# Surgical Management of Cushing's Syndrome with Emphasis on Adrenal Autotransplantation

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**Cushing's syndrome may be caused by pituitary ACTH, ectopically produced ACTH, adrenocortical tumor or medication. Cushing's disease, due to excessive pituitary ACTH resulting in adrenocortical hyperplasia, remains a complex endocrine disorder for which no single treatment is wholly satisfactory. Twenty-two patients with surgically treated Cushing's syndrome are presented: Four with benign adrenocortical adenoma, two with adrenocortical carcinoma and 16 with adrenocortical hyperplasia. The four benign adenomas were excised, with the one death due to respiratory failure and sepsis. Both patients with carcinoma and liver metastases died of their tumors. Of the 16 patients with adrenocortical hyperplasia and Cushing's disease, eight underwent subtotal adrenalectomy and thereafter eight had total intra-abdominal adrenalectomy with autotransplantation of adrenal tissue to the thigh. There was one operative death. Total adrenalectomy has now replaced subtotal resection in most clinics. All eight of the patients who had adrenal autotransplantation exhibited biopsy or functional evidence of some degree of graft survival. One patient stopped steroid replacement permanently and another developed recurrent Cushing's syndrome from the grafts. Of a total of 26 reported patients with adrenal autotransplants surveyed, 22 exhibited evidence of graft survival, 16 were able to discontinue steroid replacement therapy and three eventually developed recurrent Cushing's syndrome from the transplants. There is now strong evidence that most patients with Cushing's disease harbor a pituitary basophil adenoma, and in the future the initial surgical attack may be directed to the pituitary rather than to the adrenals.**

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CUSHING'S SYNDROME was first described over 45 years ago.[6,7] It occurs not only in man but also in other mammalian species. The physical findings which reflect the extensive metabolic disturbances may range from minimal change to spectacular clinical transformation. Yet despite the fact that this condition has been studied for decades, the basic hormonal relationships continue to unfold. For whereas the altered clinical picture in Cushing's syndrome is due specifically to the secretion of excess cortisol by the adrenal cortex (Fig. 1), the subtleties of hypothalamic stimulation of ACTH release in Cushing's disease, effected by the corticotrophin (ACTH) releasing factor (CRF), are complex. In fact, there is an increasing body of opinion that the higher centers, and specifically the cerebral cortex, may play a major role in the pathogenesis of pituitary dependent Cushing's syndrome. The definition of many of these relationships must await the isolation and quantitative measurement of CRF, but it appears possible that excessive release of CRF by the hypothalamus[13] can produce pituitary hyperplasia and nodularity. Furthermore, the fact that some patients with Cushing's disease exhibit continued psychiatric disturbances long after "eucortisolism" has been achieved by adrenalectomy is of interest in this connection. Also, persistent abnormal pituitary-adrenal relationships may be demonstrated many years after the clinical evidence of Cushing's syndrome has been abolished by adrenalectomy.[10,16,29] Spontaneous remission is rare.[27]

Even so, the results of treatment of pituitary dependent adrenocortical hyperplasia producing Cushing's syndrome are reasonably satisfactory, though some patients fail to achieve optimal permanent rehabilitation. Untreated patients with Cushing's disease are reported to have a longevity which ranges from about three to ten years. The results of removal of a benign functioning adrenocortical adenoma producing Cushing's syndrome are usually good unless irreversible physical and metabolic changes have already progressed too far. The treatment of adrenocortical malignancy or of extrapituitary malignant tumor producing ACTH is commonly noncurative.

The purpose of this communication is to present a consecutive series of 22 patients of whom 16 had bilateral adrenocortical hyperplasia (13 females), four benign cortical adenoma (all females) and two cortical carcinoma (both males). While there were some spectacular examples, patients with ectopic ACTH-

Presented at the Annual Meeting of the American Surgical Association April 26–28, 1978, Dallas, Texas.

0003-4932/78/0900/0290 $01.45 

secreting tumors were not included in this survey. Eight patients who underwent bilateral total intra-abdominal adrenalectomy had adrenal tissue transplanted to the thigh and the results achieved will be emphasized. Special pathology met included recurrent Cushing's syndrome due to excessive growth and function of adrenal slices transplanted to the thigh, pseudotumor cerebri, multiple endocrine adenomatosis (MEA), and Nelson's syndrome with chromophobe pituitary tumor and acute onset blindness 15 years following adrenalectomy. This series extended from 1955 to 1976.

## Clinical Material

The 22 surgically treated patients are presented in Table 1. Four benign cortical adenomas, all in females, were removed. One patient, who had profound metabolic changes, died from postoperative respiratory insufficiency and sepsis. The other three patients were cured. The two adrenocortical carcinomas were in men, and in both instances liver metastases were already present, preventing cure. With these comments regarding the tumors met in our patients, we shall hereinafter devote the emphasis to the patients who had Cushing's syndrome due to excessive pituitary release of ACTH causing adrenocortical hyperplasia (Cushing's disease), and especially a group of eight patients who underwent adrenocortical autotransplantation to the sartorius muscle following total intra-abdominal adrenalectomy for adrenocortical hyperplasia.

### *Diagnostic Procedures*

The diagnostic modalities employed included the history and physical examination, routine plasma chemistry measurements, plasma and urinary 17-hydroxycorticosteroid (17-OHCS) levels before and after dexamethasone suppression,[40,51] and plasma ACTH levels. Urinary 17-ketosteroids were also measured. The absence of a normal diurnal variation in the plasma cortisol level was considered highly suggestive of Cushing's syndrome.[12,41] A normal or low plasma ACTH level in the presence of elevated plasma and urinary cortisol levels suggested a functioning tumor of the adrenal cortex, and failure of suppression of plasma and urinary 17-OHCS levels by dexamethasone suggested the presence of an adrenocortical tumor or of an ectopic ACTH secreting tumor such as oat cell carcinoma of the lung. Failure to suppress an elevated plasma ACTH level with dexamethasone 2.0 mg q. six hours for 48 hours was considered to suggest the presence of an extrapituitary ACTH secreting tumor and appropriate investigations were instituted. In some patients metyrapone was used to test pituitary activity,

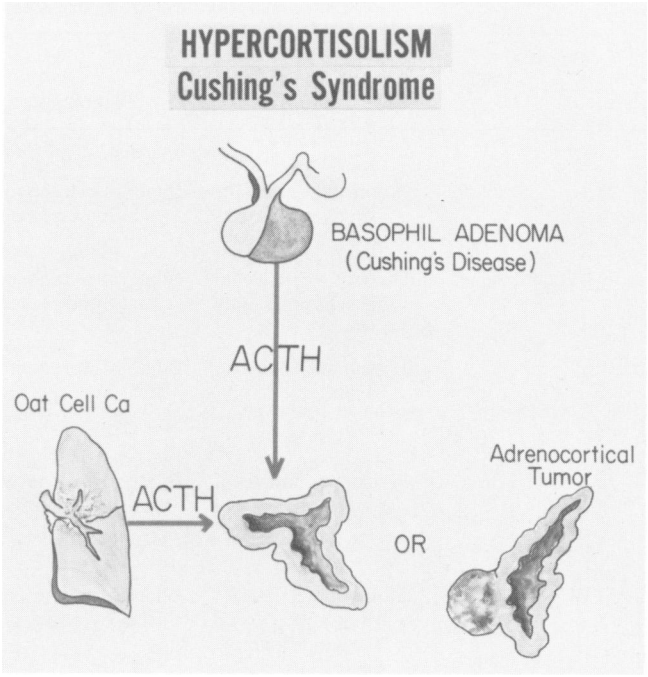


FIG. 1. Naturally occurring Cushing's syndrome may be produced by pituitary secretion of excessive amounts of ACTH (Cushing's disease), by an ectopic ACTH-producing tumor such as oat cell carcinoma of the lung, or by functioning adrenocortical tumor. Increasingly, it appears that most patients with Cushing's disease harbor a basophil adenoma of the pituitary gland.

in distinguishing between pituitary-dependent Cushing's disease and autonomous adrenocortical tumor. In general, little difficulty was met in establishing the presence of hypercortisolism and Cushing's syndrome, whether due to pituitary ACTH, extrapituitary ACTH, or autonomous adrenocortical tumor with resulting suppression of pituitary ACTH.

Radiological studies included routine adrenal and pituitary plain films and tomograms, sonography, and flush and selective arteriograms. Adrenal venograms[30] plus renal vein and caval blood sampling were carried out in the occasional patient but not routinely. Insufflation of carbon dioxide into the retroperitoneal space was not used in this series.

### *Results of Surgical Treatment of Cushing's Disease*

Sixteen patients underwent adrenalectomy for Cushing's disease, a state of hypercortisolism caused by adrenocortical hyperplasia. Without exception, adrenalectomy was carried out using an upper abdominal transverse incision, with elevation of the pancreas on the left side and with downward retraction of the duodenum on the right side.

*Hospital deaths.* There were two in-hospital deaths. One patient died early in the series when the surgeon avulsed the right central adrenal vein from the inferior

TABLE 1. *Twenty-two Patients with Cushing's Syndrome (Cumulative Data)*

| Patient | Age & Sex | Major Presenting Features | Pathology | Operation & Date | Length of Follow-up (Yrs.) | Comment |
|---|---|---|---|---|---|---|
| | | | *Adrenocortical Hyperplasia–Subtotal Adrenalectomy* | | | |
| 1. M.N. | 23 F | Moon face, hirsutism, obesity, weakness | Bilateral adrenocortical hyperplasia | Bilateral subtotal adrenalectomy, 1955 | 5 | Lost to follow-up. |
| 2. E.O. | 36 F | Obesity, voice weakness, hypokalemia | Bilateral adrenocortical hyperplasia | Subtotal adrenalectomy, 1959 | 19 | Recurrent Cushing's. Completion adrenalectomy 1962. Now well. |
| 3. B.M. | 33 F | Hirsutism, obesity, weakness | Bilateral adrenocortical hyperplasia | Subtotal adrenalectomy, 1961 Hypophysectomy, 1976 | 17 | Had pituitary irradiation before adrenalectomy. Nelson's syndrome, 1976. Now well. |
| 4. J.G. | 35 F | Weakness, hirsutism, striae | Bilateral adrenocortical hyperplasia | Subtotal adrenalectomy, 1962 | 24 hrs. | Pituitary irradiation before adrenalectomy. Died postoperative hemorrhage. |
| 5. D.W. | 18 F | Moon face, striae, hirsutism, voice change, amenorrhea | Bilateral adrenocortical hyperplasia | Subtotal adrenalectomy, 1962 | 16 | Now well but some depression. |
| 6. R.C. | 47 F | Obesity, ecchymoses, malaise | Bilateral adrenocortical hyperplasia | Subtotal adrenalectomy, 1962 | 3 months | Died at home. No autopsy. (M.I.?) |
| 7. B.M.P. | 35 F | Hypertension, weakness, obesity, moon face | Bilateral adrenocortical hyperplasia | Right adrenalectomy in California, 1970. Left adrenalectomy, 1971 | 1 | Recurrent Cushing's after unilateral adrenalectomy. Lost to follow-up at present. |
| 8. S.G. | 44 M | Ecchymoses, obesity | Bilateral adrenocortical hyperplasia | Total adrenalectomy, 1966 | 12 | Now well, on cortisone acetate. |
| | | | *Total Adrenalectomy—Adrenal Autotransplantation* | | | |
| 9. P.D. | 48 F | Easy bruisability, moon face, hypertension, weakness | Bilateral adrenocortical hyperplasia | Total adrenalectomy Adrenal autotransplantation, 1962 | 16 | Now well. Low dose cortisone replacement. Biopsy transplant positive. |
| 10. L.J. | 18 F | Hirsutism, obesity, amenorrhea | Adrenocortical hyperplasia | Total adrenalectomy with adrenal autotransplantation, 1963 | 15 | Now well. Low dose cortisone replacement. Biopsy transplant, minimal survival. |
| 11. M.He. | 38 F | Hirsutism, obesity, ecchymoses, weakness | Adrenocortical hyperplasia | Total adrenalectomy with adrenal autotransplantation, 1963 | 13 | Stable endocrine replacement. Vasculitis. Biopsy, minimal survival transplant. |
| 12. M.Ha. | 16 F | Hirsutism, striae, obesity, pigmentation, amenorrhea | Adrenocortical hyperplasia | Total adrenalectomy with adrenal autotransplantation, 1963 | 12 | Stopped all steroid replacement. Normal 17-OHCS values. Died abruptly (see text). Good transplant survival. |
| 13. S.S. | 44 F | Hirsutism, obesity, diabetes, hypertension | Adrenocortical hyperplasia | Total adrenalectomy with adrenal autotransplantation, 1968 | 13 | Stopped replacement for 2 months. Now on 5 mg cortisone per day. Is well. No transplant biopsy yet. |
| 14. S.F. | 32 F | Obesity, weakness, depression, easy bruisability | Adrenocortical hyperplasia | Total adrenalectomy with adrenal autotransplantation, 1970 | 8 | Recurrent Cushing's syndrome from transplants (1977). Excised with regression. |
| 15. V.D. | 16 M | Obesity, striae, weakness, hypertension | Adrenocortical hyperplasia | Total adrenalectomy with adrenal autotransplantation, 1975 | 3 | Now well. Transplant biopsy positive. Low dose steroid therapy. |

TABLE 1. (*Continued*)

| Patient | Age & Sex | Major Presenting Features | Pathology | Operation & Date | Length of Follow-up (Yrs.) | Comment |
|---|---|---|---|---|---|---|
| 16. J.S. | 27 M | Weakness, hypertension | Adrenocortical hyperplasia | Total adrenalectomy with adrenal autotransplantation, 1976 | 2 | Well on steroid replacement therapy. Transplant biopsy positive. |
| | | | *Adrenocortical Adenoma—Excised* | | | |
| 17. L.H. | 29 F | Striae, obesity, depression, weakness, high blood pressure | Right cortical adenoma | Excision adenoma, 1962 | 2 | Cushing's syndrome cured. Progressive renal failure. Died in 1964 of uremia. Left adrenal did not recover. Emotional disturbance. |
| 18. M.H. | 8 F | Obesity, polyuria, hirsutism, acne | Right cortical adenoma | Excision adenoma, 1964 | 14 | Cushing's syndrome cured. Emotional problems. |
| 19. J.P. | 31 F | Obesity, hirsutism, amenorrhea, depression, acne | Right cortical adenoma | Excision adenoma, 1965 | 13 | Mild emotional problems. Otherwise well. No steroid therapy. |
| 20. P.S. | 42 F | Profound Cushing's syndrome | Right cortical adenoma | Adrenalectomy | 3 weeks | Died. Respiratory failure and sepsis. |
| | | | *Adrenocortical Carcinoma—Incompletely Excised* | | | |
| 21. J.H. | 58 M | Obesity, weakness, osteoporosis, depression | Huge right adrenal carcinoma with liver metastases | Liver biopsy, 1956 | 1 month | Died of carcinoma. |
| 22. R.W. | 31 M | Mild Cushing's syndrome Hypercortisolism | Huge left adrenal carcinoma with liver metastases | Resection 1700 g left adrenal mass | 9 months | Died of carcinoma. DDD no help. |

vena cava, lost a great deal of blood, and the patient developed anuria and metabolic acidosis postoperatively with ultimate death. The other fatality occurred three weeks after operation in a woman with profound Cushing's disease of years standing due to a right adrenal adenoma. She developed postoperative respiratory insufficiency secondary in part to severe muscle wasting and debility, aggravated by pulmonary and intra-abdominal sepsis. The use of the posterior operative approach in this patient might have diminished the early postoperative respiratory insufficiency and might also have avoided the intra-abdominal infection which contributed to her death.

Of the remaining 14 such patients, one (R.C.) died unexpectedly at home in a distant town several months after operation and autopsy was not performed. Another patient (M.Ha.) died quite abruptly at home 12 years following adrenalectomy, and no special autopsy findings were reported by the coroner to explain the sudden death, though she was taking a tranquilizer medication known to cause cardiac arrhythmia in rare instances. The other 12 patients remain alive, though several have some degree of psychiatric disturbance and four increased pigmentation. One patient (B.M.) developed a large chromophobe adenoma of the pituitary (Nelson's syndrome, Fig. 2) with acute onset blindness 15 years after subtotal adrenalectomy; hypophysectomy permitted substantial visual recovery.

*Subtotal adrenalectomy for adrenocortical hyperplasia.* In the first eight patients with adrenocortical hyperplasia a subtotal adrenalectomy was performed, usually all the right adrenal being removed and leaving only a nubbin of the left adrenal drained by the left central adrenal vein. One patient is dead (R.C.), one developed recurrent Cushing's syndrome and underwent completion total adrenalectomy, one ultimately developed Nelson's syndrome (B.M.), one is well (P.D.), one patient had the operative death (J.G.), and three patients are well but have psychiatric problems.

*Total adrenalectomy.* Beginning in 1962, we began performing total intra-abdominal adrenalectomy in Cushing's disease, with autotransplantation of adrenal tissue into the thigh.[24] In our opinion, subtotal adrenalectomy should probably be abandoned.

*Other modalities.* Pituitary irradiation was employed as initial treatment in three patients in whom adrenalectomy was ultimately required. However, pituitary irradiation was employed uncommonly in our series. The only patient in our series who received DDD ther-

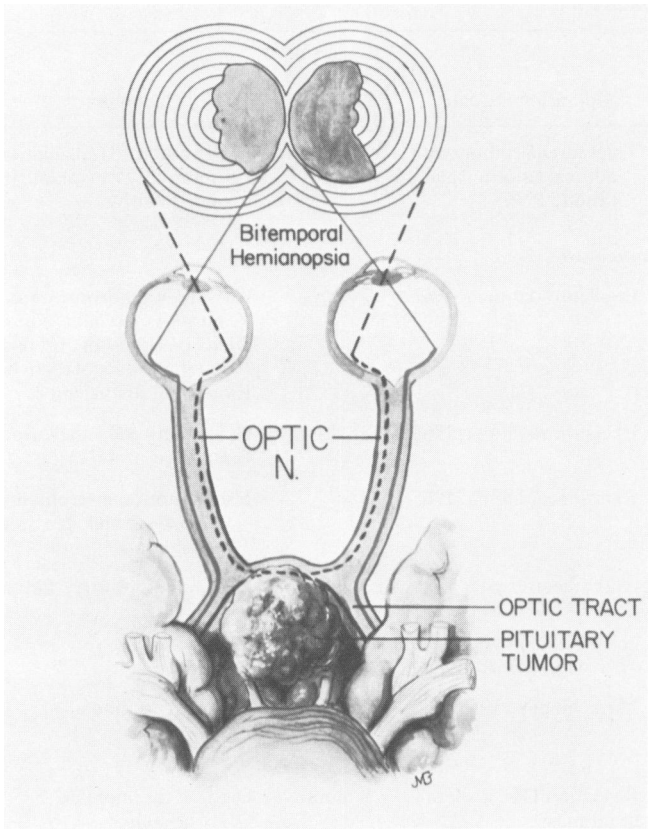


FIG. 2. Nelson's syndrome. This syndrome, long recognized, consists of the development of a chromophobe adenoma of the pituitary following adrenalectomy, often associated with increased skin pigmentation and optic nerve compression causing visual field defects.

apy was one who had liver metastases from a left adrenocortical carcinoma, and he died without improvement. Aminoglutethimide, a drug which blocks the production of cortisol, was quite useful in a patient with an incurable ACTH producing oat cell carcinoma of the lung. A severe Cushing's syndrome was reversed.

## Adrenal Autotransplantation

### *Background*

On October 26, 1962, patient P.D. (Table 1) underwent bilateral intra-abdominal adrenalectomy, and the left adrenal gland was transplanted to the right thigh with the gland's central vein being anastomosed to the distal end of the divided saphenous vein (Fig. 3). This procedure had been suggested by the need to reoperate on patient E.O. that same day, for recurrent Cushing's disease derived from a nubbin of left adrenal remaining attached by its central vein to the left renal vein. The fact that the central vein was still patent in E.O., and the fact that the nubbin had "flopped down" below or caudad to the renal vein and had achieved a parasitic arterial blood supply in this position—these findings suggested that transplantation to the thigh might preserve some degree of endogenous adrenocortical activity while avoiding the need for another laparotomy if Cushing's disease should recur: the transplant could simply be "pruned" under local anesthesia. Thus it was hoped that the transplant might a) provide sufficient adrenocortical function to avoid the necessity for life-long replacement therapy; b) diminish the likelihood or the degree of excessive skin pigmentation which occurs after adrenalectomy in some patients,[57] perhaps due to excessive MSH release; and c) reduce the possibility of the development of a chromophobe adenoma[45] of the pituitary ("Nelson's syndrome") with subsequent optic nerve compression (Fig. 2) and blindness (see patient B.M.).

After this original patient, seven additional patients were studied following adrenal autotranplantation to the thigh (Table 2), all operations being performed or supervised by the writer.

### *Technique of Adrenal Autotransplantation*

In Figure 3 are shown the progressive modifications which our technique has undergone. As mentioned, the first autotransplant was to the saphenous vein, allowing the gland to lie at the level of the fossa ovalis. This transplant survived,[24] the anastomosis to the saphenous vein remained patent, and function was achieved (Table 2, Fig. 4). Thus this appeared to represent a satisfactory technique. However, in the next patient (L.J.) the vein was found at biopsy to be thrombosed, and it was clear that the fatty bed had afforded only marginal parasitic blood supply, with minimal but definite transplant survival. Therefore, it was decided to continue to take advantage of possible long term

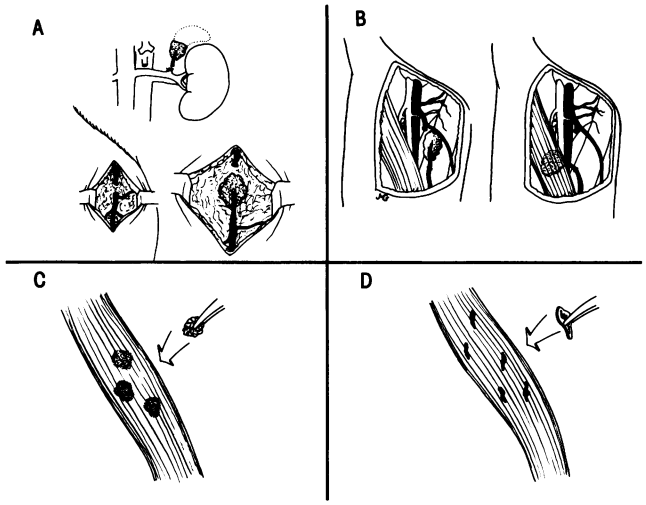


FIG. 3. Evolution of adrenal autotransplantation technique (see text).

TABLE 2. *Total Adrenalectomy with Adrenal Autotransplantation (Author's Eight Patients)*

| Patient Age/Sex | Site & Date Transplant | Technique of Transplantation | Function | Biopsy for Adrenocortical Tissue* |
|---|---|---|---|---|
| P.D. 48 F | Right thigh 1962 | Half one gland. Anastomosis to saphenous vein. | Yes. ACTH response positive. | Viable tissue. |
| L.J. 18 F | Right thigh 1963 | Half one gland. Anastomosis to saphenous vein. | Limited. | Some viable tissue. |
| M.He. 38 F | Sartorius muscle 1963 | Whole gland. Anastomosis to one saphenous vein. Implanted in sartorius muscle. Multiple longitudinal incisions in gland. | Limited. | Limited number viable cells. |
| M.Ha. 16 F | Sartorius muscle 1963 | Six gram mass implanted into sartorius muscle. Multiple incisions in gland. | Excellent. Steroid therapy stopped permanently in 1972. | Excellent adrenocortical survival. |
| S.S. 44 F | Sartorius muscle 1968 | Slices of one third each gland inserted into ipsilateral sartorius muscle. | Definite. Off Rx 2 months. | Transplants not yet biopsied. |
| S.F. 32 F | Sartorius muscle 1970 | Slices of one half each adrenal implanted sartorius muscle. | Excellent. Recurrent Cushing's disease in 1977. | Transplant slices became "adenomas". |
| V.D. 16 M | Sartorius muscle 1975 | Small slices of one adrenal implanted sartorius muscle. | Definite but steroid Rx continued. | Viable tissue. |
| J.S. 27 M | Sartorius muscle 1976 | Small slices of one adrenal gland implanted sartorius muscle. | Definite. Off steroid replacement one month. | Viable tissue. |

* Usually, questionable adrenocortical cells found in scar tissue were further identified with electron microscopy.

patency of the venous anastomosis, but to place the gland in the adjacent sartorius muscle. Yet later on, in patient M.H., it was found at the time of transplant biopsy that the adrenal mass had survived well, despite the fact that a venous anastomosis had not been employed. Therefore, in subsequent patients the adrenal gland was simply hand-sliced and the multiple slices were inserted into pockets prepared in the sartorius muscle. The site of each insertion was marked with a black silk suture cut long for ready visualization at the time of subsequent biopsy. The basic technique has not since been altered, though progressively thinner slices have been used. It is advisable to mark the site of each implant with a silver clip, in case recurrent Cushing's syndrome develops and the implants have to be excised.

### *Results of Adrenal Autotransplantation*

The degree of transplant survival and the functional activity achieved in the eight patients who underwent adrenal autotransplantation (Table 2) ranged from minimal survival and minimal activity to recurrent Cushing's syndrome due to marked enlargement of virtually all the adrenal slices implanted into the sartorius muscle in patient S.F. (Fig. 5). However, at least some adrenocortical cells survived in all seven patients biopsied thus far. The transplant in the eighth patient has not yet been biopsied, but she stopped all steroid replacement therapy for two months, before hyponatremia required reinstitution of the 5 mg of cortisone per day. Since there was such a wide variation in the results achieved in the eight subjects, each patient will be presented briefly.

## Case Reports

**Case 1.** Patient P.D., 48-year-old white woman. The patient underwent bilateral total intra-abdominal adrenalectomy on October 26. 1962 for Cushing's disease, a particular feature of which was easy bruisability and very slow healing of minor injuries leaving unsightly scars over a period of almost ten years. ACTH stimulation caused the urinary excretion of 17-OHCS to rise from a resting value of 8 μg% to 400 μg% the first day and 1,000 μg the second day, a truly remarkable reactivity. Initial pituitary irradiation failed to control the disease satisfactorily. At operation a nubbin of the left adrenal surrounding the left central adrenal vein was transplanted and anastomosed to the distal end of the divided saphenous vein (Fig. 3). Several black silk sutures were used to hold the adrenal tissue in place to prevent torsion.

Function of the autotransplant was assessed two months later in early January, 1963. An ACTH infusion produced a progressive rise from the resting plasma 17-OHCS level of 1.57 to 4.76 μg% over the course of four hours.[24] Two weeks later she was taken off steroid replacement for three days, during which the plasma 17-OHCS levels ranged at approximately 1 μg% (normal 7–25 μg%). Although neither adrenocortical crisis nor significant changes in the plasma Na, Cl, K, $CO_2$ combining power, or fasting blood sugar or BUN levels occurred, it was clear that the function of the adrenal transplant was not sufficient to permit the patient to return

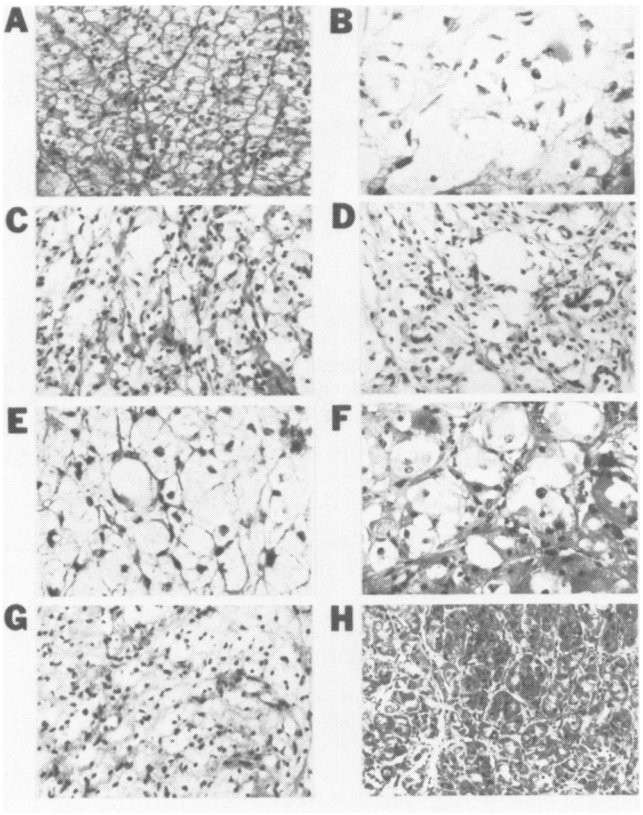


FIG. 4. Adrenal autotransplants, photomicrographs (see Table 1, patients 9 through 16 and Table 2). *A*. Microscopic appearance of excised adrenal glands for patient 14 (S. F.) who had adrenocortical hyperplasia, for comparison with the seven photomicrographs of adrenal autotransplants in seven patients (our eighth such patient has not yet been biopsied). *B*. Patient 9 (P. D.). The transplanted and biopsied tissue exhibited the normal yellowish adrenal color. *C*. Patient 10 (L. J.). Limited but definite transplant survival. *D*. Patient 11 (M. He.). Limited but definite survival of adrenocortical cells. *E*. Patient 12 (M. Ha.). Excellent transplant survival. Eventually stopped all steroid replacement therapy. *F*. Patient 13 (J. S.), definite transplant survival, with no steroid dosage for one month. *G*. Patient 15 (V. D.). Definite but limited transplant survival. *H*. Patient 14 (S. F.). Recurrent Cushing's syndrome, transplants excised with reversal (see also Fig. 5, from one of which "adenomas" this photomicrograph was made).

to her distant home without steroid replacement therapy, and such treatment was resumed.

*Biopsy* of the transplant on January 2, 1963 under local anesthesia disclosed that the adrenal tissue was grossly viable and the saphenous vein anastomosis still patent. The microscopic report stated "subcapsular portion of adrenal appears viable while central portion is necrotic. No medullary tissue present." As seen in Figure 4, adrenocortical tissue was readily recognizable.

Her *subsequent course* has been satisfactory on low dose replacement therapy. She has not been restudied in recent years for reassessment of function of the transplant. She underwent resection of an abdominal aortic aneurysm in another city in 1977, but otherwise she has been in good health and good spirits as found on recent interview.

## *Comment*

This, our initial adrenal autotransplant, was considered to have been sufficiently successful to justify further exploration of the procedure. Meanwhile, we had found two reports of adrenocortical autotransplantation in the foreign literature.[15,28]

**Case 2.** Patient L.J., 18-year-old white woman. On January 19, 1963 this girl underwent total intra-abdominal adrenalectomy with transplantation of the entire left adrenal to the sartorius muscle, using the saphenous vein anastomosis (Fig. 3). The usual timed adrenal vein blood samples were drawn for comparison with those from the antecubital vein, prior to ligation and division of the central adrenal vein.

*Function* of the transplant two months later appeared minimal and she was unable to remain entirely off replacement therapy.

*Biopsy* performed under local anesthesia on March 15, 1963 revealed that the gland had retained its usual shape and color, and it bled on incision for biopsy. The central vein and saphenous vein were thrombosed. The microscopy disclosed adrenal tissue showing coagulative necrosis and connective tissue. However, viable adrenocortical cells were present (Fig. 4).

Her *subsequent course* has not been remarkable from a purely endocrine standpoint but, possibly related to the Cushing's disease spectrum, she has continued to have considerable emotional imbalance without frank psychosis.

## *Comment*

The transplanted gland lay in fat and the venous drainage was thrombosed. It was concluded that patency of the venous anastomosis was not essential for at least partial survival of the transplant and that, since fat probably afforded little opportunity for the prompt development of a parasitic blood supply, an intramuscular position might be preferable.

**Case 3.** Patient M.Ha., 16-year-old white girl. (Cushing's Disease, Pseudotumor Cerebri, Hyperparathyroidism, and Large Gastric Ulcer). This remarkable patient was first admitted to University Hospital for acute onset of florid Cushing's disease with truly grotesque physical changes. She presently developed *pseudotumor cerebri* while under diagnostic study, with severely increased intracranial pressure and coma,[32] and required tracheostomy with mechanical ventilatory assistance for several days. Following recovery from the pseudotumor cerebri, she underwent on June 4, 1963 an uneventful intra-abdominal adrenalectomy with transplantation of a several gram portion of each adrenal to the sartorius muscle of the corresponding thigh. Both of her saphenous veins were thrombosed, due to venipunctures during her comatose period. The adrenal gland transplants were incised longitudinally at multiple sites, hopefully to permit better ingress of nutritious fluids and new blood vessels.

*Function* did not appear significant when assessed at four months. However, later on she took her replacement therapy rather irregularly and by 1972, nine years after transplantation, she had stopped her replacement therapy completely, on her own initiative. On July 21, 1972, the plasma 17-OHCS level was low, being 3.1 $\mu$g%, but on March 5, 1975 the plasma 17-OHCS level was 19.5 $\mu$g% (normal, 7–25 $\mu$g%).

*Biopsy* was performed on October 14, 1963, using the same anesthesia employed to perform *cystogastrostomy to drain a large pancreatic pseudocyst*. The transplant in each thigh exhibited the vivid yellow color of adrenal tissue and thus appeared viable. Microscopy revealed "adrenal tissue with focal areas of necrosis but approximately two-thirds appears viable" (Fig. 4).

Her *subsequent course* was complicated by hyperparathyroidism caused by hyperplastic enlargement of all four glands. At operation on October 12, 1972, all of three glands and part of the fourth were removed, returning the serum calcium level to normal.

In May, 1974 the patient was found to have a large *antral ulcer*,

with normal serum gastrin and gastric acid levels. When no improvement was achieved in three months on a medical regimen, bilateral truncal vagotomy and distal subtotal Billroth I gastrectomy was performed on August 13, 1974.

Following this she continued in tenuous emotional balance, with occasional minor seizures but otherwise in usual health. Unfortunately, in 1975 at age 28 she, abruptly, died at home. Her husband said she had been quite normal that evening and that death came without warning. The coroner concluded that sudden cardiac arrhythmia was the probable cause of death, possibly due to a tranquilizing drug known to produce cardiac arrhythmia in rare instances.

*Comment*

This patient represented an unusual instance of Cushing's disease and later hyperparathyroidism due to hyperplasia. The etiology of her large gastric ulcer was not determined. The rapid onset of Cushing's syndrome, followed by pseudotumor cerebri and coma with apnea, left her with mental and emotional changes which she exhibited in varying degrees for the rest of her life. However, she came originally from a broken home and a severe emotional environment, which encouraged speculation regarding the role of psychic stress in the development of Cushing's disease.[18]

It should be noted that the adrenal implants in the thighs gradually increased their functional activity over the course of the 12 years she was followed. It will be seen below that a patient who developed recurrent Cushing's syndrome from the adrenal autotransplants did so not until seven years after the transplantation.

**Case 4.** M.He., 38-year-old white woman. This patient was originally studied for hirsutism, obesity and multiple chronic and recurring staphylococcal infections, especially involving the glands of the axillae. It was established that she had Cushing's disease, most likely caused by adrenocortical hyperplasia. At total intra-abdominal adrenalectomy on September 7, 1963, approximately one-half of each adrenal gland was incised longitudinally at several sites and transplanted into a pocket in the sartorius muscle on the corresponding side. Early replacement therapy included hydrocortisone and cortisone, plus injections of ACTH gel as used in all these patients for maximum stimulation of the transplants.

*Function* was judged to be very low when assessed three months posttransplantation, and the patient was not able to discontinue replacement therapy.

*Biopsy* performed on December 29, 1963 revealed grossly viable yellowish adrenal tissue. However, both transplants had retracted almost out of the muscle and lay largely in fat. The microscopic picture was one of extensive necrosis and scar tissue formation, but with definitely viable adrenal tissue (Fig. 4).

Her *subsequent course* is not fully available, in that she moved away to a distant city. However, in 1976 we received a copy of a discharge letter following her treatment in the University of Iowa Hospital. At that time she appeared to have a vasculitis and was taking cortisone and Florinef. Clearly, she has continued to have various problems since her adrenalectomy for Cushing's disease.

*Comment*

This patient achieved partial though very limited survival of the transplants. Inasmuch as we have seen that years may be required for the transplants to achieve strong functional activity, the ultimate outcome of the transplants is not known at this time.

**Case 5.** S.S., 44-year-old white woman. On January 2, 1968 this patient underwent bilateral intra-abdominal adrenalectomy with transplantation of one-third to one-half of each gland to the corresponding sartorius muscle, using multiple hand slices inserted into prepared pockets which were closed with black sutures, left long for ready identification at the time of biopsy.

*Function* was evaluated at six months, at which time the plasma 17-OHCS level was found "not measurable."

*Biopsy* was not done. The endocrinologist had decided, unilaterally, that the function was so low that biopsy was not indicated, though the patient had been admitted to the clinical research center for this specific purpose. Had this writer been aware of the admission, he would have been able to assure the endocrinologist that biopsy, under local anesthesia as usual, was indicated, since viable adrenal tissue had thus far been found in all patients despite very low function in some. Unquestionably, viable tissue was present, as demonstrated by late progress as described below.

Her *subsequent course* was uneventful but notable in that in 1974 she was seen in follow-up clinic and judged "probably has mild recurrence. Will have patient stop her cortisone and will follow. Perhaps later, surgery or (pituitary) irradiation." The plasma 17-OHCS level on April 19, 1974 was 15.8 μg at 0800 hours (recall that it had been too low to measure six years earlier).

Actually, the patient did not have a recurrence at that time. Cortisone was stopped but after two months on no replacement therapy she became weak and hyponatremic, and replacement therapy was restarted. Cortisone in a maintenance dose of from 5 to 10 mg/24 hours has generally sufficed. She is well.

*Comment*

Here again, this patient achieved significant function of the transplant only after a period of years. We plan to readmit her for biopsy.

**Case 6.** S.F., 32-year-old white woman. (Recurrent Cushing's Syndrome from Adrenal Autotransplantation). On July 30, 1970 this patient underwent total intra-abdominal adrenalectomy with transplantation of adrenal slices into the left sartorius muscle. Her postoperative course was uneventful.

*Function* was not formally assessed until seven years later when she developed recurrent Cushing's syndrome. However, on July 28, 1977 the plasma 17-OHCS level was 23 μg% (normal, 7–25) and the plasma ACTH level 733 pg/ml (normal 0–100). Prior to biopsy, a dexamethasone suppression test was performed and the plasma 17-OHCS level fell progressively from 24 μg% the first day to 1.2 μg% the third day.

*Biopsy* performed on August 23, 1977 revealed hyperplasia of all eight adrenal implants that were found and excised. Actually, the implants resembled rounded adenomas of various sizes (Fig. 5) and had taken on a darkly pigmented color. The microscopic picture was reported "nodules of hyperplastic adrenocortical tissue" (Fig. 5). The overall weight of the excised adrenal tissue was 4.23 g. The plasma 17-OHCS level fell to 10 μg% postoperatively, this level suggesting that not all the implants had been found and excised.

*Steroid analyses of the biopsy tissue* revealed substantial amounts of cortisol and aldosterone, though the quantitation was inexact. Similar biochemical data were reported by others.[20]

Her *subsequent course* was one of prompt regression of the physical features of the Cushing's syndrome. However, more recently she has again gained weight. If Cushing's syndrome recurs, general anesthesia will be employed and the sartorius muscle will be excised to the extent necessary to remove all transplants.

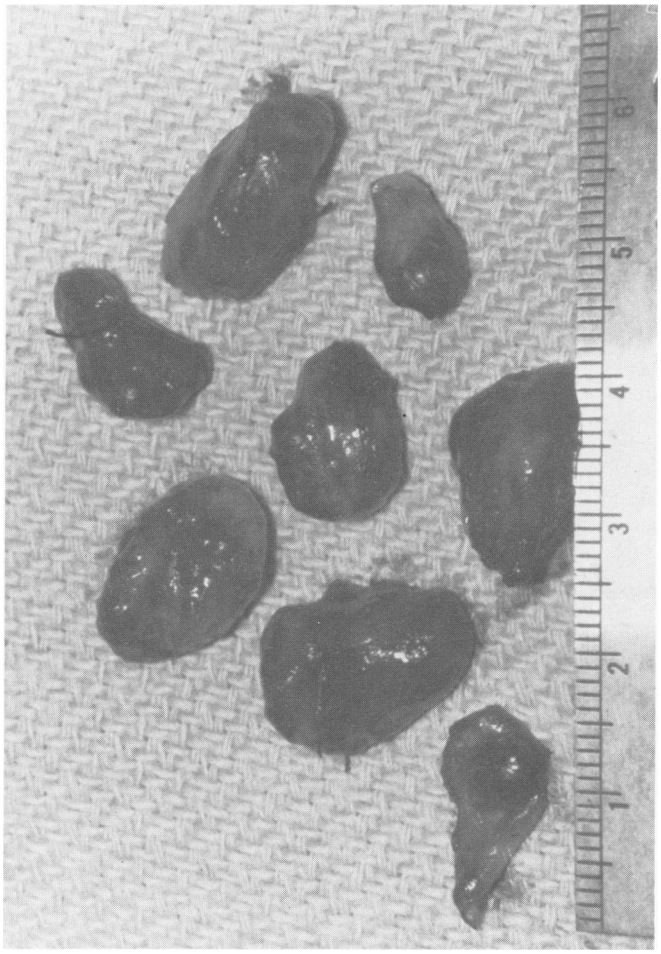

FIG. 5. Marked hyperplastic enlargement of slices of adrenal tissue transplanted to sartorius muscle (patient 14, S. F.). These "adenomas" had produced recurrent Cushing's syndrome, which was reversed by their excision (see microscopic picture, Figure 4-H). Such transplant enlargement producing recurrent Cushing's syndrome has also been reported by others.[1,39]

*Comment*

This patient was the only one of our adrenal transplant subjects to develop recurrent Cushing's disease thus far, this seven years following transplantation. Two other such instances have been reported by others.[11,39] Our patient underscored what we had already found, namely, that the adrenal transplants may take years to achieve vigorous functional activity. She has developed somewhat more skin pigmentation.

On the negative side, we clearly failed to find some of the hyperplastic implants, under the local anesthesia, and another operation may later be required. Meanwhile, she is concerned and desires that the problem of Cushing's syndrome be cured with certainty to permit orderly steroid replacement theory. Like many patients with Cushing's syndrome, she has always exhibited a considerable "functional overlay," regardless of the degree of adrenocortical activity existing at the time.

**Case 7.** V.D., 16-year-old black man. This high school football player developed obesity and marked striae which led to the diagnosis of Cushing's disease. On June 18, 1975 a total intra-abdominal adrenalectomy was performed and slices of adrenal were inserted into prepared pockets in the right sartorius muscle. The postoperative course was uneventful, hydrocortisone, cortisone and ACTH gel being administered.

*Function* at the time of biopsy was judged minimal, the plasma ACTH level being markedly elevated.

*Biopsy* under local anesthesia on November 26, 1975 revealed grossly viable adrenal tissue. Light microscopy confirmed the presence of viable adrenal tissue (Fig. 4), further supported by electron microscopy. However, there was also necrosis and extensive fibrosis.

His *subsequent course* has been satisfactory on replacement therapy. The steroid supplements have been regulated on the basis of the plasma ACTH and plasma 17-OHCS levels.

*Comment*

This boy has viable adrenal tissue in the multiple implants, and the activity of this tissue may be expected to increase in the future.

**Case 8.** J.S., 27-year-old white man. Bilateral adrenalectomy for Cushing's disease was performed on March 3, 1976, at which time multiple small pieces of adrenal tissue, 0.5–1.0 cm in size, were inserted at multiple sites in the right sartorius muscle. On April 19, 1976 cystogastrostomy was performed for a large pancreatic pseudocyst.

*Function* was assessed in January, 1978, *at which time the patient had taken no medication for one month.* However, despite his ability to survive the month without replacement therapy, done on his own initiative, he appeared definitely ill when admitted for biopsy on January 12, 1978. At this time he exhibited a marked increase in skin pigmentation as compared with photographs made preoperatively. The role of adrenocortical insufficiency in the development of his increased skin pigmentation is problematical. The sella turcica did not exhibit erosion and there were no visual defects. Nonetheless, the possibility of a pituitary tumor is not considered to have been completely excluded and careful follow-up is being conducted.

*Biopsy* on January 12, 1978 revealed viable adrenal tissue. Two of the implants were removed and microscopy revealed a "limited number of adrenocortical cells. Organizing fat necrosis and scar tissue with dystrophic calcification."

His *subsequent course* has been one of marked improvement in overall health, with adequate steroid replacement therapy.

*Comment*

Clearly, the adrenal transplants are functioning approximately two years following their insertion into the sartorius muscle. As with the other patients, only time will determine the degree of function which the transplants will achieve.

He was the only patient transplanted who developed such marked skin pigmentation, possibly due in part to the relative adrenocortical insufficiency. However, patient B.M., who had subtotal adrenalectomy without transplantation, exhibited substantial pigmentation

at the time she returned with acute onset blindness due to pituitary tumor 15 years after adrenalectomy (Nelson's syndrome). Her vision improved following hypophysectomy, but it is too early to know the extent to which the increased skin pigmentation will recede. Patient S.F., who developed recurrent Cushing's syndrome from the autotransplants, also exhibited some increase in skin pigmentation, though she herself was not particularly aware of it.

## Discussion

The diagnosis and management of Cushing's syndrome has been characterized by multiple advances over the past decade.

### *Diagnosis*

The detection of Cushing's syndrome usually begins with the recognition of the physical findings suggestive of this condition, though occasionally abnormal routine plasma chemistry values may lead to definitive endocrine laboratory investigations. Unfortunately, the full-blown physical changes which almost any physician would recognize may appear late or never in the course of the disease. Therefore, it is important to recognize the less florid or incomplete syndromes, such as easy bruisability or increasing obesity with hirsutism and menstrual irregularities, before profound osteoporosis with vertebral collapse and other pathologic changes have occurred. Incidentally, psychiatric derangements were among the earliest manifestations in some of our patients, and these persisted in a few subjects even after abolition of the hypercortisolism.

The hormonal laboratory tests provide the definitive data required for the diagnosis of Cushing's syndrome. Once the condition has been suspected on the basis of physical findings, the usually elevated plasma and urinary 17-hydroxycorticosteroids (17-OHCS) and urinary 17-ketosteroids, the absence of the normal diurnal variation in the secretion of 17-OHCS, the 17-OHCS response to ACTH stimulation and the response of 17-OHCS and growth hormone secretion to induced hypoglycemia[16,29] will further secure the diagnosis. The patient with pituitary dependent adrenocortical hyperplasia will usually exhibit a decline in plasma ACTH and 17-OHCS secretion when dexamethasone 2.0 mg per six hours is administered for two days. However, if the ACTH dependent hypercortisolism is due to an ectopic (extrapituitary) source of ACTH, as from an oat cell carcinoma of the lung, the administration of dexamethasone will have little or no effect on the plasma level of ACTH or the plasma and urine levels of 17-OHCS—this because the pituitary gland is not causing the hypersecretion of cortisol. Finally, if the hypercortisolism is due to an autonomous adrenocortical tumor, the plasma ACTH level will usually be low, and the levels of 17-OHCS in the plasma and the urine will not decline even when dexamethasone is administered in large doses. However, dexamethasone may produce some reduction in cortisol secretion in the occasional patient with cortical adenoma.

Body composition studies[25] may be suggestive but are not diagnostic. The radiological studies available have also been extended and rendered more precise. This is especially true of arteriography and tomography of both the pituitary and the adrenals. Microadenomata of the pituitary are being found with impressive frequency in patients with Cushing's syndrome due to adenocortical hyperplasia, largely through the use of arteriogram magnification and subtraction as well as increasingly discriminating pituitary tomography.[33,54] However, Wilson et al.[44] consider arteriography perhaps less indicated than transphenoidal exploration of the pituitary gland, especially since they believe that virtually all patients with Cushing's disease harbor a pituitary adenoma for which the pituitary should be surgically explored in most instances. The adrenal glands can also be outlined by angiography and tomography, and blood samples can be obtained by catheter from each renal vein or even the central adrenal vein for steroid analyses.

### *Treatment*

*Adrenocortical tumors.* The treatment of Cushing's syndrome depends upon the specific set of circumstances encountered. If the hypercortisolism is due to adrenocortical tumor,[54] the tumor is excised when possible or otherwise treated by radiation and/or with the drug DDD which attacks the zona fasciculata (cortisol) and zona reticularis (androgens and estrogens) while preserving the zona glomerulosa (aldosterone) to a considerable degree.[2,31,58] If an ectopic ACTH secreting tumor cannot be removed or destroyed by irradiation, the effects of the very high levels of ACTH in increasing cortisol production may be blocked by administration of drugs, such as aminoglutethimide which blocks the conversion of cholesterol to pregnenolone, reducing the production of cortisol; thus the Cushing's syndrome may be abolished even though the plasma ACTH level may remain very high and the adrenals intact.

### *Modalities for Management of Cushing's Syndrome Due to Adrenocortical Hyperplasia (Cushing's Disease)*

*Pituitary irradiation.*[4,38] Inasmuch as the release by the pituitary of excessive amounts of ACTH is the precipitating cause of Cushing's disease, due to adre-

nocortical hyperplasia, irradiation of the pituitary gland[4,50] has long appeared to represent an attractive mode of therapy. Unfortunately, this modality is often unsuccessful in effecting a remission, though in approximately one-fourth to one-half the patients the hypercortisolism will be controlled.

More recently, external irradiation[11] has given way to internal irradiation in some centers. Whereas only approximately 4,000–5,000 rads have usually been given from external sources, up to 12,000 rads may be given by alpha particle irradiation.[5]

The disadvantages of irradiation include uncertain control of the hypercortisolism, late recurrence in some patients temporarily improved, interference with the secretion of growth hormone and normal development in young people, and impairment of prolactin secretion in young women who may want to have children. Therefore, pituitary irradiation is perhaps best reserved for older patients and in special circumstances such as recurrence in patients who have had subtotal adrenalectomy. Pituitary irradiation has at times been used in conjunction with adrenalectomy to prevent the late development of Nelson's syndrome, but irradiation has not always been successful in this respect (see patient B.M.).

*Adrenalectomy.* In most medical centers a subtotal or now usually a total adrenalectomy currently represents the treatment most often used for the definitive management of Cushing's disease.[19,55] This effectively abolishes the hypercortisolism permanently, provided no adrenal tissue is left in the abdomen.

The disadvantages of total adrenalectomy include the need for a fairly extensive operation, permanent dependence on steroid replacement unless adrenal autotransplantation is elected, development of excessive pigmentation in some patients, and late development of a chromophobe tumor of the pituitary which may impair vision and even become malignant. Moreover, the anterior approach to adrenalectomy may result in pancreatitis and/or intra-abdominal infection in the occasional patient, while the posterior approach limits exposure. Postoperative adrenocortical crisis is no longer a problem so long as adequate steroid replacement therapy is administered.

*Pituitary surgery.* Since[37] in Cushing's disease the pituitary is the source of the excessive ACTH which stimulates the adrenal cortices to hypersecretion, the idea that initial surgical attack should be directed to the pituitary has logic and appeal. Cushing early described the pituitary basophil adenoma as the cause of Cushing's disease,[7] and the suspicion has always persisted that many patients with Cushing's disease harbor a basophil adenoma.[21,22,43,52]

Recently, with improved methods of diagnosis and surgical approach to the pituitary, it has become clear that basophilic microadenomas of the pituitary are indeed present in many if not most patients with Cushing's disease. Salassa et al.[54] at the Mayo Clinic found evidence of a pituitary microadenoma in 18 of 22 patients appropriately investigated and then explored, over a period of three years. In 17 the tumor was found and excised, with abolition of the hypercortisolism in 16. These tumors, less than 10 mm in diameter, were detected preoperatively by triaxial spiral tomograms of the sella turcica and by bilateral carotid arteriograms with magnification and subtraction techniques. As for the two patients in whom preoperative studies indicated the presence of a pituitary microadenoma but in whom hypercortisolism was not abolished, one patient died later of other causes and no pituitary tumor was found at autopsy; a pituitary tumor was found and removed in the other patient but the hypercortisolism persisted. Otherwise, in the 16 patients successfully treated, the secretion of cortisol initially became subnormal immediately after removal of the microadenoma of the pituitary but then gradually returned to normal over subsequent weeks or months. Steroid replacement therapy was administered as required. The transient hypocorticism suggested that the excessive ACTH from the tumor might have suppressed the rest of the anterior pituitary, though an effect of trauma to the pituitary is not excluded. There were no significant persisting complications of the pituitary surgery. Similarly, Wilson and Dempsey[60] explored 20 of 23 patients with Cushing's disease, also using the transphenoidal approach. In two patients large dural sinuses prevented exploration of the pituitary fossa and in a third the cryoprobe was simply applied to the anterior lobe because of such vascular structures. In still another patient the 1.5 mm basophilic adenoma was found only after total hypophysectomy and sectioning of the gland. In the remaining 16 patients, however, a microadenoma was found and excised and the hypercortisolism was corrected. Normal pituitary function was preserved in 15 of the 16 patients. The two patients who underwent hypophysectomy, one by the cryoprobe and one by surgical excision, were cured of Cushing's disease but at the cost of panhypopituitarism. One patient committed suicide on the evening before admission to the hospital and the coroner found a 3 mm microadenoma of the pituitary. Incidentally, of 250 pituitary adenomas reported by Wilson and Dempsey, 72 (28%) were "nonsecreting" and 178 (71.2%) produced a hypersecretion syndrome: human growth hormone in 83, prolactin in 59, and adrenocorticotrophic hormone (ACTH) in 36. The experience of Wilson's group with pituitary exploration in Cushing's disease has recently been updated, with even

greater emphasis on the usual presence of a pituitary basophil adenoma as the cause of the disease.[59]

*Nelson's syndrome.* In contrast to these early successes with pituitary surgery for Cushing's disease, the results of pituitary surgery in Nelson's syndrome[44-46,61] have been less satisfactory. The typical chromophobe tumor in Nelson's syndrome has been large and often invasive,[53,60] and total hypophysectomy may be indicated to prevent recurrence. Even when a pituitary tumor has been found and removed, the elevated plasma ACTH levels have at times either persisted or recurred.

The disadvantages of selective removal of pituitary microadenomata would appear to be minor, at present. However, first, few centers thus far possess the sophisticated techniques and experience required for the precise diagnosis and selective excision of these small pituitary tumors. Secondly, it is still too early to know whether permanent cure of Cushing's syndrome will be achieved in these patients. Pituitary hyperplasia may exist in some individuals.[17] However, the early results of pituitary surgery are certainly informative and encouraging.

*Medical adrenalectomy.* After it was found that the insecticide DDD produced selective destruction of the zona fasciculata and zona reticularis in the adrenals of dogs[31,47] while to a considerable extent sparing the zona granulosa, this drug was used by Bergenstal et al.[2] to treat adrenocortical cancer as noted previously. Of 18 patients so treated, seven exhibited a decrease in the size of the tumor and in cortisol secretion. In another seven patients the tumor remained the same size, but the rate of cortisol secretion declined. In the remaining four there was no change in either tumor size or in cortisol secretion.

Subsequently, others used DDD therapy for the treatment of Cushing's disease.[8] Temple, et al.[58] found that the hypercortisolism was abolished in four patients given 3 g of o, p' DDD per day. When the 17-OHCS became subnormal, dexamethasone was supplied in a dose of 0.5 mg daily, as a safeguard against glucocorticoid deficiency. Rates of aldosterone secretion were normal, and the patients adapted to sodium deprivation with virtually complete renal conservation of sodium. In a fifth patient the DDD was given for one month and then bilateral adrenalectomy performed. Except for hyperplasia and a deep yellow hue, the adrenal glands were normal both grossly and on light microscopy. However, electron microscopy revealed changes in the vesicular cristae of the mitochondria of the zona fasciculata, similar to those reported in the dog.[31] In contrast, in only an occasional section of the zona glomerulosa were there slight alterations in the lamellar cristae of the mitochondria.

Thus it is clear that DDD can produce a state of "eucortisolism" in human beings, but the late results of such therapy remain to be assessed by further investigation. The drug can produce important side effects, especially upon the liver.[31]

### *Adrenal Autotransplantation*

The role which adrenal autotransplantation is to play, combined with total intra-abdominal adrenalectomy, has yet to be determined. Following the initial experience of Franksson and his associates,[14,15] a number of other investigators[3,9,20,24,25,28,34,36,39,49,62] published their results. In Table 3 are presented 18 such patients that we have found in the literature, plus the eight of our own reported herein for a total of 26, and still others have been alluded to in foreign literature not readily available.[20,49] It was possible to stop all steroid replacement therapy in 16 of the 26 subjects. It is clear that some degree of "take" of the transplant may be expected in almost every patient, but with marked variations in "success" among patients, regardless of the operative technique employed. Adequate functional activity has been demonstrated in at least some patients with each of the transplant techniques whether the sartorius, pectoralis or rectus muscle was the recipient site. In general, ACTH stimulation tests have often failed to produce an increase in the secretory rate of the transplants, which have appeared to be already maximally stimulated by the endogenous ACTH. However, in the occasional patient exogenous ACTH will produce an increase in 17-OHCS secretion by the transplant.[24] Dexamethasone suppression of transplant secretion is possible, as demonstrated in our patient S.F. who had developed recurrent Cushing's syndrome from the transplants. Multiple thin slices would appear more likely to produce a greater mass of functioning tissue, but are harder to find if recurrent Cushing's syndrome develops.

While in some patients it may be possible to stop all replacement therapy after several months, other patients never achieve adequate function of the transplants and still others may develop recurrent Cushing's syndrome due to hypertrophy of the transplants after a period of years. The optimal site for intramuscular implantation and the optimal hormonal environment for transplant survival remain to be determined. In one of Franksson's patients adrenocortical insufficiency promptly followed excision of the transplant.[15] In two patients reported by others,[1,39] recurrent Cushing's syndrome due to hyperplasia of the transplants was reversed by excision or partial excision of the transplants, these clinical findings being paralleled by appropriate changes in the plasma and urinary 17-hydroxycorticosteroid values.

TABLE 3. *Adrenal Autotransplantation (Survey of Literature)*

| Author | Patient | Site of Transplant | Function of Transplant | Biopsy |
|---|---|---|---|---|
| Franksson et al.[15] (Stockholm, 1959) | (1) Female, Age 41 | Sartorius muscle | Steroid replacement stopped at 7 months. Excision of transplant precipitated acute adrenocortical insufficiency. | At 8 months. Normal adrenal tissue. |
| Franksson et al.[15] (Stockholm, 1959) | (2) Female, Age 45 | Sartorius muscle | Steroid replacement stopped at 5½ months. Then well for 2 years, until infection required replacement therapy. No response to ACTH. Increased pigmentation. | No biopsy reported. |
| Franksson et al.[15] (Stockholm, 1959) | (3) Female, Age 24 | Sartorius muscle | Tried drug withdrawal at 3 months but failed. Successful at 7 months. No response to ACTH. Increased pigmentation. | No biopsy reported. |
| Franksson et al.[15] (Stockholm, 1959) | (4) Female, Age 43 | Sartorius muscle | Transplanted at second operation, for recurrent Cushing's. Tried drug withdrawal at 4½ months but failed. Successful at 5 months. Low urinary 17-OHCS. | No biopsy reported. |
| Franksson et al.[15] (Stockholm, 1959) | (5) Female, Age 42 | Sartorius muscle | No attempt had been made at report, 4¼ months after operation. | No biopsy reported. |
| Ibbertson & O'Brien[28] (Auckland, 1962) | (6) Male, Age 39 | Sartorius muscle | At one month unable to withdraw drug therapy, or on several occasions thereafter. | No biopsy reported. |
| Ibbertson & O'Brien[28] (Auckland, 1962) | (7) Male, Age 41 | Sartorius muscle | At one month steroid therapy withdrawn for 1 week uneventfully and again later. ACTH and metapirone no effect. | No biopsy reported. |
| Ledingham et al.[39] (London, 1966) | (8) Male, Age 24 | Pectoralis muscle | No attempt to stop steroid therapy. ACTH no effect on urinary 17-OHCS or 17-KS. | Graft excised at 8 months. Nodule 1.0 × 0.5 cm, normal adrenal tissue. |
| Ledingham et al.[39] (London, 1966) | (9) Female, Age 64 | Pectoralis muscle | No attempt at steroid withdrawal. No response to ACTH. | Died of other causes. Autopsy showed viable transplants and pituitary basophil adenoma. |
| Ledingham et al.[39] (London, 1966) | (10) Female, Age 25 | Pectoralis muscle | Recurrent Cushing's syndrome at 3 years excision of hyperplastic transplant nodules. No response to ACTH. Enlarged pituitary fossa. | Nodular hyperplasia producing recurrent hypercortisolism. |
| Ledingham et al.[39] (London, 1966) | (11) Male, Age 34 | Pectoralis muscle | Replacement therapy stopped for 4 weeks at 4½ years. Then restarted. ACTH no effect. | |
| Ledingham et al.[39] (London, 1966) | (12) Female, Age 40 | Pectoralis muscle | At 2 years no ACTH. No effect on urinary 17-OHCS or 17-KS. | Not done. (Psychological instability precluded.) |
| Drucher, et al.[9] (New York, 1967) | (13) Female, Age 14 | Sartorius muscle | Transplanted at second operation, for recurrent Cushing's. Transplant secreted cortisol and aldosterone. All steroid replacement stopped permanently. | Viable adrenal tissue. |
| Bayer et al.[11] (Bonn, 1971) | (14) Age & Sex not given. | Sartorius muscle | Recurrent Cushing's syndrome at 2½ years. Reversed by excision of transplants. | Diffuse and nodular hyperplasia. |
| Kaplan and Shires[34] (Dallas, 1972) | (15) Male, Age 15 | Sartorius muscle (bilateral) | Replacement steroid therapy stopped permanently at 2½ months. Endocrine functions generally returned to normal. | No biopsy. |

TABLE 3. (*Continued*)

| Author | Patient | Site of Transplant | Function of Transplant | Biopsy |
|---|---|---|---|---|
| Zieleniewski & Stapor[62] (Lodz, 1972) | (16) Female, Age 41 | Rectus abdominis muscle | Steroid replacement stopped permanently 10 months post-transplant (performed at time of second operation for completion of adrenalectomy for recurrent Cushing's). ACTH increased urinary 17-OHCS at 6½ years post-transplant. | Not done. |
| Zieleniewski & Stapor[62] (Lodz, 1972) | (17) Female, Age 46 | Rectus abdominis muscle | Transplant performed at second operation, for completion intra-abdominal adrenalectomy. Steroid replacement stopped after 7 months. ACTH stimulus response in 17-OHCS at 18 months. | Not done. |
| Zieleniewski & Stapor[62] (Lodz, 1972) | (18) Female, Age 27 | Rectus abdominis muscle | Unable to stop steroid replacement at 6 months or at one year. | Not taken. |
| Hardy (Jackson) | -Eight patients reported herein | | | |
| Total patients | 26 | Transplant survived in 22. Patient off replacement therapy in 16, possibly in others. | | Recurrent Cushing's syndrome from transplant in 3. |
| | | Additional adrenal transplantation patients[20,49]. | | |

The *pathologic examination* of the autotransplants has been of special interest.[36] In our own series, the color of the adrenal tissue has ranged from the vivid yellow color of the normal adrenal cortex to darkly pigmented nodular hyperplasia (Fig. 5). Microscopically, the human autotransplants, again, exhibited a wide spectrum from only a modicum of viable adrenocortical cells scattered through areas of necrosis and fibrosis, to frank adrenocortical hyperplasia in one of our patients with recurrent Cushing's syndrome (patient S.F.). It was not possible to identify which of the three zones of the cortex had survived autotransplantation most successfully in our patients, but Kolpakov et al.[35] found in rats and rabbits that the zona glomerulosa recovered most rapidly, being almost completely recovered at two weeks, when the zona fasciculata and the zona reticularis were still in a stage of marked degeneration. The adrenal medulla had not survived in our patients and this has appeared to be the case in other reported studies. Although there have been instances when it was apparently possible to withdraw steroid replacement therapy completely at only a few weeks postadrenal autotransplantation combined with total intra-abdominal adrenalectomy, it has been our experience that the transplants may be expected to increase in function over a period of years, and as already noted our one patient who developed recurrent Cushing's syndrome (Patient S.F.) did so only after seven years, though others have reported this circumstance after only two to three years.[1,39] Actually, it would stand to reason that a progressive increase in activity could be expected from viable autotransplants, since the elevated circulating ACTH level not only persists but may increase, concomitant with a slowly improving blood supply to the transplants. Moreover, naturally occurring Cushing's disease usually develops slowly.

### *The Future of Adrenal Autotransplantation*

The data herein reported, from our clinic and elsewhere, fully establish that adrenal autotransplants to muscle may be expected to survive in most instances but to variable degrees. In a substantial percentage of such patients the steroid replacement can eventually be stopped completely or administered in minimal dosage.

On the other hand, the presence of this continuing endogenous source of cortisol does complicate the problem of steroid replacement therapy, which is otherwise clear-cut and imperative when no functioning adrenal tissue remains. Furthermore, the degree of autotransplant function is variable and the degree of functional activity to be achieved may not be fully realized for years. Next, the presence of functioning autotransplants did not prevent increasing skin pigmentation in at least one of our patients who developed recurrent Cushing's syndrome from the transplants (Patient S.F.). However, thus far no patient with actively functioning autotransplants has developed the aggressive

postadrenalectomy chromophobe tumor known as Nelson's syndrome, though further long-term follow-up is essential to decide this issue.

Therefore, to review our three objectives when in 1962 we initiated adrenal autotransplantation with total intra-abdominal adrenalectomy: 1) We and others have established that adrenal transplants can survive and function and eventually abolish the need for steroid replacement therapy in perhaps a majority of such patients, with some degree of transplant survival in most patients. 2) None of our patients with a well functioning transplant has thus far developed Nelson's syndrome with a chromophobe adenoma, though only further experience and time will settle this question. 3) The presence of a well functioning transplant has not prevented an increase in skin pigmentation in some patients.

## Acknowledgments

The author expresses appreciation to Drs. Herbert G. Langford and Jeanne R. Bonar for the opportunity to work with the patients herein reported. Dr. Bonar's laboratory performed the ACTH measurements, Dr. Robert E. McCaa's laboratory the aldosterone measurements, and Dr. J. M. Montalvo's laboratory the analyses of steroid content in excised adrenal transplant tissue.

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## Discussion

Dr. Edwin L. Kaplan (Chicago, Illinois): I agree with Dr. Hardy completely that in adrenal adenoma and carcinoma, diseases in which the treatment is clearcut—one should remove the tumor. On the other hand, the treatment of hyperplasia is still very perplexing.

One of the other modalities that he did not mention is radiation to the pituitary. Dr. Ed Paloyan has recently presented data where two individuals who were apparently cured—in quotation marks—by irradiation therapy later had recurrences. In one of them it took eight years before the recurrence of Cushing's occurred, so I think we must be wary when we use irradiation to the pituitary, and follow these patients carefully.

We have experience at the University of Chicago with one adrenal transplant. We minced the adrenal cortex, as one would do for a parathyroid transplant, and transplanted this to the muscles of the arm. This patient still requires steroid therapy. However, there is a very nice gradient of both cortisol and aldosterone, which is higher in the arm of the transplant.

I think the technique that Dr. Hardy has proposed today warrants our further investigation.

Dr. Frank Glenn (New York, New York): This report by Dr. Hardy is a great contribution to the matter of the patient who requires a total adrenalectomy. Furthermore it re-enunciates a principle of replacement for an injured or deficient part, specifically for the glands of internal secretion. These 18 cases are of significance to all of us here because Dr. Hardy has, by study of his management derived a great deal of adequate information from each one detailed that will be of value to those who pursue this type of endeavor in the future.

My interest in this disease goes back to the twelfth case in Dr. Cushing's series, when I was an assistant resident at the Brigham hospital. I have had a great deal of interest in it since.

Our total experience, in close cooperation with the endocrine group at The New York Hospital includes 113 patients with Cushing's disease who have been treated surgically. Sixty of these have had hyperplasia of the adrenals. Fifty-two have been subjected to attempted total adrenalectomy. Those in which total adrenalectomy was accomplished as determined by postoperative studies have been well supported and maintained by replacement therapy. Our longest follow-up is now 28 years.

However, replacement therapy leaves much to be desired from the patient's viewpoint. Dr. Hardy's experience will have an impact on the future management of the patient with Cushing's disease. I would suggest that for those with hyperplasia the posterior approach affords a better opportunity to look for aberrant adrenal tissue. Such tissue and any remaining adrenal tend to become exuberant when subtotal adrenalectomy is done.

Dr. Hardy has mentioned the pigmentation of the skin following total adrenalectomy. Here are two slides that further emphasize this phenomenon that I feel we lack an explanation for. Actually this is but one of many changes that follow total resection. I think it is the tip of the iceberg of many significant changes, particularly as it relates to the pituitary and hypothalamus. I have long believed that the adrenals are only one but an important link in the complex