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Serum cortisol concentrations in children with chronic renal insufficiency

Raised plasma corticosteroids may retard growth whether their source is exogenous or endogenous, as in the case of Cushing's syndrome. Fanconi (1954) postulated that adrenal hypertrophy and excess circulating corticosteroids, occurring in response to stress, might limit the growth of children with chronic renal disease. Further investigations have shown that rats rendered uraemic by either subtotal nephrectomy or induced nephritis develop adrenal hypertrophy (Deane and Masson, 1951; Morrison, 1962) and there have been reports of an abnormal diurnal rhythm and of raised midnight and morning plasma cortisol concentrations in adults with severe renal failure (Varghese *et al.*, 1969; Snodgrass *et al.*, 1970). However, in the above reports the cortisol concentrations were determined using a fluorimetric technique similar to that described by Mattingly (1962). By this method only 59% of the total fluorescence may in fact be due to the free 11-hydroxycorticosteroids, cortisol, and corticosterone (James, Townsend, and Fraser, 1967) and mistakenly raised values would be obtained in the presence of an excess of non-cortisol fluorimetric material. Cortisol may now

be estimated by the use of competitive protein binding (Murphy, 1967); this is a more specific determination and eliminates these possible errors.

Plasma cortisol concentrations show a diurnal rhythm, the lowest levels being found soon after midnight, thereafter rising to a morning peak. Any abnormality of secretion resulting in excessive values should therefore be demonstrable during the night. The nocturnal concentrations of serum cortisol have been determined by both fluorimetric and competitive protein binding techniques as part of a more comprehensive study of the growth retardation of children with chronic renal insufficiency.

Patients and methods

A method for the continuous sampling of venous blood through the night, in hourly aliquots, has been described elsewhere (Howse *et al.*, 1974). Serum cortisol concentrations were determined both fluorimetrically, by a modification of the Mattingly technique (1962) and by competitive protein binding, utilizing a modification of the technique described by Murphy (1967). Control values were obtained for the competitive protein binding technique in 5 boys with short stature who had a normal plasma cortisol response to hypoglycaemia after an insulin sensitivity test. Their mean age was 11 years (range 7 to 14 years). The hourly aliquots for serum cortisol concentration in these children were only available up to 4.00 a.m. 11 children with varying degrees of renal insufficiency were investigated and the details are shown in the Table. There were 8 boys and 3 girls; their mean age was 11 years (range 4 to 16 years). No patient was on any drug known to fluoresce or interfere with the estimation of cortisol by the competitive protein binding method.

Results

The means \pm 1 SD, for the hourly nocturnal serum cortisol concentrations determined fluorimetrically and by competitive protein binding in children with chronic renal insufficiency are shown in the Fig. The cortisol concentration in all these samples when determined fluorimetrically was higher than that obtained by competitive protein binding and the mean hourly values differed between the two methods by approximately 18 μ g/100 ml. The values obtained by competitive protein binding for the serum cortisol concentration in the renal patients were no different from those in the controls (Fig.). The renal patients showed a normal diurnal rhythm and their midnight and morning values were similar to other published normal data for plasma samples (Barnes *et al.*, 1972.)

Four of the children with chronic renal insufficiency had short stature (Table). There was no significant increase in the serum cortisol concentra-

TABLE
Clinical and laboratory findings in 11 children with chronic renal insufficiency

| Case no. | Age (year) | Sex | Height centile | Diagnosis | GFR ml/min per 1.73m ² |
|----------|------------|-----|----------------|--------------------------------------|-----------------------------------|
| 1 | 4.6 | M | 3 | Posterior urethral valves | 44 |
| 2 | 5.75 | M | <3 | Uncertain | 24 |
| 3 | 8.3 | F | 25-50 | Juvenile nephronophthisis | 30 |
| 4 | 9.5 | M | 25-50 | Bilateral dysplasia | 21 |
| 5 | 9.9 | M | 10-25 | Bilateral reflux nephropathy | 15 |
| 6 | 10.4 | M | 25 | Bilateral hydronephrosis | 30 |
| 7 | 10.5 | F | 25-50 | Mesangiocapillary glomerulonephritis | 2 |
| 8 | 13.8 | M | 50 | Bilateral dysplasia | 11 |
| 9 | 13.9 | M | <3 | Bilateral hydronephrosis | 8 |
| 10 | 15.5 | F | 25 | Schönlein-Henoch nephritis | 15 |
| 11 | 16.1 | M | <3 | Bilateral dysplasia | 10 |

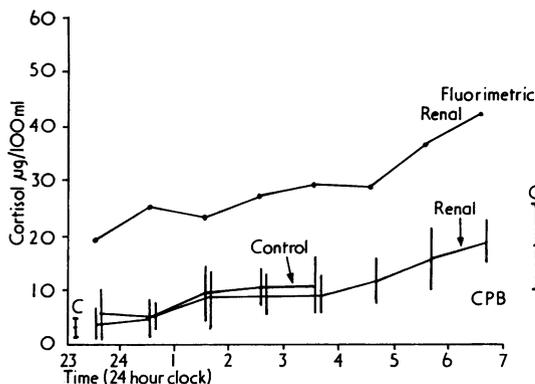


FIG.—Mean and SD for serum cortisol concentrations in control and renal patients as determined by competitive protein binding (CPB). Published normal values for the midnight and morning plasma concentrations by CPB are also shown (C) (Barnes *et al.*, 1972) together with the mean hourly fluorimetric concentrations in the renal patients.

tions determined by competitive protein binding in this group.

When the results for individual children were examined there was no obvious correlation between the difference in the serum cortisol concentrations as determined by the two methods and the glomerular filtration rate of those children with chronic renal insufficiency.

Discussion

Children with chronic renal insufficiency have a normal diurnal rhythm and normal nocturnal values

for serum cortisol concentration when determined by competitive protein binding. The growth retardation seen in these children is therefore unlikely to relate to an abnormality of serum cortisol concentration. The previously reported raised values in patients with renal insufficiency (Varghese *et al.*, 1969; Snodgrass *et al.*, 1970) have not been substantiated.

The fluorimetric method as described by Mattingly (1962) for the determination of cortisol is relatively nonspecific (James *et al.*, 1967), and the previously reported raised values in patients with chronic renal insufficiency probably included significant amounts of noncortisol and corticosterone-fluorescent material. What material this may be is under investigation, but these findings should be considered when assessing adrenocortical function in patients with renal insufficiency.

Summary

Children with chronic renal insufficiency have a normal diurnal rhythm and normal nocturnal values for serum cortisol when determined by competitive protein binding. Falsely raised values were obtained when a fluorimetric technique was used for the cortisol determinations in these patients.

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Micropenis associated with testicular agenesis

In 1962 Bergada *et al.* described 4 boys who had small, dysgenetic testes associated with micropenis, but otherwise normal sexual differentiation. More recently, Najjar, Takla, and Nassar (1974) described a family in which 5 brothers had very small testes and micropenis. This paper describes 2 further, unrelated male infants with ambiguous external genitalia who showed features of this syndrome of 'micropenis with rudimentary testes'.

Patients

Case 1. The second child of unrelated parents, born after a normal term pregnancy. At birth it was difficult to decide the infant's sex. A minute penis consisting of a small prepuce-like skin tag devoid of palpable erectile tissue was present (Fig. 1). The urethral orifice could not be seen but urine was passed from this area. Testes could not be felt in the small, fleshy scrotum. Physical examination was otherwise normal.



FIG. 1.—External genitalia in Case 1.

The patient's buccal smear was chromatin negative, and chromosome analysis showed a normal male karyotype. At the age of 3 months, the urinary 17-oxosteroid excretion was 0.4 mg/24 h.

When the patient was 4 months old, surgical exploration was carried out (Mr. Innes Williams). A vas and epididymis were present in each groin. These structures were resected. Testes could not be identified at operation and histological examination of the surgical specimens showed no evidence of testicular tissue. In view of the extreme degree of micropenis and the operative findings, it was decided that the patient would be best raised as a girl and vulvoplasty was carried out at the age of 5 months.

Case 2. This patient is the fourth child of unrelated parents. 3 older sibs are normal but 2 further pregnancies had ended in spontaneous abortions during the first trimester. The patient was born after a term pregnancy complicated by an influenza-like illness at 10 weeks which was treated with an antibiotic. Further details of this illness are not available. The pregnancy was otherwise normal.

The patient was found to have ambiguous external genitalia after delivery (Fig. 2). The penis was represented by a small, fleshy swelling approximately 3 mm × 3 mm which was partly covered by a small prepuce. The urethra opened at the base of this structure. The scrotum was small and testes could not be felt. No other abnormalities were found on examination.