The adrenogenital syndrome

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Introduction

IN 1865, de Crecchio (1865) first described a phenotypically male cadaver with hypospadias in whom he found female internal genitalia with bilateral adrenal hyperplasia. Almost a century later, Wilkins *et al.* (1951) and Bartter *et al.* (1951) independently discovered that the excessive androgenic effects of this syndrome could be suppressed by cortisone. It is now well established that the adrenogenital syndrome associated with congenital adrenal hyperplasia (CAH) is the result of inborn errors of steroidal biosynthesis (Bongiovanni and Root, 1963). Currently, five such enzymatic deficiencies in steroidogenesis, producing ambiguous external genitalia are recognised. In order to understand the diverse clinical manifestations of these defects, a knowledge of the synthesis of steroid hormones is essential. The suprarenal glands synthesise 3 main classes of hormones: mineralocorticoids, glucocorticoids and the sex hormones and a simplified scheme of the biochemistry involved is presented in Fig. 1. Any enzymatic block along the biochemical pathway results in compensatory hypertrophy of the adrenal cortex consequent on a feedback mechanism which 'instructs' the hypothalamus and pituitary gland to increase ACTH output. The abnormal quantities of sex hormones thus produced may adversely affect the differentiation of the external genitalia (but not the internal genital structures) of the developing foetus (Jost, 1953). Table I summarises the various clinical syndromes associated with each enzyme deficiency.

The incidence of this genetic disorder ranges from 1 in 490 in the Yupik Eskimos (Hirschfeld and Fleshman, 1969) to 1 in 67,000 in United States (Childs *et al.*, 1956). The actual incidence in this community is not known and during the 6-year period between 1970–76, 12 patients with adrenogenital syndrome (AGS) have been diagnosed at the University Hospital, Kuala Lumpur. It is not sufficiently realised that the AGS is a medical emergency, for delay in diagnosis and treatment may not only cause confusion in sex assignment, but may also result in fatality from Addisonian crisis. This is demonstrated in the following case reports.

Illustrative Case Reports

Case 1: RRI first presented at this hospital at $6\frac{1}{2}$ years of age. She was delivered at term, after an uncomplicated pregnancy and labour. There was no family history of consanguinity. At birth, she was assigned the female sex although the mother noticed that she had an enlarged phallus. Her early childhood was uneventful but from the age of 3 years, her growth accelerated. At 4 years, acne and pubic hair were noted and since then her clitoris had enlarged considerably. On physical examination, the child was 128 cm tall (97th percentile by Singapore standards) (Wong and Tay, 1975), the blood pressure was 100/60 mm Hg., acne was present over the forehead and malar regions, and there was a moderate growth of pubic hair. The voice remained feminine. The external genitalia revealed a large phallus 4 cm in length, separate openings were present for the urethra and vagina, but there was partial fusion of the posterior fourchette. No masses were palpable within the labial pouches. Laboratory findings included a chromatin positive buccal smear, a bone age of 9 years, normal cortisol levels and a

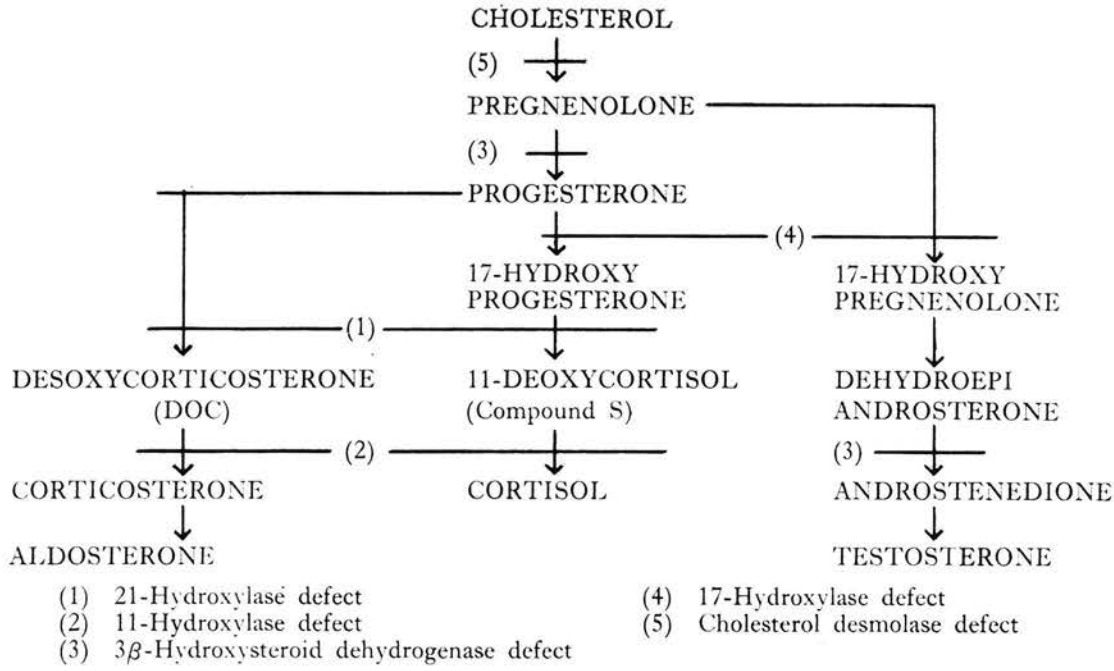

Fig. 1: Inborn Errors of Steroidal Biosynthsis Leading to the Adrenogenital Syndrome.

24-hour urinary 17-ketosteroid output of 9 mg (normal 1.5–2.5 mg for 7 years). She was treated with dexamethasone 0.25 mg b.d. This resulted in suppression of the 24-hour urinary 17-ketossteroid to 3 mg. Subsequently clitoroplasty was performed. During the next 12 months, the child remained well, became free of acne and the growth rate slowed down.

Case 2: RR2, the younger sibling of Case 1 (Fig. 2), was the product of a normal full term spontaneous delivery and appeared normal at birth. His developmental milestones were normal and he suffered no serious illnesses in early childhood. From the age of 4 years, however, his parents noticed that acne had appeared on his forehead, pubic hair had started to grow and his penis was enlarging rapidly. Examination at 5 years revealed a tall muscular boy (90th percentile in height and weight), comedones were present on the forehead, the penis was 6 cm long and there was a fine growth of pubic hair around the base. Both testes remained infantile, blood pressure was normal but skeletal maturity had advanced to 10 years of age. Laboratory studies demonstrated a normal serum electrolyte pattern, normal cortisol levels and a 24-hour urinary 17-ketosteroid output of 9 mg; the latter was readily suppressed by dexamethasone.

Comment: The above 2 cases are examples of simple virilizing adrenal hyperplasia due to a mild 21-hydroxylase deficiency. They displayed the effects of delayed diagnosis and prolonged exposure to endogenous androgenic influence, viz, advanced stature and advanced bone age, acne, pubic hair

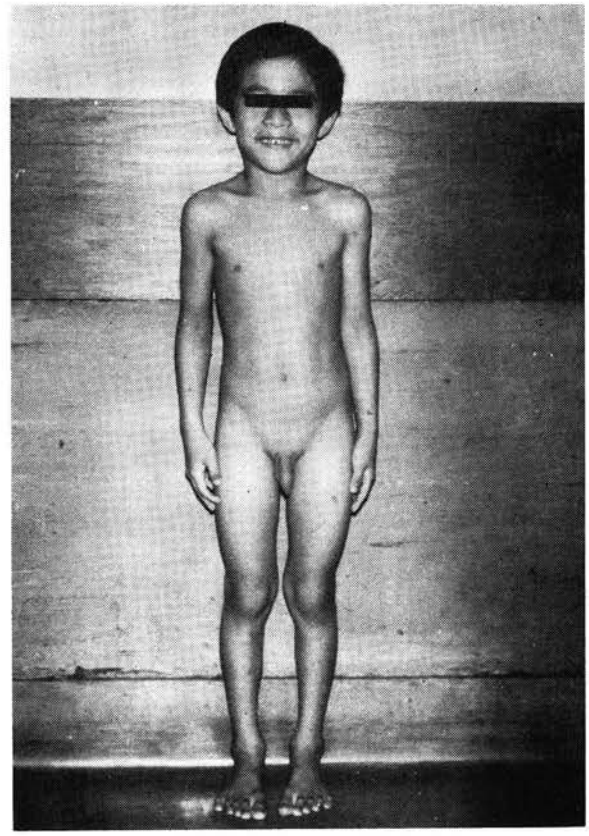

Fig. 2: RR2 (Case 2) at 5 years of age. Note tall stature and increased penile length. He also had a fine growth of pubic hair, and acne over his forehead.

Table I: Clinical Effects and Steroid Alteration in Various Forms of Adrenogenital Syndrome

Enzyme Defect	Blood Hormonal Levels	Clinical Effects	Urinary Steroid Output
21-hydroxylase (mild)	Cortisol normal Testosterone ↑ Aldosterone normal	Virilization of external genitalia in female, somatic and sexual precocity in both sexes, skin pigmentation, ultimate dwarfism in adulthood.	17-ketosteroids ↑↑ Pregnanetriol ↑↑ 17-hydroxysteroids normal or ↓
21-hydroxylase (severe)	Cortisol ↓ Testosterone ↑ Aldosterone ↓	Effects of excessive androgenization: as above. Failure to thrive, Addisonian crises in early infancy, occasional hypoglycaemia.	17-ketosteroids ↑↑ Pregnanetriol ↑↑ 17-hydroxysteroids ↓
11-hydroxylase	Cortisol normal or ↓ Aldosterone ↓ Desoxycorticosterone (DOC) ↑	Virilization as in 21-hydroxylase deficiency. Hypertension.	17-ketosteroids ↑↑ 17-hydroxysteroids (mostly tetrahydro DOC and S) ↑↑
3 β-hydroxysteroid dehydrogenase	Cortisol ↓ Testosterone ↓ Aldosterone ↓	Virilization in female, incomplete masculinization in male. Failure to thrive, marked salt wasting. Often fatal despite treatment.	17-ketosteroids ↑ 17-hydroxysteroids ↓↓
17-hydroxylase	Cortisol ↓ Testosterone ↓ Aldosterone ↓ DOC ↑	Feminization of external genitalia in male. Primary amenorrhoea and sexual infantilism in female. Hypertension.	17-ketosteroids ↓↓ 17-hydroxysteroids ↓↓
Cholesterol desmolase	Cortisol ↓ Testosterone ↓ Aldosterone ↓	Feminization of external genitalia in male. Sexual infantilism in female. Failure to thrive, severe salt wasting. Often fatal despite treatment.	17-ketosteroids ↓↓ 17-hydroxysteroids ↓↓

and an enlarged phallus. Characteristically, the gonads remain infantile and thus excludes true precocious puberty. Generally, the gonads fail to develop so that affected individuals may be expected to be infertile without therapy. In the absence of any salt losing crisis, the condition is usually not recognised in the male at birth, however, the presence of this disorder in a family should prompt a biochemical evaluation in all other siblings. It must be emphasised that these patients are unable to increase their cortisol output and are susceptible to Addisonian crisis in times of stress. This form of AGS is the most common in many reported series (Hamilton, 1972, and Jailer *et al.*, 1955). Five patients with this disorder have been diagnosed in this hospital, and all are doing well on therapy.

Case 3: C.S.J. presented at this hospital at the age of 2 months. He was the only child in the family and was delivered normally at term after an uneventful pregnancy. During the first 2 weeks of life, he thrived well and had gained 0.5 kg in weight. From the third week of life, however, he began to refuse feeds, became irritable and lethargic and had episodes of vomiting and frequent loose motions. Several changes of milk formulae were made without improvement. Physical examination revealed a marasmic infant with mild dehydration and hypothermia. His external genitalia were those of a normal male and both testes were descended. Serum electrolytes were: sodium 100 mEq/l., potassium 6.9 mEq/l., and Astrup studies revealed moderate metabolic acidosis. Soon after hospitalisation, he developed hypovolaemic shock and was resuscitated with parenteral hydrocortisone, desoxycorticosterone acetate (DOCA) and saline infusion. The electrolyte pattern returned to normal after 4 days. On the presumptive diagnosis of AGS, oral cortisone acetate, 9 α-fluorocortisone were initiated and 1 gm of salt was added to the milk each day. The baby thrived well on this regime and gained 1.3 kg over the next 3 weeks. Subsequently, he withstood common childhood illnesses without difficulty and his growth progressed along the 25th percentile. At 8 months of age, he was hospitalised for biochemical evaluation. Both steroids were withdrawn, and on the eighth day he developed fever, vomiting and diarrhoea and lost 5% of his body weight, The urinary 17-ketosteroid output at this stage was 6.9 mg per 24 hours and this was readily suppressed once the steroids were resumed. He has remained well when last examined at 3 years of age.

Case 4: I.T. (Fig. 3) was born at term in a private maternity clinic after an uncomplicated labour. She was referred at the age of 30 hours as a 'male' with hypospadias and undescended testes. Family history revealed that she was the fourth child; the

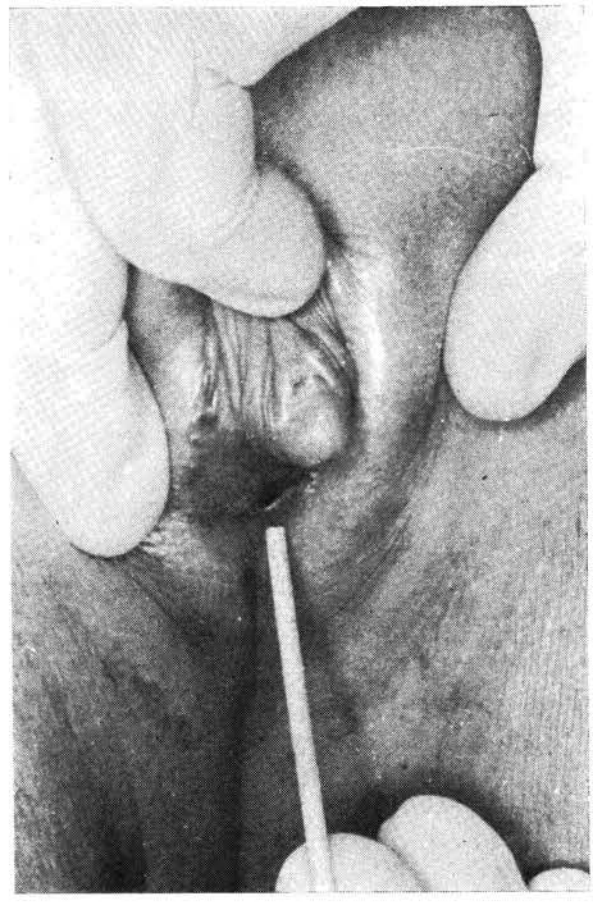

Fig. 3: The external genitalia of I.T. (Case 4). Note hypertrophic phallus, empty labio-scrotal folds and single perineal opening. Buccal smear was chromatin positive.

first, a male, had died of an unknown cause at the age of one week; the second offspring was also born with ambiguous genitalia and had succumbed to diarrhoea and vomiting at 6 weeks of age; the third child, a boy, is currently well. At the time of admission, I.T. was an alert infant weighing 3.2 kg. She had a hypertrophic phallus 3 cm long, a single perineal meatus and bifid rugose labioscrotal folds which contained no palpable masses. There was hyperpigmentation of the genitalia and the axillae. The blood pressure was 60 mm Hg. systolic and the remainder of the physical examination was normal. Buccal smear was chromatin positive and urinary 17-ketosteroids were markedly elevated. At the age of 13 days, poor feeding, lethargy and a loss of body weight were noted. There was further deterioration the next day, although serum electrolytes had remained normal. She was treated with intravenous fluids, cortisone and DOCA with good response and

discharged at 7 weeks on glucocorticoids and 9 α-fluorocortisone. Over the subsequent 4 months, the infant had 3 hospital admissions for intercurrent illnesses and for steroid dosage readjustment as her growth rate was slow and she had developed mild hypertension.

Comment: Both cases 3 and 4 demonstrate the classical features of the salt-wasting form of 21-hydroxylase defect. Symptoms of adrenal insufficiency may not appear till the second or third week of life and the diagnosis is less obvious in the male infant. Case 4, in addition, illustrates that identification of sex is frequently not possible on clinical grounds alone. Dosage schedule in these patients needs frequent adjustment. Close supervision, periodic bone age determination, and biochemical monitoring are often required to achieve optimal therapy. Three additional patients in this series had this disorder. One infant, who was on treatment died of septicaemia at the age of 4 months.

Case 5: J.A. was the product of a normal full term spontaneous delivery. She had thrived well at home but was referred at 3 weeks of age because of ambiguous genitalia. Examination revealed an active child with a blood pressure of 110/70 mm Hg. There was an enlarged phallus with a single perineal opening and the partially fused labioscrotal folds were empty. No abnormal pigmentation was noted over the genitalia or nipples. Investigations demonstrated a vagina and normal female internal genitalia on radiography, a chromosome positive buccal smear, normal serum electrolytes and a significantly elevated 17-ketosteroid and 17-hydroxysteroid output in the urine. Therapy with cortisone suppressed the urinary 17-ketosteroids and diminished the blood pressure to 80/50 mm Hg. Surgery is planned for in later infancy. The family history revealed that the child's parents are first cousins. There are five elder siblings, one of whom, a normal female, had died at the age of 15 months of bronchopneumonia. The remaining members of the family were examined and the third child, M.A., was found to be abnormal.

Case 6: M.A., (Fig. 4), a girl was already 7 years of age. At birth, the mother discovered that her

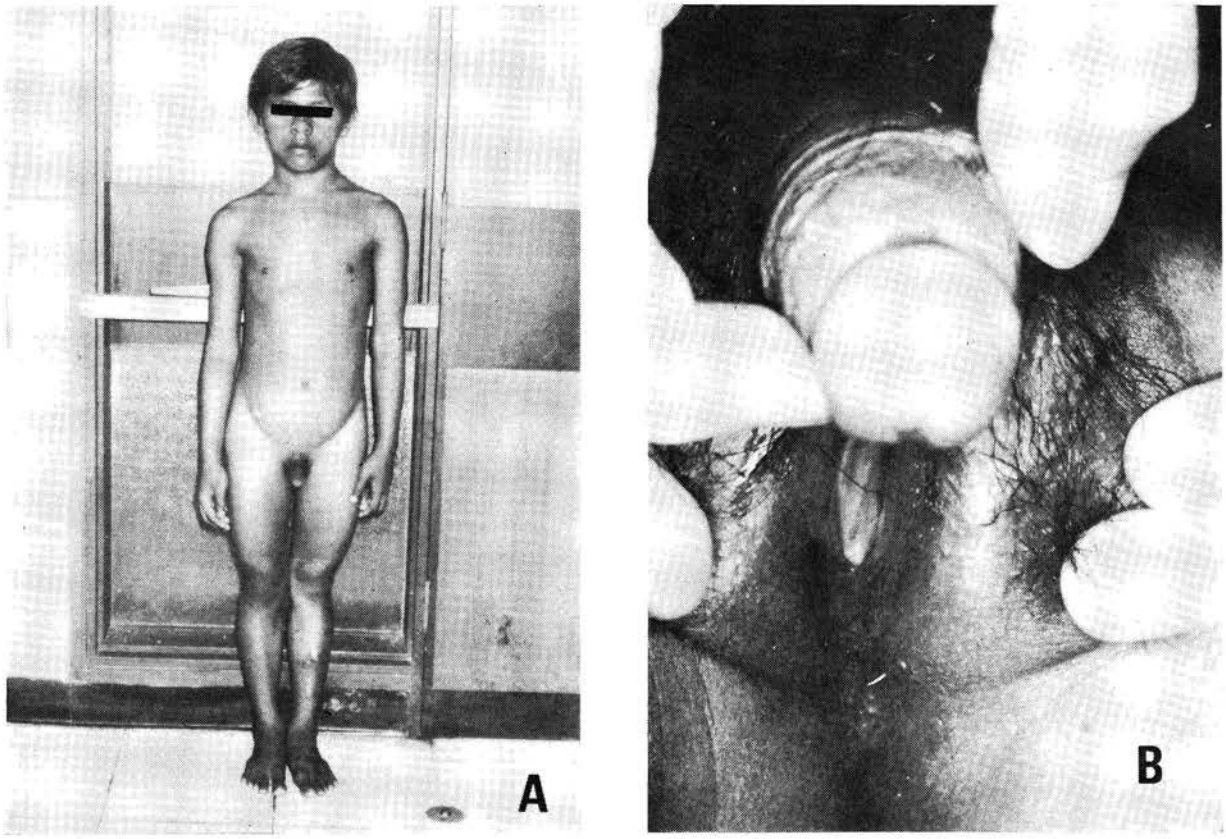

Fig. 4: M.A. (Case 6) at 7 years of age. Note (A) tall stature, masculine physique and apparently male external genitalia. Closer examination (B) revealed separate openings for the urethra and vagina. In addition, she was hypertensive.

genitalia were similar to those of J.A. She was assigned the female sex by the village midwife and was reared as a female. Over the years, however, the parents noticed that her phallus had gradually increased in size. Facial acne and pubic hair appeared at 3 years of age and her voice became increasingly hoarse from 4 years. She attended a girls' school and because of her tall stature, masculine physique and voice, she was subjected to constant teasing. In their confusion about her real sex identity, her parents dressed her in boy's jeans at home. On physical examination, her height age was 12 years, she was muscular, dark, hirsuit and had acne on her face and upper chest. Her clitoris was 7 cm long, there was a profuse growth of pubic hair, the labioscrotal folds were fused but there were separate openings for the urethra and vagina. Her blood pressure ranged from 140/110 mm Hg to 150/120 mm Hg. Nuclear sexing confirmed that she was a female, the serum electrolytes were normal, her bone age had advanced to 15 years and the urinary 17-ketosteroid and 17-hydroxysteroid excretions were markedly elevated. Three months after institution of glucocorticoids, the blood pressure and urinary 17-ketosteroids dropped to normal levels. Clitoridectomy and vulvoplasty were subsequently performed. She is now attending a different girls' school and is receiving psychological guidance to reinforce her psychosexual orientation.

Comment: In both cases 5 and 6, the diagnosis of 11-hydroxylase defect was made on the basis of elevated 17-ketosteroids, 17-hydroxysteroids and hypertension. This enzymatic defect is much rarer than the 21-hydroxylase deficiency and the history of consanguinity is thus significant (Hamilton, 1972). The somatic effects of both 11 and 21-hydroxylase deficiencies are similar and definitive diagnosis is dependent on qualitative urinary steroid determination. The problems of delayed diagnosis and confusion in psychosexual orientation are seen in Case 6. It is unfortunate that treatment at this stage will not result in any alteration of her voice. Furthermore, she is unlikely to achieve her growth potential because of the extremely advanced epiphyseal ossification.

Discussion

The diagnosis of adrenogenital syndrome is not difficult if the condition is suspected in any child presenting with ambiguous genitalia, with dehydration and salt wasting in the early weeks of life or with signs of sexual precocity. Sex chromatin determination is essential in these situations. A summary of the various disorders to be considered in the differential diagnosis of a child with indeterminate genitalia is given in Table II. The definitive diagnosis is a matter of some urgency as the correct sex will have to be assigned early to allay parental anxiety and embarrassment and to prevent psychological damage arising from confused gender role.

Table II: Differential Diagnosis of Ambiguous Genitalia

Disorder	Karyotype	Internal Genitalia	Urinary 17-KS	Laparotomy Findings
		Sex Chromatin Positive		
Virilizing AGS	XX	Female	Elevated	Not indicated
Virilization from exogenous or endogenous maternal androgens	XX	Female	Normal	Not indicated
Klinefelter variant	XXXXY, etc.	Male	Normal	Infantile hypoplastic testes
True hermaphroditism	XX, XX/XY, etc.	Mixed Wolffian and Mullerian structures	Normal	Ovary, testis, ovotestes mixed internal genitalia
		Sex Chromatin Negative		
Feminizing AGS	XY	Male with blind vaginal pouch	Absent or low	Not indicated
Incomplete testicular feminization syndrome	XY	Male with blind vaginal pouch	Normal	Testes, with vas deferens present
Mixed gonadal dysgenesis	XO/XY, etc.	Mixed	Normal	Streak gonad, testis, mixed internal genitalia
True hermaphroditism	XY, XX/XY, etc.	Mixed	Normal	Ovary, testes, ovotestes
Simple hypospadias with cryptorchidism	XY	Male, no vaginal pouch	Normal	Not indicated

There is no doubt that female infants with the AGS should be brought up as females whatever the degree of virilization of the external genitalia. Their internal organs are entirely female, they are potentially fertile and appropriate plastic repair can be performed (Mason, 1961). The converse situation of male infants with feminization is less commonly encountered, but their sex of rearing is determined largely by the morphology of the external genitalia. In the infant with a rudimentary phallus and genitalia simulating a female, no amount of reconstructive surgery will allow the child to adequately function as a male, regardless of the gonadal or chromosomal sex. It is fortunate that the 5 children who presented to us in late childhood had been assigned their appropriate sex, for any attempt at reversal of sex of rearing at that stage would have resulted in serious psychological maladjustment.

The child with CAH will, of course, require glucocorticoids for replacement therapy; the equivalent of hydrocortisone 20–30 mg per kg per day in 2–4 divided doses is recommended (Brook *et al.*, 1974). In principle, the aim is to administer the smallest dose which is sufficient to suppress androgen synthesis without producing cushingoid features and at the same time allowing for optimal growth. Thus, the dosage must be carefully adjusted with increasing age. This will require periodic monitoring of the height and weight age, skeletal maturity and the 17-ketosteroid output in the urine. Parents must be warned that therapy is life long and that under conditions of stress, such as during infection, injury or surgery, additional glucocorticoid therapy must be provided. About 30–65% of persons affected will exhibit a salt losing syndrome, with first symptoms usually appearing between the second and eighth weeks of life (Marks and Fink, 1969) as illustrated in Cases 3 and 4. Neonates with AGS should thus have regular electrolyte determinations in the early weeks of life so that this complication can be promptly diagnosed and treated. During an Addisonian crisis, urgent rehydration with intravenous saline solutions, correction of metabolic acidosis and administration of parenteral glucocorticoids and mineralocorticoids are life-saving procedures. Once the crisis has been overcome, these children need not only cortisol replacement but also salt-retaining hormones (Kenny and Vazquez, 1972) such as DOCA or 9 α-fluorocortisone and additional salt in their diet.

Surgical reconstruction of the genitalia should be performed in early childhood, preferably before the child becomes aware of the abnormality. Radiological demonstration of the internal genital structures and their relationship to the lower urinary tract is often extremely helpful in the preoperative evaluation. Completion of surgical repair does not constitute termination of therapy. Perhaps, in no other disorder is continuing tactful psychological guidance more important both for the family and the child. These aspects have been extensively discussed by Money (1975).

The AGS is inherited as an autosomal recessive trait, males and females being equally affected within sibships. The severity of the defect, with few exceptions, is consistent within one family (Rosenbloom and Smith, 1966). Prenatal detection is now possible by determination of steroid metabolites in the amniotic fluid so preventing delay in postnatal treatment (Nicols, 1970). Provided treatment is adequate, the prognosis is excellent in most cases, and is compatible with a healthy life, normal sexual function and fertility. Only one patient in our present series has succumbed to this disorder.

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