Section of Surgery

President R H Franklin FRCS

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Advances in Endocrine Surgery [*Abridged*]

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Late Results of Adrenalectomy for Cushing's Syndrome

The early effects and some of the later sequelæ of adrenalectomy for Cushing's syndrome are well known (Welbourn 1969), but the late results of a complete series of patients has not, so far as we know, been reported since the advent of cortisone made adrenalectomy relatively safe. We report here the results after five years in our first 35 patients, after ten years in our first 20, and after fifteen years in our first 8.

The response to treatment depends very much on the nature of the underlying lesion (Table 1). Of our 35 patients 3 had adrenal adenomas, which were removed surgically. They all did well and are in remission at 5, 7 and 14 years respectively. Four had adrenal carcinomas and all fared badly, none of the 4 patients living for more than a year. One patient had a bronchial carcinoma and died in a few weeks without treatment.

Table 1
Underlying pathological lesions, at review in 1969, of 35 patients with Cushing's syndrome treated between 1953 and 1964

	No. of cases		
Adrenal tumours			
Adenoma	3	7	
Carcinoma	4		
Tumour elsewhere (bronchial carcinoma)	1		
Pituitary-adrenal hyperfunction			
Pituitary tumour:			
Apparent at onset of syndrome	4 ●	9	27
Becoming manifest after adrenalectomy	3 ■		
Benign adenoma discovered at autopsy	2		
Adrenal hyperplasia without evidence of tumour elsewhere	18		

● 3 of these were invasive
■ 1 of these was invasive

Pituitary-adrenal Hyperfunction
Twenty-seven patients had pituitary-adrenal hyperfunction and bilateral adrenal hyperplasia. It is known from post-mortem evidence that about half such patients have pituitary adenomas, many of which are small and unrecognizable during life. It is known also from clinical experience that some of them are large, that some reveal themselves only after adrenalectomy, and that some are locally malignant and invade the tissues around the pituitary in an insidious and lethal manner.

Pituitary tumours: Of our 27 patients, 9, or one-third, had pituitary tumours. Four were apparent initially and 3 of these became invasive later. Three manifested themselves some time after adrenalectomy and one of these was invasive. Two small benign ones were found at autopsy. We have lost trace of one patient, but the remaining 17 have not yet shown any evidence of pituitary tumours during 5–15 years of observation.

Our policy from the beginning has been to treat patients with obvious pituitary tumours by a direct surgical attack on the pituitary and the remainder by bilateral adrenalectomy. The 4 patients with obvious pituitary tumours initially had various combinations of internal irradiation and surgical hypophysectomy, but only one, who had a simple tumour, had a good remission, which has lasted for ten years. In the other 3 the syndrome was not controlled adequately and adrenalectomy was required subsequently. Their tumours became invasive later and all 3 patients were dead within three years.

Bilateral Adrenalectomy

We were then left with 23 patients with pituitary-adrenal hyperfunction, without evidence of pituitary tumours, and we planned to treat them all by bilateral adrenalectomy. One refused operation and then had a spontaneous remission. (This patient we lost track of after a year.) The remaining 22 had bilateral adrenalectomy, which was subtotal in 21 and total in one. Subtotal adrenalectomy involved removal of the whole of one gland, nearly always the right, and about nine-tenths of the other, usually in two stages.

All those who lived for more than a few months had good remissions and lost the florid features of Cushing's syndrome. Ten patients, however, died at various times after operation, one inexplicably within a few days. Six died from cardiovascular accidents, 4 within one year of operation, one after two years and one after thirteen years. One died from an invasive tumour of the pituitary after three and a half years, and 2 from meningoencephalitis after one year and four years respectively.

Signs of pituitary tumours developed in 3 of the 22 patients after adrenalectomy – an incidence of 14%. In all 3 there was widespread pigmentation within eighteen months of operation and in 2 the pituitary fossæ were enlarged within three years. One tumour, which was invasive, ruptured and caused death after three and a half years. A benign one was removed surgically and the pigmentation faded. The presence of the third tumour is presumed, but not proved. The patient, who was 11 at the time of operation, has never had any enlargement of the fossa. He has had a normal puberty and is now, eight years after operation, still deeply pigmented.

We know that pituitary tumours can remain dormant for a very long time because we found a small one at autopsy thirteen years after adrenalectomy. But in our series all those which revealed themselves during life did so within three years.

Adrenal Function and Recurrence after Subtotal Adrenalectomy

Our hope was that subtotal adrenalectomy would restore normal adrenal function. In fact it has not done so. Of the 20 patients without pituitary tumours initially, who survived operation, 8 (40%) were weaned off cortisone at first, but their steroid excretion was low and could not be stimulated by ACTH. Two of these patients developed recurrence of the syndrome. The first recurrence was in a woman of 44, six years after operation. The adrenal remnant was re-explored, but could not be found, and she then underwent remission again spontaneously and remains well nine years later. The second occurred in a man of 32, eleven years after operation. The adrenal remnant, which weighed 8 g, was removed totally and he is now well, on cortisone, four years later.

Twelve patients (60%) could not be weaned off cortisone at first. One of them, who failed to take her cortisone when she fell ill, had an acute adrenal crisis after five years. After nine years she had a temporary recurrence which settled down again when cortisone was stopped. She died from coronary occlusion four years later.

There were, then, 3 recurrences in 20 patients – or 15%. All were treated effectively or settled down on their own. Only three, or one-third, of the 9 patients who survived ten years remained off cortisone for this period without showing recurrence.

Three further patients with invasive pituitary tumours underwent subtotal adrenalectomy when attacks on the pituitary had failed to control the syndrome. One died from a cardiovascular accident before the effect could be assessed. The other 2 failed to respond and in one of them the adrenal remnant, which had increased to 10 g, was removed four months later. The patient then underwent remission. The other patient, mentioned earlier, who died from an invasive tumour *after* subtotal adrenalectomy, did not have any recurrence of Cushing's syndrome when the tumour enlarged. In our experience, then, subtotal adrenalectomy failed to control the syndrome in half the patients with invasive pituitary tumours.

Our feeling about subtotal adrenalectomy now is that, since so few patients achieve independence from cortisone and some develop recurrence, and since close personal supervision is required during the weaning period, it is neither safe nor worth while unless the patients live close enough to be seen regularly. One of us (D A D M) continues to use the subtotal operation for the majority of patients treated in Belfast, because they live close at hand; the other (R B W) has abandoned it in favour of total adrenalectomy, and accepts the need for permanent replacement therapy from the beginning, because the patients treated at Hammersmith come from far away.

Hypertension

Hypertension is an almost constant feature in Cushing's syndrome and all but one of these

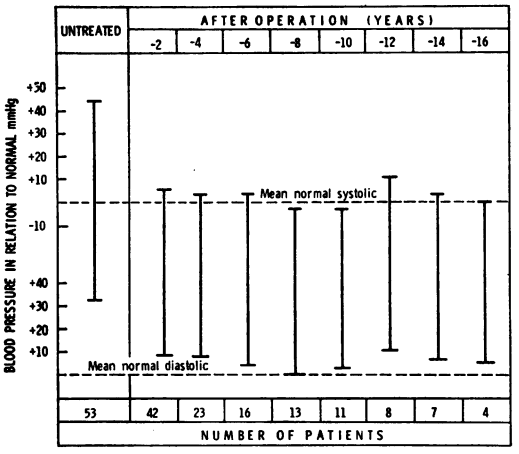

Fig 1 *Influence of surgical treatment of Cushing's syndrome on arterial blood pressure. All the blood pressure readings for each patient within each period of two years were averaged. The mean for each group was calculated from these individual means. The figures represent the amounts by which the mean pressures were greater or less than the mean values for the general population, account being taken of sex and age. Patients treated within the past five years (not in the series under review) have been included*

patients suffered from it (Welbourn 1964). Before treatment the mean systolic pressure was 45 mmHg, and the mean diastolic 32 mmHg, above the mean for the general population. Nearly half had serious complications before operation and some had atheromatous changes which were clearly irreversible. It is hardly surprising therefore that, although the blood pressure nearly always fell appreciably after operation, one-fifth of the patients died from cardiovascular accidents in the succeeding years and that 2 others have developed angina. In several, however, complications such as myocardial ischæmia and retinopathy have regressed.

Fig 1 shows the mean relative blood pressure at two-yearly intervals after operation for the whole series, together with some of the patients treated in the past five years. Within two years of operation the pressure fell to within 5 or 10 mmHg of normal and then remained there for fifteen years.

The average figures, however, conceal the course of events in individual patients. In 70% of those with benign lesions – the patients who underwent lasting remission – the pressure fell to normal or near normal and remained there. Occasionally it fell slowly and took about five years to reach normal, and sometimes it tended to rise again later, even without recurrence of the syndrome. In a few, who had been very hypertensive indeed, the pressure fell markedly, but still remained high, and in a few others it was never well controlled.

In one patient only, who had had pre-eclamptic toxæmia and hypertension before she developed Cushing's syndrome, was the blood pressure higher after adrenalectomy than it had been before.

Pregnancy

Sexual function is usually impaired in Cushing's syndrome and restored after successful treatment. Three women in our series have had 6 pregnancies between them since adrenalectomy and one woman has 3 healthy children. One patient had mild toxæmia during one pregnancy, but in all the other pregnancies the blood pressure remained normal.

Overall Survival

Fig 2 shows the numbers of patients in each group who were alive or dead in each of the first five years after treatment, and also after ten and fifteen years. Of the 22 patients with pituitary-adrenal hyperfunction and no obvious pituitary tumour initially, 5 died within the first year of adrenalectomy and one more died each year up

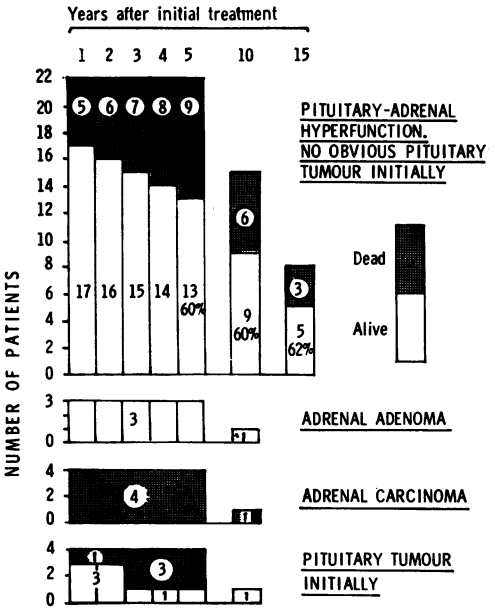

Fig 2 *Survival and mortality of 33 patients treated surgically at intervals after initial operation. For the whole series, who were treated more than five years ago, the results are shown annually for five years. For the first 18, who were treated more than ten years ago, the results are shown after ten years and for the first 8, treated more than fifteen years ago, the results are shown after fifteen years*

to five years; so that by then 13, or 60%, remained. Since then only one more patient has died – after thirteen years – and the proportions of those alive at ten years and at fifteen years were the same as at five years. All 3 patients with adenomas were alive at five years, while all 4 with carcinomas were dead in one year. Three of the 4 with pituitary tumours initially were dead in three years. The fourth was in remission and well after ten years.

This, then, is our experience of the natural history of treated Cushing's syndrome. Clearly, the first year after operation is the most hazardous. Thereafter those who survive the first five years have an excellent chance of surviving fifteen years and of leading normal lives.

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Dr D A D Montgomery (*The Sir George E Clark Metabolic Clinic, Royal Victoria Hospital, Belfast BT12 6BA*) said he felt that subtotal adrenalectomy still had a part to play in the treatment of certain cases of Cushing's syndrome due to adrenal hyperplasia, especially if effective follow up could be maintained. While agreeing that the adrenal remnant in such cases often functioned subnormally he thought that in others adrenal function returned to normal and he instanced the case of one young woman who had had a subtotal adrenalectomy sixteen years ago and whose initial subnormal response had now become normal.

Such cases might fall into the category of patients with Cushing's syndrome without pituitary tumours or other structural abnormality in the hypothalamic-pituitary region, whose adrenal hyperplasia possibly resulted from a functional disturbance of the hypothalamic-pituitary axis. If so, subtotal adrenalectomy might be an excellent method of treatment, but unfortunately there was no means as yet of detecting such patients during life. Finally, total adrenalectomy was important for control of the features of Cushing's syndrome in those patients with suspected pituitary lesions such as those with full-sized pituitary fossæ, but without sufficient evidence to make a definitive diagnosis of pituitary tumour.

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Surgical Implications of Medullary Carcinoma of the Thyroid

It is just ten years since Hazard *et al.* 1959 first described medullary carcinoma of the thyroid as a distinct entity. Williams (1967) added considerably to our knowledge of this tumour. The medullary carcinoma is a solid tumour composed of islands or nests of polygonal cells with clear or eosinophilic granular cytoplasm. A constant feature is the presence of amyloid in variable amounts in the stroma. The tumour, which is slow growing, is derived from parafollicular (C) cells which normally secrete calcitonin, and large quantities of calcitonin have now been found in tumours and in the plasma of patients with medullary carcinoma (Cunliffe *et al.* 1968). Davis (1967) reported that the incidence of medullary carcinoma in a series of 222 patients was 6·8% and similar incidence has been reported by others.

The histological material from all patients with malignant disease of the thyroid, seen in the Royal Victoria Infirmary since 1960, was examined. The distribution of tumour types is shown in Table 1. Five patients (7%) were found to have medullary carcinoma. A review of these 5 patients revealed some of the clinical and histological characteristics of this tumour and serum calcitonin levels were measured in 3. The main features of this group of patients are given in Table 2.

Table 1
Varieties of thyroid carcinoma in a series of 69 cases presenting over a period of 10 years

	No. of cases
Papillary	33 (48%)
Undifferentiated	17 (25%)
Acinar	14 (20%)
Medullary	5 (7%)

Clinical Cases
Case 1 Girl aged 19
Attended the Department of Dermatology because of acne vulgaris. She had a firm irregular goitre which had been present for about eight years. She had other symptoms. For many years she had been aware of lumps on the tongue, muscle weakness around the shoulder girdle, excessive abdominal gurgling and occasional diarrhœa. She was conscious of her unusual physique and had excess pigmentation of her