SUBTOTAL ADRENALECTOMY FOR CUSHING'S SYNDROME:

A PRELIMINARY REPORT OF 29 CASES*

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THE TERM "CUSHING'S SYNDROME" will be used in this paper to refer to the clinical picture described by Cushing.[1] The outstanding features of this syndrome are: a distinctive habitus characterized by obesity or an abnormal distribution of fat and wasting of muscle so that the face, neck and trunk appear obese while the extremities appear thin; hypertension; osteoporosis; ecchymosis; diabetes, either latent or frank, and amenorrhea or impotence. Hirsutism and acne of some degree are usually present, but other evidences of virilization are not pronounced. Generally, the skin is thin and there are distinctive purplish striations. Usually there is a pad of fat over the cervicothoracic vertebrae, the so-called buffalo hump. Frequently, there is lymphopenia, and the reaction of the urine is often alkaline. The concentration of plasma electrolytes may be normal, or a hypochloremic hypopotassemic alkalosis may be present. The urinary excretion of 17-ketosteroids may be low, normal, moderately increased, or greatly increased, depending in part on the pathologic process responsible for the clinical picture. Urinary excretion of corticosteroids (formaldehydogenic steroids) is usually increased; however, in an occasional patient with the typical clinical picture, the urinary excretion of corticosteroids is normal. Precisely what combination of symptoms justifies the diagnosis of Cushing's syndrome is a matter of opinion.

The endocrine pathologic changes of Cushing's syndrome are varied. In an occasional case there is no demonstrable endocrine lesion. In most instances, however, there is either a hyperfunctioning tumor or gross hyperplasia of the adrenal cortex. The syndrome has been observed in a few cases of thymic tumor in association with hyperplasia of the adrenal cortex,[2, 3] but the thymic tumor in such cases probably is not of primary etiologic importance. Basophilic tumors of the anterior lobe of the pituitary gland are present in some, but not all, cases. In most cases, the basophilic cells of the anterior pituitary are found to be hyalinized.[4] This change is restricted to the nontumorous portion of the pituitary when a basophilic tumor is present. While hyalinization of the basophilic cells is the most common endocrine pathologic abnormality, evidence suggests that it does not play a primary role in the causation of the syndrome.[5]

In spite of the varied endocrine lesions of Cushing's syndrome, there is ample evidence to support the concept that the syndrome in all cases is an immediate consequence of hyperfunction of the adrenal cortex. Without reviewing the evidence in detail, it can be pointed out that (1) some patients with Cushing's syndrome have

* Read at the meeting of the American Surgical Association, Washington, D. C., April 11, 1951.

been cured by removal of tumors of the adrenal cortex and (2) most of the clinical and laboratory features of the syndrome, including hyalinization of the basophilic cells of the anterior pituitary, have been pituitary, and the poor prognosis that confronts most of these patients without treatment, an attempt has been made to treat Cushing's syndrome by radical subtotal adrenalectomy.

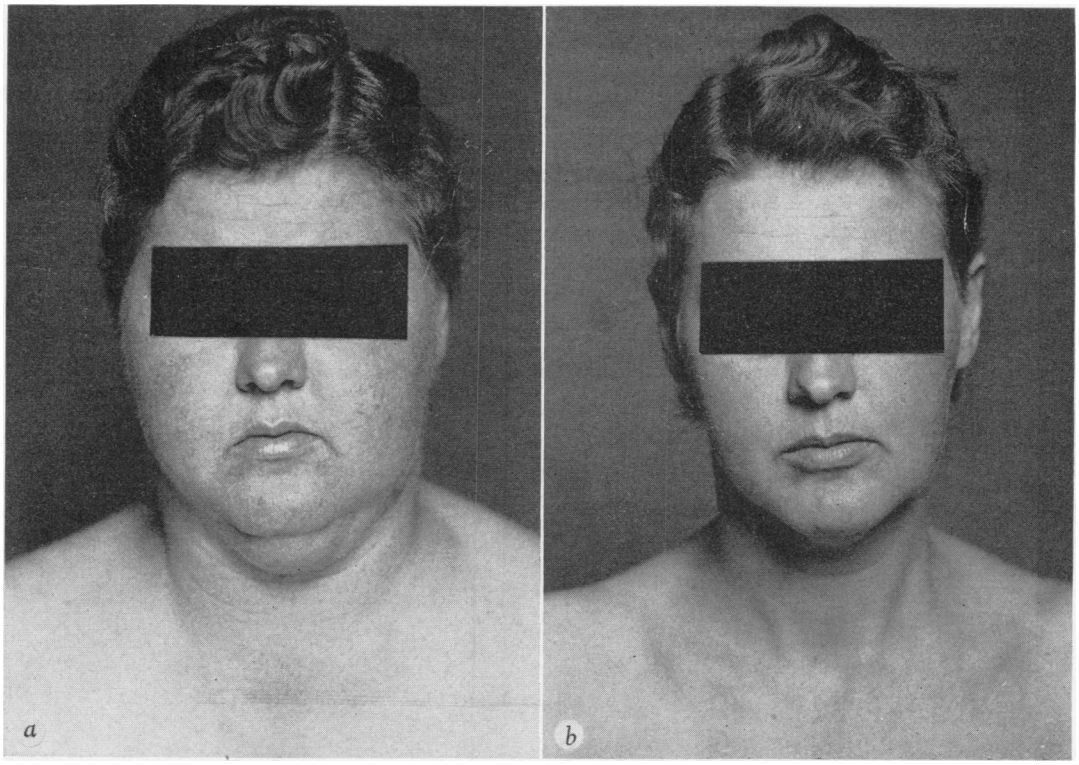

FIG. 1.—Cushing's syndrome: typical facial changes showing obesity, hirsutism, and acne present before operation. Reversion toward normal is apparent six months after radical subtotal adrenalectomy.

induced by stimulation of the adrenal cortices with exogenous adrenocorticotropic hormone (ACTH) or by administration of large doses of the adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (cortisone).[6-9] Whether hyperfunction of the adrenal cortices in Cushing's syndrome is a primary condition or a secondary phenomenon resulting from a stimulus arising in the anterior pituitary or elsewhere, the symptoms should subside if sufficient adrenal cortical tissue were removed.

With the foregoing reasoning in mind, and in view of the lack of any specific medical treatment of the condition, the uncertain response to roentgen irradiation of the

CLINICAL MATERIAL

From August, 1945, to January, 1951, radical subtotal adrenalectomy has been performed at the Mayo Clinic in 29 cases of Cushing's syndrome in which surgical exploration failed to reveal a functioning tumor of the adrenal cortex. There were six males and 23 females in the series. The youngest patient was a boy of 13 years, and the oldest, a woman of 51 years. Four patients were less than 20 years of age, and the average age was 30 years.

All of the 29 patients in the series presented a combination of clinical and laboratory findings which was considered adequate for a diagnosis of Cushing's syn-

drome. Most of the patients had the condition in severe form (Figs. 1 and 2). All had hypertension, the characteristic habitus, and some abnormality of the skin. A cervicothoracic fat pad was present in 24 cases; cutaneous striae in 20, purpuric ecchymosis in 26, acne in 18, keratosis pilaris in 19 and plethora in 28. The one patient who did not have a florid complexion had myxedema resulting from previous thyroidectomy. Twenty-five of the patients complained of muscular weakness which was usually most marked in the legs. Only four women had normal menstrual periods. Frank or latent diabetes and osteoporosis were each present in 22 cases. The excretion of 17-ketosteroids in urine was normal or low in approximately half of the cases and

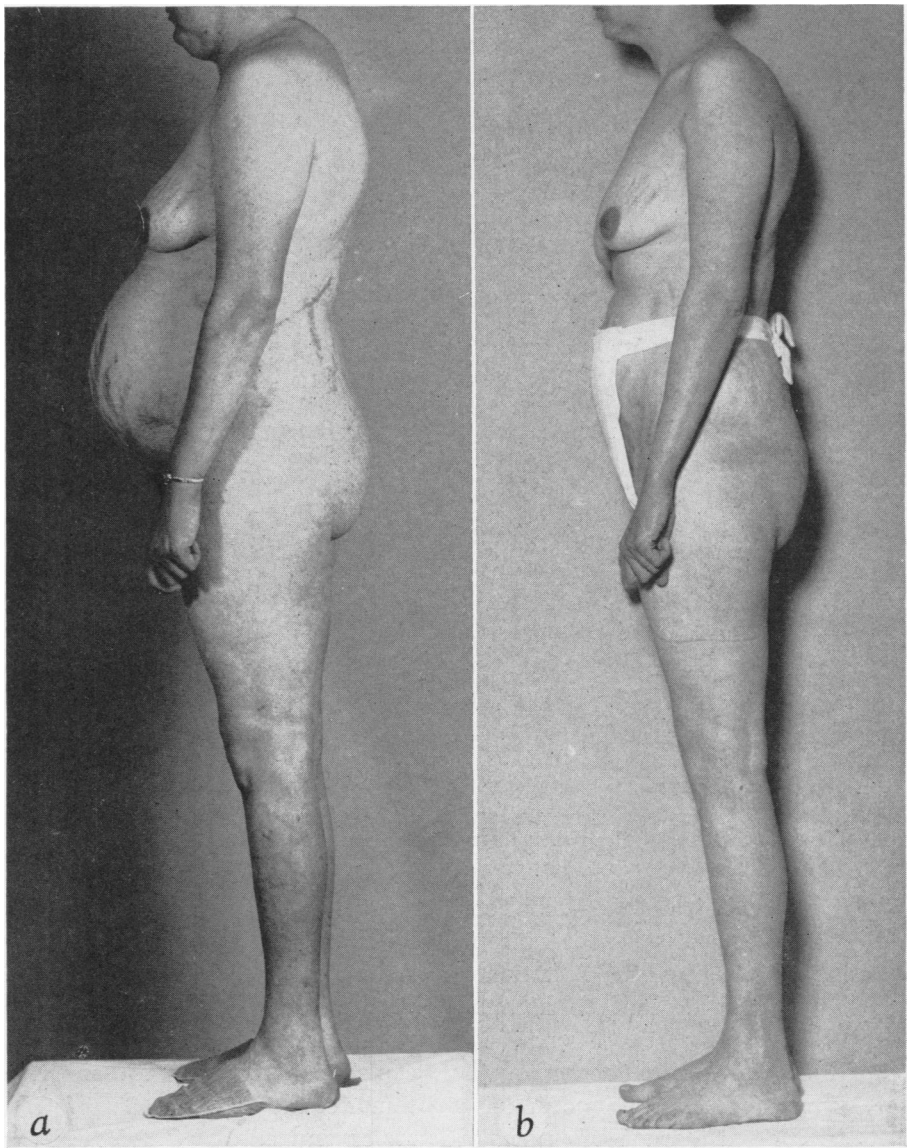

FIG. 2.—Cushing's syndrome: showing typical habitus with obesity of trunk, striae and cervicothoracic deposition of fat prior to operation. Partial or complete disappearance of these characteristics is apparent six months after operation.

elevated in the remainder. The excretion of corticosteroids in urine was normal in four cases, was not determined in two cases, and was high in the remaining 23 cases. Lymphopenia and an alkaline urine were each found in slightly more than half of the cases. Low values for plasma potassium or high carbon-dioxide combining power, or both, were present in nine cases. In 28 cases roentgenographic examination of the skull revealed no evidence of a pituitary tumor, but in one case the sella turcica was definitely enlarged by a pituitary tumor.

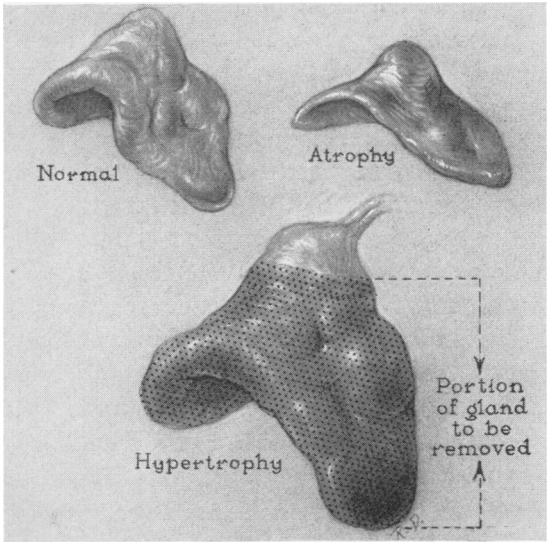

FIG. 3.—Variations in size of adrenal glands which may be found associated with Cushing's syndrome. The gland is enlarged or of normal size if no tumor is present. If a functioning tumor is present on one side, the contralateral gland is atrophic.

PREOPERATIVE AND POSTOPERATIVE TREATMENT

In the first 20 cases, aqueous adrenal cortical extract was used in both preoperative preparation and postoperative care. The usual preoperative preparation consisted of 40 cc. of extract administered intramuscularly the evening before operation and another 40 cc. administered intramuscularly just prior to the operation.

Convalescence after resection of the first adrenal gland was usually uneventful. However, since it was not possible to be certain, prior to surgical exploration, that a functioning tumor of the adrenal cortex was not present, all patients received aqueous adrenal cortical extract before the initial operation. If no functioning tumor of the adrenal cortex was found and a subtotal resection of the first adrenal was performed, the patient usually required little or no additional extract.

Prior to resection of the second adrenal gland, the patients were prepared as before the first operation. In addition, 20 to 50 cc. of aqueous adrenal cortical extract was given in a liter of saline solution during the surgical procedure. Intramuscular and intravenous administrations of extract were continued for several days following operation, the exact quantity used being determined by the clinical status of the patient. With this method of preoperative preparation and postoperative care, the immediate shocklike reaction, which occurs within the first 24 to 72 hours and which closely resembles severe acute adrenal cortical insufficiency, was averted. The usual practice was to discontinue intravenous administration of extract after a few days and then gradually reduce the quantity of extract administered intramuscularly.

After resection of the second adrenal gland, the patients usually did well for ten to 20 days, and then a delayed reaction, characterized by anorexia, increasing nausea and finally vomiting developed. The anorexia frequently progressed until the patients had such an actual aversion to food that the mere sight of food would result in vomiting. Weakness, fever and tachycardia were usually present but the blood pressure as a rule did not fall to the low levels usually observed in acute adrenal insufficiency. Abdominal pain was present in some cases and in some there were muscular and articular symptoms resembling fibrositis

and periarthritis. The chemical composition of the blood gradually became disturbed and the 24-hour excretion of 17-ketosteroids and corticosteroids reached low levels. The administration of large amounts of aqueous adrenal cortical extract (100 to 200 cc. daily) together with normal saline did not relieve this condition, which in some cases persisted for four to six weeks. Attempts to feed the patient by tube during the anorexic phase of the reaction only served to aggravate the nausea and vomiting.

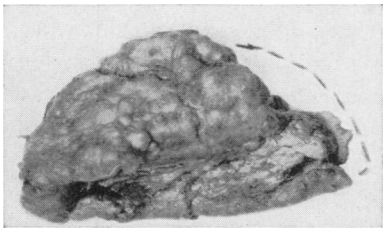

FIG. 4.—Ninety per cent of adrenal gland removed in treatment of Cushing's syndrome associated with hyperfunction of adrenal cortices. Dotted line illustrates remnant of gland which was preserved.

In the last nine cases of the series, cortisone has been used in place of aqueous adrenal cortical extract for both preoperative and postoperative care. The usual practice has been to give 200 mg. of cortisone acetate intramuscularly 48 and 24 hours before operation and another 200 mg. the morning of the operation. Since the institution of this program, the immediate postoperative shocklike reaction has been averted, with one exception, without the use of aqueous adrenal cortical extract. Moreover, it has been found that administration of cortisone for 24 to 72 hours will relieve the delayed reaction. Nausea, vomiting, anorexia, fever and tachycardia disappear. The intake of food increases from virtually nothing to 2000 to 3000 calories daily. When doses of cortisone are discontinued, the symptoms of the reaction tend to recur but may again be relieved by administration of cortisone. However, at present there is some indication that prolonged or excessive administration of cortisone following operation may make it difficult to evaluate the viability and functional capacity of the adrenal remnant and thus may be undesirable. The use of cortisone as a form of therapy for the delayed reaction is being studied further.

SURGICAL MANAGEMENT

Inasmuch as an identical clinical syndrome can be produced either by a functioning tumor of the adrenal cortex or hyperfunction of the adrenal cortical tissue in the absence of tumor, it is essential that the surgeon recognize which of these two conditions is present when the first adrenal gland is exposed, as treatment differs with the presence or absence of tumor. In the presence of tumor on one side, the contralateral adrenal gland obviously should not be removed or it may be impossible later to remove the tumor without producing permanent adrenal insufficiency. Thus it becomes essential for the surgeon either to explore both adrenals before resecting one gland or to determine with certainty from the condition of one gland whether or not there is a functioning tumor in the other gland.

Until the last year or two it was our practice to explore both glands before either was resected. More recently, with increasing experience, the plan of treatment has been determined by the appearance of the first gland exposed. This has been possible because of the consistent observation that in the presence of a functioning tumor on one side, the contralateral gland appears atrophic, whereas if so-called adrenal cortical hyperplasia is responsible for the patient's symptoms, the appearance of both adrenals is virtually identical and neither gland is atrophic.

Adoption of this plan of treatment makes it essential, of course, that the sur-

geon recognize the type of gland that is present before resection of any adrenal tissue is performed (Fig. 3). In other words, if the gland is atrophic, it is not removed and the opposite gland is then exposed with the reasonable expectation of finding a tumor. If the first gland is not atrophic, subtotal (90 per cent) resection of this gland is performed (Fig. 4). Obviously it is essential that the remnant of gland which is preserved be in a viable state and have an adequate blood supply.

Unfortunately, pathologic criteria for the recognition of adrenal cortical hyperfunction in the absence of tumor are not as well defined as the surgeon might wish. On the other hand, the pathologist can usually recognize atrophy of the adrenal histologically. Atrophy also can be recognized grossly by the surgeon with considerable accuracy as his experience accumulates, because the gland appears pale in color compared with the normal, is thin and relatively small in size. If question exists in the surgeon's mind regarding atrophy of the first adrenal to be exposed, a specimen should be taken and a frozen section made and examined immediately. If doubt still remains, the gland should not be resected until the opposite adrenal has been exposed.

If the syndrome is produced by adrenal cortical hyperplasia and subtotal (90 per cent) adrenalectomy is performed on one adrenal gland, a second operation is performed after an appropriate interval on the opposite adrenal gland. The length of this interval varies with the patient's progress but currently is usually about two weeks. Until recently it was our practice at the time of the second operation first to expose the remnant of the previously resected adrenal gland to determine its existence and apparent viability. If a viable portion of adrenal tissue was found, total adrenalectomy was performed on the opposite side. Recently, with increasing confidence in our ability to preserve a viable portion of the adrenal at the time of initial subtotal resection of one gland, we have proceeded directly with total adrenalectomy of the second gland at the second operation without preliminary exploration of the previously resected gland.

Various surgical approaches have been employed for exposing the adrenal glands simultaneously. With the patient prone on the operating table, bilateral posterolumbar incisions may be made and each adrenal exposed. Exposure in this manner is not too satisfactory but is aided by resection of the twelfth rib on each side. An anterior approach has been employed utilizing a transverse abdominal incision but if the patient is obese, as are most patients who have Cushing's syndrome, some difficulty may be experienced in obtaining exposure which is adequate for dealing with the small blood vessels which enter and leave the adrenal.

If only one adrenal is to be exposed through a given incision, a transthoracic approach has been used in an occasional case and this has afforded excellent exposure. This approach is unnecessary, however, in most cases. Our preference remains for the posterolumbar incision which is commonly employed in operations on the kidney. If it is necessary to expose both adrenals, the first incision is closed and a second incision is made on the opposite side. The adrenal is ordinarily brought to view by downward retraction of the kidney. Considerable care must be exercised to expose the entire adrenal gland, as occasionally it may have an irregular or unusual contour, and the actual extent and size of the gland may not be accurately appreciated by looking only at its presenting surface.

In 19 cases the weight of the adrenal gland which was totally removed is known; in 15 cases it weighed more than 7.5 Gm., which might be considered a maximum normal weight. The average weight of the gland in the 15 cases was 11.1 Gm. The

smallest gland which was totally removed weighed 6.6 Gm. and the largest 21.5 Gm.

RESULTS

Six of the 29 patients died. Four of the deaths occurred in the first ten cases. There have been no deaths in the last ten cases.* One of the six deaths occurred after the patient had returned home and the details of her terminal illness are unknown. Another death occurred on the day of operation. Necropsy revealed a collapsed left lung and severe hemorrhagic edema of the right lung. This patient will be referred to later. One patient had an acute venous occlusion of the right leg and died 16 days following the second operation. Necropsy revealed a thrombus of the right iliac vein which extended into the inferior vena cava to the level of the renal veins.

The other three deaths occurred 66, 53, and 33 days following resection of the second adrenal. All of these patients had stormy postoperative courses characterized by severe, protracted anorexia, nausea, vomiting, tachycardia, weakness, and fever which did not respond to treatment with large doses of aqueous adrenal cortical extract. One of the patients had severe abdominal pain just to the left of the epigastrium and a tender mass could be felt on abdominal examination a few days before death. Necropsy in this case revealed acute and chronic hemorrhagic pancreatitis. In the other two patients, necropsy revealed fat necrosis in the tail of the pancreas. In one patient a fatty liver weighing 1500 Gm. was found.

Three patients have been operated on too recently to permit an appraisal of the results obtained.

One patient who was operated on in 1947 has shown no significant improvement following subtotal adrenalectomy. At the time of the second operation, the remnant of the adrenal which was preserved when subtotal resection of the first gland was performed could not be found and, consequently, total resection of the second adrenal gland was not performed. It is possible that this patient still has considerable adrenal cortical tissue.

Due to failure of a significant remission to appear following resection of the second adrenal, three patients required a third operation and partial resection of the viable remnant. In two of these, remissions ensued, and in the third, death occurred on the day of operation, as mentioned previously.

Nineteen patients then obtained excellent remissions from Cushing's syndrome. The manifestations of the syndrome regressed over periods of several weeks or months. The characteristic habitus gradually disappeared, plethora faded, ecchymosis disappeared, the skin became thicker and purple striae lost their color. In many of the cases, hypertension disappeared and the blood pressure returned to normal levels, but in other cases a residual mild hypertension persisted. Menses became normal and three of the patients who obtained remissions have subsequently become pregnant. Muscular strength increased, and the patients have been able to perform their usual work.

To date, three of the 19 patients have had recurrences of the signs and symptoms of Cushing's syndrome. The recurrences developed after remissions lasting three years, two years, and nine months, respectively. One of these patients has had further resection of adrenal cortical tissue. Exploration of the adrenal remnant in this case revealed a globular mass of hyperplastic-appearing adrenal tissue. Ninety per cent of the remnant was removed and it weighed 6 Gm. The patient has obtained another

* In addition, since January 1, 1951, we have completed radical subtotal adrenalectomy in nine more cases of Cushing's syndrome without a fatality. A more detailed description of physiologic changes occurring in the entire series of patients as a consequence of subtotal adrenalectomy is to be the subject of a subsequent report.

remission from his Cushing's syndrome but now he has adrenal cortical insufficiency.

In all, three of the 19 patients have chronic adrenal cortical insufficiency and require daily replacement therapy. A third operation and further resection of the adrenal remnant was performed on two of these three patients as one of these failed to obtain a remission following the usual surgical procedure and as the other developed a recurrence of his disease. The third patient (the patient with roentgenographic evidence of a pituitary tumor) experienced a complete remission of his Cushing's syndrome, but developed chronic adrenal cortical insufficiency following the usual surgical procedure. One other patient may have some degree of adrenal cortical insufficiency but there is evidence that she has a small remnant of functioning adrenal cortical tissue and further observation will be necessary before definite conclusions can be reached. While typical addisonian pigmentation has occurred in the three patients who have chronic adrenal cortical insufficiency, similar pigmentation has also occurred in others who have no clinical or laboratory evidence of adrenal cortical insufficiency.

COMMENT

Although understanding of Cushing's syndrome has increased in the last decade, much remains to be learned. Present therapeutic efforts directed toward relief of this disease should be considered as representative of current thinking which may be altered in the future. Certain important concepts which have been responsible for development of the current surgical treatment of Cushing's syndrome should be mentioned. First, and perhaps foremost, was the realization that regardless of the primary cause of the disease, the clinical syndrome is dependent on hyperfunction of the adrenal cortex. The results which have been described clearly indicate that the features of Cushing's syndrome can be relieved by removal of most of the adrenal cortical tissue and these results appear to support the concept that the features of the disease are manifestations of adrenal cortical hyperfunction.

A second important observation was that in the absence of a functioning tumor, extensive resection of adrenal cortical tissue was essential if anything approaching a complete remission of the disease was to be obtained. Whereas in previous years perhaps 50 or 60 per cent of each adrenal gland might be resected in a given patient, improvement, if it occurred, was usually only moderate and of relatively brief duration. It thus became apparent that more extensive resection of adrenal tissue was necessary. It is now our opinion that approximately 90 per cent of one adrenal gland should be removed and total adrenalectomy should be performed on the opposite side if satisfactory results are to be expected. To date, we have never performed this extensive resection of adrenal tissue in less than two operative procedures.

A third observation which has been most significant in development of treatment for Cushing's syndrome is that hyperfunction of the adrenal cortices can exist in the absence of gross enlargement of the adrenal glands. Thus, it is our current practice, based on clinical experience, to proceed with extensive subtotal resection of one adrenal gland and subsequently total removal of the other adrenal gland when the patient presents unequivocal clinical and laboratory evidence of Cushing's syndrome, even though the adrenals appear to be grossly normal when exposed at operation. One must, of course, be completely satisfied with the accuracy of the clinical diagnosis if such a course is to be followed. Obviously, indiscriminate adrenalectomy in fat, hairy women would be most unfortunate.

A fourth consideration which should be emphasized is that Cushing's syndrome is generally a morbid and progressive disease, and the prognosis without treatment is poor. Such a formidable surgical procedure as radical subtotal adrenalectomy is justifiable only in view of the serious nature of the disease and the lack of other reliable methods of treatment.

It is interesting to note that experience in the surgical treatment of Cushing's syndrome has much in common with early experience in the surgical treatment of Graves' disease. In both conditions the patient suffers from hyperfunction of one of the glands of internal secretion. Preoperative preparation and postoperative care constitute major concerns in the management of both diseases. Likewise, the surgeon is confronted with the necessity of adequate removal of glandular tissue if a satisfactory remission of the disease is to be obtained. On the other hand, too extensive removal of glandular tissue must be avoided or deficiencies will result which manifest themselves as definite clinical entities, namely, myxedema or Addison's disease. To prevent these conditions, the surgeon must not only avoid removal of too much tissue but must leave the remnant of gland which is not removed in a viable state and with an adequate blood supply so that atrophy will not occur. With improvement in the preoperative and postoperative care of the patients, a better understanding of the physiologic action of various adrenal steroids and more technical experience in bilateral subtotal adrenalectomy, results should improve.

SUMMARY

Extensive bilateral subtotal adrenalectomy has been performed in 29 cases of Cushing's syndrome in which surgical exploration failed to reveal a functioning adrenal cortical tumor. There were six postoperative deaths, all of which occurred prior to the use of cortisone in both the preoperative and postoperative management. Of the 23 remaining patients, one patient experienced no improvement following operations; three patients will require further observation as the postoperative period has been too short to allow evaluation of the results, and 19 patients have obtained an excellent remission of the Cushing's syndrome. However, three of the 19 patients have adrenal insufficiency. In general, the results have been encouraging and appear to support the concept that regardless of what the primary etiology of the syndrome may ultimately prove to be, its features are contingent upon hyperfunction of the adrenal cortices. It appears entirely possible that results may be improved in the future.

BIBLIOGRAPHY

[1] Cushing, Harvey: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism). Bull. Johns Hopkins Hosp., **50:** 137, 1932.

[2] Kepler, E. J.: Report of Four Cases. Proc. Staff Meet., Mayo Clin., **8:** 102, 1933.

[3] Leyton, Otto, H. M. Turnbull, and A. B. Bratton: Primary Cancer of the Thymus With Pluriglandular Disturbance. J. Path. & Bact., **34:** 635, 1931.

[4] Crooke, A. C.: A Change in the Basophil Cells of the Pituitary Gland Common to Conditions Which Exhibit the Syndrome Attributed to Basophil Adenoma. J. Path. & Bact., **41:** 339, 1935.

[5] Kepler, E. J.: Relationship of "Crooke's Changes" in Basophilic Cells of Anterior Pituitary Body to Cushing's Syndrome (Pituitary Basophilism). J. Clin. Endocrinol., **5:** 70, 1945.

[6] Sprague, R. G., M. H. Power, H. L. Mason, A. Albert, D. R. Mathieson, P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley: Observations on the Physiologic Effects of Cortisone and ACTH in Man. Arch. Int. Med., **85:** 199, 1950.

[7] Laqueur, Gert L.: Cytological Changes in Human Hypophyses After Cortisone and ACTH Treatment. Science, **112:** 429, 1950.

[8] Golden, Abner, P. K. Bondy, and W. H. Sheldon: Pituitary Basophile Hyperplasia and Crooke's Hyalin Changes in Man After ACTH Therapy. Proc. Soc. Exper. Biol. & Med., **74:** 455, 1950.

[9] Bennett, W. A.: Personal communication to the authors.