

Treatment with higher doses of vitamin D to epileptic patients has been proposed before (Christiansen *et al.*, 1974; Hahn *et al.*, 1975; Stamp, 1974). Vitamin D treatment to these epileptic mothers might have prevented the hypocalcaemia in their children. Further investigations are needed to elucidate these problems.

Summary

Two cases are reported of prolonged hypocalcaemia with tetany in infants born at term, whose mothers had been treated with phenytoin and phenobarbitone in high doses. Both infants presented with jitteriness and tetany in the first and second weeks of life, and in both the hypocalcaemia was resistant to therapy over a longer period. An effect on the fetal vitamin D metabolism by phenytoin and phenobarbitone, resulting in defective bone mineralization and neonatal hypocalcaemia is suggested.

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Pure oestrogen-secreting feminizing adrenocortical adenoma

Adrenocortical tumours associated with raised oestrogen secretion causing feminization are rare in childhood. We have traced only 7 reported

cases (Wilkins, 1948; Fontaine *et al.*, 1954; Snaith, 1958; Mosier and Goodwin, 1961; Bacon and Lowrey, 1965; Castleman *et al.*, 1972; Leditschke and Arden, 1974). We report the clinical and laboratory findings in a boy before and after surgical removal of an adrenocortical adenoma.

Case report

A 6-year-old boy had a 4-month history of enlargement of the breasts. He had received no previous medication. His height was 122 cm (75th centile); he was not obese, had not acne or striae, his voice was not deep, and there was no facial, axillary, or pubic hair. Blood pressure was 90/60 mmHg. No abdominal masses were palpable. The breasts were 8 cm in diameter, firm and nontender. The areolae were ballooned but not pigmented; no secretion could be expressed. The penis was 3.5 cm in length and the testes, of normal consistency, measured 1.0 × 1.5 cm.

Blood count, analysis of urine, serum electrolyte concentrations, liver function tests, and radiographs of the skull and chest were all normal. Serum thyroxine was 13.5 nmol/l (10.5 µg/100 ml) (normal range 6.4-16.7 nmol/l) and the karyotype was 46,XY. The bone age was 7 years. Breast biopsy showed prominent ducts with proliferation and dilatation. Urinary 17-oxosteroid excretion was 1.7 µmol/24 h (0.5 mg/24 h) (normal for age 1.7-10.2 µmol/24 h) and total 17-oxogenic steroids 4.2 µmol/24 h (1.2 mg/24 h) (normal 3.5-14 µmol/24 h). Plasma cortisol was 276 nmol/l (10 µg/100 ml) at 9 am and 33.1 nmol/l (1.2 µg/100 ml) at midnight. The urinary steroid profile by gas-liquid chromatography by Van de Calseyde's method showed a very low excretion of adrenal androgens (Table). Urinary total oestrogens measured by Brown's method were grossly raised to 528 µg/24 h (normal adult males 5-20 µg/24 h).

Table Urinary steroid profile (mg/24 h)

	Patient	Normal adult males (mean ± SD)
Androsterone	0.46	3.8 ± 1.1
Etiocolanolone	0.16	4.0 ± 1.2
Dehydroepiandrosterone	0.19	2.3 ± 1.1
11-Ketoandrosterone	—*	0.8 ± 0.4
11-Ketoetiocolanolone	—*	0.6 ± 0.3
11-OH Androsterone	0.16	1.8 ± 0.6
11-OH Etiocolanolone	—*	1.0 ± 0.3
Pregnanediol	0.33	1.3 ± 0.6
Pregnanetriol	1.108	1.3 ± 0.6
11-Deoxytetrahydrocortisol	0.69	0.4 ± 0.2
Tetrahydrocortisone	0.78	3.8 ± 1.1
Tetrahydrocortisol	1.088	4.1 ± 1.0

*Undetectable.

Plasma testosterone was undetectable. Plasma luteinizing hormone was low (0.3 mIU/ml) and did not rise after intravenous luteinizing-releasing hormone. Intravenous pyelography showed displacement of the left kidney but no calcification. Retroperitoneal air insufflation showed a tumour in the left suprarenal region.

At surgical exploration (Professors J. H. Louw and S. Cywes) a small, round adrenal tumour (4.0 × 4.0 × 1.5 cm) was found and easily enucleated. It weighed 28 g and had a fleshy homogeneous appearance on section. Histologically it consisted of sheets, nests, and cords of cells separated by sinusoids. The cells were large with abundant granular cytoplasm, large nuclei, and prominent nucleoli. There was no evidence of necrosis or haemorrhage or of capsular or vascular invasion. Mitotic figures were scanty. Postoperatively urinary oestrogens were undetectable and remained so during the course of a 3-year follow-up. There has also been steady regression of breast size, normal growth in height, and normal adrenal function.

Discussion

Functioning neoplasms of the adrenal cortex present a variety of endocrine syndromes depending on the type of hormone produced. Virilization is associated with excessive production of androgens, Cushing's syndrome with excessive glucocorticoid secretion, while a combination of the two syndromes is not uncommon. Less often aldosterone-producing tumours may cause hypertension with hypokalaemic alkalosis, but the occurrence of feminization is rare.

Since Bittorf's first description of feminizing features produced by an adrenocortical tumour in 1919 (Gabilove *et al.*, 1965), fewer than 70 cases have been reported. Normal 17-oxosteroid levels were found in only 7 out of 52 cases in one large review (Gabilove *et al.*, 1965). When oestrogen estimations were carried out the levels were invariably raised. Feminization is even rarer in children. Only 7 cases have been reported in the world literature, all under 7 years of age, 6 in boys and only one in a girl. Virilizing features were present in 4 of the cases and absent in the other 3, including the girl. None had a Cushingoid appearance. Urinary oestrogens were raised in 6 cases and not estimated in one. Urinary 17-oxosteroids were moderately or grossly raised in all 7; urinary total 17-oxogenic steroids or hydroxycorticoids were normal in 5, raised in one, and not estimated in one other case. Histologically, 5 of the tumours resembled an adrenocortical adenoma, and long-term survival ranging from 1 to 14 years was documented in 4 of these. Two showed histological features of malignancy and ended fatally.

Probably feminization in adrenocortical tumours in children is more common than reported. One of us (F.B.) has also treated a 5-year-old girl with virilizing and feminizing features due to an adrenocortical adenoma, as well as a boy of 3 years with a carcinoma producing a mixed picture of Cushing's syndrome, virilization, feminization, and hypertension with hypokalaemic alkalosis.

Various authors tried to explain the feminization or increased oestrogen levels in their patients. Some postulated oestrogen secretion by the tumour, or extra-adrenal conversion of androgens to oestrogens. Others suggested excessive aromatization and decreased 11- β -hydroxylation of the steroid nucleus resulting in overproduction of oestrogens. The case reported here, presenting only with gynaecomastia, may be the first example of an exclusively oestrogen-secreting adrenocortical tumour in a child. In contrast to previous reports, there was no clinical or biochemical evidence of excessive androgenic or glucocorticoid activity.

In considering gynaecomastia the age and sex of the patient are most important. As an accompaniment of normal puberty it is common, though Klinefelter's syndrome may need to be excluded. In the rare cases where it occurs in a prepubertal boy raised oestrogen levels with or without evidence of other hormone production must point to an adrenocortical tumour or, less commonly, to a testicular tumour. However, the entity of idiopathic prepubertal male gynaecomastia (August *et al.*, 1972), though very rare, has been well documented and should be diagnosed by exclusion. In girls the possibility of a feminizing adrenal tumour cannot be entirely ignored, but the differentiation from the more commonly occurring premature thelarche, ovarian tumours, and precocious puberty is more difficult.

The mortality among adult males with feminizing adrenocortical tumours is high, with a less than 20% survival rate 3 years after resection (Gabilove *et al.*, 1965). The outlook seems to be more favourable in children since long-term survival has been documented in 5 out of 8 reported cases. The prognosis in our patient would therefore seem to be favourable in view of his age, the small size of tumour, the benign histological pattern, the secretion of a single type of hormone, and his present 3-year uneventful survival.

Summary

A 6-year-old boy presented with gynaecomastia. There was no clinical or biochemical evidence of excessive androgenic or glucocorticoid activity, but urinary oestrogen levels were raised. An adrenocorti-

cal adenoma, demonstrated by x-ray, was surgically removed. Oestrogen levels fell immediately. 3 years later the boy shows complete regression of the gynecomastia and no signs of recurrence.

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Wilms's tumour, hypospadias, and cryptorchidism in twins

The familial incidence of embryonal tumours of childhood is extremely low, with the exception of retinoblastoma, in which the bilateral form of the disease is usually hereditary (Sorsby, 1972). Wilms's tumour may occasionally occur in 2 or more sibs (Maslow, 1940), or in more than one generation of

the same family (Brown *et al.*, 1972), but has rarely been reported in twins.

Various congenital anomalies, including abnormalities of the urogenital tract, occur with increased frequency in patients with Wilms's tumour (Miller *et al.*, 1964). These anomalies may be found in association with each other as well as with Wilms's tumour, sometimes in members of the same family (Meadows *et al.*, 1974).

The survey of 335 families of children diagnosed as having Wilms's tumour between 1962 and 1966 in England and Wales (Ledlie *et al.*, 1970) showed only 2 cases of familial involvement; one of these was in a mother and daughter and one was in twin boys (Hewitt *et al.*, 1966). The latter case is of particular interest because of the presence of other identical anomalies in each twin, known to be associated with Wilms's tumour. This family is described in detail.

Case reports

Twin boys were born to unrelated parents. The mother was aged 22 years and had been x-rayed at 8 months' gestation; she had also been treated for hypertension during the last month of pregnancy. Delivery was uncomplicated and a common placenta found. Both twins were found to have hypospadias and bilateral undescended testes. The blood group of each twin was A Rhesus positive.

Twin 1. At the age of 15 months the mother felt a lump in the abdomen while bathing him. An intravenous pyelogram (IVP) showed that the calyces of the left kidney were distorted by a large intrarenal mass. At laparotomy a large inoperable, multifocal tumour of the left kidney was found. Biopsy confirmed the diagnosis of Wilms's tumour. He was then referred to St. Bartholomew's Hospital where he was given a course of radiotherapy, and nephrectomy was carried out one month later. The tumour had invaded the renal vein. The patient rapidly developed local recurrence and pulmonary metastases from which he died.

Twin 2. One month after the diagnosis of Wilms's tumour had been made in the first twin, the mother noticed that the other twin had started to lie on his face, something he had never done before. She took him to St. Bartholomew's Hospital where he was found to have a small left-sided abdominal mass. IVP showed appearances consistent with a Wilms's tumour of the left kidney. Nephrectomy was carried out on the same day, as for the first twin, but the tumour was found to involve only the upper pole of the kidney and to be completely encapsulated with no involvement of the renal vein. He was given a