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The Pituitary Before and After Adrenalectomy for Cushing's Syndrome

Konstantinos J. Manolas, M.D., Helen M. Farmer, B.Sc.,
H. Kenneth Wilson, M.B., D.M.R.D., F.R.C.R., A. Laurence Kennedy, M.D., M.R.C.P.(UK),
Graham F. Joplin, M.B., Ph.D., F.R.C.P., Desmond A.D. Montgomery, M.D., F.R.C.P.,
Terence L. Kennedy, M.S., F.R.C.S., and Richard B. Welbourn, M.D., F.R.C.S.

Departments of Surgery, Medicine, and Diagnostic Radiology, Royal Postgraduate Medical School and Hammersmith Hospital, London, England; and Departments of Surgery and Radiology and Sir George E. Clark Metabolic Unit, Royal Victoria Hospital, Belfast, Northern Ireland; United Kingdom

Seventy-nine patients underwent subtotal or total adrenalectomy for pituitary-dependent Cushing's syndrome (1953–1980); 76 survived the operation and 75 were followed for 1 to 27 (mean 11) years. Pigmentation, plasma ACTH, and sellar X-rays were assessed at intervals.

Pigmentation developed in 37 (5 before and 32 after operation), most frequently after total adrenalectomy. The sella was definitely enlarged in 6 of 65 patients before the operation and in 14 of 65 after it. Enlargement was more common in pigmented than in non-pigmented patients. The plasma ACTH concentration rose after adrenalectomy. It was significantly higher in pigmented than in non-pigmented patients. It was also higher after total than after subtotal adrenalectomy.

Pituitary tumors were confirmed histologically in 15 patients. The tumors presented at the same time as the Cushing's syndrome in 8 and after adrenalectomy in 7. They were malignant and fatal in 6. Pigmentation, present in 11 of these patients, developed only after adrenalectomy. In 9 other patients with benign lesions and 21 with clinically probable but histologically unconfirmed tumors, 7 were treated by hypophysectomy with or without irradiation (4 cured, 3 improved), and 4 by irradiation alone: external 3, internal 1 (all improved).

The most common variety of Cushing's syndrome is associated with excessive secretion of ACTH by the pituitary and bilateral adrenal hyperplasia. This is described as the "pituitary-dependent" type or Cushing's disease. In some 90% of such patients, the source of ACTH is a pituitary adenoma, usually a microadenoma when the patient is first seen, that is, one that is too small to be recognized by conventional radiographs and tomography [1, 2]. The reported prevalence of tumors large enough to expand the sella radiologically varies from 7.5% [3] to 23% [4]. Hyperplasia of the pituitary corticotrophs, without tumor formation, has been described in other patients [5–7]. Occasionally, tumors manifest themselves clinically by pigmentation [8] or by ocular signs [3].

Pituitary tumors often become evident for the first time after adrenalectomy. In 1955 Siebenmann [9] reported a patient who developed pigmentation and recurrence of Cushing's disease, associated with a large pituitary tumor, 2 years after subtotal adrenalectomy. Two similar patients were described in 1959 [3]. In 1958 Nelson [10] reported a patient who had developed Addisonian pigmentation, radiological enlargement of the pituitary fossa, and a very high plasma ACTH level (measured by bioassay), 3 years after adrenalectomy. This combination of features, now known as Nelson's syndrome, was observed independently by others at about the same time [3, 11–13] and in 1960 Nelson reported 9 further patients and described the syndrome fully [14]. All 10 who had undergone adrenalectomy (presumably total) for Cushing's disease had enjoyed remission but had become deeply pigmented, without recurrence, between 1 and 8 (average 3) years later. All 10 had high blood ACTH levels. The pituitary fossa had been X-rayed before operation in 7 and had been normal in all. Afterward, the fossae were enlarged in 8 and normal in 10. Some patients also had restricted visual fields.

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Reprint requests: Professor R.B. Welbourn, Department of Surgery/Endocrine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 OHS, United Kingdom.

Nelson's syndrome has been studied in several series of patients who have undergone adrenalectomy. In adults the reported incidence of pigmentation after adrenalectomy ranges from zero to 84% and that of sellar enlargement from zero to 29% [15–17]. In one recent series of 43 patients who underwent total adrenalectomy for Cushing's disease, 38 (88%) went into remission [17]. Of these, 11 (29%) developed pigmentation and enlargement of the pituitary fossa, and had a median plasma ACTH level greater than 240 pg/ml. Twenty-one (55%) had pigmentation, normal pituitary fossae, and a median ACTH level of 162 pg/ml. Six patients (16%) remained unpigmented with normal fossae and had a median ACTH level of 60 pg/ml. The median plasma ACTH level before adrenalectomy was 56 pg/ml. In a series of 27 children [18], 44% became pigmented, half of them with large and half with normal fossae, while 22% had abnormal fossae without pigmentation. Only 34% were normal. Many patients, like some of Nelson's, have been reported with visual field defects and paralysis of the ocular muscles.

Most pituitary tumors in Cushing's disease are benign adenomas and ACTH is demonstrable in their cells immunocytochemically. A few are invasive [19–23] and a very few metastasize [3, 19].

Patients remain at risk indefinitively of developing Nelson's syndrome after adrenalectomy, and in one series [22] tumors became manifest after intervals ranging from 6 months to 16 years (mean 7.4 years). External irradiation of the pituitary at about the time of adrenalectomy (4,000 to 5,000 rad within about 4 weeks) has been reported to prevent Nelson's syndrome [15], but the evidence is inconclusive [22].

Large and symptomatic pituitary tumors have been treated by surgical and radiotherapeutic means, either alone or in combination, both as initial therapy for Cushing's disease and after adrenalectomy [3, 22]. The outcome depends largely on the pathological nature of the lesion. The results of hypophysectomy by the transcranial or the transsphenoidal routes, of external irradiation with photons or protons [24, 25], and of internal irradiation with yttrium 90 or gold 198 [26] for benign tumors have been encouraging and many patients have either been cured or improved for years. On the other hand, those whose tumors are already invasive do not survive for long, whatever treatment is employed.

Nearly 25 years ago it was suggested that "adrenalectomy may enhance the growth of pituitary tumours" in patients with Cushing's disease and it was urged that "further observation of a large number of patients, with a long follow-up period, is needed before the magnitude of the hazard of a progressive pituitary tumour can be accurately evaluated" [3]. Although several studies have been undertaken, the matter has not been resolved. The detailed investigation reported here, of a large series of patients followed over many years, was planned as a further definitive evaluation.

Methods and Materials

All patients with presumed pituitary-dependent Cushing's disease [27–30] who were treated by bilateral adrenalectomy between 1953 and 1980 were studied (Table 1).

Treatments Used

Adrenalectomy. Three groups of operations were performed by 2 surgeons in 2 hospitals (RBW and TLK at the Royal Victoria Hospital, Belfast, and RBW at Hammersmith Hospital, London. One of the patients was operated on by RBW elsewhere.)

In Group I, subtotal adrenalectomy was undertaken in 34 patients, between 1953 and 1973 [27], and all had complete remission of the syndrome at first. Six suffered recurrence later and required total adrenalectomy, so that only 28 remained in this group.

Total adrenalectomy (group II) was the initial operation employed in 42 patients, between 1960 and 1979, and all had lasting remissions.

Group III included patients who had undergone total adrenalectomy after previous subtotal or partial resection. In addition to the 6 patients from group I, 3 had persistent or recurrent disease after inadequate operations performed elsewhere. All 9 underwent remission, although one subsequently relapsed and received internal pituitary irradiation (P74)[a] (see below). The mean interval between operations in the 9 patients was 10 years and the range 4 months to 21 years. For group III, "age at

[a] Numbers in brackets, preceded by *p*, refer to the series numbers of individual patients. They are numbered as follows: 38 patients with numbers between 1 and 60, are all those with pituitary-dependent Cushing's disease treated by bilateral adrenalectomy and reported in Welbourn et al. [27], where their series numbers are the same; 23 patients with numbers between 61 and 105, of the same type, treated by RBW at Hammersmith, 1968–1980; and 18 patients with numbers from 106–123 (consecutive) of the same type, treated by TLK in Belfast, 1968–1980. (The missing numbers in the first two groups belong to patients with Cushing's syndrome of other types or treated in other ways.)

Table 1. Patients, ages, and adrenalectomy groups.

Adrenalectomy group	Male			Female			Male + female		
	No. of patients	Age (years) Mean ± S.D.	Range	No. of patients	Age (years) Mean ± S.D.	Range	No. of patients	Age (years) Mean ± S.D.	Range
I	7	37.0 ± 18.1	13–52	21	37.7 ± 12.7	15–54	28	37.5 ± 13.8	13–54
II	16	28.2 ± 13.0[a]	7–48	26	40.4 ± 9.4[a]	23–61	42	35.8 ± 12.3	7–61
III	3	32.0 ± 10.1	21–41	6	47.6 ± 9.0	38–59	9	42.4 ± 11.7	21–59
Total no. of patients	26	31.0 ± 14.2[b]	7–52	53	40.2 ± 11.0[b]	15–61	79	37.2 ± 12.8	7–61

[a]Comparing ages of males and females in group II, $t = 3.534$, $p < 0.01$.
[b]Comparing ages of all males and all females, $t = 3.147$, $p < 0.01$.

Table 2. Pituitary irradiation for Cushing's syndrome in 19 patients (before or at time of adrenalectomy).

Type of irradiation	Adrenalectomy group			Total no. of patients
	I	II	III	
External				
Adequate	0	3	0	3
Inadequate	1	2	1	4
Internal				
Adequate	0	7	1	8
Inadequate	1	1	1	3
External (adequate) + internal (inadequate)	0	1	0	1
Total no. of patients	2	14	3	19

operation" and "time after operation" refer to the final operation throughout this report.

Irradiation of the Pituitary for Cushing's Syndrome. The pituitary gland was irradiated in 19 patients (24%) as part of the therapeutic regimen for Cushing's disease (Table 2), either before or at the time of adrenalectomy. Internal irradiation with yttrium 90 and/or gold 198 [31, 32] had failed to cause lasting remission in 10 patients (P32, 34, 57, 67, 68, 75, 77, 79, 81, 95), all treated before 1976, eight of whom (all except P32, 81) received adequate doses (20–50 krad peripherally to a normal fossa and 150 krad to an abnormal one). Another patient (P74), mentioned already, was irradiated (inadequately) for recurrence after bilateral adrenalectomy. He lived abroad and could not be traced after 1972 (18 months after his adrenal operation).

External irradiation was used in 7 patients. Three (P84, 96, 99) received adequate doses (4,000 rad within 4 weeks [15, 22]) at about the time of adrenalectomy. In 3 others, irradiation was the initial form of therapy and was intended to be curative, but the dosage was small and ineffective; two (P1, 4) received 2,500 rad only, while the third (P84) was given 3,000 rad on each of 2 separate occasions. The seventh (P69) patient received 800 rad, plus total adrenalectomy, when the syndrome recurred 18 months after hypophysectomy.

One patient (P55) with a large pituitary tumor had received inadequate internal and adequate external irradiation (4,000 rad) 5 and 3 years, respectively, before total adrenalectomy. The tumor had not enlarged during this time, but the Cushing's syndrome remained uncontrolled. She had a lasting remission after operation.

Irradiation of the Pituitary for Nelson's Syndrome. Five other patients, who will be mentioned again, were irradiated (3 externally, 2 internally) after they developed Nelson's syndrome.

Surgical Hypophysectomy and Pituitary Exploration. Eleven patients underwent surgical hypophysectomy, or pituitary exploration for irremovable tumors, at some time during the course of the disease. The transcranial route was used in 7: in 1 before adrenalectomy, in 4 after, and in 2 both before and after. The transsphenoidal route was employed in 4: one before and 3 after adrenalectomy.

Observations

Most patients were examined at least annually. In addition, except for the one (P74) who could not be traced, all the surviving patients were seen and investigated in 1981 or 1982. Observations made include clinical examination for evidence of pigmentation, radiographs of pituitary fossa, and measurement of plasma ACTH.

Pigmentation. Advanced Addisonian pigmentation was obvious. Patients with milder degrees were described as "pigmented" when at least 2 observers agreed. Particular attention was paid to a *change* in color and to darkness in unexposed parts, especially at pressure areas, in the palmar creases, in the mouth, on the areolae and genitalia, and in recent scars.

Table 3. Survival and death in relation to adrenalectomy groups (sexes combined).

	Adrenalectomy group			
	I	II	III	All groups
Total patients	28	42	9	79
Operative deaths	1 (4%)	2 (5%)	0 (0%)	3 (4%)
Untraced	0 (0%)	0 (0%)	1 (11%)	1 (1%)
Total patients followed	27 (96%)	40 (95%)	8 (89%)	75 (95%)
Later deaths	12 (43%)	5 (12%)	3 (33%)	20 (25%)
Interval from operation to death in years—mean (range)	4 (0.2–19)	5 (0.6–9)	5 (0.7–10)	4 (0.2–19)
Alive at final review	15 (54%)	35 (83%)	5 (55%)	55 (70%)
Interval from operation to review in years—mean (range)	18 (7–27)	8 (1–18)	10 (1–21)	11 (1–27)

Pituitary Radiographs. Plain anteroposterior and lateral films were taken routinely from the outset. In later years, coned views were obtained. Lateral tomography was used frequently when the plain films suggested abnormalities. Some earlier films had been destroyed when patients died, but in later years all were kept and those available in 1981 and 1982 were assessed by consultant radiologists who had no knowledge of the clinical findings. The fossae were assigned to 1 of 3 grades, based on the categories of MacErlean and Doyle [4], as follows: normal (categories 4 and 5), equivocal (category 3), or abnormal (categories 1 and 2).

Plasma ACTH. Routine radioimmunoassays for ACTH (N-terminal) [33] became available for Hammersmith patients in 1969 and for those in Belfast in 1972, and were then employed regularly. Blood samples from hospital inpatients were drawn at 0900 h (normal $\leq$ 80 ng/L), while those from outpatients were usually taken between 1400 and 1600 h.

Results

Analyses of survival, pigmentation, pituitary radiographs, and plasma ACTH levels were made in relation to each other and to sex, the adrenalectomy group, the time before and/or after operation, pituitary irradiation, and histological findings.

Statistical analyses included chi-squared tests (with Yates's correction for small numbers), Fisher's exact P and Student's t-test, as appropriate. The details of significant differences ($p < 0.05$) and of some that approach significance are given.

Survival and Death

There were 3 early postoperative deaths, all in women aged between 39 and 49 years [27, 30]. One (P13) died in coma of unknown cause after 3 days. The second (P76) developed profuse diarrhea, of unknown etiology, after 2 days and died from renal failure and massive gastrointestinal hemorrhage 13 days later. The third (P83), who had been bedridden for a long time, died from pulmonary embolus after 10 weeks. Twenty patients died later (Table 3). These, together with the man who was untraced (P74), are included in the following preoperative analyses (total 79), but excluded from the postoperative ones (total 75). The 20 patients who died later included 10 of each sex (38% of the males and 19% of the females). There were 55 patients alive at the time of the final review (58% of the males and 75% of the females). Since these sex differences are insignificant, males and females have been combined in subsequent analyses.

Pigmentation

Pigmentation was already present at the time of adrenalectomy in 5 of the 79 (6%) patients (3 women and 2 men). Three (P68, 72, 96) were in group II and 2 (P34, 42) in group III. The mean duration of pigmentation before the operation was 4 months, and the range 1 to 14 months. All 5 patients remained pigmented after adrenalectomy.

Pigmentation developed some time after adrenalectomy in 32 (46%) of the 70 remaining patients who were followed and who were in remission (Table 4). The incidence was similar in men (10/23, 43%) and in women (22/47, 47%). It was, however, much higher in patients in group II than in those in group I, despite the fact that the former had not been followed for as long. The incidence in those who died during the study (6/17, 35%) was less, but not significantly so, than that in the patients who survived (26/53, 49%, $p > 0.2$). Five patients (4 in group I and 1 in group II) did not require steroid

Table 4. Incidence of pigmentation after operation by adrenalectomy groups (sexes combined)[a].

Adrenalectomy group	Patients		
	Total	Pigmented	(%)
I	27	7[b]	(26)
II	37	21[b]	(57)
III	6	4	(67)
Total	70	32	(46)

[a]Excluding 5 patients pigmented before operation, 3 dying postoperatively, and 1 untraced.
[b]Comparing incidence of pigmentation in group I (7/27) and group II (21/37) $\chi^2 = 6.00$, $p(1 \text{ d.f.}) < 0.02$.

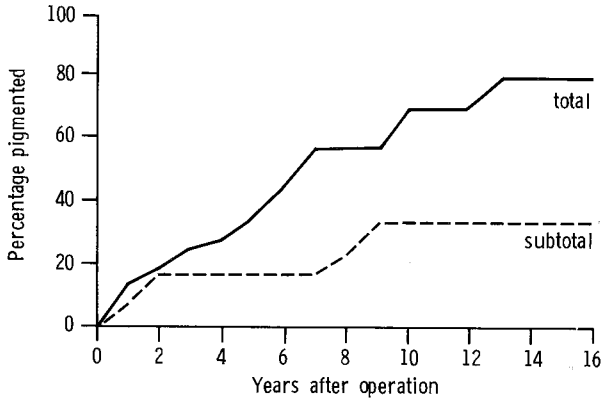

Fig. 1. Estimated cumulative probability (as percent) of developing pigmentation after adrenalectomy. (subtotal = group I, total = group II).

replacement therapy and none of these developed pigmentation. Thirty-two of the remaining 65 patients in all 3 groups, who were on replacement, became pigmented (50%). (Comparing 0/5 versus 32/65, exact p (single tail) = 0.041.)

The total number of patients who developed pigmentation (before or after operation) was 37; that is 47% of the total and 49% of the patients followed. Actuarial (life-table) calculation of the cumulative pigmentation rate (Fig. 1) [33] shows that the proportion of patients unpigmented at the time of the operation who developed pigmentation later may be expected to rise to maxima of 34% by 9 years after the operation in group I, and to 80% by 13 years in group II. If the 3 patients who were pigmented before the operation in the latter group are added, the total proportion of pigmented patients is still higher.

Pituitary Radiographs

Preoperative radiographs of the pituitary fossa were available in 65 patients (82% of 79) and postoperative follow-up films in 65 patients also (87% of 75). Both pre- and postoperative films were available in only 58 patients. The preoperative films were all taken shortly before operation. In group III patients the film taken before the last operation was used for "preoperative" analysis. In the assessment of postoperative X-ray features, the latest film available was used, except in pigmented patients in whom the first taken after pigmentation had been observed was assessed.

Definitely abnormal fossae were observed in 9% of patients before adrenalectomy (Table 5); the distribution of grades was similar in the 2 sexes. Postoperatively 22% of the patients had abnormal fossae. The type of operation did not influence the result.

Analysis of the films available both before and after the operation in 58 patients (Fig. 2) shows that 13 (22%) changed grade, all in the direction of abnormality. The 5 who were abnormal originally remained so and 1 (possibly 2) became even more abnormal afterward. The median times (and ranges) in years between operation and the recognition of a change in sellar grade were as follows: normal to equivocal, 11.2 (0.2–16.5); normal to abnormal, 4.2 (1.6–6.6); and equivocal to abnormal, 5.6 (0.3–7.0).

Table 5. Distribution of pituitary fossa grades before and after operation in all patients in whom radiographs were available. (Sexes, adrenalectomy groups, and pigmented and non-pigmented patients are combined).

Pituitary fossa grade	Before		After	
	No. of patients	(%)	No. of patients	(%)
Normal	48	(74)	39	(60)
Equivocal	11	(17)	12	(18)
Abnormal	6[a]	(9)	14[a]	(22)
All grades	65	(100)	65	(100)

[a]Comparing proportions of abnormal fossae before (6/65) and after (14/65) operation, $\chi^2 = 3.782$, $p(1 \text{ d.f.}) < 0.1$.

Plasma ACTH

Plasma ACTH measurements were obtained before adrenalectomy in 23 patients (29%), after in 58 (77%), and both before and after in 20 (27%).

Over 80% of the preoperative readings were made in patients in group II because most of the other operations were done before the assay was available. However, similar porportions ($p > 0.05$) of patients who were still alive after the different procedures were studied postoperatively. The pro-

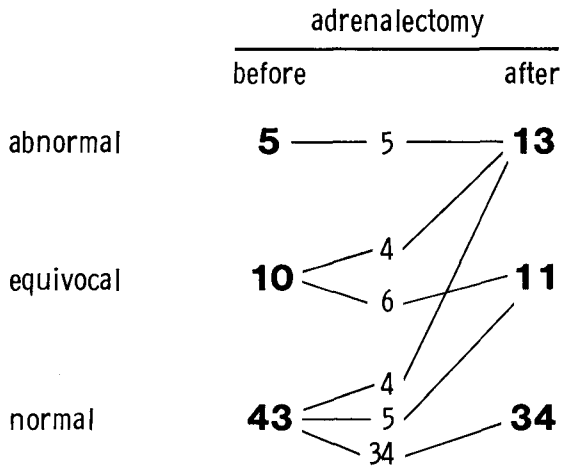

Fig. 2. Distribution of pituitary fossa grades before and after adrenalectomy in patients studied at both periods (numbers indicate numbers of patients).

portions of males and females investigated at all stages were also similar.

The preoperative readings used for analysis were the highest observed in each patient. For patients in group III the readings were made before the last operation. Similarly, for postoperative analysis the highest recorded value was used in non-pigmented patients, whereas in those who were pigmented, the first value after pigmentation had been observed was employed.

Many of the highest readings (> 800 ng/L) were reported as "greater than—ng/L" so that mean values could not be calculated. For analysis, the readings were divided arbitrarily into the following categories: normal (≤ 80 ng/L), high (81–800 ng/L), and very high (> 800 ng/L).

The distributions of categories in the 2 sexes were similar at all stages. Before the operation, approximately one-third of the patients had normal readings and two-thirds had high ones, while only 1 patient was classed as very high (Table 6). There was a marked shift toward higher ACTH values postoperatively, some of them being over 5,000 ng/L. Very high levels were observed more frequently in patients in group II than in those in the other groups.

Analysis of the 20 patients, who were studied both before and after the operation, shows that 14 (70%) moved into a higher ACTH category after the operation and that only 1 moved into a lower one (1,200 ng/L before and 165 ng/L after) (Fig. 3). After operation, however, the levels tended to fluctuate in individual patients and did not show any overall trend. Very high levels were not always permanent and fell spontaneously in 9 of the 20 patients (45%) in whom they were observed, sometimes to normal. Each year after the operation, the proportions of all readings in each category were similar.

Relationships Between Pigmentation, Sellar Grades, and Plasma ACTH Categories

Before adrenalectomy. Of the 5 patients pigmented before the operation, the fossae were normal in 3 and abnormal in 2. The ACTH level was available for only 1 patient and this was normal, as was his sellar grade. Preoperative ACTH levels were not predictive of the development of pigmentation postoperatively.

After Adrenalectomy. Each of the 3 factors has been compared with the other 2 (Tables 7, 8, and 9). The 5 patients who were already pigmented at the time of the operation have been included in this analysis. Their exclusion does not influence the main conclusions.

There was a clear relationship between pigmentation and ACTH levels. Fifty-three percent of pigmented patients developed very high levels, compared with only 12% of non-pigmented (Table 7). Similarly, far more of those with very high levels of ACTH (85%) were pigmented than of those with normal or high ones (39%). In 4 of the pigmented patients (12% of those in whom readings were available), the high ACTH levels, recorded when pigmentation was first observed, later rose further, and in one of them it became very high. However, no clear temporal relationship was observed between a rise in the ACTH concentration and the development of pigmentation. Precise ACTH readings in the 3 non-pigmented patients with very high levels were not made.

Readings were available after the operation in 3 of the patients who were pigmented preoperatively. The one whose level had been normal developed a high one (280 ng/L) and the other 2 very high levels (825 and 1,416 ng/L).

A greater proportion of pigmented than non-pigmented patients had abnormal sellae (33% and 7%, respectively), and higher proportions of patients with abnormal fossae were pigmented than of those with normal and equivocal ones (86% and 47%, respectively) (Table 8). The 13 patients whose sellar grades changed postoperatively had an incidence of pigmentation similar to that in the 45 patients with unchanged sellae.

Comparison of sellar grades and ACTH categories does not reveal any significant correlations ($p > 0.1$) (Table 9). Indeed, the highest proportion of those with very high ACTH levels (68%) was found (unexpectedly) in patients with normal sellae. Patients whose sellar grades changed had a similar distribution of ACTH categories to those in whom they remained unchanged.

Table 6. Distribution of plasma ACTH concentration categories before and after operation in all patients in whom readings available. (Sexes, all sellar grades, and pigmented and non-pigmented patients are combined).

ACTH category (ng/L)	Before		After							
			Group I		Group II		Group III		All groups	
	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Normal (≤80)	8[a]	(35)	0	(0)	1	(3)	1	(17)	2[a]	(3)
High (81–800)	14[a]	(61)	14	(88)	18	(50)	4	(66)	36[a]	(62)
Very high (≥801)	1[a]	(4)	2[b]	(12)	17[b]	(47)	1	(17)	20[a]	(35)
All categories	23	(100)	16	(100)	36	(100)	6	(100)	58	(100)

[a]Comparing the numbers of patients in each of the 3 categories before operation (8, 14, and 1/23) and after operation (2, 36, and 20/58), $\chi^2 = 18.9$, $p(2 \text{ d.f.}) < 0.001$.

[b]Comparing the patients with very high levels in groups I (2/16) and II (17/36), $\chi^2 = 4.36$, $p(1 \text{ d.f.}) < 0.05$.

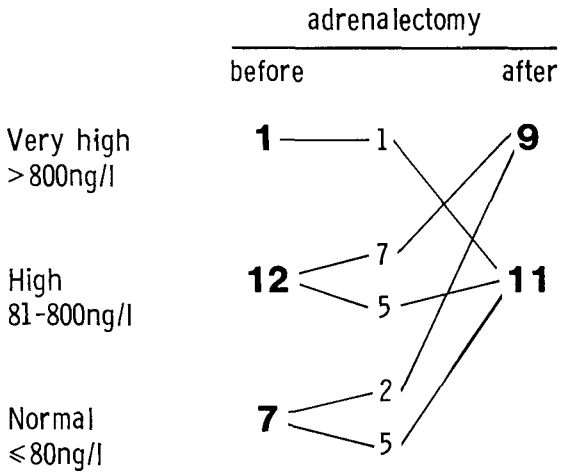

Fig. 3. Distribution of plasma ACTH concentrations before and after adrenalectomy in patients studied at both periods (numbers indicate numbers of patients).

Influence of Pituitary Irradiation

In the following analyses the 12 patients who had previously received adequate irradiation—internal in 8 and external in 4 (including 1 who received inadequate internal irradiation in addition)—are compared with patients who received inadequate irradiation or none at all (Table 2).

Pigmentation. The 5 patients who were pigmented at the time of adrenalectomy, 3 of whom had been irradiated (P34, 68, 96), have been excluded. Six, who had failed to remit after internal irradiation (P57, 67, 75, 77, 79, 95), became pigmented later. Of 3 who had been irradiated externally (P55, 84, 99), one became pigmented (P55). Of the remaining 61 patients (excluding 3 who died postoperatively and 1 untraced), 25 (41%) became pigmented.

Plasma ACTH. Plasma ACTH measurements were available after adrenalectomy in 10 of the 12 patients who had previously received adequate pituitary irradiation (7 internal and 3 external). Four (40%) were high (2 internal and 2 external) and 6 (60%) very high (5 internal and 1 external). The numbers (and proportions) in the 48 patients who had not received adequate irradiation were: normal, 2 (4%); high, 32 (67%); and very high, 14 (29%).

The differences are not significant ($p > 0.1$). Readings were available before and after the operation in 5 of the 12 irradiated patients (P67, 75, 84, 95, 96), in all of whom the levels rose, 4 of them changing category. Levels in the 2 who received external radiotherapy were high (238 and 280 ng/L) shortly after, but returned to normal within 2 or 3 years and remained so.

Pituitary Fossa Grades. The pituitary fossa grades before adequate internal irradiation and adrenalectomy (Table 2) were as follows: normal, 4 (P67, 77, 79, 95); equivocal, 2 (P57, 75); abnormal, 2 (P34, 68). The grade changed from equivocal to abnormal afterward in 1 (P57), but was unchanged in the remainder. In 1 patient (P34), however, an abnormal fossa increased in size.

The grades before adequate external irradiation and adrenalectomy were: normal 2 (P96, 99); equivocal, 1 (P84); abnormal, 1 (P55). The grades did not change in the 3 patients in whom fossae were assessed later. Thirteen fossae in the remaining 45 patients (24%), who were not irradiated (or who received inadequate irradiation), changed grade after adrenalectomy.

Pituitary Tumors

The relationships of the features that have been described to histological and to other clinical signs were examined and the effects of treatment on definite or presumed pituitary tumors were analyzed.

Definite Tumors. In the 15 patients with direct evidence of pituitary tumors, histological confirma-

Table 7. Relationship between pigmentation and ACTH category.[a]

Pigmentation	ACTH category			
	Normal	High	Very high	Total
Present				
No. (column %)	1[b] (50%)	14[c] (39%)	17[d] (85%)	32 (55%)
(row %)	(3%)	(44%)	(53%)	(100%)
Absent				
No. (column %)	1 (50%)	22 (61%)	3[e] (15%)	26 (45%)
(row %)	(3%)	(85%)	(17%)	(100%)
Total				
No. (column %)	2 (100%)	36 (100%)	20 (100%)	58 (100%)
(row %)	(3%)	(62%)	(35%)	(100%)

[a]All patients in whom data relating to both characteristics were available, including those pigmented before operation. Percentages after numbers refer to column totals and those below to row totals.

Comparing: (1) incidence of pigmentation in patients who had normal[b] and high[c] ACTH categories (15/38) with that in patients who had very high[d] categories (17/20), and (2) incidence of very high ACTH category in patients in whom pigmentation was present[d] (17/32) with that in patients in whom it was absent[e] (3/26), $\chi^2 = 11.016$, $p(1 \text{ d.f.}) < 0.001$.

Table 8. Relationship between pigmentation and sellar grade.[a]

Pigmentation	Sellar grade			
	Normal	Equivocal	Abnormal	Total
Present				
No. (column %)	19[b] (49%)	5[c] (42%)	12[d] (86%)	36 (55%)
(row %)	(53%)	(14%)	(33%)	(100%)
Absent				
No. (column %)	20 (51%)	7 (58%)	2[e] (14%)	29 (45%)
(row %)	(69%)	(24%)	(7%)	(100%)
Total				
No. (column %)	39 (100%)	12 (100%)	14 (100%)	65 (100%)
(row %)	(60%)	(18%)	(22%)	(100%)

[a]All patients in whom data relating to both characteristics were available, including those pigmented before operation. Percentages after numbers refer to column totals and those below to row totals.

Comparing: (1) incidence of pigmentation in patients who had normal[b] and equivocal[c] sellar grades (24/51) with that in patients who had abnormal[d] grades (12/14), and (2) incidence of abnormal sellar grades in patients in whom pigmentation was present[d] (12/36) with that in patients in whom it was absent[e] (2/29), $\chi^2 = 5{\cdot}170$, $p(1 \text{ d.f.}) < 0.05$.

tion was obtained from biopsy (implant or operation) or autopsy material. In 9 the tumors were benign and in 6 they were malignant and locally invasive, although not metastatic. In 8 (group A) the evidence was present when the patients were first investigated, while in 7 (group B) it appeared some time after adrenalectomy.

Comparison of the 2 groups of patients (Table 10) shows that none of those in group A was pigmented initially (although 5 became so later), while pigmentation was an early sign in 6 of the 7 in group B. It also shows that all in group A had abnormal or equivocal sellae on radiography, while 3 in group B had apparently normal fossae. The large number of unknown ACTH levels reflects the fact that many of these patients were seen before the assay became available.

In 6 of the 8 patients in group A, treatment in the form of irradiation and/or surgical operation was directed at the pituitary tumors initially. As none came under control, all then underwent adrenalectomy. Three with malignant tumors (P27, 32, 34) died within 30 months from the local effects of their tumors or from attempts to treat them. The other 3 (P57, 55, 69) received additional pituitary therapy and were alive between 13 and 18 years after their initial treatment. Two were well, but one (P57) was pigmented and had been advised further therapy.

The other 2 patients in group A (P33, 73), whose only signs of tumor initially were equivocal sellae, were treated by adrenalectomy at first. Later both became deeply pigmented and developed frankly abnormal sellae. One (P33), whose tumor was benign, underwent surgical hypophysectomy 6 years after adrenalectomy and was well 11 years later. The other (P73), who had a malignant tumor and

Table 9. Relationship between sellar grade and ACTH category.[a]

Sellar grade	ACTH category			
	Normal	High	Very high	Total
Present				
No. (column %)	1 (50%)	21 (60%)	13 (68%)	35 (62%)
(row %)	(3%)	(60%)	(37%)	(100%)
Equivocal				
No. (column %)	1 (50%)	8 (23%)	2 (11%)	11 (20%)
(row %)	(9%)	(37%)	(18%)	(100%)
Abnormal				
No. (column %)	0 (0%)	6 (17%)	4 (21%)	10 (18%)
(row %)	(0%)	(60%)	(40%)	(100%)
Total				
No. (column %)	2 (100%)	35 (100%)	19 (100%)	56 (100%)
(row %)	(4%)	(62%)	(34%)	(100%)

[a]All patients in whom data relating to both characteristics were available, including those pigmented before operation. Percentages after numbers refer to column totals and those below to row totals.

Table 10. Incidence of descriptive features in patients with definite pituitary tumors.

Features	Group A	Group B	Total
	Signs of tumor when Cushing's syndrome diagnosed	Signs of tumor developing after adrenalectomy	
No. of patients	8	7	15
Sex (male:female)	4:4	1:6	5:10
Histology (benign:malignant)	4:4	5:2	9:6
Pigmentation	0[a,b]	6[b]	6
Sellar grade			
Normal	0	3	3
Equivocal	3	1	4
Abnormal	5	3	8
ACTH category			
Normal	0	0	0
High	1	2	3
Very high	0	2	2
Unknown	7	3	10
Eye signs present	3[c]	1[c]	4

[a]Developed later in 5.
[b]Comparing incidence of pigmentation in 2 groups, exact p (single tail) = 0.00051, (double tail) = 0.00102.
[c]Developed later in 1 other.

whose plasma ACTH level rose to over 5,000 ng/L, was treated 5 years after adrenalectomy, but died 3 years later.

Three of the 7 group B patients (P1, 7, 11) became pigmented and their fossae changed from normal to abnormal between 18 months (P7) and 8 years (P1) after adrenalectomy. One had a benign tumor and was cured by hypophysectomy (P11) after 4 years, but died from an unrelated cause 1 year later. The other 2 died from spread of their tumors 2 (P7) and 4 (P1) years, respectively, after becoming pigmented. The first had no definitive treatment, while therapy in the second was ineffective. A further patient (P37) developed an equivocal fossa and a high ACTH level, but no pigmentation, 15 years after adrenalectomy. She underwent hypophysectomy and had a normal ACTH level 3 months later.

Three other patients in group B developed signs of tumor after adrenalectomy, but had normal pituitary radiographs. One (P77) was deeply pigmented and had a very high ACTH level after 10 years. Computed tomographic scanning, however, revealed a tumor with extensive extrasellar spread. Partial hypophysectomy for an apparently benign tumor and external radiotherapy caused some fading of the pigmentation and a slight fall in the ACTH

level after 3 months. A second patient (P114) developed a visual field defect and a high ACTH level within 2 years of adrenalectomy. Hypophysectomy for a benign adenoma was followed 2 years later by radiotherapy and treatment with bromocriptine. Three years later all the abnormal features had ameliorated. The third patient (P95) had had a positive biopsy when she was treated initially by pituitary implant. She did not reveal any overt sign of tumor until 5 years after adrenalectomy, when she became pigmented and developed a very high ACTH level (> 3,000 ng/L).

Probable Tumors. Twenty-one patients had features alone or in combination which, together with Cushing's syndrome, were considered (arbitrarily) to indicate the probable presence of a pituitary tumor, although histological evidence was not available. These, and the numbers of patients in whom they were observed, were: generalized pigmentation (16), an abnormal sella (4), sella observed to change from normal to equivocal (2), very high ACTH level (15), or a characteristic visual field defect (2). Four patients showed these signs initially (one was pigmented, P68), and 17 after adrenalectomy. In 5 (P68, 75, 106, 62, 39), the clinical state was considered severe enough to merit treatment and they received internal or external irradiation alone or in combination. One patient (P68) underwent hypophysectomy after pituitary implantation without tumor tissue being found. All 5 improved and were alive between 3 and 12 years after treatment of their pituitaries. Two of the 21 patients died, but it is not known if they had tumors (P42, 60).

Suspected Tumors. In 14 patients the evidence for a tumor was no more than suggestive. Ten had mild pigmentation and 7 had equivocal sellae. These signs were seen initially in 8 and after adrenalectomy in 6. One with an equivocal fossa (P105) on conventional X-rays was found with metrizamide cisternography to have an empty sella. One patient (P81) received inadequate internal irradiation as initial treatment and 2 (P84, 96) received adequate external irradiation at the time of adrenalectomy. Two of the 14 patients died from cardiovascular causes (P81, 17) and one, whose pituitary was examined postmortem, did not have a tumor.

No Clinical Evidence of Tumor. Twenty-nine patients had no direct evidence of tumor initially or during subsequent follow-up. Two of these (P10, 13), who died from unrelated causes, were found at autopsy to have small adenomas.

Influence of Type of Operation

In group I, 24 patients who did not show any evidence of pituitary tumors initially survived adrenalectomy. Nine of these (37.5%) were classed as having suspected, probable, or definite tumors later. In group II the equivalent numbers are 26 and 16 (61.5%). Although this incidence appears to be greater, the difference is not significant ($\chi^2 = 2.00$, $p < 0.1$). If those with probable or definite tumors only are considered, the corresponding numbers for group I are 24 and 7 (29%) and, for group II, 33 and 12 (36%), respectively. This difference is insignificant also ($\chi^2 = 0.08$, $p > 0.7$). Although the numbers are comparatively small, it seems unlikely that the type of initial operation (subtotal or total) influenced the development of pituitary tumors after adrenalectomy.

Discussion

Although all the patients in this series were treated by bilateral adrenalectomy, they were derived from two very different sources. The great majority (80%) were unselected, as far as we know, and their results should typify the generality of patients with pituitary-dependent Cushing's disease. However, a minority were highly selected in that either their hypersecretion of ACTH had failed to respond adequately to interstitial irradiation (15%), thereby implying that tumor had already spread beyond the sella, at least in those who received adequate doses (10%), or that pituitary implantation was impossible for technical reasons (5%). Naturally, the series did not include patients in whom these procedures had been effective, most of whom presumably had pituitary tumors that had been ablated. At Hammersmith internal pituitary irradiation is usually effective [31, 32] and adrenalectomy has not been required after this procedure since 1976 [30].

Some 90% of patients with Cushing's disease have identifiable ACTH-secreting pituitary tumors, so that the presence of the syndrome itself provides indirect evidence of such a lesion. The other features—pigmentation, radiological sellar changes, increased ACTH levels, and eye signs—may be regarded as providing direct evidence. None, however, is entirely reliable and a tumor can only be recognized for certain on histological examination, which may not be available until after death. Nevertheless, such features must be used for practical clinical purposes and for decisions about management. Our data show that histologically invasive tumors, which were only recognizable clinically by their remorseless, malignant course, were rapidly fatal in every case. All the benign ones, which were treated by surgical and/or radiotherapeutic methods, were halted or reversed in their courses and some were apparently cured. It is not possible to predict what the outcome would have been if they

had not been treated, but visual field defects were reversed in 3 (P57, 39, 75). It seems prudent to regard all direct signs, suggestive of pituitary tumors, as indications for frequent careful review. All patients with evidence of enlarging tumors or distressing symptoms should be treated.

Radiographic assessment of tumors has improved greatly since the introduction of modern computed tomographic scanning, as shown in one of our patients (P77), and such direct evidence of many more tumors will probably be forthcoming in the near future. Although definite diagnoses will still depend on histological evidence, treatment is likely to be influenced in the direction of earlier and more aggressive intervention.

Our data confirm that some patients have obvious pituitary tumors when Cushing's syndrome is first diagnosed, but that more patients develop them after adrenalectomy. Nevertheless, the numbers doing so are not great and in our series only 11 patients (6 of them with histologically confirmed tumors) are considered to have had lesions severe enough to require treatment. It is clear that direct evidence may not be available and that, when it is, it varies from one patient to another. Thus, pigmentation is not invariable (particularly before adrenalectomy) and the sella may often be normal by conventional examination. The terms "Siebenmann's syndrome" and "Nelson's syndrome" have been valuable in focusing attention on pituitary tumors in Cushing's syndrome, but they represent only certain aspects of the total spectrum of the disease.

It has never been clear whether the activity and growth of tumors are stimulated by adrenal ablation or whether they simply continue to grow at a steady rate and become apparent later because the Cushing's syndrome is cured and the patients can thereby survive. Four observations seem to support the first hypothesis and suggest that functioning adrenals have an inhibitory effect on the pituitary. These are: (a) pigmentation was less frequent after subtotal than after total adrenalectomy (Table 4); (b) pigmentation did not develop in patients with adrenal remnants whose functional capacity was great enough to obviate the need for replacement therapy, but not so great as to cause recurrence of Cushing's syndrome; (c) the plasma ACTH levels rose rapidly after adrenalectomy in pigmented and non-pigmented patients; and (d) pigmentation was absent in 8 patients with definite tumors that were radiologically evident at the time of diagnosis of Cushing's syndrome, and developed after adrenalectomy in 5 of them. It seems reasonable to suppose that more ACTH is required to cause pigmentation than to stimulate the adrenals to hyperplasia and that the cortisol excess in pituitary-dependent Cushing's syndrome usually supresses the ACTH output below the critical level causing pigmentation until it is removed by total adrenalectomy. Then, in the course of time, pigmentation develops, in our series reaching 80% by 13 years after total adrenalectomy. While the incidence of pigmentation and of very high plasma ACTH levels was greater after total than after subtotal adrenalectomy, the sellar grades and the apparent incidence of pituitary tumors were similar after the 2 operations. This suggests that subtotal adrenalectomy inhibits the functional activity, but not the actual growth, of tumors.

This study shows that the hazard of a pituitary tumor progressing after adrenalectomy is real, but that the risk is not great (about 10–15%). Nevertheless, a direct attack on the pituitary gland is to be preferred if it reduces this risk. Our observations provide a baseline against which the results of such more recent forms of treatment can be compared.

Résumé

De 1953 à 1980, 79 malades atteints de maladie de Cushing hypophyso-dépendantes ont subi une surrénalectomie subtotale ou totale. Soixante-seize ont survécu à l'opération et 75 ont été suivis de 1 à 27 ans après l'intervention. On a évalué à intervalles réguliers la pigmentation, le taux plasmatique d'ACTH et l'état radiologique de la selle turcique.

La pigmentation s'est développée chez 37 malades (5 avant et 32 après l'intervention) plus particulièrement après surrénalectomie totale.

L'élargissement de la selle turcique a été constaté chez 65 sujets étudiés, 6 fois avant l'intervention et 14 fois après celle-ci, l'élargissement étant plus fréquent chez les sujets accusant une nette pigmentation.

La concentration plasmatique en ACTH s'est élevée après surrénalectomie, le taux étant plus élevé chez les malades pigmentés et après surrénalectomie totale.

Le diagnostic de tumeur hypophysaire a été confirmé histologiquement chez 15 sujets: 8 fois au moment de la découverte du Cushing et 7 fois après la surrénalectomie. Chez 6 de ces 7 opérés la tumeur de nature maligne entraîna la mort. Onze des 15 sujets développèrent une pigmentation après la surrénalectomie.

Chez 9 autres malades qui présentaient des lésions bénignes et chez 21 qui présentaient une tumeur cliniquement probable mais qui ne fut pas confirmée histologiquement, 7 furent traités par hypophysectomie avec ou sans irradiation (4 guéris, 3 améliorés) et 4 par irradiation externe (3 cas) et interne (1 cas), tous les 4 améliorés.

Resumen

Setenta y nueve pacientes fueron sometidos a adrenalectomía subtotal o total por síndrome de Cushing pituitario-dependiente (1953–1980); 76 sobrevivieron la operación y 75 fueron seguidos por 1 a 27 (media de 11) años. La pigmentación, los niveles plasmáticos de ACTH y radiografías de la silla turca fueron evaluados periódicamente.

La pigmentación se desarrolló en 37 (5 antes y 32 después de la operación), más frecuentemente después de adrenalectomía total.

La silla turca apareció claramente aumentada de tamaño en 6 de 65 pacientes antes de la operación y en 14 de 65 después. El aumento de tamaño fue más común en los pacientes pigmentados que en los no pigmentados.

La concentración plasmática de ACTH ascendió después de la adrenalectomía. Se presentó en forma significativamente más alta en los pacientes pigmentados que en los no pigmentados. Fue más alta después de adrenalectomía total que de adrenalectomía subtotal.

Tumores pituitarios fueron confirmados histológicamente en 15 pacientes. Se presentaron al tiempo con el síndrome de Cushing en 8 y después de adrenalectomía en 7. Los tumores fueron malignos y fatales en 6. La pigmentación, presente en la totalidad de los 11 pacientes, se desarrolló solo después de la adrenalectomía. En otros 9 pacientes con lesiones benignas y en 21 con tumores clínicamente probables pero histológicamente no confirmados, 7 fueron tratados con hipofisectomía con o sin irradiación (4 curados 3 mejorados) y 4 con irradiación solamente (externa 3, interna 1), todos mejorados.

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References

1. Bigos, T.S., Somma, M., Rasio, E., Eastman, R.C., Lanthier, A., Johnston, H.H., Hardy, J.: Cushing's disease: Management by transsphenoidal pituitary microsurgery. J. Clin. Endocrinol. Metab. *50*:348, 1980
2. Fahlbusch, R., Müller, O.A.: Microadenomectomy and postoperative follow-up in Cushing's disease. J. Neurol. Neurosurg. Psychiat. *45*:277, 1982
3. Salassa, R.M., Kearns, T.P., Kernohan, J.W., Sprague, R.G., MacCarthy, C.S.: Pituitary tumors in patients with Cushing's syndrome. J. Clin. Endocrinol. Metab. *19*:1523, 1959
4. MacErlean, D.P., Doyle, F.H.: The pituitary fossa in Cushing's syndrome. A retrospective analysis of 93 patients. Br. J. Radiol. *49*:820, 1976
5. Pardee, I.H.: Basophilic hyperplasia of the pituitary in essential hypertension. Am. J. Med. Sci. *190*:7, 1935
6. Carmalt, M.H.B., Dalton, G.A., Fletcher, R.F., Smith, T.W.: The treatment of Cushing's disease by transsphenoidal hypophysectomy. Q.J. Med. [N.S. 46] *181*:119, 1977
7. Lamberts, S.W.J., Stefanko, S.Z., DeLange, S.A., Fermin, H., Van der Vijver, J.-C.M., Weber, R.F.A., DeJong, F.H.: Failure of clinical remission after transsphenoidal removal of a microadenoma in a patient with Cushing's disease: Multiple hyperplastic and adenomatous cell nests in surrounding pituitary tissue. J. Clin. Endocrinol. Metab. *50*:793, 1980
8. Cushing, H.W.: The Pituitary Body and Its Disorders. Philadelphia, J.B. Lippincott Co., 1912, case 45
9. Siebenmann, R.E.: Invasiv wachsendes, vorwiegend basophiles adenom des hypophysenvorderlappens bei Cushing-Rezidiv nach subtotaler adrenectomie. Schweiz. Z. Allg. Pathol. *18*:1189, 1955
10. Nelson, D.H., Meakin, J.W., Dealy, J.B., Matson, D.D., Emerson, K., Jr., Thorn, G.W.: ACTH-producing tumor of the pituitary gland. N. Engl. J. Med. *259*:161, 1958
11. Harrison, J.H.: ibid. (p. 374), Glenn, F., Karl, R.C., Horwith, M.: The surgical treatment of Cushing's syndrome. Ann. Surg. *148*:365, 1958
12. Rees, J.R., Bayliss, R.I.S.: Cushing's syndrome with pituitary tumour and pigmentation. Proc. R. Soc. Med. [Endocrinol.] *52*:256, 1959
13. Montgomery, D.A.D., Welbourn, R.B., MacCaughey, W.T.E., Gleadhill, C.A.: Pituitary tumours manifested after adrenalectomy for Cushing's syndrome. Lancet *31*:707, 1959
14. Nelson, D.H., Meakin, J.W., Thorn, G.W.: ACTH-producing pituitary tumours following adrenalectomy for Cushing's syndrome. Ann. Intern. Med. *52*:560, 1960
15. Orth, D.N., Liddle, G.W.: Results of treatment in 108 patients with Cushing's syndrome. N. Engl. J. Med. *285*:243, 1971
16. Cohen, L.K., Noth, H.R., Pechinski, T.: Incidence of pituitary tumors following adrenalectomy: A long-term follow-up study of patients treated for Cushing's disease. Arch. Intern. Med. *138*:575, 1978
17. Kelly, W.F., MacFarlane, I.A., Longson, D., Davies, D., Sutcliffe, H.: Cushing's disease treated by total adrenalectomy: Long-term observations of 43 patients. Q.J. Med. [N.S. 52] *206*:224, 1983
18. MacArthur, R.G., Hayles, A.B., Salassa, R.M.: Childhood Cushing's disease: Results of bilateral adrenalectomy. J. Pediatr. *59*:159, 1979
19. Sprague, R.G., Weeks, R.E., Priestley, J.T., Salassa. R.M.: Treatment of Cushing's syndrome by adrenal-

ectomy. In Modern Trends in Endocrinology (second series), H. Gardiner-Hill, editor, London, Butterworths, 1961, pp. 84–99
20. Taft, P., Martin, F.I.R., Melick, R.: Cushing's syndrome: A review of the response to treatment in 42 patients. Aust. Ann. Med. *19*:295, 1970
21. Glenn, F., Mannix, H., Jr.: Diagnosis and prognosis of Cushing's syndrome. Surg. Gynecol. Obstet. *126*:765, 1968
22. Moore, T.J., Dluhy, R.G., Williams, G.H., Cain, J.P.: Nelson's syndrome: Frequency, prognosis and effect of prior pituitary irradiation. Ann. Intern. Med. *85*:731, 1976
23. Wrightson, P.: Conservative removal of small pituitary tumours: Is it justified by the pathological findings? J. Neurol. Neurosurg. Psychiat. *41*:283, 1978
24. Kjellberg, R.N., Kliman, B.: Bragg peak proton treatment for pituitary-related conditions. Proc. R. Soc. Med. *67*:32, 1974
25. Lawrence, J.H., Linfoot, J.A.: Treatment of acromegaly, Cushing's disease and Nelson's syndrome. West. J. Med. *133*:197, 1980
26. Cassar, J., Doyle, F.A., Lewis, P.D., Mashiter, K., Van Noorden, S., Joplin, G.F.: Treatment of Nelson's syndrome by pituitary implantation of yttrium-90 or gold-198. Br. Med. J. *2*:269, 1976
27. Welbourn, R.B., Montgomery, D.A.D., Kennedy, T.L.: The natural history of treated Cushing's syndrome. Br. J. Surg. *58*:1, 1971
28. Welbourn, R.B.: Some aspects of adrenal surgery. Br. J. Surg. *67*:723, 1980
29. Davies, C.J., Joplin, G.F., Welbourn, R.B.: Surgical management of the ectopic ACTH syndrome. Ann. Surg. *196*:14, 1982
30. Welbourn, R.B., Manolas, K.J.: The role of adrenalectomy in the management of Cushing's syndrome. In Endocrine Surgery, I.D.A. Johnston and N.W. Thompson, editors, London, Butterworths, 1983, pp. 53–75.
31. Burke, C.W., Doyle, F.H., Joplin, G.F., Arnot, R.N., MacErlean, D.P., Fraser, R.T.: Cushing's disease: Treatment by pituitary implantation of radioactive gold or yttrium seeds. Q.J. Med. *168*:693, 1973
32. White, M.C., Doyle, F.H., Mashiter, K., Joplin, G.F.: Successful treatment of Cushing's disease using yttrium-90 rods. Br. Med. J. *285*:280, 1982
33. Rees, L.H., Cook, D.M., Kendall, J.W., Alin, C.F., Kramer, R.M., Ratcliffe, J.G., Knight, R.A.: A radioimmunoassay for rat plasma ACTH. Endocrinology *89*:254, 1971
34. Berkson, J., Gage, R.: Calculation of survival rates for cancer. Proc. Mayo Clin. *25*:270, 1950
35. Montgomery, D.A.D., Welbourn, R.B.: Cushing's syndrome: A report of thirteen cases and their surgical treatment. Br. J. Surg. *45*:137, 1957

Invited Commentary

Edward R. Laws, Jr., M.D.

Mayo Medical School, Mayo Clinic, Rochester, Minnesota, U.S.A.

This excellent paper from London and Belfast on the subject of adrenalectomy for Cushing's syndrome underscores much of what has been learned in recent years about the surgical management of this difficult problem. When Cushing's syndrome is caused by adrenal carcinoma or autogenous adrenal adenoma, adrenalectomy is clearly indicated, and should give satisfactory results. This situation, however, is rare, since these adrenal tumors are uncommon.

The surgeon who treats Cushing's syndrome by removal of hyperplastic adrenals msut be prepared for at least 2 categories of failure. Most important, as described in this paper, is the fact that at least 85% of such patients will have Cushing's disease, that is, a pituitary-hypothalamic source for their illness. At least 80% of these patients with Cushing's disease will have a pituitary adenoma as the source of their excess ACTH, and most of these pituitary tumors will be microadenomas ($\leq$ 10 mm in diameter) at the time Cushing's disease is initially diagnosed. A high proportion of these patients (47% as reported here) will develop Nelson's syndrome following adrenalectomy with hyperpigmentation, progressive growth of the pituitary tumor, or both. The implications are serious, not only because of the evolution of the pituitary adenoma after adrenalectomy, but also because these ACTH-producing tumors may not remain clinically benign. They are difficult to cure with surgery and/or radiotherapy and are notorious for their high recurrence rate (50%) and their ability to spread outside the sella along the base of the skull. Six of the 15 confirmed tumors in this report were "malignant and fatal."

The other potential problem in patients treated with adrenalectomy for Cushing's disease is failure to diagnose an ectopic source of ACTH. In addition bronchogenic carcinoma, pancreatic adenoma, pulmonary carcinoid, and other intra-abdominal tumors have been associated with Cushing's syndrome.

Modern endocrine diagnosis is now capable of distinguishing Cushing's disease from Cushing's syndrome in all but a few extraordinarily difficult cases, and can usually pinpoint ectopic sources of