hirsutism seemed to argue against the latter, though from other points of view this seemed to be the most probable diagnosis. The findings on investigation soon settled the point: the very high 17-KS and 17-KGS and the elevated P'triol and P'diol pointed convincingly to adrenal hyperfunction, while the prompt response to prednisone suppression ruled against an adrenal tumour. The sex chromatin indicated female genetic sex, and laparotomy confirmed the existence of normal internal genitalia. Mr. Matthews found the construction of an effective vagina more straightforward than had been expected; incision of the perineum, dilatation, and the insertion of an indwelling dilator were all that was required and grafting was not necessary. It was an advantage that the patient married soon after, and fortunate that she was able to establish normal coitus with little difficulty.

The basis for the treatment of adrenal hyperplasia with suppressive corticosteroids, following the pioneer work of Lawson Wilkins and his colleagues, is now too well known to require discussion. It is, however, very striking that, even though the patient was 24 years old, her menarche occurred only 36 days after starting definitive prednisone therapy and fertility was established soon afterwards. This dramatic response in patients with severe congenital adrenal hyperplasia is uniformly seen and is, of course, extremely gratifying.

The smooth course of pregnancy, with only a minimal rise in 17-KS excretion, necessitating no change in prednisone dosage other than the prophylactic increase at the time of delivery, was perhaps rather unexpected though none the less pleasing. In the same way the good recovery from the caesarean section, the birth of a healthy baby, the establishment of lactation, and, more recently, the re-establishment of menstruation, have all been a source of great satisfaction.

Summary

A case of female pseudohermaphroditism due to congenital adrenal hyperplasia is described. This 24-year-old patient had primary amenorrhoea and no external vaginal orifice. The surgical construction of an introitus with dilatation of the vagina, and treatment with prednisone, led to the establishment of normal menstruation. She had what was concluded to have been a tubal abortion, followed, six months later, by a normal pregnancy. This proceeded uneventfully, and at 39½ weeks a male baby was delivered by elective caesarean section. Lactation was established, the baby thrives, and, more recently, menstruation has been re-established.

It is a pleasure to record our thanks to Mr. D. N. Matthews for carrying out the plastic surgery on this patient.

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During 1960, 10,427 deaths in London were reported to the coroner; 1,694 inquests and 8,733 inquiries without inquest were held into deaths; 536 cases of suicide were investigated, compared with 522 in 1959 and 557 in 1958. Of the 536 cases, 156 were of persons over 60 years of age. Four verdicts of murder were returned compared with 13 in 1959 and seven in 1958. Sixteen deaths were caused by chronic alcoholism compared with 23 in 1959 and 22 in 1958.

USE OF CORTICOSTEROIDS IN INFERTILITY ASSOCIATED WITH HIRSUTIES AND OLIGOMENORRHOEA

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Congenital adrenal hyperplasia, caused by enzyme defects in the synthesis of cortisone, classically presents with prepubertal hirsuties, failure of breast development, and primary amenorrhoea. In this form at least, it is a rare disease. A much commoner clinical syndrome is that which presents after puberty with hirsuties, oligomenorrhoea, and infertility. It probably has a multiple aetiology (Ferriman, 1960). It may be due to a primary ovarian anomaly, to congenital adrenal hyperplasia of mild degree, or to a simple constitutional variant involving increased secretion of adrenal androgens. Certainly an adrenal factor appears to be concerned in an appreciable number of cases. Although 17-ketosteroid excretions may be normal, chromatographic separation shows that adrenal androgen secretion is frequently increased (Du Toit, 1951; Gardner, 1953; Johnsen, 1956; Perloff *et al.*, 1957; Gallagher *et al.*, 1958; Prunty *et al.*, 1958; Bush and Mahesh, 1959). Pregnanetriol excretion, another indicator of adrenal activity, is also raised above normal (Nabarro and Moxham, 1957; Gold and Frank, 1958; Prunty *et al.*, 1958).

It is now generally accepted that most of the disturbances in congenital adrenal hyperplasia may be corrected by the use of cortisone, and pregnancies have been reported (Wilkins *et al.*, 1955; Yamashita and Kozakae, 1956; de Alvarez and Smith, 1957; Wilson and Keating, 1958). It was reasonable, therefore, for its effect to be tried in the commoner clinical group of cases with which this paper is concerned, and a number of reports now indicate correction of both menstrual disturbance and infertility in a significant proportion (Jones *et al.*, 1953; Jones and Jones, 1954; Greenblatt *et al.*, 1956; Gold and Frank, 1958; Jefferies, *et al.*, 1958; Wilson and Keating, 1958; Jefferies and Levy, 1959).

This paper reports on a further group of patients with this condition.

Material and Methods

Altogether eight patients have been under study. Seven of these have fallen pregnant while under treatment with corticoids, and six have successfully borne children. One has failed to conceive.

A method of hair-scoring to be described by Gallwey and Ferriman (in preparation) has been used in six members of the group. The "hormonal" score has been found clinically useful, a score above 5 being regarded as unusual to the point of hirsuties. Marital

relations in all patients were stated to be satisfactory, and the frequency of coitus was adequate. Contraception was employed by some in the early days of marriage. The period of infertility, dating from cessation of this practice, is clearly more relevant than the date of marriage, and is therefore reported for each patient.

The optimal dosage of corticoids is unknown. Cortisone 25 mg. b.d. or prednisone 5 mg. b.d. is usually regarded as sufficient for suppression of adrenal function without producing undesirable side-effects, and these doses have usually been employed; any variation from this is stated. The common but not invariable absence of ovulatory cycles in these patients must be one factor responsible for their infertility. Other mechanisms may be involved, and it is possible that reduction of excessive androgen secretion may be necessary for the maintenance of pregnancy as well as its initiation; the frequency of abortion and miscarriage in these patients suggests such a possibility. It was decided, therefore, to continue corticoids for some months after conception. However, three patients aborted while taking corticoids, and in their subsequent successful pregnancies corticoids were discontinued three weeks after conception. Cortisone was discontinued three weeks after conception in a fourth patient on two occasions; the first pregnancy terminated in abortion three weeks later, but the second went on to termination for toxæmia at the 38th week.

Cases in which Conception Took Place During Corticoid Therapy

Case 1.—The patient was first seen at the age of 28, complaining of infertility. She was always large, and became somewhat obese from the age of 25. Menarche at 11. At first the menstrual cycle lasted four weeks, but this lengthened to five to six weeks from the age of 20. A basal temperature chart kept for one year showed cycles to be ovulatory. Height, 69 in. (175 cm.); weight, 15st. 10 lb. (99.8 kg.). Hormonal hair score, 8. Urinary excretion of 17-ketosteroids, 24.3 mg./24 hours. Prednisone 5 mg. b.d. was started on May 12, 1959, the patient then having been infertile 18 months. The basal temperature chart indicated conception on May 21. Prednisone was continued. Figures for the 24-hour urinary excretion of 17-ketosteroids had fallen to 9.6 mg. in June, but rose again to 20.3 mg. in July and September, and to 42.5 mg. in December. This apparent rise in 17-ketosteroid excretion was presumably due to interference from pregnanolone, excretion of which is increased during the later stages of pregnancy (Martin and Mills, 1958). The December figure, however, appears unusually high. Abortion threatened in the third month and again in the fourth month, and was treated by rest in bed, with continuance of the pregnancy. Prednisone was discontinued in the 34th week. Labour started spontaneously in the 35th week and she was delivered of a healthy male child weighing 5 lb. 5 oz. (2,410 g.).

Case 2.—This patient was first seen at the age of 29 in May, 1953, complaining of obesity, oligomenorrhoea, and hirsuties. Menarche at 16. Menstrual cycle, 5–16 weeks. A basal temperature chart kept for the next three years showed three out of four cycles to be ovulatory. Height, 62 in. (157.5 cm.); weight, 10 st. 8 lb. (67.1 kg.). Hormonal hair score, 15. Urinary 17-ketosteroid excretion, 19.1 mg./24 hours. Cortisone 25 mg. b.d. was started in October, 1956, the patient then having been infertile 18 months. Conception took place a few days later. Cortisone was continued and she aborted one month later. Cortisone was resumed in December. Four ovulatory cycles were followed by conception in May, 1957. Cortisone was stopped three weeks later. A full-term healthy male child was born in February, 1958.

Case 3.—First seen in December, 1956, at the age of 27, complaining of infertility. Menarche at 12. The menstrual cycle was of about 30 days' duration. Basal temperature charts showed only three out of the next six cycles to be ovulatory. Height, 64 in. (162.5 cm.); weight, 12 st. (76.2 kg.). Hormonal hair score, 11. Urinary 17-ketosteroid excretion, 28.4 mg./24 hours. Cortisone 25 mg. b.d. was started in August, 1957, the patient then having been infertile three and a half years. Three ovulatory cycles were followed by conception in October, 1957. Cortisone was continued and she aborted two months later. Cortisone was discontinued, one out of the next three cycles being anovulatory. Cortisone was resumed in April, 1958. Six ovulatory cycles then occurred, and were followed by conception in October, 1958. Cortisone was stopped three weeks later. A full-term healthy female child was born in June, 1959.

Case 4.—This patient was first seen in 1957 at the age of 39, complaining of infertility. Menarche at 15. Menstrual cycle, 28–31 days. A basal temperature chart showed six ovulatory cycles. Height, 61 in. (155 cm.); weight, 12 st. (76.2 kg.). Hormonal hair score, 13. Urinary 17-ketosteroid excretion, 16.7 mg./24 hours. Cortisone 25 mg. b.d. was started in April, 1958, the patient then having been infertile three and a half years, apart from one pregnancy at one year terminating in abortion after three months. She conceived in November, 1958. Cortisone was discontinued three weeks later. She aborted three weeks later after a strenuous day's shopping. Cortisone was resumed in January, 1959. She conceived after one ovulatory period. Cortisone was again stopped after three weeks, and abortion threatened three weeks later. She was treated by rest in bed and sedation. She stayed in hospital for two months, mostly in bed, as bleeding recurred on getting up. She left hospital eventually when four months pregnant. Mild signs of toxæmia appeared later in pregnancy. A healthy female child was delivered by caesarean section at term.

Case 5.—The patient was first seen in November, 1956, at the age of 25, complaining of hirsuties and oligomenorrhoea. Menarche at 16. The menstrual cycle varied from six weeks to six months. Height, 63 in. (160 cm.); weight, 8 st. 7 lb. (54 kg.). A basal temperature chart kept for seven months showed six cycles, of which five were ovulatory. No obesity. Hirsuties, present from her teens, involved the lip, chin, breasts, lower abdomen, and thighs. Prednisone 5 mg. b.d. was started in June, 1958, the patient then having been infertile for approximately four years, apart from a pregnancy at three years terminating in abortion at three months. Two ovulatory periods, in July and August, were followed by conception in October. Prednisone was discontinued after six months. The patient was delivered of a full-term healthy male child in June, 1959.

Case 6.—The patient was first seen in September, 1957, at the age of 24, complaining of obesity and hirsuties. Marked obesity had developed from the age of 20. Menarche at 17. Menstrual cycle, five to six weeks. Height, 62 in. (157.5 cm.); weight, 13 st. 6 lb. (85.3 kg.). Hirsuties of two to three years' duration affected the face, breasts, sacral area, lower abdomen, and thighs. Prednisone 5 mg. b.d. was started in March, 1958, the patient then having been infertile approximately five years. This was increased to 5 mg. t.d.s. in December, and shortly after that she conceived. She discontinued tablets of her own volition one month later, and abortion occurred in April, 1958. She has failed to keep further appointments.

Case 7.—This patient was first seen in June, 1954, at the age of 29, complaining of oligomenorrhoea. Menarche at 13. Menstrual cycle, one to two months. Basal temperature charts kept for the next three years showed mostly anovulatory cycles. Height, 63 in. (160 cm.); weight, 15 st. (95.3 kg.). The hormonal hair score was only 3. However, a frankly hirsute sister with oligomenorrhoea and a hormonal hair score of 9 was seen later. The patient's urinary 17-ketosteroid excretion was 15.6 mg./24 hours. It is believed,

therefore, that this patient belongs to the group under discussion. A wedge resection of the ovaries was carried out in 1955. The ovaries were normal in size, but contained a number of small follicular cysts. Ovulatory activity was not improved. Cortisone 25 mg. b.d. was started in July, 1957, the patient then having been infertile seven years, apart from one pregnancy at 2 years, terminating in miscarriage after 4-5 months. She conceived in October, 1957, after two doubtfully ovulatory periods. Cortisone was continued, and she aborted six weeks later. She continued to take cortisone and, after two menstrual cycles with short progestational phases, conceived in February, 1958. Cortisone was stopped three weeks from conception. Mild toxæmia developed later in pregnancy, and labour was induced at the 38th week. A healthy male child weighing 6 lb. 8 oz. (2,950 g.) was born in October, 1958.

Cases in which Conception Did Not Take Place During Corticoid Therapy

Case 8.—The patient was first seen in 1954 at the age of 20, complaining of abdominal pain; she was found to be pregnant. Menarche at 16. Menstrual cycles were regular at monthly intervals until the age of 18, when they lengthened to between two and nine months. Height, 62 in. (157.5 cm.); weight, 9 st. (57.2 kg.). Hormonal hair score, 8. Urinary 17-ketosteroid excretion, 12.2 mg./24 hours. One healthy male child had been born out of wedlock in 1954. She married the child's father in 1955 and practised contraception until 1957. She then discontinued this practice and expressed a wish for a child. Cortisone 25 mg. b.d. was started. She discontinued the tablets of her own volition six months later. There had been no improvement in menstrual behaviour nor had pregnancy ensued. She has been followed for a further two and a half years and conception has not taken place. Salpingography has shown patent fallopian tubes.

Discussion

Important features of those cases in which pregnancy occurred during corticoid therapy are illustrated in the Chart. It must be pointed out that in two cases the periods of infertility prior to treatment were rather short

Data relating to patients who became pregnant on corticoid therapy.

—18 months. However, it is suggestive that seven out of eight patients became pregnant within a few days to nine months from starting corticoids, after periods of infertility ranging from 18 months to 7 years. The time relationships involved are particularly suggestive, and this is brought out in the Chart, where periods of infertility are contrasted with duration of corticoid therapy prior to conception. Taken in conjunction with

the experience of others reported above, the evidence presented here is thought to justify further trial of corticoid therapy in this group of cases.

A tendency to abortion seems to be a feature of the syndrome, both spontaneously and after the use of corticoids. It was of common occurrence prior to operation, for example, in the large series of cases treated with wedge resection of the ovaries by Stein (1955). It has been common in the reported series treated with corticoids, and occurred during treatment in no fewer than five of our patients. The question arises whether corticoids should be continued throughout pregnancy. Neither our own nor other series provide any clear answer to this. What seems fairly clear is that threatened abortion needs prompt treatment along traditional lines with rest and sedation.

Summary

The effect of corticosteroids is reported in eight patients suffering from hirsuties, oligomenorrhoea, and infertility. Seven fell pregnant and six successfully bore children. A comparison between the duration of therapy prior to contraception and the preceding periods of infertility suggests that corticosteroids were responsible for the relief of infertility in at least some of the patients. A tendency to abortion was common. Three patients had experienced abortions prior to treatment, and five aborted during treatment. The literature is reviewed. It is concluded that corticosteroids may have a part to play in the treatment of these patients.

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