Total Adrenalectomy for Cushing's Disease

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THE SURGICAL TREATMENT of Cushing's syndrome was most unsatisfactory until replacement therapy became available slightly more than 20 years ago. There were sporadic case reports of attempted surgical therapy but the patients usually died in the early postoperative period of adrenal insufficiency. When cortisone became readily available for replacement therapy, interest in the surgical treatment became great. Total bilateral adrenalectomy was first performed at The New York Hospital more than 20 years ago[1] and to date has remained the therapy of choice for the majority of patients with Cushing's disease.[2] Since that time many other forms of therapy have been advocated which include subtotal adrenalectomy, unilateral adrenalectomy with and without x-ray therapy to the pituitary. Various types of radiotherapy to the pituitary, yttrium implantation to the pituitary have been employed as well as hypophysectomy. All types of therapy have one or more drawbacks and there is no universal acceptance of any one.[5]

Presented at the Southern Surgical Association Meeting held at Hot Springs, Virginia, December 6–8, 1971.

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Although there has been considerable debate regarding the cause of Cushing's disease the information gained from (1) ACTH radio-immunoassay, (2) dexamethasone suppression tests and (3) the occurrence of hyperpigmentation post-adrenalectomy strongly suggests that the hypothalamus and pituitary are of primary importance in its etiology. If Cushing's disease is a disorder of the hypothalamic-pituitary tract, and we believe it is, the adrenal merely reacts to an over supply of ACTH. Hyperpigmentation frequently occurs in totally adrenalectomized patients. This is presumably related to continued abnormal hypothalamic-pituitary over activity.

At The New York Hospital-Cornell Medical Center over a period from 1950–1971, we have had the opportunity to study and treat 95 patients with Cushing's syndrome.

The patients with other aspects of Cushing's syndrome such as those with adrenal adenoma, adrenal carcinoma and the ectopic ACTH syndrome, present far fewer therapeutic problems than the larger group with adrenal hyperplasia or hyperfunction which we classify as Cushing's disease. Surgical extirpation of the tumor, benign or malignant, will alleviate or cure the patient's symptoms in most instances. The group with extra-adrenal carcinomas producing ACTH usually can be treated only palliatively except in very rare instances.

At The New York Hospital-Cornell Medical Center, 42 patients with adrenal hyperplasia were selected for total adrenalectomy. This report reviews and analyzes those patients with Cushing's disease who

have undergone total adrenalectomy. The report will emphasize several aspects of the postoperative period. These aspects include the progression of cardiovascular disease and its accompanying complications involving the heart, the great vessels, kidney and brain, the progression of hypothalamic-pituitary disease with hyperpigmentation and/or pituitary tumors, and the problem of adrenal insufficiency.

Cushing's Disease and Hyperplasia of the Adrenal Cortex

In our series, 49 patients had cortical hyperplasia without clinical evidence of pituitary involvement. There were 44 females and 5 males, with an age range from 11 to 72 years, the mean age was 28.

Forty-two of the 49 were operated upon for total bilateral adrenalectomy. The procedure was done in one or two stages. Although complete removal of all adrenal tissue was attempted and attained in the opinion of the surgeon, two patients exhibited evidence of residual functional cortical substance.

Seven other patients were selected for total adrenalectomy but for various reasons only one adrenal was removed. Two of these later received radiation to the pituitary and five did not. One of these later underwent hypophysectomy because of enlargement of the pituitary.

We believe that we failed in our objective of attempted total adrenalectomy in two of the 42 patients. Residual adrenal tissue was strongly suggested by their clinical course.

Case Reports

Case 1. A 54-year-old woman with long-standing and advanced Cushing's disease was operated upon for total removal of both adrenal glands. In the opinion of the surgeon this was accomplished. However, the symptoms persisted. Some hyperpigmentation soon appeared and was progressive. Her clinical course after operation was almost unaltered. The disease persisted and she died 3 years after operation. In the absence of an autopsy we do not know if any adrenal tissue was present.

TABLE 1. *Cushing's Syndrome*

Hyperplasia	49
Adenoma	27
Carcinoma	10
Extra-adrenal carcinoma	1
Pituitary involvement	8
Total	95

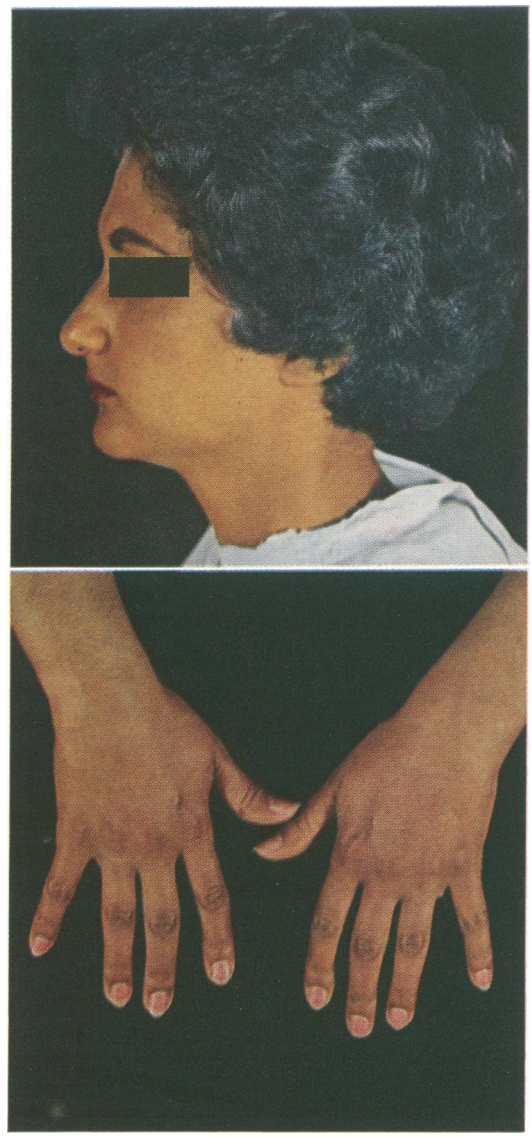

FIG. 1. Hyperpigmentation 4 years following total adrenalectomy. A 19-year old girl within 1 year after total adrenalectomy developed hyperpigmentation of the face and extensor surfaces of the extremities and hands. This has remained since its appearance.

TABLE 2. *49 Patients with Cushing's Disease Due to Hyperplasia—1950–1971*

Attempted total adrenalectomy	42
Unilateral adrenalectomy without radiation	5
Unilateral adrenalectomy with radiation	2
Total	49

Case 2. A 54-year-old woman with advanced Cushing's disease had one adrenal gland removed in October of 1966 and the other was removed 15 months later in January of 1968. The surgeon believed all adrenal tissue had been excised. Her clinical course did not improve. One year later she received radiation to the pituitary without benefit. A hypophysectomy was done in 1971. Immediately the symptoms began to recede. She is now improving but has symptoms of cardiovascular disease.

There was one death in the early postoperative period due to a massive pulmonary embolus. Nine deaths have occurred at intervals of 3 months to 14 years after operation.

Of the late deaths (9) seven were related to cardiovascular disease, one to a malignant tumor of the pituitary 10 years after total adrenalectomy and one patient in whom death might be ascribed to neglect or failure to take substitution therapy. This occurred 14 years after adrenalectomy and we lack specific information that might prove or disprove that such was the case. One of the seven died 3 months after operation and is considered a therapeutic failure with progressive cardiovascular disease.

All patients selected for total adrenalectomy have been in consultation and free discussions with those associated with their medical care in the community in which they live. The risks and disadvantages of having to have replacement therapy for the remainder of their lives is emphasized as well as improvement in prognosis afforded by total adrenalectomy. They are instructed in the administration of:

Cortisone 25–37.5 mg.
Florinef * 0.1 mg. } oral, daily

Factors that influence the utilization of these and the manifestations of inadequate dosage are repeatedly dwelt upon with the patient.

TABLE 3. *Two Failures in 42 Attempted Total Adrenalectomies—1950–1971*

Sex	Age	Clinical Course	Survival
1. F	54	Hyperpigmentation	3 years (dead)
2. F	54	Hyperpigmentation Hypophysectomy	6 years (living and active)

TABLE 4. *Results of Attempted Total Adrenalectomy in 42 Patients—1950–1971*

Deaths	10
Postoperative (1)	
Late (9)	
Living and well (up to 20-year follow-up)	29
Lost to follow-up	3
Total	42

* Fludrocortisone acetate.

TABLE 5. *10 Deaths Following Attempted Total Adrenalectomy, 1950–1971*

Cause of Death	Age	Time from Operation
Postoperative (1)		
1. Embolus, pulmonary	66	
Late (9)		
1. ? Neglect of substitution therapy	40	14 years
2. Hypertensive C-V disease	46	13 years
3. Pituitary tumor	22	10 years
4. Hypertension, cardiovascular disease	47	9 years
5. Embolus, massive pulmonary	31	5 years, 4 months
6. Hypertensive C-V disease	57	3 years, 3 months
7. Hypertensive C-V disease—CVA	38	1 year, 3 months
8. Hypertensive C-V disease–CVA	72	4 months
9. Cause undetermined	33	3 months

TABLE 6. *Follow-Up in 42 Patients Undergoing Attempted Total Adrenalectomy—1950–1971*

Time	No. of Patients
15–20 years	11
10–14 years	10
5–9 years	9
1–4 years	4
Under 1 year	2
Dead within 1 year	2
Postoperative death	1
Lost to follow-up	3
Total	42

The quality of life following total adrenalectomy and the daily self medication for replacement has been far better than we had anticipated. The longest follow-up is 20 years; the patient has married but had no children. Four women have been pregnant, two of whom had two pregnancies, resulting in six living infants amongst this group of patients.

Six patients have undergone major surgical procedures without difficulty.

Hyperpigmentation has been much more frequent after total adrenalectomy in our experience than has been reported by others.

Discussion

The emphasis in this review has been on patients who have had total adrenalectomy for Cushing's disease. The risk and burden the operation imposes has been evaluated in terms of morbidity and mortality. The parameters of well being, the control and regression of the disease have been described in parallel to continuation of symptoms and sequelae of those not operated upon. That only one death occurred in the early postoperative period amongst 42 patients in whom total adrenalectomy was attempted is significant, particularly in view of the patient's age of 66 and with an advanced Cushing's disease of long-standing.

TABLE 7. *Pregnancies Following Attempted Total Adrenalectomy—1950–1971*

No. of Women	No. of Pregnancies
4	6

TABLE 8. *Major Surgical Procedures Following Total Adrenalectomy 1950–1971*

Operation	No. of Patients
Amputation, leg	2
Cholecystectomy	1
Gastrectomy	1
Mastectomy	1
Open reduction for fractured hip	1
Total	6

Patients with untreated Cushing's syndrome suffer progressive damage to the cardiovascular system, that in our experience is the most life threatening component of hypercortisolemia. Particularly disturbing is the evidence presented here that even among those patients effectively treated with bilateral adrenalectomy there persists a propensity for vascular disease. Pre-existing hypertension which often was adequately improved by surgery had been present in all patients who developed evidence of cardiovascular disease. Preoperative hypertension was noted in 34 patients. Of these, evaluation studies were feasible in 28 patients. Twenty-one patients became normotensive postoperatively.

The problems encountered were myocardial infarction, cerebrovascular accidents, pulmonary emboli, vascular insufficiency leading to amputation. The frequency of vascular complications suggests that prompt and effective therapy is of utmost importance for patients with hypercortisolemia.

TABLE 9. *21 (50%) of 42 Patients Developed Hyperpigmentation Following Attempted Total Adrenalectomy—1950–1971*

Progressive after onset	6
Persisted after onset without change	15
Total	21

TABLE 10. *Hypertension* in 42 Patients With Attempted Total Adrenalectomy—1950–1971*

Preoperative hypertension		34
Postoperative death	1	
Died within 1 year	2	
Too recent for evaluation	1	
Lost to follow-up	2	
Preoperative normal blood pressure		8
Total		42

* Greater than 140/90.

The role of pathologic changes in the cardiovascular system of patients with Cushing's syndrome has long been recognized as a basis for its serious life threatening complication. Hypertension almost always present, even in the very young, is dramatically reduced in Cushing's disease by total adrenalectomy. The extent and degree of cardiovascular disease is sometimes difficult to evaluate. In most instances the longer the disease has been present the greater is the degree of vascular disease. Total adrenalectomy may slow or interrupt its progress but does not reverse the changes that have taken place. In the group who have survived, and there are 29, most are well and active. The longest follow-up is 20 years. This patient is married but has no children. The remaining patients have been followed from 18 years to six months. Development after operation in the younger patients has been normal. Schooling has not been a problem. Sexual maturity does not seem to have been impaired in either men or women. There have been six pregnancies with living infants in four women. Although the activities of these patients are commensurate with other individuals of comparable age the routine of self administered oral replacement therapy must be emphasized from time to time to prevent complacency. As a group they do not complain.

TABLE 11. *Complications Occurring Among 34 Patients Who Were Hypertensive Prior to Attempted Total Adrenalectomy—1950–1971*

Complications	No. of Patients
Myocardial infarcts	5
Death due to C-V disease	3
CVA	2
Pulmonary infarcts	2
Sudden unexplained death	1
Total	13

In this series there has been less morbidity and fewer deaths than in that reported by Welbourn and Montgomery.[8] In this series, of 27 patients with Cushing's disease there were ten late deaths of which six were related to cardiovascular disease. Plotz, Knowlton and Ragan,[6] 20 years ago, demonstrated clearly the inexorable progression of cardiovascular disease and early death in inadequately treated patients. Pituitary ablation as well as total adrenalectomy is followed with a decrease in blood pressure among those who are hypertensive.

The frequent occurrence of hyperpigmentation in patients totally adrenalectomised provokes discussion of the relationship between therapy and this particular sequela.[3, 4, 7, 9] Is the hyperpigmentation a direct sequela of bilateral adrenalectomy or is it the hyperpigmentation and occasional pituitary tumor part of Cushing's disease appearing in patients who are now surviving long enough to demonstrate this aspect of the disease? There are certain observations which lead us to believe that hyperpigmentation and pituitary enlargement are inherent components of Cushing's disease which are emphasized by the increased survival of patients effectively treated with total adrenalectomy. It is recognized also that the reduced concentrations of plasma cortisol following operation and substitution therapy by physiological replacement of cortisol may to some extent lessen the degree of suppression of hypothalamic-pituitary function. However, persistence of the hypercortisolemia does not in itself consistently and sufficiently suppress the hypothalamus-pituitary unit. It is for this reason that we may see some patients with

Cushing's disease presenting initially with apparent pituitary tumors and/or hyperpigmentation. In our series, six of 42 patients developed progressive hyperpigmentation and two of these had had therapy directed at diminishing function of the pituitary. One patient underwent total hypophysectomy with complete regression of the hyperpigmentation. Another patient, now 7 months post-conventional radiation of the pituitary has not had a decrease of the hyperpigmentation. Fifteen additional patients have definite hyperpigmentation which has not progressed and represents no difficulty.

The occurrence of pituitary tumors, if indeed enhanced by adrenalectomy would be a significant deterrent to this form of therapy. Of 42 patients, two or possibly three presented with evidence of pituitary tumor. Only one patient had had x-ray evidence of a change in the size of the sella turcica post-adrenalectomy. Five additional patients have had progressive hyperpigmentation without evidence of an increase in the size of the sella turcica or visual field defects.

A variety of medical and surgical conditions have been encountered in this group of patients in the period following adrenalectomy. Adrenal insufficiency most frequently accompanied transient gastrointestinal disturbances when the patient failed to follow advice regarding the need for additional cortisone, fluid and electrolyte replacement. In order to minimize this complication, patients are given printed cards with instructions for themselves and family and also special instructions for physicians. Additional medical as well as surgical problems were not particularly unique for this diverse patient population.

Summary

Total adrenalectomy was attempted in 42 patients for Cushing's disease with hyperplasia and/or hyperfunction of the cortical tissue. This was successful in 40. There was one operative fatality. Follow-up studies reveal 29 are living and indulging in ordinary activity, nine have died from three months to 14 years after operation. Three were lost to follow-up. Hypertension present in 34 patients before operation returned to normal pressure range afterwards in 21. Cardiovascular disease seems to have been brought under control in many but not reversed. Hyperpigmentation was observed after operation in 21 or 50 per cent.

Substitution therapy so essential in totally adrenalectomized patients has been remarkably satisfactory. On the basis of this experience it is concluded that the results of total adrenalectomy for Cushing's disease is relatively predictable and definitive. It is accomplished with a low morbidity and mortality. If done early it interrupts the progress of the disease.

References

1. Glenn, F., Peterson, R. E. and Mannix, H., Jr.: Surgery of the Adrenal Gland. New York, The Macmillan Company, 1968, p. 93.
2. Horwith, M. and Stokes, P. E.: Cushing's Syndrome: Experience with Total Adrenalectomy. Advances Intern. Med., 10:259, 1960.
3. Lerner, A. and McGuire, J. S.: Melanocyte-stimulating Hormone and Adrenocorticotrophic Hormone: Their Relation to Pigmentation. N. Engl. J. Med., 27:539, 1964.
4. Nelson, D. H., Meakin, J. W. and Thorn, G. W.: ACTH-producing Pituitary Tumors Following Adrenalectomy for Cushing's Syndrome. Ann. Intern. Med., 52:560, 1960.
5. Orth, D. N. and Liddle, G. W.: Results of Treating Cushing's Syndrome. N. Engl. J. Med., 285:243, 1971.
6. Plotz, C. M., Knowlton, A. I. and Ragan, C.: The Natural History of Cushing's Syndrome. Am. J. Med., 13:597, 1952.
7. Shimizu, N., Ogata, E., Nicholson, W. E., Island, D. P., Ney, R. L. and Liddle, G. W.: Studies on the Melanotropic Activity of Human Plasma and Tissues. J. Clin. Endocrinol., 25:984, 1965.
8. Welbourn, R. B. and Montgomery, D. A. D.: Later Results of Adrenalectomy for Cushing's Syndrome. Proc. Royal Soc. Med., 63:609, 1970.
9. Welbourn, R. B., Montgomery, D. A. D. and Kennedy, T. L.: The Natural History of Treated Cushing's Syndrome. Brit. J. Surg., 58:1, 1971.