THE SUPRARENAL CORTICAL SYNDROME WITH PRESENTATION OF TEN CASES

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In the past two years nine patients presenting clinical pictures similar to that named by Gallais[10] "le syndrome génito-surrénal" and by Krabbe,[15] "adrenal hirsutism," have been examined at The Mayo Clinic. In this paper we are reporting again an additional case in which operation was performed in 1924 and which was reported at that time by Keyser[13] and Walters.[28] Although considerable variation may be encountered, the syndrome is generally characterized by hirsuitism, amenorrhœa, hypertension, and hyperglycæmia and by obesity of the face, trunk and abdomen. Acneform eruptions, cutaneous infections and osteoporosis also have been common symptoms.

One patient was not subjected to operation. In nine cases surgical exploration of one or both suprarenal glands was performed. If a tumor was found it was removed. If the suprarenal glands were thought to be hyperplastic, a portion of each gland was removed. Two cases of bilateral hyperplasia were encountered, five cases of unilateral tumor, and two cases in which the suprarenal glands were essentially normal. In two of the five cases within four months after removal of a suprarenal tumor, all symptoms had practically disappeared, and the patients reverted to their normal appearance. A third patient of the five from whom a cortical tumor was removed four weeks ago has already shown definite evidence of a return to normal. In the remaining two cases of the five, the patients died. Since the first case was reported by William Cooke,[3] in 1756, many similar cases have been reported by Thornton, Bovin, Collett,[2] Holmes and others, but a series as large as the one presented here, studied in a reasonably short period, is thought to be exceptional.

Tumors involving the suprarenal cortex occur with much greater frequency than those arising from the medullary substance. Structurally, the cortex takes its derivation from the intermediate cell mass, coelomic epithelium which later gives rise to the urogenital fold and the wolffian body, from which, in turn, arise the ovary and testis. Because of this common ancestry disturbances of these ductless glands may produce heterosexual changes characteristic of patients presenting the suprarenal cortical syndrome. On the other hand, the medulla of the gland is derived from the embryonic sympathetic nervous system. The most important tumors of the medullary portion

of the suprarenal gland are the paragangliomas, benign in character, characterized clinically by attacks of paroxysmal hypertension. Relief in such cases, over periods of more than six years, has resulted following removal of suprarenal paragangliomas by C. H. Mayo,[18] by Shipley,[24] and by Porter and Porter.[21]

Clinically and experimentally, Marine[17] and Jaffé[11] have shown that an intimate relationship exists between the suprarenal body and the other ductless glands. Further support of their thesis is the fact that in the past three years Cushing[5] has collected a group of fourteen cases, the clinical picture of which has been similar to that in cases of tumor of the suprarenal cortex. Ten of his patients were found to have basophilic adenomas of the pituitary body, and the remainder had pituitary tumors which were not definitely classified. Sometimes the tumors were so small that it was necessary to study the pituitary body in serial section in order to demonstrate their presence. Inasmuch as in most such cases examination of the suprarenal gland gives no evidence of tumor, but frequently the cortical portion of the structure is hypertrophied, it becomes necessary to approach the problem from the other angle, namely, to determine whether or not patients with syndromes suggesting tumors of the suprarenal cortex may not also have adenomas of the pituitary body. But recent experience may serve to cast some light on this problem. Two of our patients were proved to have bilateral hyperplasia of the suprarenal glands, and in both instances the pituitary body was normal when examined histologically. In each case, serial sections of the pituitary body were made. Layton, Turnbull and Bratton[16] reported two similar cases with cortical hyperplasia and normal pituitary bodies. One of our two patients, just mentioned, had normal convalescence from her operation until, on the tenth day, mild parotitis developed. Tonsillitis followed, then extensive cervical cellulitis with pneumonia, and the patient died. At necropsy the hypophysis was removed and was examined in serial sections, but it did not contain adenomas. The combined weight of the suprarenal glands was thirty-five grams, which is estimated to be more than twice normal. There were two small cortical adenomas in the left suprarenal gland, three to four millimetres in diameter. The thymus was atrophic and was replaced by fat. The ovaries were small and sclerotic, containing small cysts.

In the second case (Case VI) the patient's condition on admission was so poor that surgical exploration of her suprarenal glands could not be considered, and she succumbed two months after admission. Necropsy disclosed a normal pituitary gland, both grossly and on microscopical examination of serial sections with special stains. Both suprarenal glands were enlarged and hyperplastic, and had a combined weight of forty-nine grams. A thymic tumor, about five centimetres in diameter, was present. There was a small abscess of the pancreas. The thyroid gland contained multiple, degenerating, colloid and fetal adenomas with intra-adenomatous parenchymatous hypertrophy, graded 2. In Case VIII of this series in which there was diffuse

hyperplasia and hypertrophy of the suprarenal glands, the clinical picture was so similar to that presented by the other patients that the diagnosis was at once suggested. The suprarenal glands, on exploration, were found to be about twice normal size.

In two additional cases, bilateral exploration of the suprarenal glands was carried out without gross evidence being found of suprarenal tumor, hypertrophy or hyperplasia. Specimens removed from each suprarenal gland, in both cases, showed no evidence of hyperplasia on microscopical examination. One year subsequent to exploration in one of these cases the patient died at her home. The hypophysis was removed and was sent to us for examination. It contained an adenoma, five millimetres in diameter, composed of basophilic cells. In a second case the sella turcica was slightly but definitely enlarged, and the posterior clinoid process was slightly eroded. This patient is still living.

THE SIGNIFICANCE OF HYPERTROPHY AND HYPERPLASIA OF THE SUPRARENAL CORTEX

That adenomatous tumors of the cortical portion of the suprarenal gland will produce the clinical syndrome described is apparent from the fact that after removal of the adenoma, reversion of the patient to a normal status has taken place in three of our cases as well as in the cases of Holmes, of Collett and of others whose reports have appeared in the literature. An analogy might well be drawn between hyperfunctioning adenomas of the thyroid gland and of the suprarenal glands. A similar analogy might be drawn between parenchymatous hypertrophy of the thyroid gland with exophthalmic goitre and the hyperplasia of the suprarenal gland, the former with the development of hyperthyroidism and the latter with the development of the suprarenal cortical syndrome. Whether the condition is the result of tumor or of hyperplasia and whether it is referable to the thyroid gland, or the suprarenal glands, apparent hyperfunction may follow. Bilateral reduction of the mass of functioning suprarenal tissue, if sufficiently radical, might be expected to restore normal conditions, as does similar reduction of parenchymatous thyroid tissue in Graves' disease. In the most recent case in which the suprarenal cortical syndrome was present, half of the left suprarenal gland and four-fifths of the right were removed. In this case each appeared to be at least twice normal size and hyperplastic.

In two of three patients with proved hyperplasia of the cortex of the suprarenal gland, this hyperplasia could not be attributed to the presence of a basophilic adenoma of the pituitary body, for complete post-mortem examination was obtained, and on serial section of the pituitary body no adenoma was present. The possibility that an anatomically normal pituitary body might be overfunctioning and thus producing hyperplasia of the suprarenal glands is, of course, not excluded, but the possibility appears to us to be extremely improbable.

SUPRARENAL CORTICAL SYNDROME AND PITUITARY BASOPHILISM

Eight of our ten cases seem to be instances of primary disease of the suprarenal cortex. In one, a basophilic adenoma of the pituitary body was found on post-mortem examination. In a second case, the patient had evidence, on röntgenographical examination, of enlargement of the sella turcica, with erosion of the floor and of the posterior clinoid processes. This patient is still living, but röntgenographical evidence of a pituitary tumor is present. In both of these cases, the suprarenal glands appeared to be normal in size at surgical operation, and sections of them, removed for microscopical examination, revealed no abnormalities. A point that should be held in mind is the not infrequent presence of adenomas of the hypophysis, suprarenal cortex, and other glands of internal secretion, in the absence of any physiological disturbances. G. Roussy and C. Oberling,[22] reviewing the histology of pituitary adenoma, stated that in systematic examination of the pituitary glands recovered at necropsy in forty-one cases, they have found microscopical adenomatous foci in about 10 per cent. of cases. The "Lancet" (London) in commenting on their studies stated "the incidence of these chance adenomas in necropsy material is certainly a problem that demands attention."

Costello[4] recently has been engaged, at the clinic, in examining 1,000 hypophyses obtained at random in post-mortem examinations in cases in which there was no history of endocrine abnormality. Each hypophysis was sectioned serially at intervals of one millimetre. Approximately 20 per cent. of them contained adenomas, but only about a fifth of these were basophilic. With the random incidence of basophilic adenoma, less than 4 per cent., as the foregoing seems to indicate, it must be more than a coincidence that the pathologist should have found basophilic tumors of the pituitary body in one of ten cases in which the syndrome of "pituitary basophilism" had been recognized, and that Cushing[5] should have been able to report fourteen proved instances in the twenty-two cases he has described. The possibility is entertained that a possible basophilic tumor of the hypophysis incites the hyperplasia and the growth of adenomas in the suprarenal glands. From the evidence at hand in this disease, however, one might speculate equally logically that the dominant part is taken by the suprarenal gland, even in cases in which basophilic tumors of the hypophysis were present. As Cushing[6] stated: "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."

We find ourselves in complete agreement with this position. The answer to the question of dominance must wait, it would seem, until the hormones of the hypophysis and those of the suprarenal cortex have been isolated in satisfactory purity and in sufficient amounts so that the spontaneous disease can be reproduced experimentally. In the meantime, the following conclusions may serve as a guide in treatment:

In our experience, cortical adenoma and hyperplasia of the suprarenal cortex are encountered in a large percentage of cases in which is present the peculiar syndrome described herein. Removal of the adenomas is highly beneficial, and reduction of the mass of cortical tissue in cases in which there is bilateral suprarenal hyperplasia may be helpful, as is the analogous reduction of diffuse hyperplastic thyroid tissue in exophthalmic goitre and of hyperplastic parathyroid tissue in hyperparathyroidism as described by Albright, Churchill and Castleman.[1] The suprarenal glands can be explored with very little surgical hazard; therefore, it seems that this ought to be done in all cases in which the syndrome in question is encountered and a positive differential diagnosis cannot be made. If a cortical tumor is found, it should be removed. If the suprarenal tissue is hyperplastic, its mass may be reduced by resection, with later treatment of the hypophysis by Röntgen-rays. This we believe to be a better plan than to reverse this procedure and to depend primarily on treatment directed at the hypophysis. Treatment of the hypophysis by Röntgen-rays was ineffective in controlling the syndrome in one case in which a basophilic pituitary adenoma was present, had no effect in the other case, in which a pituitary tumor is suspected, and cannot be expected to help in cases in which suprarenocortical adenoma is present.

SURGICAL CONSIDERATIONS

We have found the lateral, posterior lumbar incision, the patient lying on the side, to be a satisfactory method of exposing a suprarenal gland. The incision is similar to that used in approaching the kidney, and, with the kidney retracted downward, excellent exposure of the suprarenal gland is obtained, permitting performance of whatever surgical procedure is indicated. This approach has the advantage of avoiding opening the general peritoneal cavity; thus, it carries reduced surgical hazard. Its disadvantages, as compared with the transperitoneal abdominal approach, are that it is impossible to compare the two suprarenal glands simultaneously, and that a little delay is caused by the necessity of changing the patient from one side to the other in order to expose the opposite suprarenal gland. Whichever incision is chosen, in female patients, the ovaries should be examined by palpation after an opening has been made in the peritoneum. This is to determine the presence or absence of ovarian tumors, such as arrhenoblastomas, described by

Meyer[19, 20] and Strassmann[25] and by Taylor, Wolfermann and Krock,[26] and which is reputed to impart masculine characteristics to women. Other advantages to opening the peritoneum for intra-abdominal exploration are to examine the liver for metastasis and to determine where aberrant pathological suprarenal tissue may be present, as reported by Kolodny.[14]

A serious but controllable hazard accompanies resection of hyperfunctioning tumor of the suprarenal cortex. Such a tumor, it may be supposed, takes over the principal part of the production of cortical hormone, placing what normal cortical tissue is present in a condition of physiological desuetude. Actual atrophy may follow, as in Cases II and V, in which the opposite suprarenal gland appeared to be extremely small. When the tumor is removed, the functionally indolent or atrophied cortical tissue remaining proves incapable of supplying an amount of hormone necessary for life, with the result that symptoms of temporary cortical insufficiency develop, as was observed after operation (Case I and also Case V). An entirely analogous complication has been met by those who have removed hyperfunctioning tumors of the parathyroid bodies in cases of hyperparathyroidism. The concentration of serum calcium in these cases, previously elevated above normal, drops precipitately after operation to levels below those necessary to prevent tetany, and unless corrective measures are resorted to, the patient may die. However, if the patient can be sustained for a period, the remaining indolent parathyroid tissue seems to resume activity and to provide what hormone is required. The cortical insufficiency following resection of cortical tumors of

TABLE I

Summary of Cases

Case	Suprarenal glands at Operation	Suprarenal glands at Necropsy	Pituitary body at Necropsy	Pituitary body at Clinically	Result
I	Carcinoma			Normal	Local recurrence
II	Carcinoma			Normal	Living, symptoms dispelled
III	Carcinoma			Normal	Improving (?)
IV	Carcinoma (?)	Bilateral hyperplasia (?)	Not examined	Normal	Died at home; necropsy
V	Carcinoma	Carcinoma	Normal	Normal	Died post-operatively
VI	Not operated on	Bilateral hyperplasia	Normal	Normal	Dead; necropsy
VII	Bilateral hyperplasia	Bilateral hyperplasia	Normal	Normal	Died post-operatively
VIII	Bilateral hyperplasia			Normal	Improving (?)
IX	Normal	Not examined	Basophilic adenoma	Normal	Died
X	Normal			Enlarged sella turcica; eroded posterior clinoid processes	Living

the suprarenal glands can be combatted effectively by injections of cortical hormone and treatment with salt and water as recommended by those who have been developing the treatment of Addison's disease.

SUMMARY.—The records of ten cases in which the suprarenal cortical syndrome was present, are reviewed. (See Table I.) In the past two years, since the advent of active preparations of the cortical hormone, eight patients have been operated on, with one operative death from apparently accidental cause. There was one non-operative death (Case VI). In the tenth case, in which operation was performed in 1924, the patient died of what appeared to be suprarenal insufficiency. This fatality might have been prevented had active suprarenal cortical hormone been available for temporary use. In five of the cases, suprarenal tumors were encountered; in three, diffuse hypertrophy and hyperplasia, and in two, suprarenal glands of normal appearance. Surgical removal of the tumors was followed, in three cases, by rapid return to normal of previously abnormal physical metabolic conditions. Two patients with tumor died. The pituitary and pineal bodies of one of these patients were not examined, of the other, they were examined and found normal, although serial sections of the pituitary body were not made. Necropsy in two of the three cases of diffuse hypertrophy and hyperplasia did not reveal (in one case operation not performed) abnormality of the pituitary body or ovaries. The patient in the third case of hypertrophy and hyperplasia recently has been operated on, and is in good condition; the röntgenogram of the sella turcica is normal. In one of the two cases in which the suprarenal glands were of normal appearance at operation, the patient died at home several months after operation. Post-mortem examination of the pituitary body, by Robertson and Kernohan, revealed a basophilic adenoma. The patient in the other case is living; the röntgenogram of the sella turcica discloses distortion suggestive of pituitary tumor. It would seem, from this experience, that surgical exploration of the suprarenal glands is advisable whenever the syndrome is encountered unless definite evidence of pituitary tumor is present. The hazard attending removal of tumors, or resection of large portions of hyperplastic suprarenal glands has been reduced to a minimum.

FOUR CASES OF ADENOMA OF THE SUPRARENAL GLAND

CASE I.—A married woman, twenty-five years of age, had always been well until the onset of the illness for which she came to the clinic. She was referred, August 28, 1933, by Dr. W. P. Freligh, of Albert Lea, and Dr. J. J. McGroarty of Easton, Minn., with the diagnosis of an affection of the suprarenal glands. The woman had been examined for life insurance in December, 1932, and had been accepted. The blood-pressure then had been normal, but menstrual flow had diminished in amount and duration; two months before we saw the patient menses had ceased. Her weight had increased in the past year from 145 to 165 pounds (sixty-six to seventy-five kilograms). The extra fat affected the face, neck and trunk, whereas the legs and arms remained unchanged in contour. In this period, also, hair had begun to grow on the lips, cheeks, arms and legs, whereas previously the patient had had very little body hair. The general appearance had changed to such an extent that friends had failed to recognize the patient. (Fig. 1*a*.) She complained, in addition, of great loss of strength, of an acneform eruption of the face

and of bruising easily. Increased thirst, with polyuria, had been present for two or three months.

The face was full and round, and the body fat was distributed as described. The shoulders were rounded, largely because of fat in the upper thoracic region. The blood-pressure was 180 millimetres of mercury systolic and 120 diastolic. Long, fine hair grew over the face, arms and legs. The skin was dry; that of the face was highly colored and mottled. Acne was present on the face and thorax, and atrophic, purplish striations affected the thighs and lower part of the abdomen. One specimen of urine contained 1.08 per cent. or sugar; the value for blood sugar, fasting, was eighty-two milligrams per 100

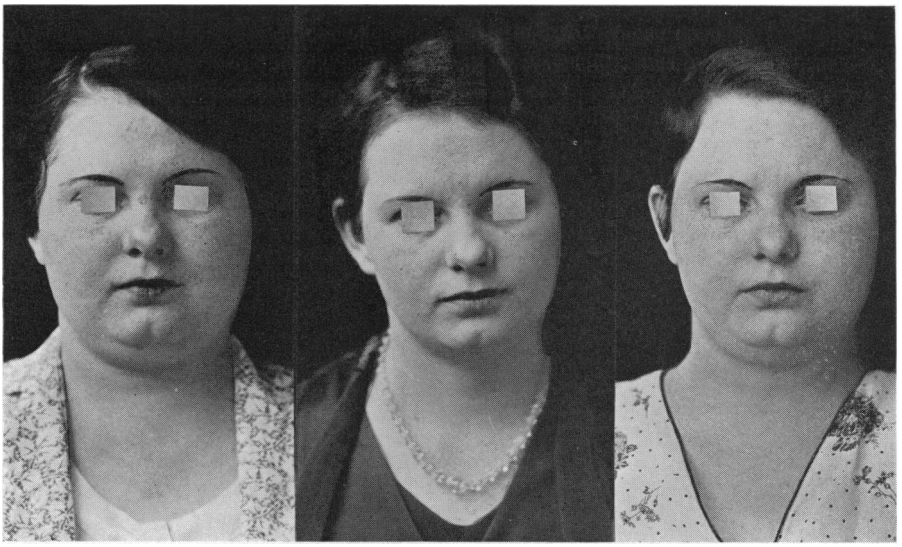

FIG. 1.—(Case I.) (*a*) Appearance of patient September 1, 1933. A tumor of the right suprarenal gland was removed September 11, 1933. (*b*) Appearance of patient March 14, 1934. (*c*) Appearance of patient May 29, 1934, when tumor had recurred.

cubic centimetres. The basal metabolic rate was + 1 per cent. The sella turcica was normal röntgenologically, and the perimetric fields were normal. The value for hæmoglobin was slightly elevated, 17.5 grams. per 100 cubic centimetres but the erythrocyte count was normal. There was slight osteoporosis of the spine. On intravenous urogram revealed the pelvis of the right kidney to be rotated outward and displaced downward, suggesting an overlying tumor.

It was decided that the suprarenal glands should be explored. This was done September 12, and a yellowish, soft, friable, encapsulated mass, ten to 12 centimetres in diameter, was found in the place of the right suprarenal gland, and extending as high as and attached to, the diaphragm. The tumor was so friable that it had to be removed piecemeal. (Fig. 2.) It was removed, except for a very minute portion attached to the vena cava. This was crushed with clamps. Examination of the tissue showed it to be an adeno-carcinoma containing tissue of cortical origin. (Fig. 3.)

The patient continued to bleed rather profusely from the operative site and was taken to the operating room, the incision was opened, and the generalized oozing was controlled by gauze packs and transfusion of blood. A few hours after operation, symptoms developed suggesting cortical insufficiency. Accordingly, the patient was treated with cortical hormone, infusions of solution of sodium chloride, and transfusion of blood.

March 21, 1934, the patient weighed 147 pounds (sixty-seven kilograms) and her appearance, her friends told her, was as it had been before her illness. The excessive

hair had disappeared, and the blood-pressure was normal. Menstruation had returned and recurred regularly. Her former strength had not been regained entirely and some acne persisted. (Fig. 1*b*.)

May 11, 1934, the patient returned to the clinic, stating that in the past three or four weeks there had been a return of symptoms, weakness, palpitation, increased appetite, and a gain of six pounds (2.7 kilograms). The last menstrual period was on April 3. A purplish color had returned to the striæ.

On physical examination a mass, approximately 12.5 centimetres in its greatest diameter and ten centimetres in its lesser diameter, was found in the right portion of the middle zone of the abdomen. The blood-pressure was 180 systolic and 120 diastolic. The face was a little fuller. Metastatic growths were not felt on pelvic examination nor in the pouch of Douglas. The patient was sent for post-operative Röntgen therapy.

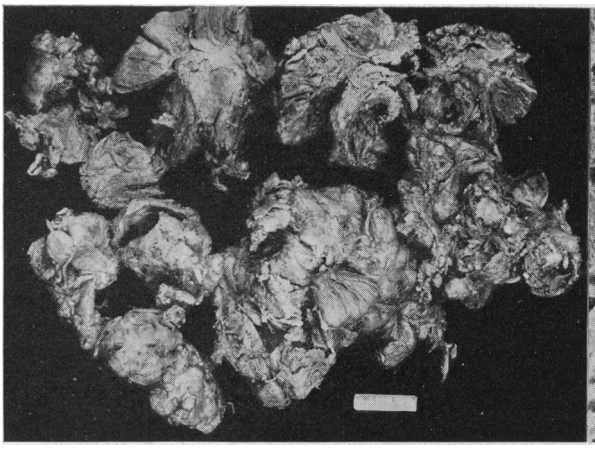

FIG. 2.—(Case I.) Tumor of right suprarenal gland; it was friable and became fragemented as removed.

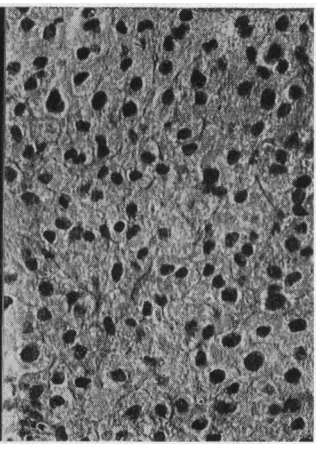

FIG. 3.—(Case I.) Section of the tumor.

CASE II.—A girl, aged nine years, was referred to us in September, 1933, by Dr. O. S. Ely, of St. Paul. There was nothing significant in the family history. Birth and development had been normal, and the patient had been a healthy child until the onset of the present difficulty for which she was brought to the clinic. When the child was four years of age, the mother had observed unusual development of the breasts, generalized growth of hair over the body, and deepening and coarsening of the voice. A year later the pubic hair had become abundant and the external genitalia had developed abnormally. At eight years of age the child had menstruated for four days, and afterward there had been some menstrual spotting at intervals of about two months. The mentality and personality had undergone no great changes, but the child seemed to spend most of her time at home and to shun the company of other children. In her selection of companions she showed no preference for members of either sex. She was in the fifth grade at school and was doing well with her lessons.

At examination the child apparently was placid, her features suggesting an age considerably greater than her actual age. Her height was fifty-three inches (134.6 centimetres) which was well within the normal range for girls nine years of age, but her weight was 103 pounds (forty-seven kilograms), about thirty-six pounds (sixteen kilograms) more than the normal for her sex, age, and height (according to Bolwin, Wood tables, American Health Association). The most striking abnormalities were: (1) obesity affecting principally the trunk, neck and face; (2) hypertrichosis of the face and body, especially prominent in the axillæ and on the mons veneris; (3) purplish,

atrophic striations over the abdomen, thighs, and buttocks; (4) additional development of the breasts and external genitalia; and (5) acne of the face and trunk. (Fig. 4*a*.)

The blood-pressure in millimetres of mercury was 132 systolic and 97 diastolic. Urinalysis gave negative results. The basal metabolic rate was —20 per cent. The concentration of hæmoglobin was 17.2 Gm. per 100 cubic centimetres. Erythrocytes numbered 4,620,000 and leucocytes 8,400 per cubic millimetre of blood. The sella turcica appeared normal, and no thymic shadow was observed on röntgenological examination. Development of the bones was commensurate with that of a child aged twelve years. The response to the test for glucose tolerance was normal, but one specimen of urine obtained before the test had slight reducing power. The concentration of serum phosphorus was 4.1 milligrams per 100 cubic centimetres; the value for phosphatase was normal. The concentration of serum calcium was 10.9 milligrams, and 11.7 milligrams

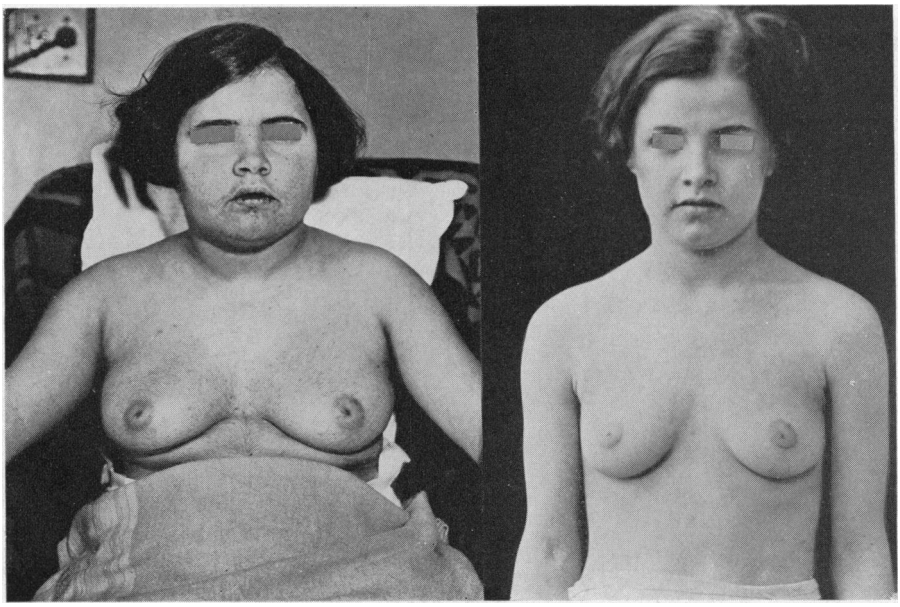

FIG. 4.—(Case II.) (*a*) Appearance of patient November 14, 1933. A tumor of the cortex of the left suprarenal gland had been removed October 31, 1933. The effect was not apparent when this photograph was made. (*b*) Appearance of patient March 14, 1934.

per 100 cubic centimetres. The outlines of the kidney in the intravenous urogram were normal.

Surgical exploration was performed in October, 1933. The right suprarenal gland was about half the usual size. A section removed for microscopical examination was normal histologically. The position of the left suprarenal gland was occupied by a large, encapsulated tumor measuring six by four by two centimetres, a portion of which projected into an enlarged suprarenal vein. The tumor was completely removed and was found to be a cortical adenoma.

Cortical hormone, 21 cubic centimetres, was administered during the first six days after operation. There was some fever for twelve days, but otherwise the post-operative period was uneventful.

Within three weeks the weight had fallen, and the excessive hair was beginning to disappear. Later, the skin became smooth, the voice became pitched higher, and the breasts and external genitalia became smaller. Also, the child began to be more playful, and instead of wanting to be at home with her mother, as before, she now preferred to associate with other children. Her appetite was reduced, and, indeed, the patient became

rather finicky in the choice of her food. There has been no menstrual flow of any kind since the operation, and that part of the hair of the head which has grown since operation is lighter in color and finer than the old hair.

Examination, March 31, 1934, showed the weight to be seventy-two pounds (thirty-three kilograms) which represented a loss of thirty-one pounds (14 kilograms). The blood-pressure was ninety-eight millimetres of mercury systolic and sixty-two diastolic. The basal metabolic rate was —9 per cent. The skin of the face was somewhat redundant, as a result of the loss of weight, but was otherwise clear and healthy in appearance. The proportions of the body were normal except that the breasts, although smaller, were still of the adult type, and breast tissue was palpable. The face, back, and extremities were hairless, and only a few hairs were left on the thorax. The genitalia were still of almost adult size, but the clitoris was definitely smaller than it had been.

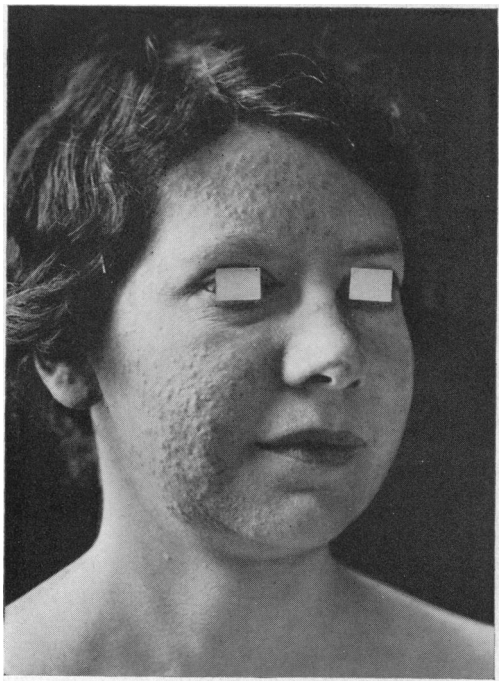

FIG. 5.—(Case III.) Appearance of patient on admission to clinic in April, 1934, aged thirty-nine years. An encapsulated tumor of the left suprarenal gland was removed April 27, 1934.

CASE III.—An unmarried woman, aged thirty-nine years, in December, 1933, complained of fullness in the epigastrium, but on December 18 she noted that she had increased thirteen pounds (5.9 kilograms over her usual normal weight). There appeared to be swelling of the legs, face and hands, and an acneform eruption appeared on the face. The hair of her scalp began to fall out. The skin became dry. However, during this time she noted hair appearing on her legs and on her chest. February 20, the patient had gained ten pounds (4.5 kilograms) over a short period, and April 5 she gained three pounds (1.4 kilograms). There had been gradual, persistent weakness since the onset of her symptoms.

On physical examination, a marked, acneform, papillary eruption, with comedones, was noted on the face. (Fig. 5.) She was not particularly obese. The face appeared swollen. There was an increase in the amount of hair on the face. Hair was noted on the chest, around the nipples, on the legs and thighs, as well as in the mid-abdominal region. The breasts were underdeveloped. The clitoris was normal. The blood-pressure gave evidence of hypertension; the systolic pressure varied from 162 to 170 millimetres and the diastolic, from 102 to 104; the pulse rate was 102 beats per minute. Röntgenograms of the head, chest, and lumbosacral portion of the spinal column were practically normal, except for evidence of slight osteoporosis of the lumbosacral portion. The urine, basal metabolic rate, and values for blood urea, sugar, chlorides, serum calcium and phosphorus were normal. Sugar tolerance was normal.

Operation was performed April 27, 1934, and an encapsulated tumor of the left suprarenal gland, 2.7 by 2 by 1.5 centimetres, weighing 5.4 Gm., was removed. (Fig 6.) Microscopical examination of the tumor revealed it to be an adenocarcinoma grade I.

Following operation the patient was given "Eschatin," and saline solution was injected intravenously; the woman appeared to be making an uneventful convalescence.

After dismissal from the hospital, she complained of weakness, anorexia and vomiting. May 23, twenty-six days after operation, jaundice appeared and the liver was found to be enlarged. The value for serum bilirubin was seven milligrams for each 100 cubic centimetres of blood, and the van den Bergh reaction was direct. Bile was present in the urine and fæces. One week later the value for serum bilirubin rose to 12.5 milligrams and the liver had become further enlarged.

Under treatment with intravenously injected solution of glucose and saline, the jaundice gradually disappeared and the liver decreased in size. At the time of the patient's dismissal, June 27, 1934, the value for serum bilirubin was normal, her face had largely regained its normal contours, and the comedones had decreased at least half

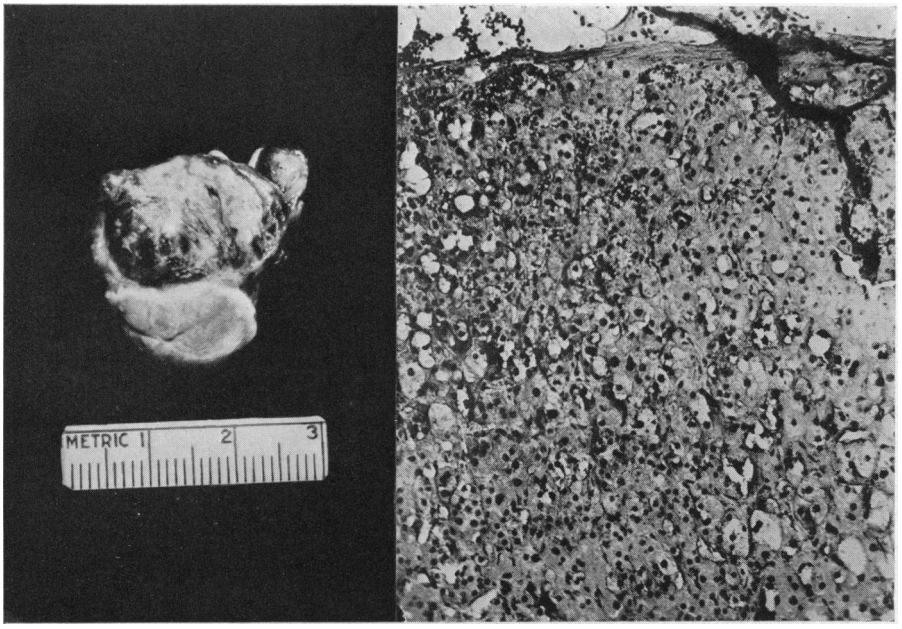

FIG. 6.—(Case III.) (*a*) Encapsulated tumor of left suprarenal. (*b*) Section of the tumor.

in size and number. The blood-pressure was 130 millimetres of mercury systolic, and seventy-six diastolic. The woman's strength was improving.

CASE IV.—The patient, aged thirty years, was referred to the clinic by three physicians of Spokane, Washington: Drs. John T. Bird, Charles M. Anderson, and R. F. E. Stier. The woman suffered from profound muscular weakness of the trunk and all four extremities. She had been well until two months before admission, when she had become exceedingly weak, and hair had begun to grow on her face. Her face had changed in color. At about the same time, sugar had appeared in the urine. Within one month after the onset of her illness, she had become bedridden because of weakness and swelling of her legs. She had lost twenty-five pounds (11.3 kilograms). Suddenly, her menses, which heretofore had been regular, practically had ceased. Before her admission to the clinic she had been treated, without success, with insulin and various preparations of the endocrine glands.

The patient's face was florid and fat. Her chin and upper lip were hairy. The tissues of her neck and face were putty-like and loose, but did not pit on pressure. The muscles of the lower extremities, shoulder girdle, and trunk were weak almost to the point of paralysis. However, power of the muscles of the forearm was only slightly reduced. She was unable to support her own weight, to turn over in bed, or to elevate her arms to

comb her hair. The liver was enlarged to about one palms breadth (approximately eight centimetres) below the level of the costal margin, and pitting œdema was present from the toes to about the level of the eighth thoracic vertebra. The tendon reflexes of all the extremities were absent except those of the triceps brachii and jaw. The blood-pressure was 118 millimetres of mercury systolic, and seventy diastolic. The only other findings of note were slight secondary anæmia, and glycosuria and hyperglycæmia of high grade. The consulting neurologist believed the muscular paresis to be the result of a disturbance of metabolism rather than of any of the known forms of myopathy, or of lesions of the nervous system. Normal spinal fluid supported his interpretation. Röntgenograms of the sella turcica were not made. The ocular fundi were normal.

We felt that the patient probably had a carcinoma of one of the suprarenal glands, with extension by way of the renal vein to the vena cava. The left suprarenal gland was explored April 26, 1932, and a tumor 2.5 by 5 by 1 centimetre, involving the entire left suprarenal gland, was removed. Microscopically, this tumor was interpreted to be a carcinoma of the suprarenal gland, although the pathologist noted that it resembled a primary hepatic-cell carcinoma. Convalescence was rather stormy. Signs of post-operative suprarenal deficiency appeared, and were controlled by administration of "Eschatin." The diabetes became difficult to treat because of instability of the concentration of blood sugar, with its attendant insulin reactions. The daily requirements for insulin suddenly dropped from sixty-five units to ten units. The patient was dismissed from the clinic and died at home about six weeks after operation.

The outstanding findings at necropsy, as reported by Doctor Stier, were carcinoma of the entire head of the pancreas, with metastatic nodules in the peritoneum and over the dome of the diaphragm. The lesser omental cavity was filled with involved lymph-nodes. The liver was almost completely replaced by tumor tissue. At the site of the previously removed suprarenal gland there was no evidence of tumor or of suprarenal gland. The portal vein appeared as a rope-like mass which was completely filled with tumor tissue resembling the carcinoma in the pancreas. The right suprarenal gland was almost identical in size and color to the left, which had been removed at operation, and the histological pictures of the two glands were identical. Neither the pituitary gland nor the thyroid gland was examined.

A CASE OF CARCINOMA OF THE SUPRARENAL GLAND

CASE V.—A married woman, aged thirty-seven years, the mother of ten children, was admitted, February 7, 1923, complaining of goitre, weakness, and skin trouble. Since her last pregnancy, three years before, she had not menstruated. Two years before her admission, the patient had noticed an enlargement in the thyroid gland; since that time it had increased but slightly. However, moderate nervousness, occasional tremor, intermittent attacks of precordial pain, and a jerking sensation in the heart had been noted. Intolerance to heat, perspiration, fatigue, and dyspnœa, with choking sensations, all brought out on moderate exertion, had been troublesome. Her appetite had increased, and she had gained thirty pounds (13.6 kilograms), but in spite of this she had lost strength and vigor. The patient complained of a slight mental dullness.

Eighteen months before her admission, blotchy erythrema had appeared over the shoulders and chest, followed by a papular, and later by a pustular, eruption. The skin had become oily, and numerous blackheads had appeared in association with the pustules. This acneform eruption had spread gradually over the entire body, with the exception of the hands and feet. Six months after the onset of the cutaneous lesion, the hair of the face, arms and chest had begun to increase in amount. This hirsutism had become so excessive that the patient recently had been forced to shave the face, and as the body hair had increased in amount, that of the scalp had become thin.

For the preceding year the patient had been troubled with a salty taste in her mouth, and six months before admission a form of stomatitis had developed. The voice had become increasingly coarse for more than a year. During this time the patient also had

suffered from a dull, aching pain in the back, which had been made worse by stooping or exercise.

At the time of examination, the patient weighed 130 pounds (fifty-nine kilograms) and was apparently well nourished. The skin immediately impressed the observer with its oiliness. Distributed over it with fair uniformity were papules, encrusted pustules, and numerous comedones; these were generally surrounded by an area of dull erythema. A marked degree of hypertrichosis of the face, chest and limbs was noted. The hair of the head was coarse and stringy, and diffuse alopecia was present. The thyroid gland was definitely enlarged, with a small, firm adenoma in the lower pole on the right side; aside from râles in the bronchi, and röntgenological evidence of old tuberculosis at the apex of the right lung, examination of the chest gave negative results. The abdomen was diffusely tender, and a smooth mass was palpable below the left costal margin, anteriorly. The urine contained a moderate amount of albumin, and sugar was present in the twenty-four-hour specimens, in amounts varying from 5.9 to 6.5 Gm. Examination of the blood revealed hæmoglobin, 80 per cent. (Dare); erythrocytes, 5,290,000, and leucocytes 12,900 per cubic millimetre, with normal differential count. The value for blood sugar was from 0.111 to 0.143 milligrams per 100 cubic centimetres. The concentration of blood urea was normal. The blood-pressure ranged from 124 systolic and 90 diastolic to 180 systolic and 110 diastolic. The pulse rate varied from 100 to 130 beats per minute, and the temperature from 98° to 100° Fd Röntgenograms revealed a normal sella turcica. The basal metabolic rate varied from + 15 to + 28 per cent.

Exploration was made, February 28, 1923, through a left oblique incision. A large tumor was separated from the left kidney and removed between clamps. The tumor was about twenty-five centimetres in diameter. The patient recovered well from the anæsthesia, but within twenty-four hours elevation of pulse rate and temperature, and onset of drowsiness ensued. A low, indeterminate systolic blood-pressure was noted. This continued for twenty-four hours, during which time a transfusion of citrated blood was given. This was followed by a slightly favorable reaction. The blood-pressure continued low; the pulse and temperature, elevated. Epinephrine was given subcutaneously and by rectum. On the fourth day, the patient went into coma and died after several hours of unconsciousness. The tumor removed at operation corresponded closely with those described by Glynn and others as malignant suprarenal hypernephromas. At necropsy, hypoplasia of the right suprarenal gland, early hæmorrhagic bronchopneumonia, terminal acute hepatitis, and nephrosis, were observed. The habitus was that of a male. Acne, and hæmorrhagic fat necrosis in the pancreas also were noted. The follicles of the thyroid gland were distended with colloid, and the epithelium was flattened. The pituitary and pineal bodies and the ovaries were normal.

THREE CASES OF HYPERPLASIA OF THE SUPRARENAL GLAND

CASE VI.—A woman was referred to us by Dr. W. F. Baillie, of Fargo, N. D. She came to the clinic first in 1914(aged twenty-eight years, because of a hyperfunctioning adenomatous goitre for which she underwent operation. Following operation she remained well until 1924, except for attacks of abdominal pain necessitating, elsewhere, in 1921, appendectomy and drainage of the gall-bladder. She returned to the clinic in 1924, when aged thirty-eight years, because of recurring hyperthyroidism. In the meantime she had been married and had borne one child, who was then aged six. The left lobe of the thyroid gland was resected. The basal metabolic rate at the time of dismissal was − 7 per cent.

Following this visit she remained well until 1928, when she again returned to the clinic because of further gall-bladder colic, necessitating cholecystectomy. (Fig. 7*a*.) At this time her weight was 215 pounds (97.5 kilograms), the blood-pressure was 150 systolic and 90 diastolic, and the basal metabolic rate—14 per cent.

The woman remained well until the onset of her last illness, which began rather suddenly in April, 1932, three months before her last admission to the clinic. She had not

been pregnant again. She stated that she had always had a slight growth of hair on the face, but that it had been insignificant until about three months before admission, when the hair had grown rapidly and daily shaving had become necessary. At the same time, her face had become fat and florid. Two months before admission, after an attack of influenza characterized chiefly by diarrhœa, her health had begun to fail rapidly. Intense glycosuria had appeared, and symptoms suggesting hyperthyroidism had developed. Her menstrual periods had ceased with the onset of her illness. Her weight rapidly had decreased from 240 to 208 pounds (108.8 to 94.3 kilograms). Her legs had become exceedingly weak. Her constant complaint, after the illness had become well established, was that her "head felt funny" and that her vision blurred.

As in the preceding cases, the woman's face was round, hairy, and dusky red. (Fig. 7*b*.) She was unable to support her own weight because of weakness of her legs. Her skin was warm and moist. There was a fine tremor of the fingers. The tissues of the neck hung in loose folds. The thyroid gland could not be felt. The pulse was of the

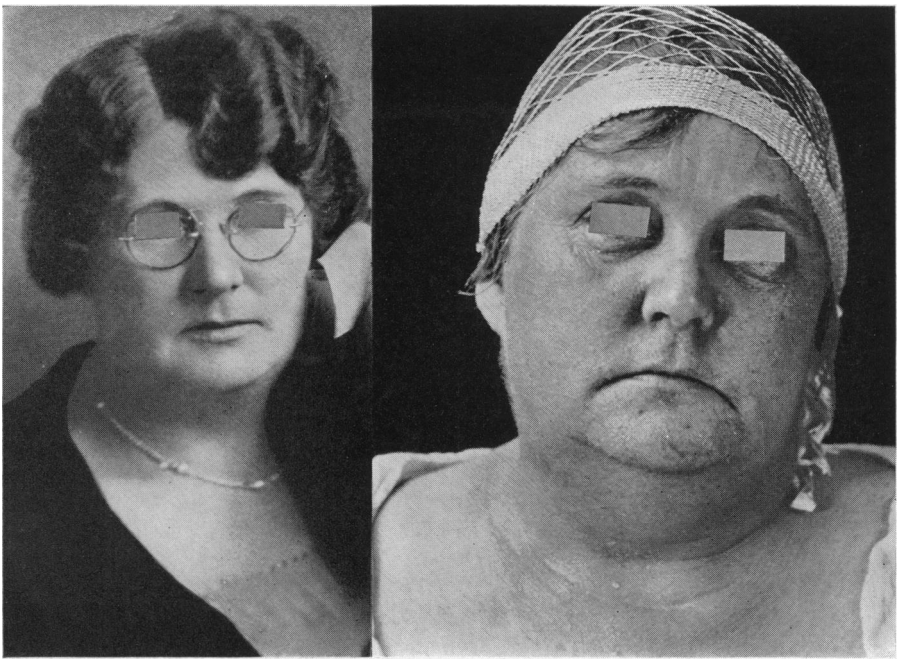

FIG. 7.—(Case VI.) (*a*) Appearance of patient in 1928, aged forty years. (*b*) Appearance of patient on admission to clinic in 1932, aged forty-five years. Died two months later. Necropsy revealed hyperplasia of suprarenal glands and a normal pituitary body.

water-hammer type, and at times there was a marked capillary pulse. The legs were slightly œdematous. The blood-pressure averaged about 176 systolic and 80 diastolic. The retinal arteries were slightly narrowed, the veins slightly full, the discs normal. There was a small hæmorrhage below, and nasal to, the left disc, and a small amount of exudate inferotemporal to the right disc, thought to be associated with diabetes or hypertension rather than with any intracranial lesion. The perimetric fields were normal, and the sella turcica was normal to röntgenographical examination. Besides the unusual physical findings, there was evidence of unusual metabolic disturbance; namely, spontaneous, persistent alkalosis associated with low concentration of the chloride ions in the blood, unusually low total blood volume, and arterial and venous blood of inexplicably low oxygen content. The diabetes was intense. At times mild tetany was present.

Cortical tumor of one of the suprarenal glands was considered as the most likely diagnosis. Owing to the unusual features of the condition, we were reluctant to recommend surgical exploration. It was decided to give a course of Röntgen treatment to the hypophyseal region, and if her condition improved to repeat the treatment in a month. If her condition did not improve, we could then consider exploration of the suprarenal glands. One course of Röntgen therapy was followed by some subjective, but temporary, improvement. The woman shortly began to fail rapidly, and finally she died about two months after admission.

Necropsy disclosed a normal pituitary gland, both grossly and on microscopical examination of serial sections with special stains. Both suprarenal glands were enlarged and hyperplastic, and their combined weight was forty-nine Gm. A thymic tumor, about five centimetres in diameter, was present. There was a small abscess of the pancreas, which communicated through several tracts with the duodenum. The thyroid gland was identical histologically with the specimens obtained at operation; namely, there were multiple, degenerating, colloid and fœtal adenomas in a colloid thyroid gland, with intra-adenomatous parenchymatous hypertrophy, graded 2. The ribs broke easily between the fingers.

CASE VIII.—An unmarried woman, thirty-two years of age, a stenographer, came to the clinic January 15, 1934, with complaints of nervousness and irritability of several years duration. Slight abrasions of the shins would fail to heal for months. Menses never had been regular, but for the past six months menstruation had ceased altogether. During the past year the patient had had a ravenous appetite, and had gained twenty-five pounds (11.3 kilograms). A beard had grown on her face, so that she had resorted to shaving.

Examination revealed that the excess of fat was confined to the trunk and face and spared the extremities. The abdomen was protuberant, and there was a conspicuous prominence over the upper thoracic and cervical portions of the spinal column, due apparently to a pad of fat. The face was definitely broadened. Coarse, dark hair was distributed over the chest, abdomen and thighs. The face had been shaved. The skin was dry and rather dusky, and atrophic striations were present over the thighs and lower part of the abdomen. These were bluish. The thyroid gland was slightly enlarged, soft, and symmetrical. The blood-pressure in millimetres of mercury was 168 systolic and 118 diastolic. The basal metabolic rate, in one determination, was —15 per cent. The value for hæmoglobin was 15.4 Gm. per 100 cubic centimetres of blood and erythrocytes numbered 4,460,000 per cubic millimetre. The urine was free of sugar by the qualitative Benedict test. The concentration of blood sugar was not determined. Osteoporosis of the thoracic portion of the spinal column was noted at röntgenological examination. The value for serum calcium was 10.0 milligrams per 100 cubic centimetres, and for serum phosphorus 2.7 milligrams per 100 cubic centimetres.

Bilateral surgical exploration of the suprarenal glands disclosed that both were definitely enlarged. Portions removed for microscopical examination seemed normal histologically. Convalescence from the operation was uneventful until the tenth day, when it became complicated by mild parotitis. Tonsillitis followed; then extensive cervical cellulitis with pneumonia, and the patient died.

At necropsy, the hypophysis was removed and was examined by serial sections. It did not contain adenomas. The combined weight of the two suprarenal glands was 35 Gm., estimated to be more than twice normal. There were two small, cortical adenomas in the left suprarenal gland, measuring respectively three and four millimetres in diameter. These are of questionable significance. The thymus was atrophic and was replaced by fat. The heart weighed 345 Gm. The ovaries were small and sclerotic. They contained small cysts.

CASE VIII.—A married woman, aged thirty years, presented herself August 5, 1933, complaining of swelling of the feet and legs, sugar in the urine, some diminution of vision, and myopia. The blood-pressure was 150 millimetres of mercury systolic and

100 diastolic. Röntgenological examination of the sella turcica gave negative results. The urine contained a trace of sugar. The value for blood sugar was 154 milligrams per 100 cubic centimetres.

January 10, 1934, the woman returned, and at this time the basal metabolic rate was —4 per cent. The face had taken on the moon-shaped, downy appearance of patients with the cortical adrenal syndrome. Her blood-pressure was 150 systolic and ninety diastolic. A diagnosis of suprarenal cortical syndrome was made, and cortical hyperplasia, rather than tumor, was suspected.

May 22, 1934, bilateral exploration of the suprarenal glands through posterolumbar extraperitoneal incisions revealed enlargement of both glands, each of which measured approximately seven centimetres in length, 3.5 centimetres in width, and about eight millimetres in thickness. Suprarenal tumors were not seen or felt. A portion of the left suprarenal gland, two centimetres in diameter, and a portion of the right suprarenal gland, three by two centimetres, were removed. Microscopical examination revealed hyperplasia of suprarenal tissue. Post-operative convalescence was normal. The patient regained strength. Her blood-pressure returned to normal, 124 millimetres of mercury systolic and sixty-two diastolic. Much of the swelling of the face, and the acne disappeared. The urine became sugar-free without insulin, and remained so even after the diet had been increased to 250 Gm. of carbohydrate, and later, when no dietary restrictions were imposed. The values for carbon dioxide combining power and plasma chlorides became normal and the potassium content increased markedly.

A CASE OF BASOPHILIC ADENOMA OF THE PITUITARY

CASE IX.—The patient was a woman, aged thirty-four years. Until the illness for which Dr. D. D. Lyon, of Olympia, Wash., referred her to the clinic September 5, 1932, she always had been robust and athletic. Her menses, which had begun at the age of twelve years, had remained normal until March, 1930, when they rather suddenly had ceased. Following removal, elsewhere, of both oviducts and part of one ovary, menses had become reëstablished for about a year. In February, 1932, menstruation had ceased again. Four years before her admission to the clinic her appearance had begun to change. She had grown stout, and hair had begun to appear on her face. She thought that she was becoming round-shouldered. Simultaneously, her health had begun to fail. She had suffered from headaches, abdominal colic, palpitation of the heart, a sense of retrosternal pressure, and her legs had become weak. She had bruised easily, and hæmorrhagic areas often had appeared on the skin, even though she did not injure herself. Her feet and legs had begun to swell. In the course of four years, her appearance had changed to such an extent that her friends no longer had recognized her. A few weeks before her admission to the clinic, after a slight injury, she had begun to have intense backache, with pain referred across the lower part of the abdomen.

On examination, the buffalo type of obesity was obvious. The face was florid, and telangiectasis was present over the cheek bones. A beard would have been present had the hairs not been plucked. Numerous areas of ecchymosis were present on the extremities. When the blood-pressure was taken, petechiæ appeared on the arm above where the cuff had been applied. There were a few striæ on the abdomen, which was protuberant. The legs were moderately œdematous. The blood-pressure was 160 millimetres of mercury systolic, and 118 diastolic. Slight amounts of sugar and albumin were present in the urine. The sella turcica was normal. The perimetric fields likewise were normal. The retinal arteries were generally constricted, and slight sclerosis of hypertension type was present. Röntgenograms gave evidence of a compression fracture of the eleventh thoracic vertebra, and of gibbus. At operation, January 4, both suprarenal glands appeared to be essentially normal. Nevertheless, it was thought best to remove about half of each gland. The excised tissue was essentially

normal to microscopical examination. One course of Röntgen therapy has been given to the thymic and pituitary regions.

The patient died of bronchopneumonia at her home, January 6, 1934. Permission for a limited post-mortem examination was secured by her physician, who sent the pituitary gland to the clinic for examination. Serial sections of it were made, revealing a basophilic adenoma five millimetres in diameter.

A CASE OF QUESTIONABLE PITUITARY TUMOR

CASE X.—A woman, a Russian Jewess, aged twenty-seven years, was referred to the clinic, September 5, 1932, by Dr. Richard J. Gordon, of Chicago. The patient had never been married. Until the onset of the illness which brought her to the clinic, she had enjoyed good health. Her menstrual periods had been somewhat irregular, but otherwise normal. Four years before she came to the clinic, coarse black hair had begun to grow on her face, and a heavy growth of hair over the rest of the body. A year later the beard had become so pronounced that she had had it removed by electrolysis. She had increased in weight and decreased in height. Her general health had remained good, however, until about a year before she came to the clinic. During this year her feet and ankles had begun to swell, and she had complained of weakness. On her arrival at the clinic, her chief complaints were of weakness and concern over the changes which had occurred in her appearance.

The face was broad, fat, florid and hairy. The large abdomen, with its purplish striæ, contrasted sharply with the thin legs and arms. There was an extensive growth of hair on the back, legs and buttocks. Other outstanding features were marked hypertension, osteoporosis of the skull and spinal column, reduction of the total volume of blood, and latent diabetes. The sella turcica was slightly but definitely enlarged, and the floor of the sella and the posterior clinoid processes were slightly eroded. The perimetric fields were normal. There was general constriction of the retinal arteries, also old choroiditis, with a cystic type of degeneration below the right macula, and glial excess on the right disc, nasally, with extension along the superior nasal vessels. At exploration, September 17, both suprarenal glands were found to be essentially normal in appearance except for slight enlargement of the left. About half of each gland was removed. The tissue removed was normal suprarenal tisue on microscopical examination, except for the presence of an adenoma microscopical in size. Recovery from the operation was uneventful, and the patient was dismissed from the clinic after having been given one course of Röntgen therapy to the pituitary gland. So far as we have been able to learn, there has been no material change in her condition.

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