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ACTH Secreting Pituitary Tumours

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The majority of pituitary adenomas seem to be hormone secreting and the functionless tumour relatively rare. Prolactin and growth hormone secreting adenomas are the most common and a few tumours contain two types of cells and secrete both polypeptides. Corticotrophin (ACTH) secreting tumours are less common and those secreting thyrotrophin and gonadotrophin have only occasionally been described.

An ACTH secreting tumour in a patient with intact adrenal glands will cause adrenal hyperplasia, increased production of cortisol and the development of Cushing's syndrome. Overproduction of cortisol and Cushing's syndrome may be due to a cortisol-secreting adenoma or carcinoma of the adrenal cortex, or to excess ACTH of 'ectopic', or of pituitary origin. Cases of Cushing's syndrome due to excess ACTH production by the pituitary may be differentiated from the others and referred to as having Cushing's disease. One of the unresolved problems of Cushing's disease is whether the primary defect is in the hypothalamus or pituitary. The report by Nelson *et al.* (1960) of pituitary tumours becoming apparent after adrenalectomy for Cushing's syndrome was taken as evidence that the primary cause was a pituitary adenoma. More recently, however, Garcia *et al.* (1976) have described hyperplasia of corticotrophin producing cells in a similar situation. There is no answer to this question at the present time, but patients with Cushing's disease are being seen and have to be treated. Data on patients with Cushing's syndrome seen at the Middlesex Hospital between 1954 and 1976 will be reviewed with particular reference to the treatment to be advised.

PATIENTS AND METHODS

In the period 1954-76, 68 patients who had, or had had, Cushing's syndrome were seen at the Middlesex Hospital. In 12 it was primarily of adrenal origin, and in 9 an ectopic ACTH syndrome was diagnosed. The remaining 47 were made up as shown in Table 1. Of the patients not treated surgically, two refused operation, two were treated with X-ray therapy to the pituitary, two were elderly and had mild Cushing's syndrome, and one was not treated because of advanced vascular disease.

Plasma ACTH measurements were made initially by Dr J. G. B. Miller using a C-terminal antibody, and subsequently by Dr Lesley Rees at St Bartholomew's Hospital using an N-terminal antibody.

Table 1.

Patients with obvious pituitary tumour	3
Patients treated by total adrenalectomy	28
Patients treated by hypophysectomy	1
Patients not treated surgically	7
Patients who had had adrenalectomy elsewhere referred for follow-up	6
Patients who had had adrenalectomy elsewhere referred for treatment of Nelson's syndrome	2

Patients with a Pituitary Tumour at the Onset

There were three patients in this group. One presented with a temporal hemianopia and had his first operation before the features of Cushing's syndrome became apparent. These were noted three years later and he had a further operation and X-ray therapy, but died shortly afterwards. At autopsy a widely invasive pituitary tumour was found. This case has been reported in full (Shrank and Turner, 1960). The second patient presented with a visual field defect and obvious Cushing's syndrome. She was treated by transfrontal surgery, X-ray therapy and, finally, bilateral adrenalectomy. She was well when last seen four years later. The third presented with Cushing's syndrome and a 3rd nerve palsy. Despite trans-sphenoidal surgery and X-ray therapy the invasive tumour in the pituitary progressed relentlessly and the patient died 21 months after presentation. These cases are fortunately not common. They are very difficult to treat. If the local condition can be controlled by surgery and X-ray therapy, adrenalectomy may be undertaken if the Cushing's syndrome persists. Welbourn *et al.* (1971) have pointed out that adrenalectomy should not be delayed too long in these patients. The tendency of these tumours to be locally invasive and even to metastasise has been reviewed by Rovitt and Duane (1969).

Cushing's Disease — Hypothalamic or Pituitary Origin

In 1944, Heinbecker reported degenerative changes in the hypothalamus in four patients with Cushing's disease in whom detailed histological examination of that part of the brain was made. James *et al.* (1968), on the basis of dynamic endocrine tests of hypothalamic-pituitary function, suggested that the primary defect was in the hypothalamus or higher brain centres. This view was supported by Besser and Edwards (1972). Evidence of a primary pituitary origin was given in Cushing's original report (1932). It was supported by Plotz *et al.* (1952), who reviewed the literature and found reports of 58 patients coming to autopsy, in 35 of whom a pituitary adenoma was found. More recently, Burke *et al.* (1973) studied biopsy material obtained in the course of radioactive isotope implantation for the treatment of Cushing's disease. In 33 satisfactory biopsies 64 per cent showed the presence of a pituitary adenoma. Hardy (1973) reported the cure of

five patients by the removal of a small central pituitary adenoma by trans-sphenoidal microdissection. This data was updated by Vezina, at the Fifth International Congress of Endocrinology in July 1976, to 20 cures out of 25 patients treated in this way.

Mason (1972) has, however, pointed out that the presence of a pituitary tumour could be secondary to hypothalamic release of corticotrophin releasing factor (CRF) and is not necessarily evidence of primary pituitary disease. Liddle (1973) has emphasised that this question will not be solved until CRF has been identified and can be measured.

Nelson's Syndrome

The appearance of a pituitary tumour after adrenalectomy for Cushing's disease was described by Nelson *et al.* (1958) and Rees and Bayliss (1959). Both these patients developed increasing pigmentation and a visual field defect after adrenalectomy for Cushing's disease. It is possible that the pituitary tumour was present before adrenalectomy, but that the high circulating level of plasma cortisol inhibited both ACTH secretion and growth of the tumour. After adrenalectomy and reduction of plasma cortisol to the normal range, the negative feed-back of the high plasma cortisol is lost, ACTH secretion rises, causing pigmentation, and the tumour grows with first radiological then clinical manifestations.

There are, therefore, four phases in the development of Nelson's syndrome – rising ACTH levels, increasing pigmentation, radiological changes in the pituitary fossa and, finally, clinical evidence of a pituitary tumour. It is difficult to assess the incidence of Nelson's syndrome after adrenalectomy for Cushing's disease because of lack of detail in many of the published reports. Salassa *et al.* (1959) reported 122 patients, 8 of whom had evidence of pituitary tumour on presentation; in 5 of the remainder a tumour became apparent after adrenal surgery. Ernest and Ekman (1972) reported 4 patients who developed a pituitary tumour, and 3 with marked pigmentation without evidence of a tumour, in 38 patients surviving adrenalectomy who had no evidence of a tumour before operation. Besser *et al.* (1972) reported 14 patients with normal pituitary fossae before operation, 4 who developed radiological abnormalities after operation and a further 3 who developed severe pigmentation. Bennett *et al.* (1973) described 90 patients surviving adrenalectomy and noted that 10 had developed pituitary adenomas.

Middlesex Hospital Series

There are 44 patients in this series who could have had a pituitary tumour as the cause of their Cushing's syndrome. Two of these should be excluded from any assessment of the frequency of pituitary tumour in this condition because they were referred after having developed evidence of a tumour. Seven patients were not treated surgically: three of these died and were examined at autopsy at the

Middlesex Hospital. In one an adenoma of the pituitary was found; in the other two the initial report was of hyaline changes in the basophil cells. However, recent re-examination of the blocks (Dr Helen C. Grant) has revealed a small pituitary adenoma in both cases. In the patient treated by trans-sphenoidal surgery no discrete adenoma could be found, but the tissue was removed in small pieces.

Of the 34 patients treated by adrenalectomy, 19 have evidence of pituitary tumour or overactivity. One patient died from carcinoma of the colon three years after adrenalectomy for long-standing Cushing's syndrome. None of the clinical features of Nelson's syndrome had developed, but a small central pituitary adenoma was found at autopsy. Evidence of pituitary overactivity varies in its severity and the categories in Table 2 have been noted—

Table 2.

1. No clinical evidence—but ACTH level may be slightly increased	16 patients
2. Marked pigmentation and ACTH < 1000 ng/litre	8 patients
3. Very marked pigmentation and ACTH > 1000 ng/litre	4 patients
4. X-ray evidence of enlarging fossa + pigmentation	3 patients
5. Neurological evidence of pituitary tumour + pigmentation	3 patients

The time course of the development of pigmentation and treatment adopted in the 10 patients in groups 3, 4 and 5 are shown in Fig. 1. It will be noted that two patients had pituitary apoplexy, with 'cure' in one and transient remission in the other.

It is important to look at the age and sex of these patients in relation to the development of less severe (Group 2: Table 2) and more severe (Groups 3, 4 and 5) Nelson's syndrome. Five men under 35 years of age were included in the study; only one developed evidence of Nelson's syndrome (Group 2). Twelve women over 35 had adrenalectomy for Cushing's disease; three developed this complication, one in Group 4 and the other two in Group 2. However, of the 17 women operated on before they were 35 years old, nine had serious manifestations (Groups 3 to 5) and five came into Group 2. These figures suggest that young women having an adrenalectomy for Cushing's disease are particularly at risk for the development of Nelson's syndrome.

ACTH Levels

ACTH levels are available in 27 patients who have had adrenalectomy for Cushing's syndrome. These are shown in the right-hand column of Fig. 2; nearly all are above the normal range. In contrast, the levels in 18 patients on treatment for Addison's disease and 6 on replacement therapy after total adrenalectomy are shown in the left-hand column. The figures were surprising because these patients were all apparently well and performing their normal duties. The ACTH levels in

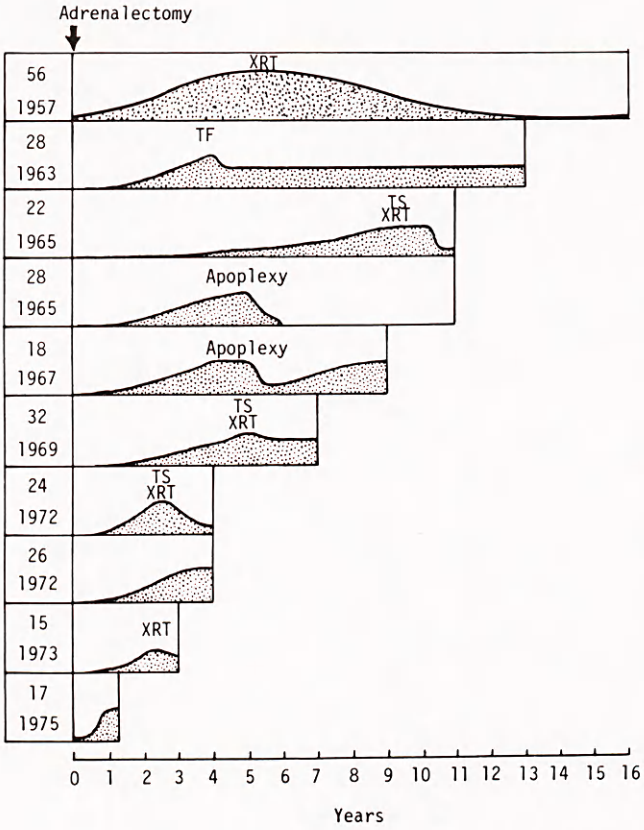

Fig. 1. Time course in 10 women who developed severe manifestations of Nelson's syndrome. On left, age and year of adrenalectomy. Stippling indicates degree of pigmentation and treatment undertaken is shown where appropriate. TF – transfrontal surgery. TS – trans-sphenoidal surgery: XRT – deep X-ray therapy.

most patients were measured in the course of a routine afternoon out-patient clinic. In the majority, plasma cortisol levels were measured at the same time as the plasma ACTH, and the results are shown in Fig. 3. This does not show the sharp distinction reported by Williams *et al.* (1961). The patients with Addison's disease and the highest ACTH levels had rather low levels of plasma cortisol and it might be argued that they were not adequately treated. However, one patient had a plasma cortisol of over 250 nM/litre and a simultaneous ACTH level of 907 ng/litre.

The most remarkable patient with Addison's disease shown on Fig. 2 had a fasting plasma ACTH of 4800 ng/litre. He does not appear on Fig. 3 because no simultaneous cortisol estimation was made. More detail is given in Fig. 4. He is

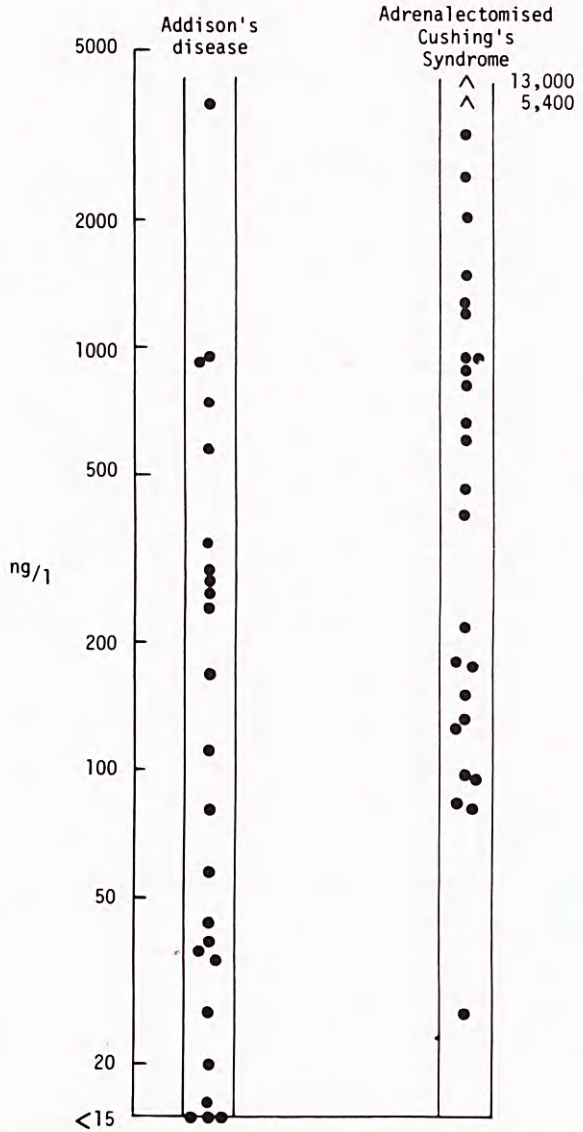

Fig. 2. Left-hand column – ACTH levels in patients with Addison's disease (18) or after total adrenalectomy for carcinoma (6). Right-hand column – ACTH levels after adrenalectomy for Cushing's syndrome (27). Patients all on their usual replacement therapy.

believed to have Schmidt's syndrome, having been diagnosed as hypothyroid at the age of two years and Addisonian when he was 13. He was maintained on 30 mg cortisone and 0.1 mg fludrocortisone each day. In 1973 he was noted to be

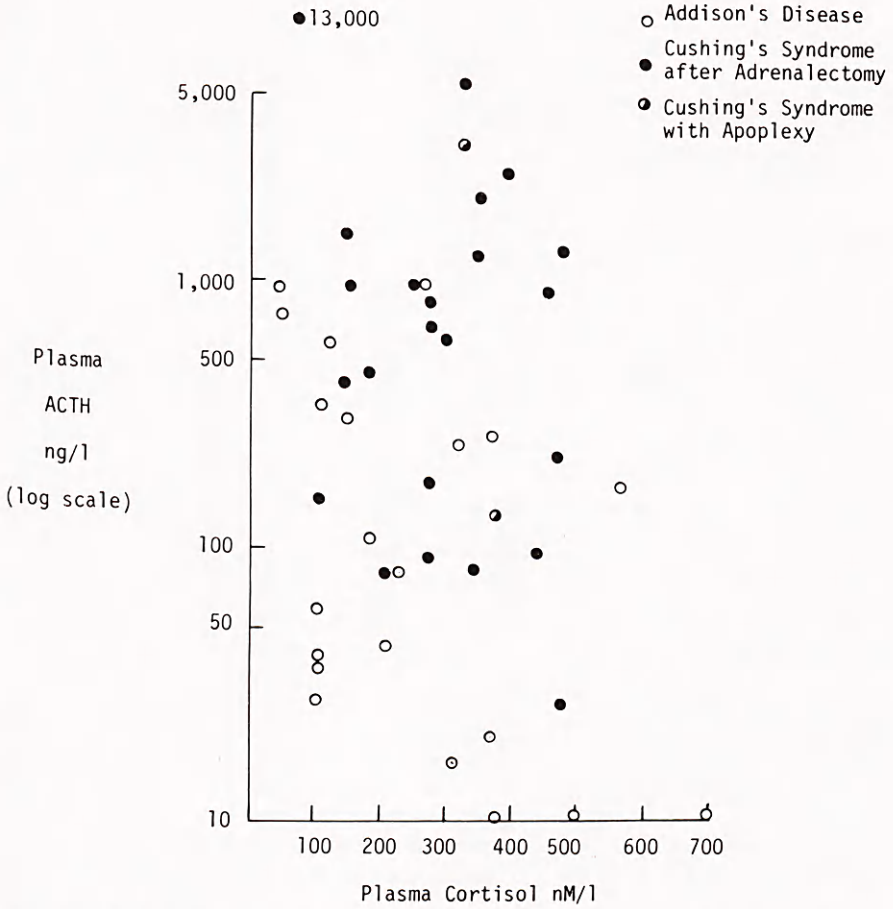

Fig. 3. Simultaneous plasma cortisol and ACTH measurements in some of the patients shown in Fig. 2.

markedly pigmented and his pituitary fossa was at the upper limit of normal on X-ray. It was thought that this might be a case of Cushing's syndrome without hypercortisolism, similar to that described by Liddle's group (Dexter *et al.*, 1970). However, when he was given dexamethasone the plasma ACTH was readily suppressed (Fig. 4). He was subsequently put on to a modified regime with a small dose of dexamethasone at bedtime. On this programme ACTH is undetectable and his pigmentation has faded. Figure 4 also shows the slow disappearance of the dexamethasone from the circulation (kindly measured by Professor Vincent Marks of the University of Surrey). We have had another deeply pigmented Addisonian patient who responded well to a small dose of dexamethasone at bedtime.

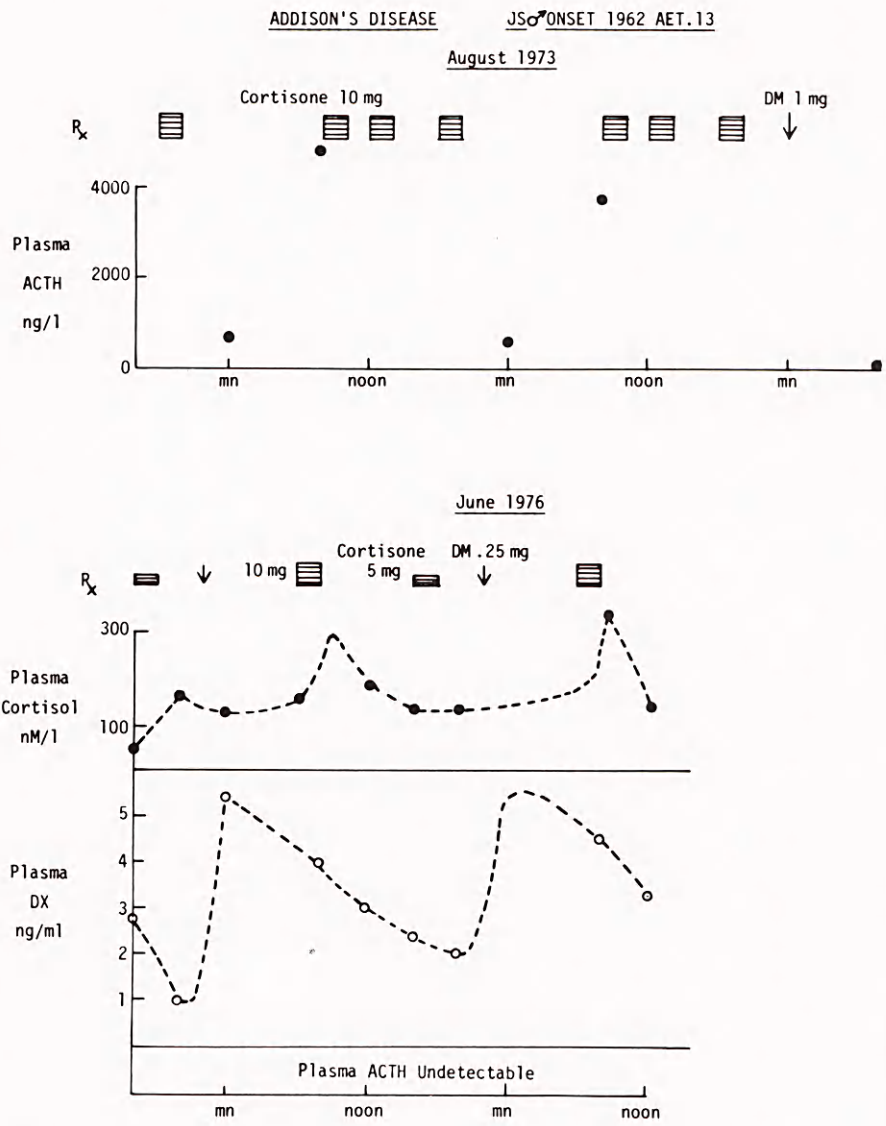

Fig. 4. J. S. Schmidt's syndrome + marked pigmentation.

(*Above*) August 1973. Patient J. S. on cortisone acetate 10 mg t.d.s. + fludrocortisone 0.1 mg/day and thyroxine 0.3 mg/day. Showing very high fasting plasma ACTH and lower MN level. 8 a.m. level easily suppressed by 1 mg dexamethasone at MN.

(*Below*) June 1976. On cortisone 10 mg a.m., 5 mg 1 p.m., dexamethasone 0.25 mg bedtime, fludrocortisone 0.2 mg/day, thyroxine 0.3 mg/day. ACTH not detectable in any sample. Pigmentation faded.

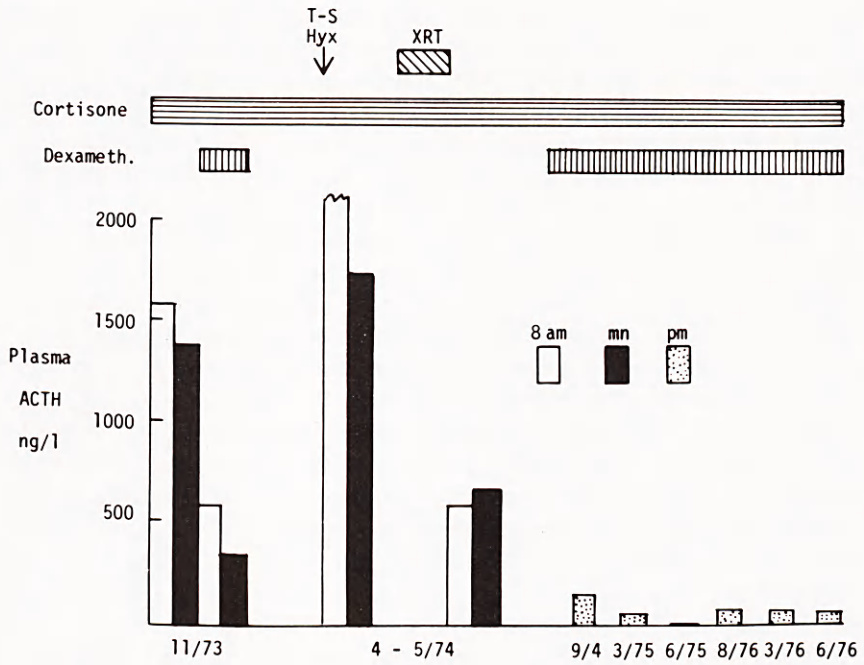

Fig. 5. The treatment of Nelson's syndrome. Patient R. B. Adrenalectomy 1972, aged 24. Pigmentation and high ACTH levels November 1973. Transient reduction of ACTH on adding dexamethasone but enlarging pituitary fossa and diplopia necessitated trans-sphenoidal surgery + X-ray therapy April-May 1974. Pigmentation regressed, ACTH levels normal.

Patients with Nelson's syndrome show some reduction of ACTH levels if given reduced cortisone during the day and a small dose of dexamethasone at bedtime. The reduction, however, is inadequate (Fig. 5).

The Treatment of Nelson's Syndrome

Patients who have had total adrenalectomy for Cushing's syndrome due to adrenal hyperplasia are now followed carefully to see whether they are developing any evidence of Nelson's syndrome. Simultaneous cortisol and ACTH measurements are made and the degree of skin pigmentation noted. Initially, this is done at three month intervals; after one year the interval is extended, but annual review seems desirable. Tomograms of the pituitary fossa and accurate visual field plotting are undertaken annually.

Deepening pigmentation and ACTH levels exceeding 1000 ng/litre are a source of anxiety but not necessarily an indication for active intervention unless the pigmentation is worrying the patient. Active treatment is probably necessary if X-rays show evidence of an enlarging pituitary, and certainly if the visual fields or

oculomotor nerves are affected. There are a number of approaches to treatment. If there is a suprasellar extension of the tumour, transfrontal surgery may be needed and can be supplemented by insertion of an Yttrium-90 pack into the fossa (Welbourn *et al.*, 1971). Transnasal implantation of radioactive Yttrium pellets gives good results in some patients (Cassar *et al.*, 1976). The results of heavy particle therapy recently reported by Lawrence *et al.* (1976) are encouraging, with reduction of pigmentation in 6 out of 9 patients.

In this series three patients were treated by deep X-ray therapy, four by trans-sphenoidal pituitary surgery (this includes two referred to Mr R. A. Williams for this operation) and one by transfrontal surgery. Of the three treated by external irradiation, one who received 5800 rad lost her pigmentation and the plasma ACTH fell to a low level; the other two received smaller doses and the results were not impressive. Of the four treated by trans-sphenoidal surgery and X-ray therapy, two had reduction of ACTH levels and disappearance of pigmentation (Fig. 5); in the other two the ACTH level has dropped but not to normal and the tumour seems to be controlled. The patient treated by transfrontal surgery followed by external irradiation is still pigmented but the tumour and ACTH levels are stabilised.

The Treatment of Cushing's Disease — The Doctor's Dilemma

When a patient with Cushing's disease has obvious evidence — radiological or clinical — of a pituitary tumour, there is little doubt that the initial treatment should be directed at the pituitary. We have encountered this only in a small proportion of patients, although Macerlean and Doyle (1976), using sophisticated radiological techniques, reported evidence of a pituitary abnormality in 10 out of 86 patients. It is the young patient with a radiologically normal pituitary fossa who presents the greatest problem to the physician. If he recommends total adrenalectomy the Cushing's syndrome will certainly be cured but there is continuing anxiety about the possibility of an invasive pituitary tumour appearing. Orth and Liddle (1971) recommend irradiation of the pituitary (4000 to 5000 rad). About half the patients were not improved and subsequently had adrenal surgery. This has the advantage that Nelson's syndrome does not seem to develop in patients who have had pituitary irradiation prior to adrenalectomy. We have been hesitant to advise pituitary irradiation as a first line of treatment for women who hope to have children.

In theory it is better to direct one's treatment at the pituitary, and Burke *et al.* (1973), from the Hammersmith Hospital, reported 60 per cent of cures with implantation of radioactive gold or Yttrium. However, a 50 per cent incidence of hypogonadism in these patients seems unacceptably high. The data on heavy particle irradiation is incomplete, and although Lawrence *et al.* (1976) reported remissions in 62.5 per cent of 41 patients, there is no record of gonadotrophin status. In our hands, trans-sphenoidal surgery, which has been used in 3 older

women with long-standing Cushing's syndrome, has been disappointing. Two of the women were found to have invasive tumours and subsequently needed adrenalectomies, and the third was cured but at the cost of panhypopituitarism. Hardy (1973) reported better results but, although full details are not available, it would seem that they were treated while still at the stage of having a central microadenoma that could be dissected out, leaving normal pituitary tissue in the fossa.

There is another hazard in directing the initial treatment to the pituitary – the condition we have called the 'occult' ectopic ACTH syndrome. We have already reported two patients with this condition (O'Riordan *et al.*, 1966). These were young women with what appeared to be typical Cushing's disease. In one aged 20, evidence of a bronchial carcinoma appeared six months after pituitary irradiation. The second was found to have a bronchial carcinoid on routine chest X-ray one year after adrenalectomy, and when this was removed pigmentation regressed. A third patient has been seen more recently. Mrs V. J., aged 23 in 1966, complained of weight gain and amenorrhoea. Investigations over the next two years gave varying results, but in the autumn of 1968 she had florid Cushing's syndrome with psychotic manifestations. After preparation with aminoglutethimide, total adrenalectomy was performed and recovery was complete. Four years later the patient commented that she was getting very sunburnt. In 1973 a routine chest X-ray showed a small opacity and this was removed. The pigmentation cleared and plasma ACTH dropped from 660 ng/litre and is now in the normal range. Histological examination showed a carcinoid tumour with lymph gland involvement.

In the treatment of the older patient with Cushing's syndrome due to adrenal hyperplasia it seems reasonable to start with pituitary irradiation. On account of the severity or complications it may be reasonable to undertake adrenalectomy at the same time, but in the less severe case 6 to 12 months may be allowed to elapse and the situation then reassessed. The dilemma remains with the young woman; adrenalectomy leads to a dramatic cure, but the incidence of pigmentation and invasive pituitary tumour is very high. Looking at the data collected over 20 years it seems clear that something must be done to the pituitary before, instead of, or at, the time of adrenalectomy. Whether this should be trans-sphenoidal surgery or X-ray therapy depends on the surgical expertise available and the results of more detailed experience of both forms of treatment.

CONCLUSIONS

Cases of Cushing's syndrome due to adrenal hyperplasia (excluding those associated with the ectopic ACTH syndrome) are probably due to an ACTH secreting pituitary tumour. Whether the tumour is a primary pituitary disorder or secondary to excess hypothalamic corticotrophin releasing factor is not known.

If the tumour is readily detectable when the patient presents with features of

Cushing's syndrome, treatment is difficult and pituitary surgery and irradiation as well as adrenalectomy are often needed. If the pituitary tumour is not detectable at the time of presentation it may grow after adrenalectomy. This gives rise to Nelson's syndrome, which comprises skin pigmentation, raised plasma ACTH levels, radiological evidence of pituitary fossa enlargement and visual field and oculomotor defect. In 34 patients treated by adrenalectomy, there was excess pigmentation in 18 patients, ACTH levels exceeded 1000 ng/litre in 8, radiological changes in the fossa were found in 6, and neurological changes in 3. These abnormalities were found most often in women under 35.

The treatment of Nelson's syndrome may be by pituitary irradiation and/or pituitary surgery. The dilemma that arises over the treatment of Cushing's disease is reviewed. In the older patient it is suggested that pituitary irradiation should be tried first, followed by total adrenalectomy if successful response to irradiation is not obtained. In younger women the incidence of Nelson's syndrome after total adrenalectomy is unacceptable and it is suggested that pituitary irradiation should be given at the same time as total adrenalectomy. Attention is drawn to the 'occult' ectopic ACTH syndrome in cases of apparently straightforward Cushing's disease. Treatment directed to the pituitary in these patients will be useless.

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