Two Cases of Cushing's Syndrome

TUMOUR AND BILATERAL HYPERPLASIA

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SUMMARY

Two patients, one with Cushing's syndrome and one with Cushing's disease, are presented. In the first case the syndrome was caused by a tumour of the right suprarenal gland which was treated by unilateral adrenalectomy, and the second case was diagnosed as hyperplasia of the left suprarenal gland, eventually leading to removal of all cortical tissue. Subsequently the typical features of Nelson's syndrome developed.

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Cushing's syndrome in children has been well documented, although it is a rare condition.[1] The majority of cases have been caused by adrenocortical tumours.[1-4] A much rarer cause is cortical hyperplasia.[5]

This report describes two patients who presented with Cushing's syndrome, the first case being caused by a tumour of the right suprarenal gland, and the second case due to hyperplasia of both suprarenal glands.

CASE REPORTS

Case 1

A 13-month-old female was first seen on 1 June 1959. The parents complained that she was extremely irritable and had gained an excessive amount of weight during the previous 5 months. She was their second baby, birth-weight 3,2 kg, and pregnancy and delivery had been normal. At 5 months she was able to sit up and appeared normal to the parents. At the age of 8 months excessive weight gain was noticed, and at the age of 10 months her parents noticed excessive hair growth on the forehead, with markedly ruddy cheeks, resulting in the nickname 'Ruby'.

Family history revealed that their first baby had died at the age of 2 months from a meningocele. A grandmother had diabetes mellitus, an aunt had had a goitre and another aunt had died of cancer.

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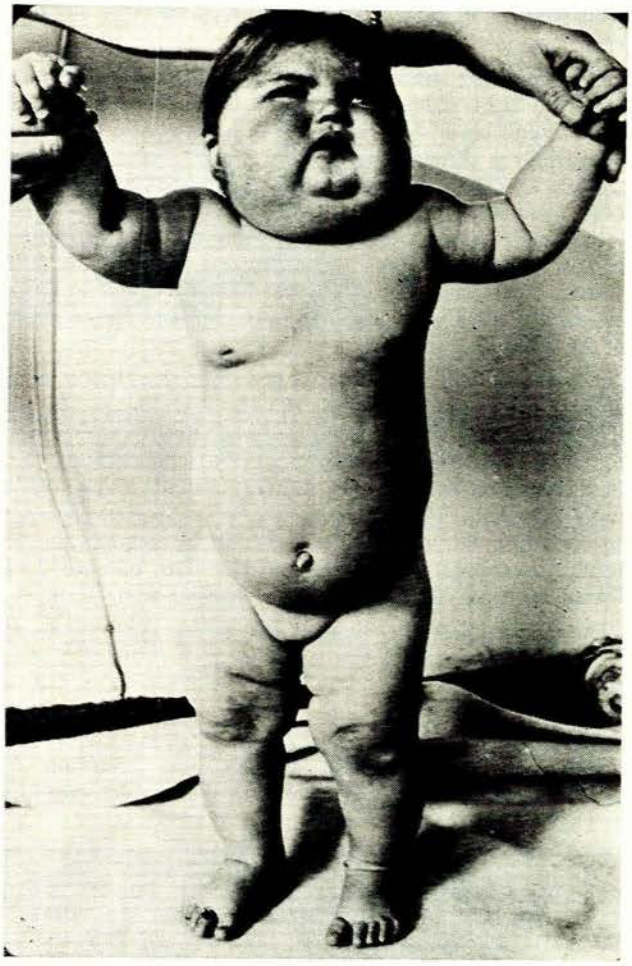

Fig. 1. Case 1, age 13 months, full-blown appearance of Cushing's syndrome.

On examination the baby showed the typical appearance of Cushing's syndrome (Fig. 1). Her weight was then 10,9 kg (85th percentile), height 66 cm (below 3rd percentile), skull circumference 42,9 cm (below 3rd percentile). She was short and obese, with a mild microcephaly. Her cheeks were unusually red, with obvious growth of hair low over the forehead, and she had no acne or striae. A prominent interscapular fat pad was present. Her blood pressure was 140/90 mmHg (normal 90/60). No other abnormalities were found and no mass was palpable in the abdomen.

Laboratory tests showed a haemoglobin of 16,4 g/100 ml, haematocrit 64%. No eosinophils were seen. Her

serum electrolytes were normal. The urinary 17-ketosteroids were 1,4 mg/24 hours (normal range: 0 - 1,5 mg/24 hours) and the urinary 17-hydroxycorticosteroids were 2,3 mg/24 hours (normal range: 0,5 - 1,0 mg/24 hours). X-ray examination revealed generalised enlargement of the heart. The spinal column showed slight but definite osteoporosis. Tomography of the abdomen showed an ill-defined mass above the right kidney. No calcifications were seen. The diagnosis of Cushing's syndrome caused by a tumour of the right suprarenal gland was made, and a laparotomy in this region was performed on 11 June 1959.

At operation a smooth encapsulated tumour was found above the right kidney and was removed. Hydrocortisone was administered before surgery and continued postoperatively in diminishing doses. The size of the tumour was 6,5 × 7 × 4,5 cm, weight 120 g. Section showed a fleshy mass and focal areas of necrosis. No yellow areas of suprarenal tissue were seen. On microscopy the capsule did not show any signs of infiltration of tumour cells. In some areas mitotic activity was noted. A diagnosis of cortical adenoma was suggested, although carcinoma could not be excluded.

Follow-up: One month after operation her blood pressure had dropped to 130/90 mmHg and her weight to 9,1 kg. Her cheeks were still red, but the typical moon face was less striking. Two months after operation her blood pressure was 120/85 mmHg, weight 8,6 kg. The moon face had disappeared (Fig. 2). Eight months after the operation blood pressure was 110/70 mmHg, and 15 months postoperatively 90/60 mmHg. The parents were pleased with her progress, and she looked well.

The parents left the vicinity and never reported back.

Case 2

This little boy, 7 years of age, was seen on 25 May 1963, the parents having observed a sudden increase in weight during the previous month. They noticed that the fat deposits were mostly on his trunk and face and did not affect his extremities to the same extent. He did not have an abnormal appetite. They also noticed that his face was often flushed without any apparent cause. He did not complain of any headaches, nausea or vomiting. He is the fourth of 7 children, but the other siblings are all normal and healthy. He had had the ordinary children's diseases and was quite well until the excessive weight gain started. There was no family history of endocrine disorder.

Examination revealed the typical facial appearance of Cushing's syndrome. His height was 110 cm (below 3rd percentile), and weight 24 kg (75th percentile). Blood pressure was 135/115 mmHg. The fat deposits were mostly on his trunk and face, with a buffalo hump between the scapulae. The rest of the clinical examination was negative.

Laboratory investigations showed a haemoglobin of 15 g/100 ml, haematocrit 45%, white cells 18 400, differential count normal, with no eosinophils seen. Fasting blood sugar was 90 mg/100 ml, urinary 17-ketosteroids 5,4 mg/24 hours (normal range: 1,0 - 3,5 mg/24 hours), and urinary 17-hydroxycorticosteroids 17,5 mg/24 hours (normal range: 1,5 - 4,5 mg/24 hours). Intravenous pyelography did not show any displacement of the kidneys or any other abnormalities. Retroperitoneal nitrogen dioxide studies revealed that the left suprarenal gland was larger than the right one, but of normal shape. A diagnosis of hyperplasia was made, and surgery advised.

First laparotomy on 11 June 1963: The surgeon found the left suprarenal gland to be about three times the size of the right one, and it was removed. The right gland was left *in situ*. The weight of the suprarenal gland was 10 g, and after stripping the surrounding fat it weighed 7 g. It measured 7 mm in its greatest thickness. Histological examination showed some increase in the size of the cortex and a relatively inconspicuous medulla. No nodules were detected, and the histological features were consistent with the diagnosis of hyperplasia of the suprarenal cortex.

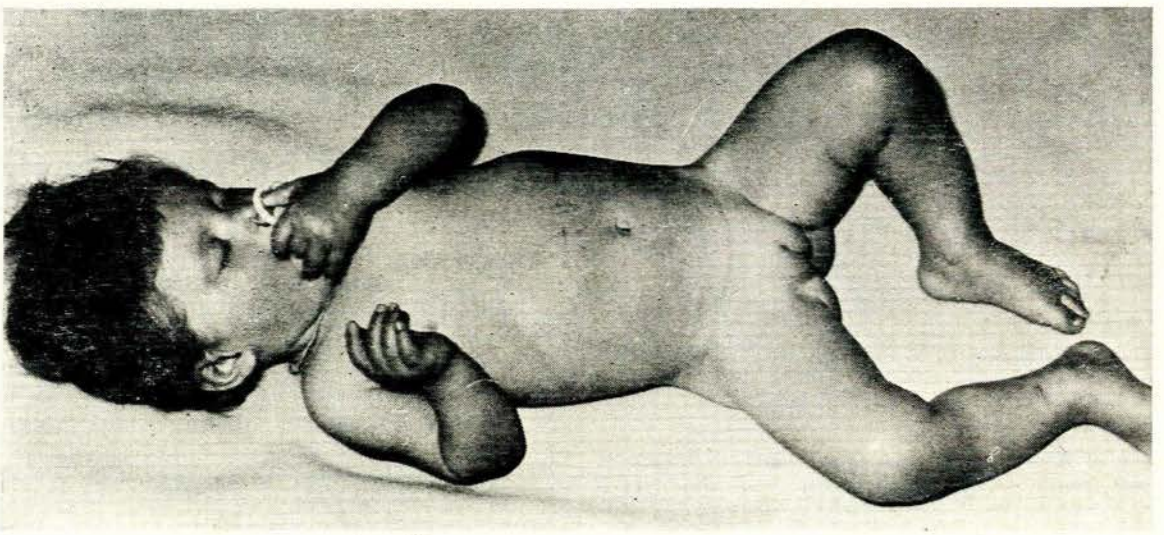

Fig. 2. Case 1. Two months after operation.

His postoperative recovery was without complications, his supporting doses of steroids (prednisone) were gradually diminished, and he was discharged home after three weeks to be maintained on prednisone 2,5 mg daily. Six weeks after this operation examination revealed that his Cushingoid features were disappearing, his blood pressure had dropped to 120/95 mmHg, his urinary 17-ketosteroids had dropped to 2,5 mg/24 hours and the 17-hydroxycorticosteroids to 6,5 mg/24 hours. As there was the possibility of pituitary gland involvement as the primary cause of this hyperplasia, further special investigations were done. His visual fields were normal, and have always remained normal during many subsequent tests. X-ray examinations of the pituitary fossa were also found to be normal, and have remained so up to the present time.

Four months after his first laparotomy, the original abnormal clinical features reappeared. His blood pressure rose to 130/115, the urinary 17-ketosteroids increased to 4,3 mg/24 hours, and it was thought that the right suprarenal gland had become hyperplastic.

Second laparotomy on 4 November 1963: The surgeon removed nine-tenths of the right suprarenal gland. Histological examination showed abundant cortical tissue, a very small medulla, and no tumour cells were detected. His postoperative course was without incident, and he was maintained initially on high doses of steroids, which were slowly diminished. Eleven days after the operation the urinary 17-ketosteroids dropped to 3,1 mg/24 hours, and he was discharged home on a maintenance dose of 5 mg oral hydrocortisone daily. The typical Cushingoid features disappeared completely and he progressed well.

Third laparotomy: Thirteen months later he was admitted to another hospital with an acute obstruction of his ileum due to adhesions from the previous operations. An emergency operation was done under cover of high doses of steroids, and his obstruction relieved. His postoperative recovery was without complications, and he was discharged home 10 days later.

Regular follow-up examinations showed his condition to be stationary, with a blood pressure ranging between 100/80 and 120/90 mmHg. During June 1965, 19 months after his last adrenalectomy, his maintenance dosage of hydrocortisone was discontinued. During the next 8 months his condition remained satisfactory. A significant rise of blood pressure to 130/100 mmHg was then noticed, soon followed by the appearance of the typical Cushing's syndrome. His urinary 17-ketosteroids rose to 7,4 mg/24 hours, and the urinary 17-hydroxycorticosteroids to 25,6 mg/24 hours. The one-tenth remnant of cortical tissue left at the second operation had now become hyperplastic. The pituitary gland was again examined as before, and no abnormalities were found.

Fourth laparotomy on 30 March 1966: The surgeon at this stage removed all the adrenal tissue that could be found on the right side. Histological examination showed only hyperplasia of the cortical tissue, and no medullary tissue was found.

The postoperative period was again without incident, the usual regimen of high doses of steroids just before and after the operation applied. Gradually diminishing the doses of steroids, he was eventually maintained on oral hydrocortisone 5 mg every third day. Regular follow-up showed the features of Cushing's syndrome to have disappeared completely, and his blood pressure ranged from 110/85 to 120/90 mmHg. He maintained this condition for the next 18 months, when he started to complain of headaches, and subsequent examinations revealed some weight gain. He had now developed gynaecomastia (Fig. 3) and generalised hyperpigmentation of his skin. His blood pressure was 125/105 mmHg. However, there was no Cushingoid facies. It was thought that the excessive weight gain was caused by the hydrocortisone maintenance therapy. He was put on a diet, and actually lost some weight. However, it soon became apparent that he was again de-

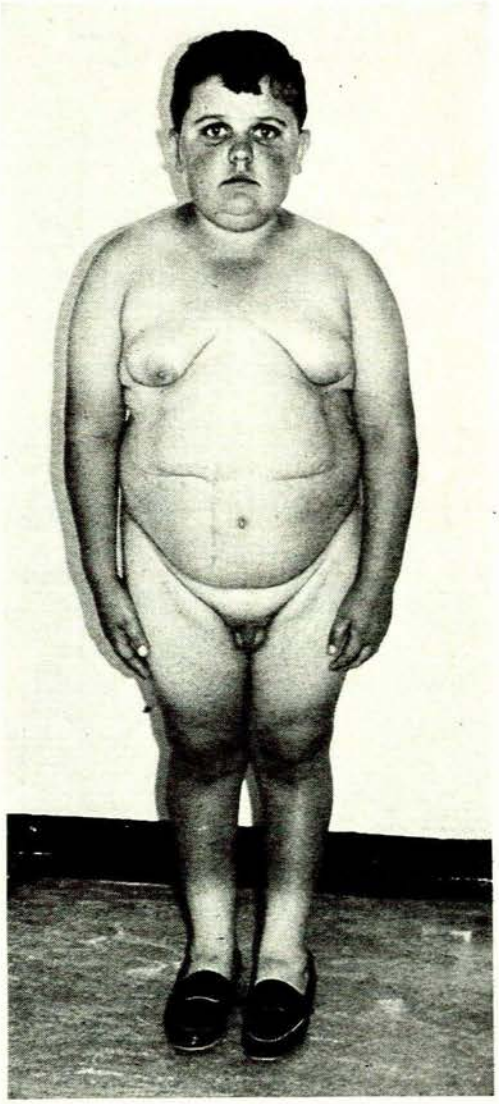

Fig. 3. Case 2. Before fourth adrenalectomy. Note gynaecomastia.

veloping the typical Cushing's syndrome appearance, and that there must still be residual cortical tissue somewhere which had become hyperplastic. In view of the fact that both suprarenal glands had been removed it was important to establish the exact site of any cortical tissue which had become hyperplastic. He was readmitted to hospital, and investigations again showed increased urinary 17-ketosteroids of 13 mg/24 hours (normal range: 1,5 - 4,5 mg/24 hours) and urinary 17-hydroxycorticosteroids of 19 mg/24 hours (normal range: 2,5 - 7,0 mg/24 hours). Dexamethazone did not suppress his urinary steroid output. Fifty units of ACTH produced an increase of his plasma cortisol from 20 to 31 μg/100 ml after a period of 8 hours. This proved the presence of some hyperplastic cortical tissue.

In order to establish the exact site, a catheter was inserted through the right femoral vein high up into the vena cava inferior. Twelve blood specimens were taken at regular 2,5 cm distances (Fig. 4) in order to determine the plasma cortisol levels. As can be seen from Fig. 5, there was a sharp increase in plasma cortisol concentration at levels 7 to 9 (Fig. 4), which corresponded with the original level of the suprarenal glands.

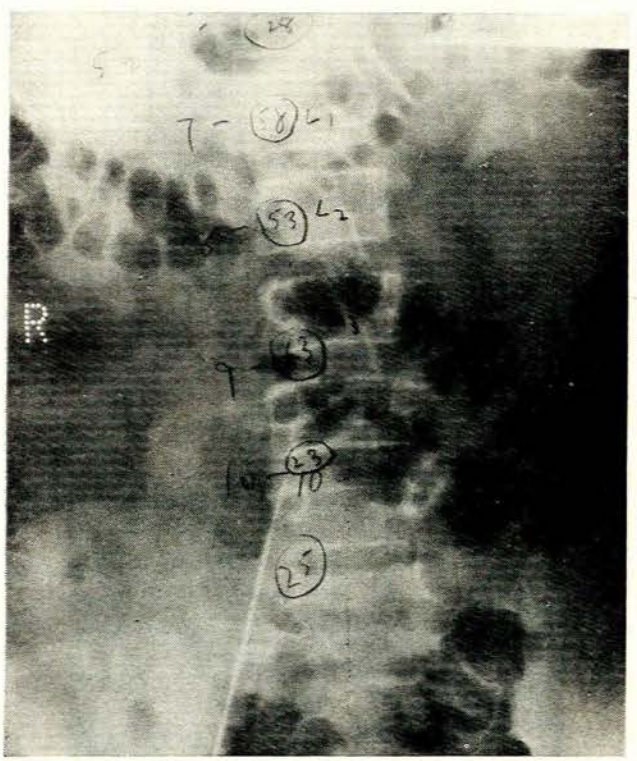

Fig. 4. Case 2. Levels of sampling.

Fifth laparotomy on 11 April 1969: A mass of adrenal tissue of 2,5 cm in diameter was removed from the left adrenal area, where the very first adrenalectomy had been performed (Fig. 6). The postoperative period was well controlled with hydrocortisone in high doses. He was discharged on a maintenance therapy of hydrocortisone

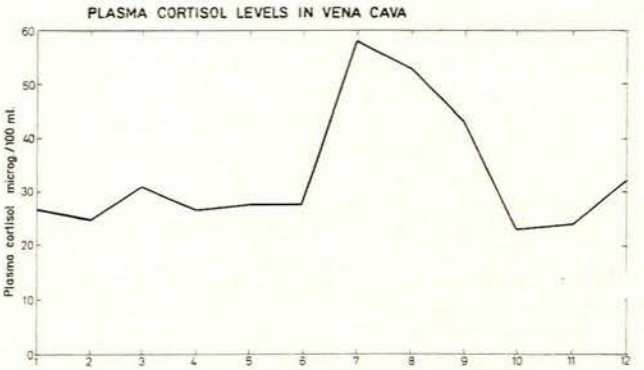

Fig. 5. Case 2. Plasma cortisol concentration at different levels.

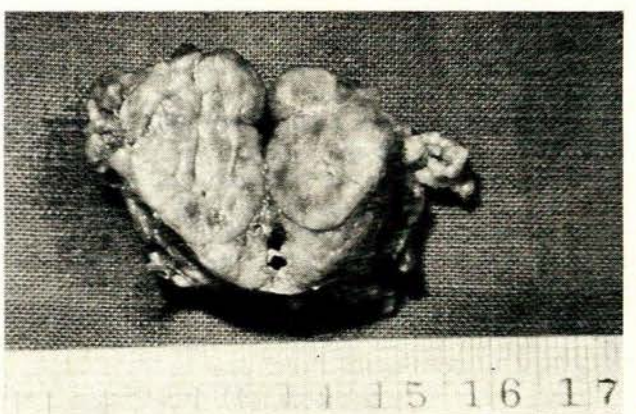

Fig. 6. Case 2. Left hypertrophied adrenal cortex removed at last operation.

20 mg and fluorocortisone acetate 0,1 mg daily. He remained well for the following 6 months. His previous Cushingoid appearance diminished, including the gynaecomastia, although at present he still shows mild hyperpigmentation of his skin (Fig. 7). His blood pressure ranged from 100/80 to 105/95 mmHg.

Six months after this operation he developed an acute follicular tonsillitis which caused a typical postadrenalectomy shock-reaction. When he was examined after being ill for approximately 24 hours, his blood pressure was imperceptible, he was cyanotic, mildly dehydrated, and the pulse could not be felt. This was regarded as proof that all his adrenal tissue had been removed. He was treated with intravenous fluids and high doses of hydrocortisone, and recovered from shock within 24 hours. A tonsillectomy was performed some time later under cover of high doses of hydrocortisone, and there were no complications.

He is still seen at monthly intervals, and seems to be doing quite well. His gynaecomastia is slowly receding, but his skin pigmentation seems to be increasing slowly. His most recent control examination, done on 28 July 1973, showed his height 152 cm, weight 55,4 kg, blood pressure 120/73 mmHg. He is obviously short of stature, and slightly overweight for his height.

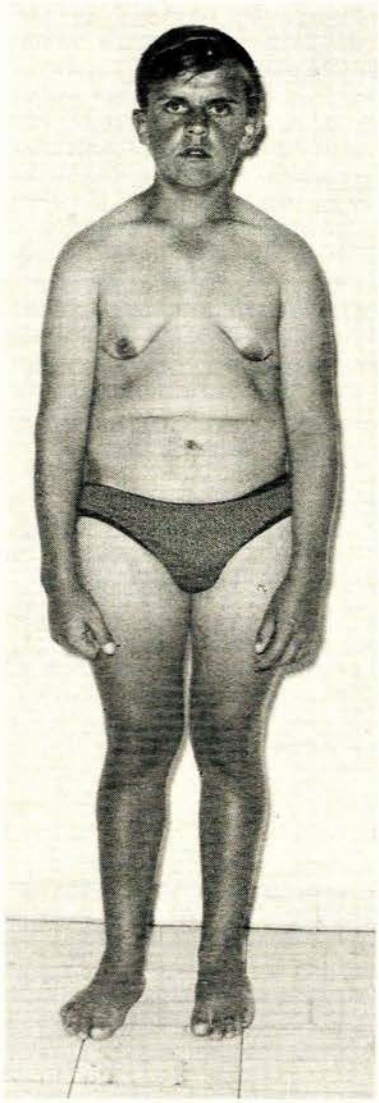

Fig. 7. Case 2. Three years after complete adrenalectomy. Note smaller breasts.

Although X-ray examinations of his sella turcica and examinations of his visual fields did not show any abnormalities, it was decided to determine his serum and cerebrospinal fluid ACTH levels, determinations of which have recently become available. The serum ACTH concentration was 350 pg/ml (normal range 0 - 100 pg/ml) and the cerebrospinal fluid ACTH concentration was 188 pg/ml (normal range 0 - 80 pg/ml). All laboratory investigations were carried out by one of us (W.M.P.).

DISCUSSION

Cases of Cushing's syndrome in children have been described before the typical description by Harvey Cushing in 1932.[6] Cushing's syndrome in children before the age of one year is usually caused by tumours of the suprarenal gland, and most of these are malignant. It is unusual to find a benign adenoma producing this syndrome in an infant. Three such cases have recently been reported.[7]

A survey of both suprarenal adenomas and carcinomas was done by Fraumeni and Miller,[8] who collected 62 cases from 12 large hospitals. They found a preponderance of females (43 girls and 19 boys). Eberlein and Winters[9] also noticed this particular sex distribution, since no other childhood cancer occurs more often in females.

The term Cushing's disease is now reserved for those patients in whom hyperplasia of the suprarenal cortices is caused by a tumour of the pituitary gland, whereas all other cases, including iatrogenic disease, are known as Cushing's syndrome.

In case 1, the clinical symptoms and signs, laboratory findings, hospital course and pathological findings, were those typical of Cushing's syndrome as described by Gilbert and Cleveland.[7]

In contrast to the female preponderance seen in children with suprarenal tumours, there is no difference in sex distribution in Cushing's disease caused by hyperplasia.

In case 2, the diagnosis of unilateral hyperplasia of the left suprarenal gland was made by nitrogen dioxide insufflation and confirmed by surgery, the left suprarenal gland being three times the size of the right gland. It was considered that this was one of those occasions when one finds one suprarenal gland affected initially.

The modern treatment of hyperplasia of the suprarenal glands causing Cushing's disease is either by radiation of the pituitary gland, subtotal adrenalectomy or total adrenalectomy,[10] and the decision to carry out a subtotal adrenalectomy at that time (1963) was based on reluctance to radiate the pituitary gland in such a young child, even if an adenoma could be demonstrated.

Costello,[11] as early as 1936, examined 1 000 pituitary glands at routine autopsies, and the clinical diagnoses and causes of death ranged from cardiac failure, hypertension, and nephritis to carcinomatosis. He found 225 pituitary glands to have one or more adenomas, some minute and some so large as to have almost destroyed the entire gland. The most notable observation was that there was nothing in the history or clinical findings in any of these cases where adenomas were found to suggest the presence of any pituitary dysfunction. He did not, however, mention the presence of any clinical features of Cushing's syndrome or any hyperplasia of the suprarenal glands.

Although remission was observed in some cases treated with pituitary radiation, it did not provide any permanent relief, and subtotal or total adrenalectomy became the accepted form of treatment.[10,12] Hypophysectomy was considered a proposition in our case 2, but no local neurosurgeon was prepared to perform this operation on a boy 7 years of age. This may not even be effective, since small remnants of the pituitary gland may continue to secrete ACTH.[6,12]

Two subsequent operations were necessary before complete total adrenalectomy was accomplished. Fully aware of the fact that a pituitary tumour could be the primary cause of the hyperplasia, and that total adrenalectomy could enhance the further development of such a tumour,[6] its presence could never be established by the available

clinical investigations. Owing to the age of the patient, requests for radiation were refused by the radiotherapists.

The raised serum and cerebrospinal fluid levels of ACTH may be indicative of a pituitary tumour, or a raised output of the hypothalamus-pituitary axis as the result of increased secretion of corticotrophin-releasing factor (CRF) by the hypothalamus. This would lead to uncontrolled ACTH production.[6] Proof of this theory must come from the demonstration of increased corticotrophin-releasing factor (CRF) in the spinal fluid and blood in patients with Cushing's syndrome, as suggested by Eberlein and Winter.[6] In 1960 Nelson *et al.*[13] reported a clinical syndrome of cutaneous pigmentation with a pituitary tumour developing some time after adrenalectomy for Cushing's syndrome, now referred to as Nelson's syndrome.[14] Aarskag and Tveteraas[10] reported a similar hyperpigmentation of the skin in their patient—a little girl who developed Cushing's syndrome at the age of 1 month, on whom total bilateral adrenalectomy was carried out at the age of 4 months, and 8 months after the adrenalectomy patchy skin pigmentation was noticed. This increased during the next few years until she developed the full clinical picture of McCune-Albright's syndrome with skin pigmentation, polyostotic fibrous dysplasia, and sexual precocity.

It is suggested that the skin pigmentation seen in the post-adrenalectomy syndrome may be due to excessive secretion of melanocyte-stimulating hormone (MSH) or, since MSH and ACTH so closely resemble one another chemically, to the direct action of ACTH.[13,14]

Kleerekoper *et al.*[14] determined the ACTH levels in the plasma and spinal fluid of their 3 adult patients who developed increased skin pigmentation after bilateral adrenalectomy. In their first case very high levels of ACTH in the serum and spinal fluid were found (serum ACTH 5 460 pg/ml and cerebrospinal fluid ACTH 4 500 pg/ml). This patient showed clinical evidence of a developing pituitary tumour. The other 2 cases showed high plasma ACTH levels, but low cerebrospinal fluid values and a pituitary tumour could not be demonstrated.

The serum and cerebrospinal fluid levels of ACTH of our case 2 were raised, but were very much lower than the abovementioned figures, which would indicate mild hyperfunction of the pituitary gland at this stage; but when these levels increase to those found by Kleerekoper *et al.*[14] in their first case, one should very seriously consider extracellular spread of a tumour and regard this as an indication for surgery or radiation.

A most striking feature of case 2 was the development of gynaecomastia 18 months after the complete adrenalectomy. At first this was thought to be due to the onset of puberty. This is seen frequently in normal adolescent boys and is thought to be due to secretion of oestrogens as well as androgens by the pubertal testes.[15] The incidence of pubertal gynaecomastia was found to be 38,7% in a group of 2 369 examinations made of 1 890 normal boys, of which 27% persisted through 2 seasons and 7,7% for 3 seasons.[16] It is thus a very common finding, although their cases were not as severe as our case 2. It is not unusual for both breasts to enlarge at disproportionate rates—surgical removal is rarely indicated, but may be necessary when enlargement is so striking as to cause serious emotional disturbance to the patient.[15]

The gynaecomastia was very obvious in our case (Fig. 3), and at one stage plastic surgery was considered. At present the gynaecomastia seems to be regressing, and it is thought that excessive amounts of oestrogens were probably excreted by the pubertal testes, due to the physiological hormonal inequilibrium produced by the adrenalectomies at different stages and by an overactive pituitary gland.

We have not come across any reports in the available literature of gynaecomastia developing after total adrenalectomy for hyperplasia of the suprarenal glands. This finding is still being investigated further and may be reported on at a later stage.

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