Although this stimulation test appears to unmask some underlying adrenal abnormality in a proportion of the parents it is difficult to understand why, if the syndrome is due to a non-sex-linked recessive gene, all the parents are not abnormal. It is also difficult to understand why the degree of expression of the defect appears to be additive in the manner described. However, the small number of families investigated, as in other series, makes any conclusion difficult. More extensive application of the test to a larger series of parents and siblings of affected parents would seem to be justified.

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Diagnosis and Management of Congenital Adrenal Hyperplasia

The commonest form of congenital adrenal hyperplasia (CAH) is that with a C21-hydroxylation defect which results in virilization with or without salt loss. Clinical diagnosis is most difficult in infant boys since virilization may not be apparent with any degree of certainty. If the virilized boy presents in later childhood other causes must be remembered including adrenocortical carcinoma and adenoma, precocious puberty and interstitial cell tumour of the testis. Virilization is readily observed in girls and amongst other causes the possibility of the mother having received a progestational agent during pregnancy must be considered.

Attempts have been made to diagnose the condition *in utero*, e.g. by Merkatz *et al.* (1969). Unfortunately the amounts of 17-oxosteroids (17-ketosteroids, 17-KS) and pregnanetriol in the amniotic fluid are not sufficiently abnormal to enable the diagnosis to be reached in any particular instance.

Provided the child is not dehydrated time can be taken to investigate the patient fully, but where there is salt loss and dehydration urgent treatment is required. The determination of plasma electrolytes and the 11-oxygenation index (11-OI) is desirable. The plasma electrolytes are characterized by a raised potassium, reduced sodium and often a raised urea. The 11-OI reflects the efficiency of the last stages of cortisol biosynthesis. It was first introduced by Hill (1960) and later modified by Edwards *et al.* (1964). It measures the ratio of adrenocortical steroids without an oxygenation function at the C-11 position to those with oxygenation at C-11. The upper level of normal is 0·7 and levels of 0·9 to 6·7 have been observed in untreated children with CAH. The method has several advantages: it can be performed on a random sample of urine (about 20 ml), it is unaffected by the administration of a salt-retaining steroid and salt, and a subjective result from the chromatograms can be obtained in four hours. Urine for this determination should not be collected until the infant is 8 days old since abnormally high values may be obtained in younger infants who do not have CAH (*see* Fig 1); this is probably the result of late maturation of cortisol biosynthesis. Also in infants with CAH the 11-OI may not be raised until the eighth

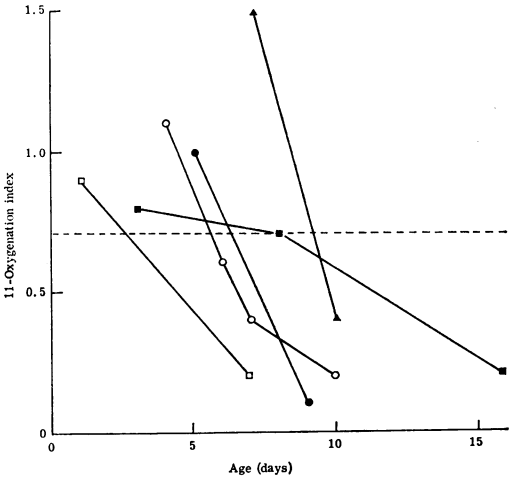

Fig 1 *Variation of the 11-oxygenation index in 5 normal infants with late maturation of cortisol biosynthesis*

day (*see* Fig 2). Generally salt loss is not seen until the end of the first week of life at the earliest. Exceptionally the 11-OI may not be raised until as late as 3 months of age. A raised 11-OI is occasionally seen too in very ill patients without CAH. It presumably indicates a failure of cortisol production. A variety of factors could account for this including nutritional deficiencies, anoxia and

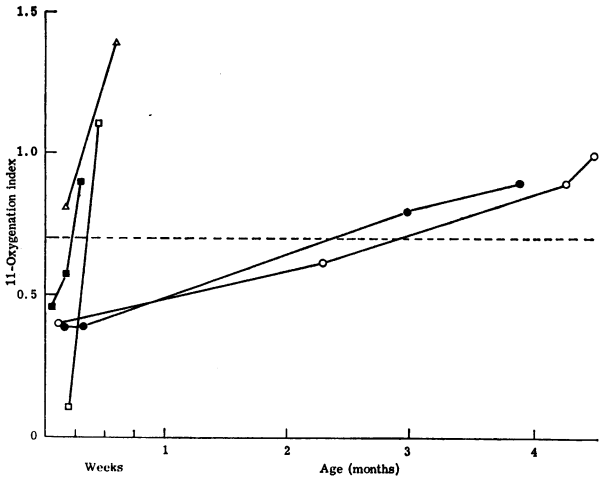

Fig 2 *Variation of the 11-oxygenation index with age in patients with untreated congenital adrenal hyperplasia. The pattern seen in subjects S G (○———○) and C E(●———●) is exceptional*

the development of pathological lesions in the adrenals. Provided urine is not collected earlier than the eighth day of life and the result is assessed in the light of other clinical and biochemical findings, this determination is most helpful.

In the past much emphasis has been placed upon demonstrating a high urinary excretion of 17-KS. Apart from the difficulty of collecting a 24-hour urine, particularly from a virilized girl, the somewhat raised excretion of 17-KS in the normal neonate can render interpretation of the result difficult. Normal values for the excretion of 17-KS have been given by Prout & Snaith (1958), and after the first month of life the excretion should be less than about 1 mg per day until 6 years of age. These patients also show an elevated excretion of pregnanetriol to levels as high as about 0·29 mg/kg bodyweight/day compared with the normal of 0·01 mg/kg bodyweight/day (Bongiovanni *et al.* 1959). The method is time consuming and does not serve as an emergency procedure.

Biochemical confirmation of the diagnosis may not be requested until days or weeks after treatment with glucocorticoids has been commenced. In such treated patients the 11-OI will of course be normal. Whilst continuing steroid therapy the child should be injected with adrenocorticotrophic hormone (ACTH; 20 physiological units Armour gel twice daily) for four to seven days, and daily random urines collected for the estimation of the 11-OI. If the child has CAH there will be a steady increase in the value of the 11-OI (*see* Fig 3). In contrast, in subjects without CAH the 11-OI will decrease. This provides a safe method for establishing the diagnosis since the withdrawal of steroids is avoided.

Treatment includes the correction of dehydration and salt loss; administration of a glucocorticoid and of a salt-retaining steroid when necessary, confirmation of the sex of the child and possibly surgery at a later date. The parents of such a child, especially if the external genitalia are equivocal, require much support. Other sibs should be examined since undiagnosed CAH with virilization and no salt loss may have been missed. Excellent accounts of treatment have been given by Hubble (1960), Raiti & Newns (1964), Wilkins

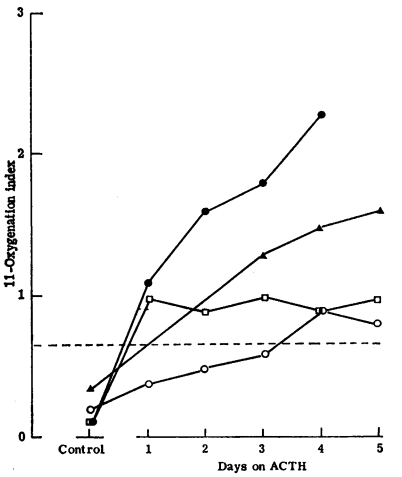

Fig 3 *The response of the 11-oxygenation index to ACTH in patients receiving steroids for the treatment of congenital adrenal hyperplasia*

(1965) and Visser (1966). If there is any doubt about the diagnosis or if laboratory facilities are inadequate, then in the salt-losing form treatment should be commenced without delay. If possible a random urine for the 11-OI should be collected into a few drops of chloroform before corticoids are given, but deoxycortone acetate and 9α-fluorohydrocortisone will not interfere with the estimation. Such preserved urine can be sent by post if necessary. It is better to overdose with a glucocorticoid rather than give insufficient, and very high doses are required initially.

Once the child has been stabilized the dosage of steroid should be reviewed regularly in the light of the child's growth in height and weight, skeletal maturation and urinary excretion of 17-KS. It is unnecessary to stop the administration of steroid during collection of the 24-hour urine for 17-KS. Using a few drops of chloroform as preservative, the urine can be posted to the laboratory. In our experience the 11-OI has not proved sufficiently sensitive for the long-term follow up of patients.

The dose of steroids should be increased during surgery and infections, and if vomiting occurs the steroid should be injected. Tragedies due to failure to inject the dose during infections with accompanying vomiting are not unknown.

A fuller account of the data on the 11-OI will be published elsewhere.

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The following paper was also read:

Congenital Adrenal Hyperplasia due to 17-Hydroxylase Deficiency

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