneous extravasations. Blood examination showed 5,800,000 erythrocytes and 12,000 leucocytes (poly-morphonuclears 77 per cent), with a haemoglobin of 85 per cent. The systolic blood pressure was consistently high, averaging 185 mm. Hg.

There were no clear therapeutic indications and she was discharged. She reentered the hospital again in July 1911, at which time, owing to the assumption that her continued cephalalgia might be due to intracranial pressure, an oldtime subtemporal decompression was performed, a wet brain being disclosed without subsequent protrusion at the site of the bone defect. She also at this time complained so greatly of 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 rapidly acquired adiposity of peculiar distribution in an amenorrhoeic young woman. At the time, Dercum's adiposis dolorosa (usually a menopausal disorder) Bartel's and Fröhlich's adiposogenital dystrophy (commonly associated with hypophysial-duct tumors) and the adipositas cerebralis of Aschner and Erdheim (due to hypothalamic lesions) were but vague terms; and the possible relation of the basophilic elements in the anterior pituitary to the reproductive functions was not 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 pinealomas but with adenomatous or hyperplastic 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 soon reported similar cases, to believe that the source of the trouble in all probability lay in the adrenal gland. To this I shall return.

The case of Minnie G. further: Because of her continued complaints with an increase of weight up to 151 pounds, on Dr. Stetten'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 hyperaemic and congested with hazy margins, while the fields of vision were contracted and the acuity considerably reduced. Her blood-pressure fluctuated around 180/110, on one occasion reaching 210/140. She was still somewhat polycythemic, the erythrocytes slightly exceeding five million, the highest count having been 5,248,000 with a haemoglobin estimation of 105 per cent. Several differential blood counts were essentially within normal limits.

She was for a time studied by my medical colleague, Dr. Christian. On the basis of a defective excretion of phenolsulphonephthalein and the presence in the urine of a slight trace of albumin with occasional hyaline casts, he felt that a vascular type of nephritis was the probable cause of her hypertension. She was again discharged with no therapeutic recommendations.

On November 15, 1922, after an interval of nine years, she was for the second time admitted to the Brigham Hospital. It was then learned that her menses, after complete cessation for ten years, had late in 1913 again become irregularly re-established; also that in 1917 she had had an exploratory operation for a stone in the left kidney, but she was uncertain whether a calculus had actually been found.

The blood-pressure at this time averaged in the neighborhood of 160/95; the blood-count showed 5,240,000 erythrocytes; the basal metabolism was 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 reread] an unmistakable diffuse decalcification of the bones. Renal pyelograms were made, no trace of stone or other renal abnormality being disclosed. There was no evidence of advancing nephritis and on the whole she seemed at least no worse than in 1913. She accordingly was discharged once more without further light having been thrown on the nature of her disorder.

From correspondence it may be gathered that she at present (1932) is in reasonably good health though some of the stigmata of her malady still persist.

In the intervening years six other examples 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 amenorrhoea, had become rapidly obese with a peculiar tense and more or less painful adiposity chiefly affecting head, neck and trunk. They were all plethoric in appearance, all had become abnormally hirsute, all but one showed purplish cutaneous striae. Vascular hypertension with a high red blood count and haemoglobin percentage was usually present, and all complained of aches and pains and general enfeeblement. 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 Minnie G. had been reported in 1912, descriptions of polyglandular syndromes closely resembling hers 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. Such of these cases as have come to my attention may be given in the chronological order in which they appeared in print. The first of them was recorded in 1913 by Dr. H. G. Turney of London.15

Fig. 5. Case 1. To show acrocyanosis with scars and ecchymoses of lower limbs.

Miss A. O., a previously healthy and normal young woman, in 1907 when 20 years of age, suddenly ceased menstruating and began to grow obese. Three years later, she observed a tendency for her extremities to bruise easily. She gradually became increasingly round-shouldered (kyphotic) thereby losing two and a half inches (6.4 cm.) in height. Her chief complaints were of pain in the back.

The face was extremely fat and florid and the texture firm. The hair of the head was dry and somewhat scanty, as was the pubic and axillary hair, but there was a growth of fine short hair over the back and upper legs. Notable were the large pendulous mammae and the great obesity of the abdomen, which had the contour of a full-term pregnancy (cf. Figs. 6, 7).

The obesity of the trunk was in marked contrast to the somewhat thin extremities which below the knee were of a dark brownish color, interspersed with recent ecchymoses. The skin had a parchment-like texture. Numerous broad, red, atrophic striae were present over the abdomen and thorax. An apparent partial absorption of the posterior clinoid processes was shown by cranial roentgenograms. A glistening subretinal exudate was present in the right eye, probably from an absorbed haemorrhage. The systolic blood-pressure was high, varying between 200 and 185 mm. Hg. There had been a tendency to polycythemia, the erythrocytes on one occasion having been counted at eight million and on another at six million. The urine contained no albumin. Carbohydrate tolerance was normal.

The subsequent history of this patient was briefly given in a later article by Dr. Parkes Weber. Several spontaneous fractures occurred from time to time, involving sternum, clavicle, and ribs. Multiple ulcers and subcutaneous abscesses developed, and in May 1914, seven years from the symptomatic onset of the disorder, death ended the story.

An autopsy was performed. The body was that of an hirsute woman with “abundant hair on the chin” and multiple subcutaneous abscesses and ulcers. There was found a chronic nephritis, an hypertrophic ventricle of the left heart, a fatty infiltrated liver, and an enlarged left suprarenal gland of “bulky cortex.” The ovaries were small. The bones showed calcareous deficiency (“fibrous osteitis” and were so soft they could be easily cut with scissors. “Nothing abnormal was found in the pituitary and thyroid glands.” [How thorough an examination of the former was made is not stated.]


Dr. Turney at the time of his report, while the patient was still living, apparently favored a pituitary origin for the symptoms, but this opinion may have been modified by the post-mortem findings; Dr. Parkes Weber, on the other hand, in his subsequent discussion of the case appears to have regarded it as unquestionably due to a primary adrenal disorder. The next example of which I have knowledge was reported two years later (1915) by Dr. John Anderson of Glasgow. 17


A women, at the age of 23, in association with a menstrual irregularity which in two years was followed by total amenorrhoea, became increasingly obese, the adiposity sparing the limbs. The adipose areas were tender on palpation. She suffered much from headaches, pains in the chest and eyeballs, the eyes having become somewhat exophthalmic. She acquired a reddish complexion and facial hirsuties, developed a tendency to petechial haemorrhages and purpuric outbreaks on her arms and legs, the slightest contusion provoking ecchymoses. The systolic blood-pressure was 185 mm.; the red blood count approximated five million. Muscular weakness became extreme, and she finally died from increasing asthenia. The whole course of the malady was something over five years.

At the postmortem examination, arteriosclerosis with "chronic interstitial nephritis" was found. The ribs were brittle and easily fractured. The kidneys were normal; the ovaries and uterus were senile in character; the thyroid was slightly enlarged; the parathyroids were normal, the thymus atrophic. In the medulla of one of the suprarenal glands which were "slightly enlarged" was a small pea-sized tumor resembling a small-celled sarcoma. This was found to be an adenoma composed to have basedow's disease. This was excluded as was also cardio-renal hypertension; and under the belief that the condition was ascribable to a sympathtico-adrenal disorder the left adrenal gland was surgically removed with a fatality a few days later from a generalized peritonitis. The autopsy showed a cardiac hypertrophy, hyperplastic arteriosclerosis, skeletal osteoporosis with spinal curvature, the bones being easily cut with a knife. The pituitary body, while macroscopically normal, was found on section to contain within a compressed mantle chiefly composed of basophilic elements a tumor "resembling a small-celled sarcoma." This was found to be an adenoma composed of chromophobe cells some of which contained eosinophile [sic] granules. The thyroid was small; the remaining adrenal was hyperplastic; the ovaries fibrotic.

In his discussion of the case, the author, if correctly understood, was inclined to regard it as a form of acromegaly, the hyperpituitary changes being confined to the thickened and cyanotic face; the other symptoms were ascribed to a secondary adrenal origin. 19

Chronologically the next fairly unmistakable case of which I have knowledge was described in Professor Zondek's monograph (1923) on the ductless glands among other examples of so-called pluriglandular insufficiency.


This concerned a 24-year-old Russian woman who had previously been normal in all respects and in good health. At the age of 19, amenorrhoea set in and she began rapidly to grow adipose, accumulations of fat being limited to the head and trunk, while the extremities remained thin (Figs. 8, 9). She began to lose the hair of her head, whereas on the cheeks and upper lip a somewhat definite beard began to appear; and as time


19 It may be assumed from the postmortem findings that this was a typical example of pituitary basophilism. The case has not been counted because of the absence of adiposity of the trunk which is so marked a feature of all the others. It suggests that the disorder may not necessarily be accompanied by abdominal obesity.

Glycosuria was found and the urine at one time showed as much as 3 per cent of sugar. The skin became pigmented, suggesting an adrenal disorder. The cutaneous dryness from lack of normal secretion strongly suggested myxoedema. Hence there were polyglandular disturbances which appeared to affect the function of the adrenals, thyroid, ovary and pancreas. She finally died of an intercurrent erysipelas.

An autopsy was performed. A marked osteoporosis of the skeleton was found, it being easily possible to cut the vertebral bodies with a knife, the spongy part of the bone having largely disappeared. There was follicular atresia of the ovaries, marked lipomatosis of the pancreas, an increase of colloid in the abnormally small thyroid, hypoplasia of the thymus, and capillary dilatation of the parathyroid glandules. [The adrenal glands are not mentioned and presumably would have been had they shown any change.]

The pituitary body showed no apparent abnormality until examined microscopically when it was found: "that the anterior lobe was enormously reduced and diminished mesially to a narrow ledge. As contrasted with this finding, the intermediary layer, as well as the posterior lobe, was rather more than normally developed. Between the gliomatous fibres of the posterior lobe, there were enlargements of the intermediary spaces, the exact nature of which, whether hydropical enlargements or myxomatous degenerations, could not be determined. In the vicinity of the diminished anterior lobe a tremendously developed fibrous tissue was encountered, into which the glandular elements of the anterior lobe gradually passed over. As to the kind of destroying process, involving particularly the anterior lobe, no definite decision was possible, this being the more difficult, as there were nests of an adenomous-like structure enclosed in the masses of fibrous tissue. The identity of these cells with the anterior-pituitary cells could not with certainty be determined, but Professor Benda, who saw the specimens, favored more the diagnosis of a tumor arising from the hypophysial duct."

This briefly reported case, in which some clinical details are unfortunately lacking, was, properly enough, regarded as one of pluriglandular nature, the most significant postmortem findings seemingly having been the lesion of somewhat obscure nature in the anterior pituitary. The adrenal glands at least we may assume to have shown no abnormality. Attention may be drawn to the fact that, as in the two preceding cases, the bones were described as being markedly softened and fragile, so much so indeed, that in his discussion of osteomalacia Zondek refers to this case (loc. cit., p. 285) as illustrating one type of the disease.

In the following year, 1924, Drs. B. S. Oppenheimer and A. M. Fishberg of New York published a paper in which the association of non-nephritic hypertension with suprarenal tumors.
hypertension with suprarenal tumors was under discussion. Two illustrative cases were given. The first of them was that of a man said to have had an acromegalic appearance who was found after death to have had a tumor of the suprarenal cortex associated with cardiac hypertrophy. It is merely stated that the head and neck organs were negative, no specific mention being made of an histological examination of the pituitary body. It need scarcely be said that adenomas of the adrenal and cardiac hypertrophy are common in acromegaly. However, I have no wish to pick possible flaws in this highly interesting paper but rather to call attention to the authors' second case which bears a close resemblance to those under discussion. The essentials of the clinical history are as follows:

Case 5. [Patient of Drs. Oppenheimer and Fishberg.]


S. G., an undersized child, 12 years of age, was admitted to the Montefiore Hospital complaining of weakness and adiposity. In her sixth year she suddenly began to put on flesh and became disproportionately adipose, gaining about 75 pounds (34 kg.). She was seen by many physicians and treated symptomatically with various glandular preparations. About a year prior to her admission the parents noticed a change in coloration of the skin and the patient developed a tendency to fall asleep. A routine urine examination revealed 4 per cent of sugar. Polyuria and nocturia developed about this time. At the age of 11, hair began to grow on the face, axilla and pubis. The patient had never menstruated.

**Physical examination.** An undersized child, appearing many years older than her actual age (Figs. 10–12). She was exceedingly obese and had a very red, plethoric facies. There was a well marked growth of hair on the chin and lower cheeks; pubic and axillary hair was abundant. The skin was dry and on the abdomen were pigmented striae. There were abscesses on the back and neck, a mycotic infection of the nails, and ulcers on the legs. There was no oedema whatever.

The heart was enlarged to the left. The sounds were of good quality, the second sound being accentuated over the aortic area. There were no murmurs. The blood pressure was 190 systolic, 130 diastolic.

The urine contained sugar but no acetone bodies. There was a heavy cloud of albumin but neither casts nor cellular elements were found. Phenolsulphonephthalein elimination, 45 per cent (after intravenous injection). The basal metabolic rate was normal. The blood showed 260 mg. of sugar per hundred cubic centimeters; erythrocytes, 4,500,000; white cells 11,800 with 78 per cent polymorphonuclears; haemoglobin, 90 per cent (Sahli). Roentgenologically the sella turcica was slightly larger than normal and showed bone absorption in the neighborhood.

The patient was placed on an anti-diabetic diet and digitalized. The urine rapidly became normal; the sugar and albumin disappeared completely. At one time signs

Figs. 10–12. Drs. Oppenheimer and Fishberg's patient with "adrenal hypertension" (1924).
and symptoms of broncho-pneumonia appeared but cleared up. The abscesses of the neck and back finally healed. At this juncture, the parents insisted on removing her from the hospital and she died three weeks later. Though no postmortem examination was obtained, the clinical picture, in the authors' words, "was so characteristic of suprarenal hyperplasia as to leave little doubt of the diagnosis."

It can be seen that the syndrome presented by this patient, though it was of preadolescent onset, bore a close resemblance to that of the others so far presented: a rapidly acquired adiposity sparing the extremities, a plethoric facies with pigmented abdominal striae, an exaggeration of the secondary sexual characters accompanied by a growth of hair on cheeks and chin, vascular hypertension, and glycosuria. Her precocious secondary sex-characters were unaccompanied by any signs of menstruation.

The close resemblance to the original case of Minnie G. shown by these last four patients, in their symptomatic history, in their physical appearance, and in their clinical findings, is unmistakable. They are examples unquestionably of a highly similar polyglandular disorder the interpretation of which to this point remains highly obscure in spite of the three postmortem examinations. A tendency to chronic nephritis with cardiac hypertrophy probably secondary to the hypertension was noted in Cases 2, 3 and 5. A peculiar softening of the bones was mentioned in all three autopsied cases. The adrenal glands showed a unilateral enlargement in Case 2, a pea-sized adenoma in Case 3, and are not mentioned in Case 4. The pituitary body was said to be normal in Case 2, to show a minute adenoma (type undesignated) in Case 3, and an "adenomatous-like structure" of undetermined nature in Case 4.

We now come to a particularly well recorded example of the disorder published in 1926 from which something more definite can be learned. I have taken the liberty of quoting fully from the author's vivid description of the case.


"The patient, Mrs. E. B., aged 28 years, an Englishwoman, suffers from a 'coarse' plethoric-looking type of obesity, chronic purpura (Fig. 13), and large 'striae cutis distensae' ('striae atrophicae') of the trunk and limbs. The purpura recurs from time to time in the form of 'crops' of cutaneous petechiae and ecchymoses. Constriction of the veins of the arm at once produces ecchymoses. The 'striae' are of different dates and vary correspondingly in color, the newer ones being purplish, the older ones paler. The face is coarsely hyperaemic. The obesity is shown chiefly in the trunk, by the large fatty pendulous breasts and the corpulent projecting abdomen (Fig. 14).

"The limbs are not specially large, and the legs below the knees are relatively thin and have a striking appearance. They show transverse 'striae' (like the thighs do), and besides petechiae and ecchymoses there is a peculiar brownish discoloration, especially over the anterior surface, resulting probably from previous multiple haemorrhages. Moreover, a good deal of the skin in front of both legs has become shiny or parchment-like owing to some atrophic change. In spite of the obese appearance of her trunk, her body-weight is actually

22 Parkes Weber, F.: Cutaneous striae, purpura, high blood-pressure, amenorrhoea and obesity, of the type sometimes connected with cortical tumours of the adrenal glands, occurring in the absence of any such tumour—with some remarks on the morphogenetic and hormonal effects of true hypernephromata of the adrenal cortex. Brit. J. Dermat., 1926, 38, 1-19.

Fig. 13. Case 6. Dr. Parkes Weber's patient (1926) showing cutaneous hemorrhages and striae ascribed to adrenal hyperplasia.
pressure was 220 mm. Hg., the brachial diastolic blood-pressure was 170 mm. Hg.

There is slight bilateral exophthalmos. The basal metabolism is like that of a nulli-para; there is no sign of any intra-abdominal disease. By roentgen-ray examination the dorsum sellae turcicae gives only an extremely faint shadow, but the pituitary fossa appears of normal size. There is slight bilateral exophthalmos. The basal metabolic rate is 20 per cent above the normal. . . . There is slight hairiness of the chin and upper lip. The Wassermann reaction is negative. . . .

"The history is that the patient was a twin, her fellow twin being born dead. Her father and mother are both living, aged 50 and 49 respectively, and the blood-pressure of each of them is high. They have had eleven children, of whom only four are living. . . . She was married in December, 1922, and has never been pregnant. Her menstrual periods ceased suddenly about September, 1921, but she had three slight periods again after her marriage. Since then (March, 1923) there has been complete amenorrhoea. About March 1922, she already began to get fatter, especially in the face and abdomen. But it is only since about March, 1923, with the onset of permanent amenorrhoea, that her chief symptoms have gradually developed: headaches, pains in her whole body, attacks of dyspnoea (accompanied by a sensation of suffocation), feelings of sickness (for which she sometimes induces vomiting by putting her finger in her mouth), frequent slight, epitaxis, the 'coarse' type of obesity already mentioned, the cutaneous 'striae,' the purpura, the slight exophthalmos.

"The patient died on July 4th, 1925, in an attack clinically resembling acute pulmonary oedema. She had had a similar attack previously in the hospital, relieved apparently by blood-letting."

At the postmortem examination: There was no tumour in either adrenal gland, but the medullary substance was apparently rather in excess. The left ventricle of the heart was hypertrophied. There was slight chronic interstitial nephritis (slight renal sclerosis). In the anterior lobe of the pituitary gland there was a minute adenoma consisting of basophil cells. There was no evidence of disease in the thyroid gland or in the ovaries; the latter were said to have been rather small but histologically normal.

Microscopical examination "The pituitary gland: Its three parts can be easily distinguished. In the anterior part is a rounded nodule (3X4X5 mm. in the hardened sections) of basophil cells, in alveolar arrangement (with some minute calcareous spots), contained in a thin connective-tissue capsule; it is evidently a basophil adenoma. The remainder of the anterior part and the middle and posterior parts of the pituitary gland are of normal appearance. In the anterior lobe-spur of the pedicle of the pituitary gland there are many relatively large epithelial islands (Erdheim) [cf. Case 4]. This is remarkable, but must not be considered pathological. No special immigration of cells from the middle lobe into the posterior lobe can be made out."

Dr. Weber states in conclusion: "In my opinion it belongs to a group of cases characterized by complete amenorrhoea and by symptoms [given in the title of his paper] sometimes connected with cortical adrenal tumours, occurring in the absence of any such tumour. The main features cannot be explained by the small adenoma of the pituitary gland found at the post-mortem examination."

In search of further information regarding this important case, Dr. Weber was written to and he obligingly forwarded the original paraffin block from which further sections of the tumor have been made. He also referred me to Professor Herbert M. Turnbull of the London Hospital who first recognized the nature of the lesion as a basophil adenoma and who kindly sent me the accompanying photographs (Figs. 15, 16) from the single section in his possession.
Fig. 15. Case 6. The anterior basophil adenoma (aniline blue-fuchsin, X10). Kindness of Professor H. M. Turnbull.

Fig. 16. Case 6. From the centre of the basophil adenoma to show the blue basophil granules in the often multi-nuclear cells (aniline blue-fuchsin, X1020). Kindness of Professor Turnbull.
Much has been learned since 1926 concerning the influence of the pituitary body on the development and regulation of the genital system, and Dr. Weber would have been more likely today than at that time to suspect the probable influence on his patient's syndrome of a pituitary adenoma which was then so easily explained away in favor of an adrenal influence even in the absence of any definite microscopical abnormality in these latter glands.

It was at about this time that it had become possible by crude chemical methods to separate the growth and sex hormones from bovine hypophyses and though Dott and Bailey in a study of the pituitary adenomas in the Brigham collection had stated in 1925 that basophil adenomata occur only in the form of minute intraglandular nodules that give rise to no known clinical manifestations, some of us soon began to suspect that this was probably a matter of not knowing what to look for.

This at least was the conclusion arrived at as the result of a survey of the then known facts regarding the dual anterior pituitary hormones which, chiefly for our own information, my junior co-worker, Dr. Harold Teel, and I shortly afterward came to put together. The prepared mind was what enabled Dr. Teel during his house officership at the Lakeside Hospital in Cleveland for the first time to predict the presence of a basophil adenoma which, as will be told, was confirmed at autopsy. Case history, which unfortunately is lacking in many details, may be briefly summarized as follows:


An exceedingly obese and abundantly hirsute young woman, 20 years of age, admitted to hospital in a comatose condition due to a meningococcal meningitis, was under clinical observation for only three days before she died. Owing to her physical condition, a personal history was not obtainable, but it was learned that at the age of nine she had a continuous menstrual flow lasting four months. Subsequently, at the age of 14, she was said to have attained a normal adolescence, but her periods were subsequently most irregular. From the age of 15 she had grown exceedingly stout, the maximum weight of 306 pounds (93.4 kg.) having been recorded seven months before her hospital admission. Because of excessive fatigability she had consulted a physician at about that time, when and she found she had a basal metabolic rate of +38, her enlarged thyroid was roentgenologically radiated. This was said to have caused little or no symptomatic improvement.

At autopsy, a suppurative meningococcic leptomenigitis was found to be the obvious cause of death. The pituitary body appeared to be of normal size, but suggesting from the patient's general appearance what might be found, Dr. Teel had the gland serially sectioned and a small though unmistakable basophil adenoma measuring 2.5 mm. in diameter was disclosed (Fig. 17). There was a persistent thymus, a slight enlargement of the thyroid, questionable enlargement of the pancreatic islets, and a definite enlargement (90 gm.) of the suprarenals with no histological change of structure, no definite secondary adenomata being present in any of these organs. The ovaries were enlarged apparently from increase in stroma; there was a single large corpus luteum with a small central haemorrhagic area and several smaller ones in various stages of organization.

The only true neoplastic growth was the small anterior-pituitary adenoma to which the other endocrine changes were regarded as purely secondary.

**THE SYNDROME AS IT OCCURS IN THE MALE**

To this point, examples have been presented of this peculiar polyglandular syndrome as it occurs in women who seem to be more commonly victimized than do men. Why this should be so, if it is actually so, is not fully apparent. It is perhaps reasonable to assume that the combination of amenorrhoea, adiposity and heterosexual hirsuties may excite the attention of physicians and be recorded as a freakish disorder more often than would corresponding maladies in men.

However this may be, five cases of the same or a comparable disturbance, three of them with and two without autopsy, can be cited in the male. The first case, unfortunately unaccompanied by photographs of the patient, was briefly reported after careful study by Dr. E. D. Friedman of New York. The essentials only need here be given.

**Case 8. [Dr. Friedman's case.] Obesity. Hypertrichosis. Vascular hypertension. Glycosuria.**

E. C., a student, 19 years of age, complained of obesity, hypertension and recurrent pains in the region of the spine for six months. He was an undersized young man who at the age of ten in the course of two months had grown rapidly stout. Treatment with thyroid extract was without avail. His abdomen became pendulous and face ruddy. More recently he had been having shooting pains in the region of the spine, chest, and abdomen. He was thought to have "kidney trouble." There was shortness of breath, palpitation and tremor on exertion, dimness of vision and occasional headaches with impairment of memory. Nycturia was present; libido absent.


28 Friedman, E. D. An unusual hypophyseal syndrome. N. York M. J., 1921, 114, 118.
**Physical examination.** The patient was round shouldered and short (136.5 cm.; 4 ft. 7 in.), obese (46.4 kgm.; 102 lbs.), with an erythematous face and a pendulous, distended abdomen. The mammæ were well developed, the genitals small, and the fat distribution was of feminine type. There was an overgrowth of hair at the bridge of the nose and the body was covered with a fine lanugo. The heart was somewhat enlarged to the left. The skin, which was dry, showed ringworm in the axillæ and pubes; erythema and telangiectasis of the face; and "striae distensae" on the abdomen and thighs.

Blood-pressure was 198/110 and there were two minute haemorrhages in the outer side of the left optic disc. The basal metabolic rate was —5 per cent. The urine showed glycosuria with a faint trace of albumin; the phenolsulphonephthalein excretion was diminished. The blood showed 95 per cent haemoglobin, 4,860,000 erythrocytes, 13,400 white cells of which 76 per cent were polymorphonuclears. Chemical examination disclosed, in mgm. per cent, an excess of non-protein nitrogen (46.6); of cholesterin (308); and of sugar (240).

Roentgenograms: of the skull, showed markedly atrophic and thin bones of sella and sphenoid; of the hands, "a development of bones such as is usually seen in persons about 13 years of age." [Dr. Friedman informs me that the patient died of pneumonia in November of the year in which his report was made: there was no autopsy.]

It was recognized that this boy's syndrome had no relation to hyperpituitarism (acromegaly) nor to hypopituitarism (syndrome of Fröhlich). This condition nevertheless was thought to be of pituitary origin though the tendency to hypertrichosis and high cholesterin content of the blood suggested an involvement of the adrenals.

In the same year as the foregoing (1921) a highly suggestive example with a detailed post-mortem examination was recorded by Dr. Hermann Mooser from the Pathological Institute of Zurich then under the direction of Professor Busse. Though the protocol specifically states that the pituitary body was normal, the case so definitely fits into the polyglandular syndrome under consideration it cannot properly be neglected any more than can examples of acromegaly without gross changes in the pituitary body be excluded in a general consideration of acromegaly.

**Case 9.** [Dr. Mooser's case.] Acute painful obesity sparing extremities. Cutaneous pigmentation. Spinal deformity from osteoporosis. Duration three years. Autopsy: osteomalacia with multiple fractures; cardiac hypertrophy; atheromatous vessels; contracted kidneys; acute pancreatic necrosis; testicular atrophy. Pituitary body large but said to be normal.

**Clinical history.** The patient, aged 27 (born in 1890), the eldest of eleven children, one of them a pituitary dwarf, was an unmarried merchant, a polylinguist, and fond of sport. Previously spare and of slight build (Fig. 18) at the age of 24, while in military service during the autumn of 1914, he began to grow so stout as scarcely to be recognizable. The adiposity was so rapidly acquired that broad striae atrophicae appeared over the trunk and extremities. The tension of the skin was such it gave the disagreeable feeling of being electrically stimulated. Ere long, he began having pain in his spine, which the military surgeon thought indicated a tuberculous spondylitis and he was sent to a sanatorium. There his disorder was diagnosed as adiposo-genital dystrophy of pituitary origin.


The adiposity, which was confined to face, neck and trunk (Fig. 19), progressively increased and the suffering from his tense skin which greatly disturbed his sleep became scarcely endurable. In the course of the next six months he became so weak he could scarcely hold a pencil or feed himself. He was given heliotherapy, which he bore badly, as it provoked alternating attacks of hyperaemia, cyanosis and sweating lasting from a few minutes to half an hour.

At first, there was little complaint of headache, but this for a time became more marked and later on again subsided. He was made sleepless by trembling of the body, noises in the ears, dreams and visions. He also complained of visual disturbances on moving his head. Ophthalmoscopic investigation, apart from a slight lessening of visual acuity, showed no abnormality. He had a marked polydipsia which obliged him to get up three or four times at night. The genitalia became dystrophic. The urine examination showed during 1916–1917 a slight trace of albumin with a few hyaline casts and no sugar; amount was not recorded.

His height diminished from 165 cm. in 1914 to 158 cm. in 1917. The body circumference increased from 91 cm. in November 1915 to 96 cm. in January 1917, with a gain in weight from 52 to 63.9 kgm.

Roentgenological studies in 1916 showed that the contours of the sella turcica were scarcely visible, the bones porous. An examination a year later showed these conditions to be still more advanced. There was apparent destruction of the bodies of the mid-thoracic vertebrae associated with a gibbus which was diagnosed in 1915 as osteitis vertebrae; in 1916 as spondylitis tuberculosa; in 1917 recognized as part of a non-tuberculous generalized porosity or decalcification of the skeleton.

Following a brief period of asthmatic dyspnoea and haemoptysis, he died on November 27, 1917, three years from the onset of symptoms.

Postmortem examination. The body was that of a man whose head, neck and body were exceedingly adipose in marked contrast to his relatively thin extremities. The abdomen was likened to a pillow, the circumference being 90 cm. at the level of the navel. The color of the skin was everywhere strikingly brown, the region of the pelvis being of a lighter color, presumably from the fact that during his periods of heliotherapy this region was protected by swimming tights. Radiating scars were present on inner surface of thigh and upper arm. The hairiness of the lower body was normal in distribution.

Head: The inner part of the calvarium showed sharply circumscribed red spots, the largest of which had a diameter of 5 to 3 cm. The cerebral vessels were markedly atheromatous. The sella turcica was not enlarged. The hypophysis measured 14 by 8 by 7 mm. The neurohypophysis was plainly evident. The organ was put immediately in formalin. The base of the sella turcica was of red but smooth bone.

Thorax: Subcutaneous fat 3.5 cm. thick. The ribs were found to be greatly softened; the upper part of the sternum greatly thickened. The heart was enlarged; the aorta atheromatous; the

Professor Busse’s detailed protocol is herein greatly abbreviated.
thymus not to be identified in the abundant mediastinal fat. The thyroid gland was fibrotic, difficult to cut, and contained but little colloid.

**Abdomen:** Panniculus 4.5 cm. thick; omentum exceedingly large and fat; perirenal fat abundant. The adrenal glands, though buried in fat, were of average size and of normal appearance. In the pancreas was found an area of central necrosis. The testes were small.

The investigation, particularly of the bones, showed that the thickened sternum was due to the callus of a healing fracture; several ribs also showed old healed fractures. The manubrium was intensely red and soft, and contained great holes of soft marrow. The ribs were easily cut, as was true of the spinal column, part of which was removed. The greatly compressed bodies of the vertebrae, in places only 1 cm. thick, were so soft they could easily be cut with a knife.

The gross pathological diagnosis: Lipomatosis; osteomalacia (seu rachitis tarda); multiple fractures of the ribs; vertebral collapse; hypertrophy of the cardiac ventricles; arteriomegaly of the cerebral vessels; atheromatosis of aorta and of the cerebral vessels; encephalomalacia of the right occipital lobe; fibrino-purulent peritonitis; necrosis of the pancreas; hypoplasia of the thymus; granular atrophy of the thyroid.

The principal histological findings of note were those relating to the peculiar structure of the softened bones. The kidneys showed slight glomerular fibrosis; the cerebral vessels an endarteritis proliferans. No abnormality was found in the adrenals, pineal or pituitary glands.

The small [from a Swiss standpoint] thyroid showed an increase of intralobar connective tissue with small and atrophic intermedial follicles; the single parathyroid detected was closely attached to the capsule of the thyroid, measured 4 by 3 by 2 mm., and showed an increase of connective tissue. The thymus could scarcely be identified in the mediastinal fat. The pancreatic islets were relatively few and atrophic in the part of the gland that had escaped necrosis. The testes also showed fibrosis with atrophic changes, though some active spermatogenesis was still present.

The outstanding symptomatic features of this remarkable case were: (1) The suddenly acquired, and peculiarly disposed, painful obesity; (2) The softening of the bones affecting the entire skeleton but more particularly the vertebrae, leading to multiple fractures (cf. Case 2); (3) The ultimate enfeeblement with fatality at the expiration of three years. In view of the slightly contracted kidneys, the enlarged heart and the arteriovascular changes found after death, vascular hypertension was probably present during life. Plethora was not particularly emphasized nor purplish abdominal striae, but pigmentation of the skin was noted by the pathologist.

The author, in his analysis of the case, comes to the conclusion that the disorder represents a polyglandular deficiency, and ascribes the skeletal decalcification to sclerosis of the parathyroid glandules; the adiposity was taken to be chiefly thyroidal in origin though something was to be said in favour of a pancreaticogenous insufficiency. A possible pituitary origin was discussed only insufficiently as to point out the lack of resemblance of the syndrome to that of adiposogenital dystrophy. Whether the gland was scrutinized for the possible presence of an adenoma is not apparent. The gross measurements were certainly in the upper limits of normal.

The next case, also with autopspy, figures in a report made from Professor Biedl’s clinic in Prague in 1924 by Dr. William Raab on the general topic of hypophysial and cerebral adiposity, or what is commonly called adiposogenital dystrophy. The subject was approached largely from its roentgenological aspects, and it was a mere chance that in 1920 when preparing for my Lister Lecture I happened to hit upon the fact in reading this paper that in one of the patients (Case 2) a basophil adenoma had been disclosed at autopsy. The photographs of the patient were so striking and bore such a close resemblance to the appearance of a patient at the time under observation in my own wards (cf. Case 11) that I felt little doubt but that they had been afflicted in all certainty with the same disorder. The translation of Dr. Raab’s brief note of his case is as follows:


"Karel W., a man aged 31, showed gigantism of moderate degree (192 cm.), with very long extremities, externally well-developed genitalia and distribution of hair of normal masculine type. Patient complains of suffering from headaches for the past two weeks previous to his admission into the clinic and claims to have taken on 10 kgm. in weight during the same [sic] short period. This was confirmed by the family doctor. The libido had always been rather low; he had been impotent for the past fortnight.

"There is a marked obesity of the face which appears, therefore, considerably disfigured when compared with former photographs (slit-eyes), and a marked adiposity of the abdomen (Figs. 30, 41). There is no adiposity of the long, slender extremities and of the nates. The abdomen is tremendously prominent and shows flame-shaped striae of dark-red color which are, in part, more than 2 cm. broad. The hips reveal the same feature. Weight 96 kgm. (211 pounds). The X-ray plate shows a sella which, while not being excessively large, reveals


33 In view of the postmortem findings of advanced testicular atrophy and decalcification of the skeleton, the disease presumably was of longer duration than this statement would indicate.
nevertheless the characteristic deconfiguration produced by a process enlarging the intrasellar space. Diagnosis: tumor hypophyseos.

"The headaches improving and the weight remaining unchanged, the patient left the clinic, but returned in a few weeks, feverish and suffering from excessive pains in the lumbar vertebral column. Shortly afterwards he acquired a streptococcal phlegmon of the hand and died from acute sepsis in spite of generous incisions and amputation of his arm.

"The autopsy revealed an operculum sellae which was, as usual, concave; the pituitary body was scarcely enlarged; the posterior lobe was softened supposedly by postmortal changes. The pathologist emphatically denied the presence of a growth. Histologically, however, a small basophil adenoma was discovered which had almost entirely replaced the posterior lobe and showed central softening—a verification of the clinical diagnosis. An osteoporosis of extreme degree involving the vertebral column and the long bones accounted for the vertebral pain."

Further details of the postmortem examination of this case were given in a separate report in the same year (1934) by Professor E. J. Kraus34 of Prague who has been kind enough to send me sections of the pituitary body (cf. appended Figs. 22, 23) for study, and whose personal description is translated as follows:

Fig. 22. Case 10. The basophilic adenoma from Dr. Raab's patient. Tumor lying between pars anterior above and pars nervosa below. (Hematoxylin and eosin, X9). Kindness of Professor Kraus.

Fig. 23. Case 10. The adenoma of the Raab-Kraus case (hematoxylin and eosin X850) showing a cluster of basophilic cells, many of them multinuclear.
contains much colloid, reveals enlarged vesicles, a partly cubic, partly flat epithelium, and a delicate interstitial tissue. Three parathyroid glands (weight together 0.16 gm.) are strikingly infiltrated by fat tissue, and here and there occur rather large nests of oxyphil cells. The pancreas (weight 94 gm.) shows marked post-mortal autolysis as do also the adrenal glands. The two testes (without the epididymes) weigh 18.3 gm. The canalules of the testes have a delicate tunica propria. Spermatides, spermatoblasts and spermatozoa are wanting; only heads of spermatozoa are found in a very few canalicules. The epithelium for the most part shows four or five rows; the amount of lipoid is somewhat diminished; the epididymes histologically normal.

Professor Kraus, if I understand him correctly, looked upon the hypophysial tumor as “an incidental finding” without relation to the clinical features shown by the patient, whereas Dr. Raab believed that the adenoma in some way influenced the secretory activities of the posterior lobe, the relation of which (pituitrin) to adiposity he has made the special object of study. With neither of these views do I find myself in accord; and inasmuch as Professor Kraus not only was one of the first to describe basophilic adenomas, but has since made other important contributions to the subject, his seeming reluctance to correlate the adenoma with the clinical syndrome is the more surprising. This may be explained by the fact that only in later years, largely through the work of P. E. Smith and his collaborators, has the functional importance of these cells been pointed out. However this may be, I quite agree with Professor Kraus’ opinion that the adipose syndrome presented by this case was something wholly different from that seen in adiposogenital dystrophy, which is a deprivation syndrome due usually to inactivation of the hypophysis by compression. The adipose disorder under consideration, on the contrary, is almost certainly due to a hyper-secretory influence of some kind, and since the adrenal glands, apart from their postmortem change, were supposedly normal in this case whereas an adenoma was found in the pituitary body, the latter would seem to be the most probable primary seat of the trouble.

We may now turn to the next of the male patients whose syndrome bears so close similarity to the foregoing case that even without a postmortem examination it may safely be ascribed to a lesion of the same primary sort. Fortunately the somewhat meagre clinical record for the preceding case, in which many details are missing, can now be supplied:


E. G. F., a dentist 30 years of age, referred for therapeutic recommendations by Drs. R. T. Woodyatt and A. R. Colwell of Chicago, entered the Brigham Hospital August 11, 1930, with the principal complaints of pain and weakness, loss of strength, irritability, polyuria and polyphagia.

Family and personal history. The patient was one of twelve children of healthy parents, both living and well, none of this large family having had any known endocrinological disorders. He had been married for ten years and was the father of two children, the first of whom died following an instrumental delivery at birth, the second being a healthy girl one year of age. Until the past year the patient had always enjoyed excellent health. He was a tall man, standing over six feet, his normal average weight having been 160 pounds.

Present illness. This, he thinks, started five years before admission, when he began slowly to grow round-shouldered and stout. In the course of the next three years he gained 25 pounds and during the fourth year there was a more rapid gain of 35 pounds, his weight reaching 220 pounds (100 kgm.). He then began limiting his diet and finally succeeded in losing a few pounds, but under this régime he soon found himself without energy, easily fatigued, unable to concentrate his mind on his work, and fits of unnatural irritability alternated with periods of depression.

At this juncture he consulted a physician who restored some carbohydrates to his self-imposed dietary restrictions. He immediately felt better but his weight quickly increased, his abdomen became prominent, and for the first time he noticed a peculiar disposition of localized masses of fat on his face and neck. These fat deposits, which appeared in symmetrical regions over the head (cheeks, temples, orbital region, supramental and suprasternal regions, as well as over the cervicodorsal spine), were at first soft, but tended to become increasingly firm and tense. They moreover were accompanied by most uncomfortable “drawing sensations,” presumably from stretching of the cutaneous nerves. The tense skin over these swellings acquired a peculiar florid reddish-bronze color and showed telangiectases so altering his appearance that he was scarcely recognizable to his friends (cf. Figs. 27, 28).

About this time (December 1929) he began to have an excessive thirst associated with a polyuria which was more marked at night when he would be obliged to void at least five times a night. An excessive thirst associated with a polyuria which was more marked at night when he would be obliged to void at least five times a night is true—namely, an adrenal hypoplasia is accompanied by few basophils. He suggests that the “hypercholesterinämie” of hypertension may be the common basis or at least play an important rôle.
from four to six times. He experienced also susceptibility to fatigue, forgetfulness, restlessness, palpitation on slight exertion, swelling of the feet and ankles, generalized weakness, and impotence. A distinct loss of body hair was observed.

In January 1980, he was found to have a glycosuria and this led to his admission to the Presbyterian Hospital in Chicago where, by Drs. Woodyatt and Colwell, his condition was carefully investigated at various periods during the course of the next six months. They found, to make the story short:

(1) "A slight leucocytosis of from 10 to 18 thousand, with some preponderance of neutrophilic polymorphonuclear elements; erythrocytes in normal limits."

(2) "A variable glycosuria and hyperglycaemia, together with increased nitrogen excretion. On a diet with a daily glucose value of 201 grams, there was a daily excretion of 5.7 grams sugar (glucose) which was controlled by 50 units of insulin daily. This glycosuria was looked upon as a truly diabetic phenomenon, but it was accompanied by an unexpectedly great and wholly unrelated polydipsia and polyuria, the largest daily excretion observed having been 67.0 cc. Attempts to modify this polyuria by pituitrin injections up to a dosage of 3 cc. in twelve hours were wholly ineffective."

(3) "Azoturia. On a diet containing 81 gm. of protein daily (13 gm. nitrogen), there was a daily nitrogenous excretion of 20–24 gm. despite approximate caloric balance. This loss was later balanced by increasing the protein intake. Since then there has been a continuous excretion in the urine of 90 to 30 gm. daily."

(4) "Blood chemistry: urea N. 19.0; uric acid 3.8; creatinine 1.1; total N. P. N. 36.0; chlorides 466; calcium 7.1–8.9; cholesterol 147.5 (all values in mg. per 100 cc. blood); CO₂ 77.7 vol. per cent. Wassermann reaction negative."

(5) "Basal metabolic rate: minus 10% to plus 1% on repeated readings."

(6) "A moderate degree of vascular hypertension, from 165/70 to 178/100, without evidences of arteriosclerotic change."

(7) "The administration of iodine was without effect. One of the fat pads on the front of the neck was removed for study and proved to be fatty tissue of customary pannicular type."

Finally, when a suspicious enlargement of the pituitary fossa was roentgenologically detected suggesting a possible pituitary or hypothalamic disorder, he was referred to the Brigham Hospital for an opinion.

*Physical examination* (on admission). This showed (Figs. 24–26) a tall (184.2 cm.), extremely abdominous, and somewhat round-shouldered man with patchy
adiposity of the face, neck and trunk, and comparatively spare extremities (weight 86.8 kgm.). All his movements, such as those incidental to rising from a chair, were obviously made with great effort, as though his limbs were scarcely strong enough to support his huge body. His face was peculiarly florid and dusky, and on forehead, cheek bones, temples, and chin were deposits of fat which were tender to the touch and covered by tense, glistening skin (Figs. 27, 28). Similar accumulations of fat were present on the anterior aspect of the neck and over the cervico-thoracic region in the back.

Owing to the puffiness of his face and eyelids, the palpebral slits were narrow, the eyes being injected and somewhat prominent. Vessels of the fundus oculi were exceedingly tortuous and the edges of the discs were blurred, but there was no measurable swelling. The fields of vision were normal.

Wide purplish striae radiated from the groins over the abdomen and smaller striae were present over medial aspects of both thighs (Fig. 29). There was some pitting oedema about the ankles and some swelling of the hands, so that he was unable to remove a ring. He was partially bald and the hirsuties of the extremities and axillae was scanty, but there was abundant hair on the
chest which was normal in deposition and texture. The skin of the axillae, groins and crotch was pigmented and soily.

He was free from headache, but complained greatly of discomforts associated with the adiposity and also of variable pain in the back and shoulders. Roentgenograms were made of the entire skeleton, which in Dr. Sossman’s opinion showed no evidence of decalcification.

The pituitary fossa was not enlarged but the posterior clinoids appeared to show some absorption. No acromegalic changes were present. The spine and pelvis, so far as could be seen, were normal.

The blood examination, frequently repeated, averaged 6,000,000 red cells, 16,700 white cells, 85 per cent of them being polymorphonuclears. Haemoglobin was variously estimated at 90 to 100 per cent. The basal metabolic rate was −10 per cent; a specific-dynamic test with a 200 gm. steak-breakfast showed (possibly because of his nitrogen imbalance) a rise only to +4 per cent at the end of a four-hour period. The systolic blood-pressure was over 170 mm. of Hg, indicating a moderate vascular hypertension. There were no renal elements or albumin in the urine.

When admitted to hospital, he was still on the somewhat restricted diet which finally had been worked out by Dr. Woodyatt as most effective in caring not only for the diabetes but also for the increased nitrogen output. In order to balance this and to keep up the patient’s strength, it had been found necessary to increase the protein in the diet from 200 to 475 grams. He was taking in addition 65 units of insulin daily, divided into two doses, 40 in the morning and 25 at night. This, however, had been found in Chicago, as it was found here, to be most variable in its effect. His polyphagia was most striking. He was hungry all the time, and even when allowed a full meal, of which he would partake greedily, he would feel ravenous again after an hour’s interval.

Laboratory studies. During his long hospital sojourn of 71 days, his condition was investigated from every angle, both when under dietary restrictions and when free from them. Various authorities on diabetes and the blood, coming among them Dr. Reginald Fitz, Dr. W. P. Murphy, and Dr. E. P. Joslin, saw him in consultation but had no therapeutic suggestion to make. Under the supervision of one or another of them frequent detailed studies were made of the blood and during the entire period daily record was kept of the total protein, total nitrogen, total uric acid, and total sugar elimination in the urine, both diurnal and nocturnal.

Soon after his admission, a study of the fasting blood was made in Dr. Murphy’s laboratory the morning after he had been on a wholly unrestricted diet for comparison with the findings after a period of dietary restriction, with the results shown in the subjoined table of blood studies.

During the 24 hours prior to the test on the morning of August 18th, the diet was estimated to contain 412 gm. carbohydrate, 188 gm. protein, and 286 gm. of fat with an approximate glucose value of 546 gm. The corresponding urinary output had been 5410 ccm. containing: 15.5 gm. sugar; 36.4 gm. total nitrogen (127.5 gm. total protein); and 855 gm. uric acid.

During the 24-hour period preceding the August 22nd test, the diet contained 95 gm. carbohydrate, 178 gm. protein, and 177 gm. fat with a glucose value of 212 gms. The corresponding urinary output had been 4550 ccm., containing: 15.5 gm. sugar; 36.4 gm. total nitrogen (127.5 gm. total protein); and 1505 gm. uric acid.

During the month of August, also, acting on the assumption that a basophil adenoma might conceivably show a sex-maturing substance in the urine similar to that present during pregnancy, a series of observations was made by Dr. W. G. Gaiser to test this point. The urine was highly toxic for immature rats but the survivors showed no change in ovaries or seminal vesicles at the end of 120 hours. Similar tests on immature mice were equally without result.

On September 12, 1900, during a period when he was again on a restricted diet without insulin [he showed on this particular day a fasting blood sugar 0.214, with the elimination of 4500 cc. of urine containing 24.4 gm. sugar, 188 gm. total protein, 29.2 gm. total nitrogen, and 1405 mgm. total uric acid], an estimation in Dr. Joslin’s laboratory was made of his plasma lipids (the patient’s brother and an insulinized case of diabetes of nine years’ duration serving as controls), with the following results:

<table>
<thead>
<tr>
<th>Plasma lipids</th>
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<tbody>
<tr>
<td>CHOLESTEROL</td>
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<tr>
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<tr>
<td>mgm. per 100 cc.</td>
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<tr>
<td>Normal average</td>
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<tr>
<td>The patient, E. G. F. Controls</td>
</tr>
<tr>
<td>Patient’s brother</td>
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<tr>
<td>A 9-year diabetic</td>
</tr>
</tbody>
</table>

Though the patient’s fatty acids and total lipids were considerably in excess of the controls, they were regarded as “approximating those seen in cases of mild or moderate diabetes in the days before the introduction of insulin.”

[29] Attention may be drawn to two recently published papers by Anselmino and Hoffman (Klin. Wehnschr., 26 Dec. 1931, pp. 2880–86) in which the presence in the anterior pituitary of what is called a metabolizing (Steifneccheal) hormone is claimed. This appears to be related to but is separable from the gonad-stimulating hormone. Its injections increase the acetone-body content in the blood by accelerating fat combustion.
As weeks passed, he became increasingly more feeble, was reluctant to get out of bed, and appeared rapidly to be going downhill, the progressive loss of strength causing him great concern. Not only did he suffer from pain in his hips and shoulders but from such extreme sensitiveness of his face he could not bear the pressure of a pillow against it. It was very difficult to make him comfortable in bed, recoupe being finally had to an air mattress. He ceased to take an interest in his surroundings; became so feeble he was unable even to turn in bed; and he finally acquired a carbuncular infection at the lower end of his spine which began rapidly to spread. Knowing that other patients with this syndrome had died either from or with ulcerative cutaneous infections (cf. Case 10), it was feared that his end was near.

From the outset, he had been pleading for an exploratory operation which was considered impracticable, but in view of the growing conviction that his trouble must be due to a basophil adenoma, which might conceivably be amenable to radiation, he was given, between October 14th and 17th, four x-ray treatments. During their course, he felt particularly miserable, but by the 19th his downward progression for the preceding month was unmistakably checked. The improvement in his general condition was so striking it must have been due to a carbuncular infection of the lower spine which began rapidly to spread. The carbuncular infection of the lower spine began to show improvement, and though he was unable as yet to get out of bed, he at this juncture (October 21, 1930) insisted on being taken home. There he continued rapidly to improve and the infected area on his back and hip soon healed.

According to his frequent letters he continued to complain of the backaches and of the painful sensations in the tense, adipose areas; and on March 6, 1931, he must be due to a basophil adenoma, which might conceivably be amenable to radiation. He had gone for the winter, stating that he was still improving and no longer showed sugar on an ordinary diet, though he was unable as yet to make efforts to move himself about, was conscious of a diminution in thirst, and of lessening in his discomforts. The carbuncular infection of the lower spine began to show improvement, and though he was unable as yet to get out of bed, he at this juncture (October 21, 1930) insisted on being taken home. There he continued rapidly to improve and the infected area on his back and hip soon healed.

According to his frequent letters he continued to complain of the backaches and of the painful sensations in the tense, adipose areas; and on March 6, 1931, he reported a further gain in weight up to 235 pounds. But on the whole, he made steady progress and by July 1931, was able to walk a half-mile or more at a time without over-fatigue. In October 1931, he stated that the "tumour-like growths" of his head had nearly disappeared, and two months later he wrote from Florida, where he had gone for the winter, stating that he was still improving and no longer showed sugar on an ordinary diet, even without insulin.

The sudden improvement following radiation of the patient's pituitary body was looked upon as something more than mere coincidence. As will be pointed out in the next section, the average duration of life of the fatal cases had been in the neighborhood of five years and all the patients succumbed to progressive enfeeblement associated in most of the cases with terminal infections, a happening which in this particular instance there was every reason to anticipate when recourse was finally had to radiotherapy.

The exhaustive laboratory studies of the blood and urine gave no information of value though attention may be called to the consistently high non-protein nitrogen percentages and to the high cholesterol reading, on a single occasion, of 246 mgm. per cent. In this connection it is interesting that Professor Kraus, after the painstaking enumeration of the number and condition of the basophilic elements in the anterior pituitary in various pathological states, expresses the conclusion in a recent paper (loc. cit., 1928) that a definite relationship exists between the number of these cells, those of the adrenal, the blood-pressure and cholesterol metabolism.

Another matter to which attention may be called is the fact that the patient's diabetes, like that complicating cases of acromegaly, was far more difficult to regulate and control by insulin than is the diabetes primarily of pancreatic origin. What, if anything, this may have to do with the known counter-effect of posterior lobe extract (pituitrin) on the action of insulin needs further ventilation.

Another unmistakable example of this same disorder, recently reported by Dr. Wieth-Pedersen of the Rigshospital of Copenhagen, has been called to my attention by a Danish student in our Medical School. The author gives a detailed report of two cases both of which showed marked striae distensae cutis to which factor attention is particularly drawn. One of the patients had a malignant adrenal tumor with metastases, the other a pituitary tumor associated with adrenal hyperplasia, the syndrome in both having been ascribed to the adrenal factor.

The first case was that of a woman, 158 cm. in height, with headaches, puffy skin (without hypertrichosis), dimness of vision, increase of 16 kg. in weight, with reddish-blue striae distensae, hypertension 245/150, cardiac enlargement and polydipsia. She died a year after the onset of symptoms. An adrenal tumor 12 by 6 cm. with metastases was found at autopsy. The pituitary body was said to be normal but was not examined microscopically. An abbreviated report of the second case follows:

Case 12. [Dr. Wieth-Pedersen's patient.] Delayed adolescence, Plethoric adiposity with striae, Albunimuria, Hyperglycaemia, Glocosuria. Vasular hypertension. Cardiac hypertrophy. Duration 4 years. Autopsy: pituitary adenoma (type unverified); adrenal hyperplasia.

Clinical history. A young man, 24 years of age, entered the hospital May 6, 1930, and died there three months later. He had always been well but his puberty was delayed until the age of 20 when he began to grow abnormally and the color of his face and hands became bluish red. He had polyphagia, polydipsia, and polyuria. He perspired freely when at work. He needed to shave only twice weekly. There was no headache or dizziness. His vision had become impaired in later years and he

had lost some weight under treatment during the nine months prior to admission.

**Physical examination.** The appearance was that of a man older than his age. He was of slight stature. Height 161.5 cm. (5 ft. 3 in.); weight 61.8 kg. (135 lbs.). There was quite marked adiposity, localized around abdomen, thorax and face, the extremities not being affected. No dyspnoea while resting. The teeth were carious. The thyroid gland was covered by a cushion of fat, but not enlarged. No peripheral adenitis. No cardiac enlargement was detected. There were numerous pigmented naevi on the chest.

On both sides of the abdomen were reddish striae distensae, 1 cm. in width and 5 to 6 cm. in length; otherwise nothing abnormal. The external genitalia were not hypoplastic. The face and hands showed a deep red-blue color. There was cyanosis of the lower legs with spots of light brownish pigmentation which contrasted with the varices which were present. At the time of the examination there was a four days’ growth of beard which amounted to 2 mm. at the most. The hair on the head, eyebrows, axillae and pubis was normal.

The urine contained sugar and albumin with a few hyaline casts. Blood-pressure 190/170; haemoglobin 98 per cent (Sahli). Wassermann negative. The cranial roentgenograms showed no abnormality; the sella was normal (10 by 12 mm.) with no evidence of a destructive process. The epiphyseal lines in both knees and wrists were open, corresponding with 16 to 17 years of age. No signs of atherosclerosis.

The basal metabolic rate was approximately normal.
Renal function was unimpaired. The eyes were normal, except for a polar cataract visible in both of them. Blood urea [non-protein nitrogen?] 44 mgm.%; fasting blood sugar, highest estimate 203 mgm.%. No ketonuria 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 headache, of pains in the ears, and became dull and sleepy. On one occasion, he had subjective dimness of sight, marked dizziness, and vomited, the blood-pressure registering 185/150 with a rapid pulse. The abdominal striae grew more pronounced and finally reached all the way up to the axillae on both sides. Ecchymoses occurred from time to time on the legs and arms; his left hand became oedematous. On August 1st, the patient became dyspnoeic and cyanotic 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 thorax and even to axillae. The skin was without oedema, apart from that on the left forearm and back of hand. The growth of the hair was natural, except the beard, which was scanty. Broncho-pneumonia was found, also marked growth of the hair was natural, except the beard, which was scanty. Broncho-pneumonia was found, also marked hypertrophy of the left ventricle and atheroma of the aorta and common iliacs. The mesentery was exceedingly fat. The kidneys were slightly granular. 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 headache, of pains in the ears, and became dull and sleepy. On one occasion, he had subjective dimness of sight, marked dizziness, and vomited, the blood-pressure registering 185/150 with a rapid pulse. The abdominal striae grew more pronounced and finally reached all the way up to the axillae on both sides. Ecchymoses occurred from time to time on the legs and arms; his left hand became oedematous. On August 1st, the patient became dyspnoeic and cyanotic and died that evening.

The thyroid gland was small (each lobe measuring 3 by 1.3 cm.) and firm. The right adrenal was normal, but the left was hyperplastic, weighing 27 grams; the tissue on fresh section appeared normal, but the medullary portion was oedematous and of a brownish-green color. The pituitary gland, on removal of the brain, was found to be replaced by a soft tumor-like growth of reddish color, which measured 3 by 2 by 2.5 cm. The brain itself was oedematous, the ventricles moderately dilated.

Microscopical examination. The thyroid gland showed changes like those found in a colloid struma, the epithelial lining of the follicles being low cuboidal, with no proliferation and no increase of connective tissue. The pancreas showed slight increase of connective tissue, with an unusual number of islets. The left adrenal gland had a normal structure without oedematous cell proliferation. Toward its centre, there was some oedema and congestion of the vessels without cell degeneration. The hyperplasia was evenly distributed between cortex and marrow, the two structures being indistinguishable. The kidneys showed no definite change, though casts were found in the tubules.

Hypophysis: The tumor tissue consists of a coarse network of rather delicate connective tissue, often containing thin-walled, wide, congested vessels. Although there are postmortem changes, one is of the impression that the network of connective tissues with its branches all throughout has been covered by cells of epithelial nature. These cells are polygonal, at times somewhat extended, and containing a nucleus of varying sizes and shape with a dark nucleolus. Quite often there are seen large plump complexes of nuclei, a few mitoses. These cells form, as a rule, a quite dense layer and line irregularly-shaped vacuoles which are filled with granular material consisting of necrotic 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 ascribed the polyglandular disorder in the first of them to the adrenal tumor. In the second case, he laid chief emphasis (as did Dr. Parkes Weber in Case 6) upon the unilateral adrenal hyperplasia. He however ascribed the delayed puberty, retarded ossification and the adiposity to a pituitary effect as an example of dystrophia adiposo-genitalis [sic].

Collation of Symptomatic and Pathological Data

The twelve patients whose case histories have been presented, as will have been noted, were all relatively young adults. Their average age at the onset of the malady, so far as can be estimated (Case 10 being eliminated for want of information) has been 18 years; the youngest was six (Case 5) and the oldest 25 (Case 11).

In stature, the female patients all appear to have been definitely undersized. Where heights were given, the tallest (Case 6) was 159 cm. (5 ft. 3 in.), the shortest (Case 1), 145 cm. (4 ft. 9 in.). Two of the male patients, on the other hand, were tall: Case 9, 192 cm. (6 ft. 1½ in.); Case 11, 184.2 cm. (6 ft. 1½ in.).

The average duration of the disease from onset to death in the cases where definitely stated (Case 10 again eliminated) has been slightly over five years, the extremes being three (Case 9) and seven (? years) (Case 8).

The following features are characteristic of all cases: (1) A rapidly acquired, peculiarly disposed and usually painful adiposity (in one instance representing a 40 per cent gain in weight) confined to face, neck and trunk, the extremities being spared; (2) A tendency to become roundshouldered (kyphotic) even to the point of measurable loss of height (cf. Cases 2 and 9) associated with lumbo-spinal pains; (3) A sexual dystrophy shown by early amenorrhoea in the females and ultimate functional impotence in the males; (4) An alteration in normal hirsuties shown by a tendency to hypertrichosis of face and trunk in all the females as well as the preadolescent males (Cases
8 and 12) and possibly the reverse in the adult males; (5) A dusky or plethoric appearance of the skin with purplish lineae atrophicae; (6) Vascular hypertension, present in all cases except Cases 4, 7 and 9 where no mention was made of blood-pressure; it varied from the highest recorded in Case 6 of 250/170 to the lowest in Case 11 of 178/100; (7) A tendency to erythraemia, a count exceeding five million having been present in five of the nine cases in which blood counts were recorded; (8) Variable backaches, abdominal pains, fatigability and ultimate extreme weakness.

Other features less consistently recorded have been as follows: Acroeyanosis (e.g., Cases 1, 12); Purpura-like ecchymoses, whether from bruising or occurring spontaneously (Cases 1, 2, 3, 6, 12); Aching pains in the eyes, associated with slight exophthalmus (Cases 1, 3, 6, 11), with transient diplopia (Case 1), with suggestive papilloedema (Cases 1, 6, 11), with dinness of vision (Cases 8, 9, 12), with subretinal exudate (Case 2) and retinal haemorrhage (Case 8); Extreme dryness of skin (e.g., Cases 1, 2, 4, 6, 8), with pigmentation (e.g., Cases, 1, 4, 6, 11, 12); Polyphagia, polydipsia and polyuria (e.g., Cases 11, 12); Oedema of the lower extremities was noted in several cases and in Case 12, of the hand; A susceptibility to pulmonary infections (Cases 5, 6, 8, 9, 12); Albuminuria of slight degree with occasional casts was found in six patients (Cases 1, 5, 6, 8, 9, 12); A sense of suffocation and difficulty in swallowing were occasionally noted (Cases 1, 6); Insomnia was a not uncommon complaint; An increase of non-protein nitrogen and of cholesterol in the blood was recorded in the only patients (Cases 8, 11 and possibly 12) in which it was estimated; A polymorphonuclear leucocytosis was noted in Cases 1, 3, 6, 8, 11.

Secondary endocrine disturbances conceivably affecting the adrenal glands were suggested not only by the hypertension, by the pigmentation (particularly noted in Cases 1, 4, 9, 12) but by the terminal extreme weakness; on the part of the pancreatic islets, by the glycosuria (Cases 4, 5, 8, 11, 12); conceivably 12) in which it was estimated; A polymorphonuclear leucocytosis was noted in Cases 1, 3, 6, 8, 11.

Postmortem findings. The malady appears to leave the patients with a definite susceptibility to infections. Death in the nine fatal cases, eight of which came to postmortem examination, was ascribable to, or associated with, multiple cutaneous abscesses and ulcers (Cases 2, 5), intercurrent erysipelas (Case 4), acute pulmonary complications (Cases, 5, 6, 12), intercurrent meningitis (Case 7), a streptococcal phlegmon (Case 10), pancreatic necrosis (Case 9). Chronic nephritis of mild degree was found, in the absence of any definite clinical signs, in Cases 2, 3, 6, 9 and 12; hypertrophy of the cardiac ventricle in Cases 2, 6, 9 and 12; and vascular atherosclerosis was noted in Cases 3, 9, 12. An osteoporosis of the skeleton most marked in the spine was specifically described in six (Cases 2, 3, 4, 6, 9, 10) of the eight autopsies, Cases 7 and 12 being the exceptions and in these it may have escaped notice.

The ductless glands. A basophilic adenoma of the pituitary body was found in Cases 6, 7 and 10; an undifferentiated adenoma in Cases 3 and 12; what was described as an adenomatous-like structure in a fibrosed area of the anterior pituitary was noted in Case 4; and in Cases 2 and 9, the gland was said to be "normal." The thyroid was described as slightly enlarged (colloidal) in Cases 3, 7, 10, 12; as small in Case 4; as fibrotic in Case 9. The parathyroids were described as normal in Case 3; to have shown capillary dilatation in Case 4; to be fibrotic in Case 9; and infiltrated with fat in Case 10. The suprarenal glands in Cases 2 and 6 showed a cortical hyperplasia; in Case 3, a small adenoma; while in Cases 4, 7, 9 and 10, no abnormality was noted. The ovaries and uterus were said to be senile in Case 3; in Case 4 to show atresia; in Case 6, to be small but normal; and in Case 7, to show hypothyrotrphy with signs of increased functional activity. The testes in Cases 9 and 10 showed atrophy of the spermatogenous epithelium.

Discussion and Recapitulation

In ascribing this obscure polyglandular syndrome to a pituitary rather than to an adrenal source, I am aware that much might be said in favour of the latter seat of origin. Indeed, it was my original belief in the case of Minnie G. that her malady was in all probability associated with an adrenal tumor. What light the contemporary literature served to shed on the subject was strongly in favour of such an interpretation, containing, as it did, numerous examples of precocious sexual development in children or of the masculinization of women who were found to have large suprarenal tumors. A striking example was that reported in 1911 by Launois, Pinard and Gallais of a bearded and amenorrhoeic woman who showed plethoric adiposity with an abundance of purplish lineae over the trunk. A supra-
renal tumor of cortical type with metastases to liver and lungs was found at autopsy in association with what was said to be a normal pituitary body, though the sella turcica was said to have measured 18 mm. in its largest diameter which, to say the least, is at the upper limit of normal for her age, this being 14.4 mm. according to Erdheim and Stumme's measurements.

About this same time, twenty years ago, I had the opportunity in London to see with Dr. Gordon Holmes a striking example of masculinization or heterosexual virilism in a woman from whom an adrenal tumor was subsequently removed by Sir Percy Sargent with prompt restoration of the patient's original normal feminine appearance and reactions. This woman had a lean, mannish habitus quite unlike the highly plethoric and adipose individuals herein depicted, and the case may possibly have unduly coloured my impressions of hyperadrenalism of which, to be sure, several differing types have been described. Primary adrenal tumors, therefore, 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 occurs after experimental pituitary dwarfism or gigantism. And if the acidophilic adenomas of acromegaly inevitably cause hyperplasia not infrequently associated with actual adenomata of the adrenal cortex, it is reasonable to assume that basophilic adenomas may well enough do the same.

An excess or deficiency of anterior-pituitary hormones, in other words, secondarily affects the function of the adrenal cortex with established certainty, whereas nothing comparable to this occurs in the reverse direction. Hence, if further study should prove that adrenal tumors in the absence of any demonstrable change in the pituitary body may cause a polyglandular syndrome in many respects similar to that under discussion, it may well enough be assumed that, when the same features characterize the syndrome of a basophilic adenoma, they in all probability are secondarily ascribable to a hypersecretory influence of adrenal cortex even in the absence of any histologically appreciable abnormality as exemplified by the Parkes Weber and by the Raab-Kraus cases cited above.  

The disorders under discussion in all probability are much more common than would appear from the present assembly of twelve examples which with four exceptions have been restricted to cases in which a postmortem examination has been held. Acromegaly was once looked upon as a rare disease, and in its extreme form may still be so considered. However, one encounters on every hand persons with unmistakable traces of pituitary acidophilia (acromegalic overgrowth) so mild in its effects medical advice has not been sought; and the same is probably true of persons affected by transitory or mild degrees of pituitary basophilia.

I am quite aware that in ascribing the disorder to the basophilic elements, even were their association with maturation and the ovulatory mechanism established beyond peradventure, 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 (cf. Case 11) in the urine of patients with basophilic adenomas if the polyglandular disorder under consideration is actually due to the hypersecretory effect of such a lesion? (2) Whereas premature sexual maturity appears to characterize the disorder in children of either sex, why, in adult women, should amenorrhoea occur together with an apparent reversal of the secondary characters of sex? (3) If in this syndrome we are actually dealing with an oversecretion of the gonad-stimulating factor, why should atretic ovaries be found in the females instead of over-follicularized or over-luteinized ('mulberry') ovaries such as occur in immature or adult female rats after repeated injections with extracts containing one or the other gonad-stimulating factors? (4) If the polyglandular features of the disorder are partly due, as premised, to a secondary hyperplasia of adrenal cortex, why has this not been observed in rats after injection with the gonad-stimulating extracts whereas it is a striking effect of injecting growth-promoting extracts? An answer to these and other questions

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45 Smith and Engle, as may be recalled, found that pituitary transplants in the immature female rat produced precocious sexual maturity even after bilateral adrenalectomy. Loc. cit., 1927.
46) The hypophysial hyperplasia which occurs in pregnancy, described by Erdheim and Stumme (1909), is composed of modified chief cells which are non-granular. One would assume that this means the cells are not advanced to secretory maturity. The source of the gonad-stimulating substance in the urine, unless it is provided by the placenta (cf. Collip), is therefore not clear.
will doubtless in time be forthcoming.

A chronological recapitulation of the facts that have chiefly served to throw light on this subject during the past twenty years are as follows: (1) Primary anterior-pituitary disorders are commonly produced by adenomas; (2) Adenomas of the endocrine series are as a whole functionally active lesions; (3) Even minute adenomatous tumors of parathyroid glandules and pancreatic islets may lead to serious constitutional derangements of hypersecretory type; (4) Pituitary adenomas are of three principal varieties—neutrophil, acidophil and basophil, no constitutional disorder heretofore having been definitely ascribed to the last; (5) There is experimental evidence to suggest that the basophilic elements of the anterior pituitary secrete the sex-maturing hormone; and finally, (6) A polyglandular syndrome hitherto supposed to be of cortico-adrenal origin characterized in its full-blown state by acute plethoric adiposity, by genital dystrophy, by osteoporosis, by vascular hypertension, and so on, has been found at autopsy in six out of eight instances to be associated with a pituitary adenoma which in the three most carefully studied cases (Cases 6, 7, 10) has been definitely shown to be composed of basophilic elements, the lesion in one instance (Case 7) having been clinically predicted before its postmortal verification.48

Conclusions. Of all subjects that engage the attention of the profession at the present day, that of endocrinology particularly lends itself to the temptation of impressionistic speculation. During the past ten years, innumerable syndromes of so-called polyglandular type, some of them bearing a certain resemblance to that under consideration, have often been described in print. Examples of “diabetes in bearded women,” of rapidly acquired obesity, of hypertension, of masculinization in the female and of sexual precocity in children of either sex, often associated with hyperplasias or tumors of one sort or another of the suprarenal glands, have been so many and varied as to baffle analysis.

Some of these syndromes have unquestionably been due to cortico-adrenal tumors and in not a few instances, indeed, such a tumor has been removed at operation with definite amelioration of symptoms. What is more, in similar states suprarenal tumors have been found after death in the absence of any recognizable abnormality in the pituitary body, though all too often the protocol refers to the examination of this structure either in the briefest terms or not at all.

While there is every reason to concede, therefore, that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal, or with adrenal tumors, the fact, that the peculiar polyglandular syndrome, which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the adrenal cortex other than a possible secondary hyperplasia, will give pathologists reason in the future more carefully to scrutinize the anterior-pituitary for lesions of similar composition.

48 Since Erdheim and Stumme’s classical paper (Über die Schwangerschaftsveränderung der Hypophyse. [III. Adenome der Hypophyse.] Ziegler’s Beitr., 1909, 46, 1–182), no one appears to have made a systematic search for the presence of adenomata in supposedly normal pituitary glands. These authors found adenomas in approximately one out of ten of the glands that were serially sectioned.