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Complications of Treated Cushing's Syndrome

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Fifty-two patients with Cushing's syndrome are reported with emphasis on post treatment complications. Seven patients, cured of their disease following appropriate therapy, had a recurrence of adrenal hypersecretion from one to ten years later. This occurred after all modalities of treatment, but was more common after sub-total adrenalectomy. Pituitary adenomas were found in two cases. Pseudotumor cerebri, psychiatric complications, hyperthyroidism and hyperpigmentation were observed. One patient developed progressive hyperpigmentation despite pituitary radiation. Thirteen of fifty-two patients had malignant disease including three endometrial carcinomas, one rectal carcinoma and one adenocarcinoma of the mandible. Despite the remarkable improvement in the prognosis for patients with Cushing's syndrome, this population continues to be at high risk for late complications and warrants close follow-up medical care.

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IN 1952, Plotz and co-workers reported a 50% five-year mortality in patients treated for Cushing's syndrome.¹ As therapeutic modalities were refined, understanding of the disease advanced by sophisticated steroid assays and adrenal replacement therapy widely used, the outlook for the patient with Cushing's syndrome improved progressively. A 1971 review describing 108 patients with Cushing's syndrome documented this dramatic improvement.² With the exception of adrenal or ACTH producing malignancies, present therapy is now considered curative in most instances. Nevertheless, late and serious complications are still reported in treated patients.^{3,4} We report here our experience with 52 patients with Cushing's syndrome seen at the Henry Ford Hospital from 1950-1970. Particular attention is given to the problem of recurrent Cushing's syndrome in patients treated and restored to a eucortical condition. Case reports of seven such patients are presented in detail. In addition, other complications which were encountered are discussed.

Methods and Patients

All patients seen from 1950-1970 with the diagnosis of adrenal hypercortisolism are included. Diagnoses were established using routine assay procedures

for urinary 17 hydroxysteroids⁵ and 17 ketosteroids.⁶ Responses to metyrapone, ACTH and dexamethasone suppression⁷ were also studied in most cases. Plasma cortisol was measured routinely since 1960. In a few patients the urinary free cortisol was also measured to confirm the diagnosis.

As shown in Table I, six patients had cortisol producing adrenal adenomas, four had adrenal carcinomas, 39 patients had adrenal hyperplasia (nodular hyperplasia was noted in one of these patients), and three patients had putative ectopic ACTH syndrome but the diagnoses were not verified by ACTH assay. There were 38 females and 14 males ranging in age from 2 months to 71 years. Peak incidence of disease occurred in the fourth decade. The mean follow-up (Table I) for patients with adenomas was 14 years and with hyperplasia 9.2 years. The patients with adrenal cancer or ectopic ACTH syndrome all died within four years of diagnosis.

Treatment

The initial therapy employed and the results are shown in Table II. For the purpose of this paper, a cure is defined as a permanent reduction of cortisol secretion to normal basal levels, either with or without steroid replacement, and disappearance of associated clinical abnormalities. A recurrence is diagnosed in those patients with Cushing's syndrome who achieved documented clinical and laboratory evidence of normal or subnormal cortisol secretion and subsequently developed clinical and laboratory findings of adrenal overactivity. Patients classified as failures, although usually demonstrating improvement after initial treatment, continued to excrete elevated glucocorticoids.

All six patients with adrenal adenomas were successfully treated with unilateral adrenalectomy and cured of their disease. Of the four patients with adrenal carcinoma, two were treated with surgical excision. One achieved a temporary slight amelioration of hypercorticism while the other was completely eucorticotoid for one year. His case history is described later. The other two patients were explored, but their carcinomas were unresectable. All four patients were subsequently treated with orthopara' DDD with improvement in circulating cortisol levels.

Sixteen of 39 patients with adrenal hyperplasia underwent total adrenalectomy as initial therapy and 15 of these were cured. The one recurrence will be discussed. Fourteen patients received initial therapy with pituitary radiation. Six were cured. Two, whose case histories are presented later, experienced a recurrence. Six were failures requiring additional treatment.

Five patients with adrenal hyperplasia were treated by unilateral adrenalectomy followed by pituitary radiation. Two of these patients were cured, while the other three patients required further therapy. Three patients with adrenal hyperplasia were treated initially with subtotal adrenalectomy. One patient has done well without further treatment. Two recurred and they will be discussed.

Two of the three patients with ectopic ACTH were cured of their hypercorticism but died of their underlying disease while one with an associated pheochromocytoma died at surgery.

Table III shows the treatment received by the six patients with persistent disease after radiation. Three immediately underwent a bilateral adrenalectomy resulting in a permanent

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**TABLE I
CUSHING'S SYNDROME 1950-1970**

Adrenal Diagnosis	Number	Ages		Sex		Follow-Up In Years	
		Range	Mean	F	M	Range	Mean
Adenoma	6	32-56	42	5	1	1-19	14
Carcinoma	4	15-45	33	1	3	0.2-4	1.2
Hyperplasia	39	0.2-71	36	30	9	0-20	9.2
Ectopic ACTH	3	6, 46, 59		2	1	0-4	1

**TABLE II
PRIMARY TREATMENT**

Diagnosis	Treatment	Number	Cure	Recurrence	Failure
Adenoma	Unilateral Adrenalectomy	6	6	0	0
Carcinoma	Surgery & Ortho Para' DDD	4	0	1	3
Hyperplasia	Adrenalectomy	16	15	1	0
	Radiation	14	6	2	6
	Unilateral Adrenalectomy & Radiation	5	2	0	3
	Subtotal Adrenalectomy	3	1	2	0
	Not treated	1			
Ectopic ACTH	Adrenalectomy	3	2	0	1*

*Died at Operation

**TABLE III
FOLLOW-UP TREATMENT OF SIX RADIATION FAILURES**

Treatment	Number	Permanent Cure	Recurrence	Failure
Bilateral Adrenalectomy	3	2	1	0
Unilateral Adrenalectomy	2	0	0	2*
Under Observation	1			

*Both cured with total adrenalectomy

cure in two. In the third, after a 10-year remission, recurrent, overactive adrenal tissue was located by radioactive iodocholesterol scanning and was suc-

cessfully removed. Two of the six radiation failures were subjected to unilateral adrenalectomy which was unsuccessful, necessitating a total adrenalectomy for

eventual cure. One patient is still under observation.

Cushing's syndrome recurred in seven patients after initial treatment had resulted in a documented clinical and laboratory cure. This incidence of over 13% was a significant complication in our series. Case histories of these seven patients follow.

Case Reports

Case #1. This school boy was first seen in December of 1967 at 12 years of age for evaluation of obesity, acne and growth failure. Basal 17 hydroxysteroids were 17.3 mg and 17 ketosteroids 15.7 mg per day. There was marked hyper-responsiveness to ACTH with a rise in 17 hydroxysteroids to 100 mg per day and 17 ketosteroids to 51 mg per day. In February of 1968 he was treated with 4,500 roentgens to the pituitary gland and two months later basal 17 hydroxysteroids and 17 ketosteroids had fallen to normal levels of 5.5 and 7.3 mg per day, respectively. This was associated clinically with a "catch-up growth spurt" as he had a 7¼ inch increase in height over the next 16 months. In 1969 the growth rate decreased and symptoms of recurrent disease appeared. Evaluation in September of 1970 revealed a plasma cortisol of 17.1 mcg% when checked at 8 a.m. which suppressed inadequately to 6.5 mcg% following 1 mg of dexamethasone. No additional treatment has been given, although recurrence of his disease has been documented.

Case #2. This 25-year-old woman was seen in July 1953 for progressive weight gain, menstrual irregularities and hirsutism. Basal 17 hydroxysteroids and 17 ketosteroids were 19.5 and 12.1 mg per day and 17 hydroxysteroids rose to 56.2 mg per day with 20 units of ACTH gel over a two-day period. Pituitary radiation was administered at another hospital nearer her home in August 1953 and by the fall of that year complete remission had occurred. The radiation dose is not known; 17 hydroxysteroids were 3.8 mg per day and 17 ketosteroids 4.4 mg per day.

She had no further difficulty until 1958 when she developed weakness, fatigue, depression and recurrent disease, verified by laboratory testing. Plasma cortisol was 31 mcg% without diurnal variation and basal urinary 17 hydroxysteroids were 22.4 mg per day. In March of 1959 another course of pituitary radiation was administered. By February of 1960, she was asymptomatic and basal urinary 17 hydroxysteroids were 4.8 mg per day and 17 ketosteroids 6.8 mg per day. Three years later she again noted symptoms of hypercorticism and urinary 17 hydroxysteroids had risen to 18.9 mg per day with a urinary free cortisol of 610 mcg per 24 hours. A total bilateral adrenalectomy was done in May of 1963. She has had no further difficulty since then and has been maintained on full replacement therapy. She has developed progressive hyperpigmentation, without enlargement of the sella turcica.

Case #3. In 1951, at the age of 34, this patient had a complete resection of the left adrenal gland and 90% resection of the right adrenal for Cushing's disease. Replacement therapy consisted of prednisone 5 mg daily until 1959 when it was decreased to 2½ mg daily and eventually discontinued in 1960. When first seen at this hospital her skin was deeply pigmented and she was weak and cachectic. Basal 17 hydroxysteroids were 5.7 mg and 17 ketosteroids 2.2 mg per day. Eighty units of ACTH for several days produced no increase in glucocorticoid production. The diagnosis of Addison's disease with a maximally stimulated small adrenal remnant was confirmed and the patient discharged with 9-alpha flurohydrocortisone prescribed. In 1964 signs and symptoms of recurrent Cushing's disease developed. The mineralocorticoid was discontinued and plasma cortisol was 9.6 mcg%, with no diurnal variation. She remained apparently eucortical until 1970 when adrenal insufficiency was again documented. Plasma cortisol was 0.5 mg%. Since that time the patient has required 20 mg hydrocortisone daily. The adrenal remnant initially appeared to be insufficient to maintain normal corticoid production. With time, the gland size probably enlarged in response to persistent ACTH stimulation and the recurrent Cushing's syndrome resulted from the additive effect of exogenous and endogenous glucocorticoids. The explanation for the adrenal failure five years later is not apparent. This patient has

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no pituitary enlargement or other evident endocrine abnormality.

Case #4. This patient was 22 years old in 1950 when the diagnosis of Cushing's disease was made and she was treated with a 90% left adrenalectomy at another hospital. She was first seen at Henry Ford Hospital in 1955 with symptoms of recurrent Cushing's disease. 17 hydroxysteroids and 17 ketosteroids were 36.7 and 36.2 mg per day and rose with ACTH to 74.6 and 59.4 mg. When right adrenal tissue weighing 16 grams was removed, it presented the histologic changes of nodular adrenal hyperplasia. The postoperative urinary 17 hydroxysteroid level was 4.6 mg per day but the patient shortly developed symptoms of steroid insufficiency and required full steroid replacement therapy for over seven years. Thereafter she developed hypertension, and when dermal atrophy was also noted replacement therapy was discontinued. By 1963 she had distinct features of Cushing's disease and the recurrence was substantiated by laboratory investigation. Basal 17 hydroxysteroids and 17 ketosteroids were 37.3 and 26.9 mg per day, rising to 56.2 and 26.5 with ACTH. Use of 2 mg per day of dexamethasone caused no suppression, but urinary 17 hydroxysteroids fell to 8.4 mg per day with use of 8 mg of dexamethasone. The left adrenal remnant was removed. It weighed eight grams and also showed nodular cortical hyperplasia. Clinical remission was again achieved.

Case #5. This patient was 25 years old when the diagnosis of Cushing's disease was made in 1968 and a total bilateral adrenalectomy was performed elsewhere. Under treatment elsewhere, she was given full replacement doses of cortisone daily over the next year. She first presented at Henry Ford Hospital in 1969 with severe psychiatric symptoms and florid signs of Cushing's disease. Cortisone was discontinued and the plasma cortisol was greater than 40 mcg% in the morning, with afternoon values of 35 mcg%. Basal urinary 17 hydroxysteroids of 16.5 mg per day rose to 51.3 mg with ACTH and fell to 12.5 mg per day when using 8 mg of dexamethasone a day. She was treated with psychotropic drugs and 5,000 roentgens to the pituitary. Five months later her clinical

status was improved, urinary 17 hydroxysteroids were 9.7 mg per day and the AM plasma cortisol was 14 mcg. The patient remained amenorrheic and emotionally unstable, however, and within a few months the level of plasma cortisol increased to 22.6 mcg%. Treatment with ortho-para' DDD was initiated and after five months of treatment a complete remission occurred. Within six months the blood pressure again rose, the patient gained weight and noted increased bruising. Pigmentation increased although the skull x-ray was normal. Plasma cortisol exceeded 20 mcg% without diurnal change. Because she refuses further surgery the patient is maintained with ortho-para' DDD 3 gm daily along with 10 mg of hydrocortisone and is asymptomatic.

Case #6. This patient was 43 when first seen for evaluation of Cushing's syndrome in 1967. 17 hydroxysteroids were 87 mg per day and 17 ketosteroids 16.3 mg per day. There was no suppression with dexamethasone or stimulation by ACTH. An adenoma was removed and, although the pathology was suggestive of carcinoma, the lesion appeared to be entirely encapsulated. Furthermore, the normal urinary 17 ketosteroid levels, characteristic for adenoma, supported the impression of a benign lesion. Steroids were discontinued after a six-month period and the patient experienced no further difficulty until the Cushing's syndrome recurred almost two years after the original surgery. Pulmonary metastases were present and the patient was treated with ortho para' DDD and radiation. He responded temporarily, but then gradually deteriorated and died despite extensive chemotherapy.

Case #7. This 26-year-old mother of one child developed Cushing's syndrome in 1961 with laboratory data characteristic of adrenocortical hyperplasia. When 4,000 roentgens of cobalt teletherapy to the pituitary gland failed to produce any evidence of remission, bilateral total adrenalectomy was performed and revealed adenomatous hyperplasia of both glands. Complete remission occurred and the patient was successfully delivered of her second child 18 months later. Steroid therapy in the form of 20 mg hydrocortisone and intermittent 9 alpha

flurohydrocortisone was continued until March, 1972. At that time persistent edema, headache and weight gain led to discontinuation of hormone therapy. Progressively rising plasma and urinary cortisol levels were recorded over the next six months. Radioactive iodocholesterol scanning* demonstrated the presence of recurrent tissue in the left adrenal bed and the nodular hyperplastic remnant was removed with a resultant cure. Progressive pigmentation has occurred in subsequent months.

Additional Complications

As shown in Table IV, 10 patients with adrenal hyperplasia became pigmented after treatment. One of these patients died suddenly with hemorrhage into a pituitary adenoma 11 years after adrenalectomy. The sella was not enlarged. One patient developed an enlargement of the sella turcica following adrenalectomy. This was associated with moderate skin pigmentation, hypothyroidism and low growth hormone levels which were unresponsive to insulin-induced hypoglycemia. She was treated subsequently with pituitary irradiation.

Five patients had psychiatric problems of a magnitude severe enough to necessitate hospitalization. Hyperthyroidism occurred in one patient two months after adrenalectomy and pseudotumor cerebri developed in another patient while his adrenal disease was active.

With the exception of ACTH producing neoplasms an increased incidence of non-adrenal cancer has not been reported in Cushing's syndrome. In our series, however, there were 13 patients with malignant disease (Table V). Four

*Performed in cooperation with Drs. Martin F. Sturman and William H. Bierewaltes, Division of Nuclear Medicine, University of Michigan, Medical Center, Ann Arbor, Michigan.

**TABLE IV
COMPLICATIONS**

Dermal Pigmentation	10
Intense	5
Moderate	5
Hyperpigmentation with Sella Enlargement.....	1
Psychosis after Adrenalectomy	5
Hyperthyroidism Two Months after	
Adrenalectomy.....	1
Pseudotumor Cerebri.....	1

**TABLE V
CANCER IN CUSHING'S SYNDROME**

Para Endocrine Syndrome	
Lung Cancer and Thyroid Cancer.....	1
Neuroblastoma	1
Medullary Thyroid Cancer and	
Pheochromocytoma	1
Adrenal Cancers.....	4
Occurring During or after Hypercorticism	
Endometrial Cancers.....	3
Rectal Cancer.....	1
Thyroid Cancer.....	1
Adenocarcinoma of the Mandible	1
TOTAL.....	13

malignancies were functioning adrenal carcinomas. Three patients were felt to have malignancies secreting ACTH. One of these had carcinoma of the lung, bilateral adrenal hyperplasia and an occult thyroid cancer noted at autopsy. A child with bilateral adrenal hyperplasia, successfully treated with bilateral adrenalectomy, died four year later with a central nervous system neuroblastoma. The third patient died at the time of her adrenalectomy. A previously unsuspected pheochromocytoma and medullary thyroid cancer were found at autopsy.

Six additional patients developed carcinomas following therapy. Three of these were endometrial cancers diagnosed two, eight and ten years after

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TABLE VI
DEATHS

	Number	Ages
I. Endocrine Related (10)		
Adrenal Carcinoma	4	16, 46, 29, 45
Ectopic ACTH	3	10, 59, 46
Addisonian Crisis	1	40
Pituitary Apoplexy	1	27
Untreated Cushing's Disease	1	2 mo.
II. Other (2)		
Renal Failure and Diabetes	1	61
Fractured Leg with Fat Emboli	1	81
TOTAL	12	

treatment. One patient had rectal cancer and another a mixed papillary-follicular thyroid cancer two years after adrenalectomy. One patient with an adrenal adenoma developed an adenocarcinoma of the mandible 17 years after adrenal surgery. Two patients had pituitary tumors after removal of hyperplastic adrenals.

Table VI lists the 12 deaths which occurred in this group of 52 patients. Ten deaths were directly related to the endocrine disturbance. Four patients died from carcinoma. Three other patients died with cancers known to be associated with the ectopic ACTH syndrome. One patient died at home three months after surgery probably of adrenal insufficiency. One child died at the age of two months, before definitive therapy could be initiated. This child, born with Cushing's disease, has been reported previously.⁸

One patient died 11 years after her Cushing's disease had been treated by bilateral adrenalectomy. Although she had noted progressive hyperpigmentation since treatment, sella turcica enlargement did not appear for 11 years and she had delivered two normal babies while on replacement therapy. A

chromophobe adenoma was subtotally removed when increased intracranial pressure developed rapidly. The patient responded well postoperatively only to develop fatal cardiopulmonary arrest the night after surgery. One diabetic patient died with renal failure more than 20 years after adrenalectomy and another had a pulmonary fat embolus after a hip fracture.

Discussion

Results of our treatment are in keeping with previous reports. Unilateral adrenalectomy for a solitary adrenal adenoma was curative in all patients so treated and all patients with adrenal carcinoma eventually died of their disease. External pituitary radiation was successful in 6 of 14 patients with bilateral hyperplasia. Radiation and unilateral adrenalectomy together or subtotal adrenalectomy were successful in a smaller number of patients. Our results with radiation are comparable to those reported by others.^{9,10}

Although Crougns and Docter have reported beneficial immediate effect of pituitary radiation and unilateral adrenalectomy, this procedure has been

abandoned in our practice, as long term results are no better than either adrenalectomy or pituitary radiation alone.¹¹ Originally this procedure was also performed to confirm the adrenal pathology, but it is no longer necessary with current diagnostic procedures.

Total adrenalectomy was also curative although there were two recurrences. Siegal and co-workers and Scheingart's group also reported recurrence after total adrenalectomy.^{3,4} Whether this rare complication may result from adrenal remnants left inadvertently at the time of surgery or whether ectopic adrenal tissue is present and activated by prolonged and intensive ACTH production may be difficult to determine. The use of ortho para' DDD as an adrenotoxic chemical suitable for therapy has made clarification of the problem less crucial. However, iodocholesterol scanning in such patients may aid in precise localization of adrenal tissue, making repeat curative surgery possible.

Recurrences after asymptomatic periods lasting from one to ten years appeared following all modalities of therapy, but were more common after subtotal adrenalectomy. In the series reported by Welbourn, recurrence was also more frequent after sub-total adrenalectomy.¹²

Our approach to therapy in patients with bilateral adrenal hyperplasia is as follows: a) pituitary radiation in patients with mild disease in whom an expected period of observation will not be associated with deterioration in the patient's condition; or b) total adrenalectomy in patients with more aggressive disease. In addition, pituitary radiation probably should be administered to patients with progressive hyperpigmentation. The patient in Case # 7 had received no radiotherapy. She was

deeply pigmented, but x-rays had not demonstrated sella turcica enlargement until 11 years after her adrenal surgery. Unfortunately, little data is available to document radiation effectiveness in this pituitary disorder. Orth reports no cases of Nelson's syndrome in patients previously treated with pituitary irradiation.¹³ However, our patient (Case #2) had two courses of radiation, one of which produced a remission in her Cushing's disease, only to develop intense pigmentation following her eventual adrenalectomy. Although radiation may help prevent Nelson's syndrome, it apparently will not prevent the disorder in all patients with adrenal hyperplasia.

Intermittent Addison's disease (patient in Case #3) alternating with Cushing's disease is a rare complication of subtotal adrenalectomy. In reviewing this phenomenon, Egda has suggested that the adrenal remnant may undergo fluctuating steroid production, making control difficult.¹⁴

A large number of our patients developed serious complications during an extended period of observation. These complications, after treatment, seem directly related to Cushing's syndrome. Several patients developed medical problems not usually associated with endocrine disorders.

The finding of 13 cases of malignancy in our group has not characterized the patients in other series. In 1952, Plotz reported the cause of death in 114 cases of Cushing's syndrome and reviewed the existing literature to that time. He found six tumors of the thymus, four of the pancreas and one sympathicoblastoma. Excluding those with adrenal or pituitary tumors, 10% of patients had neoplasms. Most of these cases were probably examples of the ectopic ACTH syndrome. In the series reported by

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Welbourn, no note is made of non-endocrine neoplasia except for one patient who died with cancer of the cecum. Although finding of increased malignancy may be due to chance variation, the three cases of endometrial cancer in 39 females are of interest. Even though association between Cushing's syndrome and neoplasia must be conjectural, it has been postulated that malignancy may be associated with a deficient immunological state. Con-

ceivably, high levels of corticosteroids interfere with the normal immunological mechanics which retard a tendency to develop neoplasm.¹⁵

Despite the generally satisfactory prognosis for patients with Cushing's disease, serious complications may arise. Even patients successfully treated for the disorder appear to be at high risk and need continued observation.

References

1. Plotz CM, Knowlton AL and Regan C: The natural history of Cushing's syndrome. *Amer J Med* **13**:597-614, 1952
2. Orth DN and Liddle GW: Results of treatment in 108 patients with Cushing's syndrome. *N Eng J Med* **285**:243-7, 1971
3. Siegal AM, Kreisberg RA, Hershman JM and Owen WC: Recurrent Cushing's disease following "total" adrenalectomy. *Arch Int Med* **129**:642-7, 1972
4. Schteingart DE, Conn JW, Lieberman LB and Beierwaltes WH: Persistent or recurrent Cushing's syndrome after "total" adrenalectomy. *Arch Int Med* **130**:384-7, 1972
5. Silber RH and Porter CC: The determination of 17, 21-dihydroxy-20 ketosteroids in urine and plasma. *J Biol Chem* **210**:923-32, 1954
6. Drechter IJ, Heisler A, Scism GR, Stern S, Pearson S and McGavack TH: Determination of urinary steroids; preparation of pigment-free extracts and simplified procedure for estimation of total 17-ketosteroids. *J Clin Endocr* **12**:55-65, 1952
7. Liddle GW: Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. *J Clin Endocr* **20**:1539-60, 1960
8. O'Bryan RM, Smith RW Jr, Fine G and Mellinger RC: Congenital adrenocortical hyperplasia with Cushing's syndrome. *JAMA* **187**:257-61, 1964
9. Liddle GW and Shute AM: The evolution of Cushing's syndrome as a clinical entity. *Adv Int Med* **15**:155-75, 1969
10. Hartog M, Doyle F, Fotherby K, Fraser R and Hoplin GE: Partial pituitary ablation with implant of gold 198 and yttrium 90 for Cushing's syndrome with associated adrenal hyperplasia. *Brit Med J* **2**:392-5, 1965
11. Crougths RJM and Docter R: Immediate effect of unilateral adrenalectomy followed by external pituitary irradiation on cortisol secretion rate in subjects suffering from pituitary dependent Cushing's syndrome. *J Clin Endocr* **33**:912-6, 1971

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12. Welbourn RB, Montgomery DAD and Kennedy VL: The natural history of treated Cushing's syndrome. *Brit J Surg* **58**:1-16, 1971
13. Orth DM and Liddle GW: Letter to the editor. *N Engl J Med* **285**:1264, 1971
14. Egdahl RH and Melby JC: Recurrent Cushing's disease and intermittent functional adrenal cortical insufficiency following sub-total adrenalectomy. *Ann Surg* **166**:586-95, 1967
15. Leibowitz S and Schwartz, RS: Malignancy as a complication of immunosuppressive therapy. *Adv Int Med*, Vol 17, 1971 Year Book Medical Publishers