In the present study methandienone did not appear to have any marked virilizing side-effects, if one excludes those patients who had high levels of endogenous or exogenous corticoids. Acne, increased sebaceous secretion, and changes in facial, body, and scalp hair were uncommon, while voice changes have not occurred. In the two women with Cushing's syndrome, however, and in four patients receiving either prednisone or triamcinolone, methandienone did produce some androgenic effects, though these were never of a very severe degree, and did not necessitate the discontinuation of the drug. The increase in libido that occurred in some patients is of interest, and may indicate some androgenic action.

The relative lack of androgenic effect of methandienone in this series is particularly relevant in that initially we were uncertain of the dosage necessary to produce anabolism, and consequently in the early periods of our study we used an excessively high dose. From our present studies of nitrogen balance, doses of 0.2–0.4 mg./kg. body weight per day are capable of producing marked nitrogen retention and gain in weight. Initially many of the patients were given methandienone in doses in excess of 1 mg./kg. body weight per day.

In the rat, Desaulles *et al.* (1959) found that inhibition of oestrus could be brought about only by high doses of methandienone (30 mg./day)—methyltestosterone and norethandrolone being 30 times more active inhibitors of the oestrous cycle. They also found methandienone to have a very weak progestational effect, large doses (70 mg./kg.) being unable to produce a complete progestational type of secretory epithelium in castrated female rabbits sensitized with oestrone.

Foss (1960) found no suppression of the menses in two women given 25 mg. and 50 mg. of methandienone daily, though the drug caused suppression of the menses in one 14-year-old girl. In the small number of premenopausal patients in the present series who had normal and regular periods prior to starting methandienone, the drug has completely suppressed menstruation. The suppression of menstruation in these patients had persisted for from 100 to 200 days at the time of reporting this study. The suppression of menstruation and of menopausal symptoms is probably due to methandienone inhibiting the function of the pituitary gland.

Methandienone appeared to have no progestational effect. It caused no rise of body temperature, nor was there any withdrawal bleeding.

The increased sense of well-being found in many patients while on methandienone was of considerable therapeutic value. It did not occur in patients who were not symptomatically ill at the time of being given the drug, but was most pronounced in the older or chronically ill patient.

This sense of well-being may be attributable to the anabolic or possibly some other action of methandienone, rather than to any androgenic property. These changes were not similar to the euphoria seen in some patients on cortisone or in some patients with disseminated sclerosis or general paresis of the insane. It did not consist of unjustified cheerfulness, but occurred at a time of positive nitrogen balance, weight gain, and symptomatic improvement. It did not cause the undesirable psychological manifestations often seen with cortisone, such as nervousness, restlessness, and insomnia, nor did it ever produce a psychotic state.

Summary

During the past two years the effects of methandienone have been studied. Androgenic effects were slight or absent when a dose of the drug capable of producing marked anabolism was given, and, in several cases, even when the dose used was greater than that required to produce the maximum therapeutic effect.

Methandienone may suppress menstruation and menopausal symptoms when these are present.

In many patients, especially in the old or chronically ill, methandienone produced a sense of well-being and increased confidence. Unlike the effects of corticoid or corticotrophin administration, restlessness, nervousness, or insomnia did not occur.

REFERENCES

- Desaulles, P. A., Krähenbühl, Ch., Schuler, W., and Bein, H. J. (1959). *Schweiz. med. Wschr.*, **89**, 1313.
Dorfman, R. I., and Shipley, R. A. (1956). *Androgens*, p. 368. Wiley, New York.
Foss, G. L. (1960). *Brit. med. J.*, **1**, 1300.
— and Simpson, S. L. (1959). *Ibid.*, **1**, 259.
Wynn, V., Landon, J., Kamerau, E. (1961). *Lancet*, **1**, 69.

PREGNANCY IN AN ADRENAL PSEUDOHERMAPHRODITE TREATED WITH CORTISONE

BY

A. STUART MASON, M.D., M.R.C.P.

Consultant Endocrinologist, the London Hospital

Congenital adrenal virilism is caused by an inborn error of metabolism in which an inherited enzyme defect is responsible for excessive production of androgens and a diminished secretion of other cortical hormones (Jailer, 1953; Mason and Morris, 1953). The beneficial effects of cortisone, or its synthetic analogues, were demonstrated first by Wilkins *et al.* (1952): androgen production drops to normal and feminine characters emerge.

An obvious criterion of success in long-term therapy is the maintenance of a normal pregnancy. This paper records successful pregnancy and the birth of a normal child to a patient whose congenital adrenal virilism was not treated until adult life.

Case History

The patient, born in 1928, was seen at the London Hospital in 1954 complaining of amenorrhoea and beard-growth. At the age of 4 years enlargement of the clitoris had been noted and pubic hair was present at the age of 7. By the age of 11 she had a considerable amount of body hair, and facial hair growth had just begun. Subsequently this became so marked that daily shaving was required. Throughout childhood she grew faster than her contemporaries but stopped growing in her thirteenth year. From infancy until her fourteenth year she had suffered from episodic attacks of severe vomiting which prostrated her for two or three days. These attacks were usually precipitated by minor infections but became less severe and less frequent as she grew up. She had never menstruated.

Family History.—Four sisters were normal, but the fifth was suspected of having a genital abnormality. This girl (aged 8 years) was examined in 1954 and found to be an adrenal pseudohermaphrodite with virilism and a high 17-ketosteroid excretion. Treatment with cortisone diminished the virilism and in due course she went through a normal female puberty and achieved a regular menstrual cycle.

Examination (1954).—Female aged 25, height 4 ft. 10 in. (147 cm.). Limbs short in relation to height and very muscular. A diffuse brown pigmentation involved the skin and was accentuated over the fingers and present in the palmar creases. No buccal pigmentation was found. There was marked bitemporal recession of the scalp hair. The whole body was covered with coarse hair, the pubic hair spreading upwards to the umbilicus. The face was heavily bearded. There was no breast development. The genitalia were examined under anaesthesia. The clitoris was erectile and very hypertrophic. The urethra was separate from a normal vagina. The uterus was infertile, a sound passing only 1 in. (2.5 cm.). A salpingogram showed normal fallopian tubes. All other systems were normal. The blood-pressure was 120/70 mm.Hg.

Investigations.—Serum electrolytes were normal. Urinary 17-ketosteroids varied from 36 to 41 mg./24 hours. Total eosinophil count remained unchanged four hours after the intramuscular injection of 30 mg. of A.C.T.H.

Progress

The patient was treated with oral cortisone 25 mg. t.d.s. Her 17-ketosteroid excretion declined rapidly and then remained at between 6 and 12 mg./24 hours. After two months' treatment there was a definite growth of breast tissue and the skin pigmentation had faded. Menstruation occurred at that time, and from then onwards a regular menstrual cycle was established. Her scalp hair grew over the temporal areas but there was no significant change in the rate of beard growth.

After one year's treatment a further examination under anaesthesia was made. The uterus had enlarged and a sound passed 2 in. (5 cm.). Cortisone therapy at a total daily dose of 75 mg. was continued throughout, but as a result of the examination the 17-ketosteroid excretion rose temporarily from 15 to 31 mg./24 hours.

Subsequent progress on continued treatment was uneventful, but soon after marriage she conceived (last menstrual period June, 1959). She remained well throughout the pregnancy without any change in the dosage of cortisone. There was no hypertension, oedema, or albuminuria. In the 36th week a glucose-tolerance test was normal, the serum electrolytes were normal, but the excretion of 17-ketosteroids was 31 mg./24 hours. At the 38th week labour was induced by rupture of the membranes, but the head failed to descend properly owing to the small size of the pelvis, and the baby was delivered by caesarean section. The infant was a normal female, weighing 6½ lb. (3,060 g.). Lactation began normally but had to be suppressed, as retracted nipples prevented the baby sucking.

Prior to the caesarean section 200 mg. of hydrocortisone was injected intramuscularly; otherwise, oral cortisone was continued at a dose of 75 mg. daily. Ten days after delivery the 17-ketosteroid excretion was 16 mg./24 hours. The puerperium was normal and the operation wound healed normally.

Discussion

Despite severe and prolonged virilization with primary amenorrhoea, the patient, at the age of 25, responded to cortisone therapy, which initiated a normal adult sex cycle that culminated in pregnancy. Fortunately she was born with a normal vagina and not the urogenital sinus commonly found in adrenal pseudohermaphrodites. The progressive virilization from childhood onwards was responsible for the android pelvic shape that prevented normal delivery. The association in her of a normal vagina and severe post-natal virilism illustrates the fact that the genital deformity at birth is related to the stage of embryogenesis at which abnormal adrenal function begins and is not correlated with the degree of adrenal androgen secretion in later life.

Gans and Ser (1959) reported a normal pregnancy in an adrenal pseudohermaphrodite treated with cortisone

from the age of 16. Plastic repair of a urogenital sinus had been performed, but the baby was delivered by caesarean section because the lower genital tract was not regarded as suitable for normal delivery. Delivery by caesarean section was necessary for the patient recorded by Taylor (1958) because the android pelvis did not permit normal delivery. The diagnosis is somewhat dubious in the two cases reported by Wilson and Keating (1958) as the virilism appeared to be pubertal in onset, but their second patient required a caesarean section because of a contracted pelvis. The node of delivery in these cases depends on the size of the birth canal, and it is to be expected that the pelvis proportions will not be sufficient to allow normal delivery.

A rise in the 17-ketosteroid excretion as pregnancy progressed was found in the above case and in that of Gans and Ser. De Alvarez and Smith (1957), whose patient miscarried at the fourth month of pregnancy, had suggested that any rise of 17-ketosteroid excretion during pregnancy might be dangerous. However, these two pregnancies were normal throughout and the therapy remained unchanged. The rise in 17-ketosteroid excretion might be due to changes in intermediary metabolism or to increased pituitary activity despite continued cortisone therapy. A rise subsequent to the stress of anaesthesia was noted in the case reported here. The same mechanism may have been responsible for this and for the pregnancy change.

A history of vomiting attacks in childhood suggested that our patient suffered from recurrent minor episodes of Addisonian crisis. All patients with this type of adrenal disturbance are liable to adrenocortical insufficiency in response to stress. Consequently intramuscular hydrocortisone was given in addition to the regular dose of cortisone at the time of caesarean section. There was no evidence of adrenal insufficiency after operation, and it is suggested that such precautionary therapy is essential in all cases at the time of delivery, whether the birth is natural or by caesarean section.

The child born to our patient was a female with no genital deformity and with no evidence of adrenal insufficiency during her first weeks of life. The patients of Taylor and of Gans and Ser also gave birth to normal female infants. The children have not inherited their mothers' endocrine disorder, and their development was not affected by cortisone therapy.

Summary

A case of familial adrenal pseudohermaphroditism is described. Cortisone therapy initiated a normal menstrual cycle when the patient was 25 years old. Subsequent pregnancy was normal in all respects, but delivery had to be by caesarean section. A normal female child was born.

I am grateful to Mr. A. Brews for his help and interest in this case.

REFERENCES

- de Alvarez, R. R., and Smith, E. K. (1957). *Obstet. and Gynec.*, **9**, 426.
- Gans, F., and Ser, J. (1959). *Acta endocr. (Kbh.)*, **30**, 424.
- Jailer, J. W. (1953). *Bull. N.Y. Acad. Med.*, **29**, 377.
- Mason, A. S., and Morris, C. J. O. R. (1953). *Lancet*, **1**, 116.
- Taylor, E. S. (1958). *Amer. J. Obstet. Gynec.*, **76**, 396.
- Wilkins, L., Gardner, L. I., Crigler, J. F., jun., Silverman, S. H., and Migeon, C. J. (1952). *J. clin. Endocr.*, **12**, 257.
- Wilson, R. B., and Keating, F. R. (1958). *Amer. J. Obstet. Gynec.*, **76**, 388.