CORTISONE TREATMENT OF THE ADRENOCORTICAL SYNDROME WITH SPECIAL REFERENCE TO STEROID EXCRETION DURING CONTINUED AND DISCONTINUED THERAPY

By

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Until 1950 the treatment of the adrenogenital syndrome was exclusively surgical and good results were obtained only in cases of adrenocortical tumours. In most cases of adrenocortical hyperplasia the disease recurred in spite of extensive resections of the adrenals. The attempts at medical treatment performed by Wilkins and collaborators were not successful until the introduction of cortisone in the therapy (Wilkins et al., 1950; Wilkins et al., 1951). They found that the increased excretion of 17-ketosteroids (17-KS) decreased to normal values after few days' treatment. Subsequently continued treatment with small doses of cortisone kept the excretion within normal limits. The clinical signs of increased androgen production too were arrested or disappeared, partly or completely (Wilkins et al., 1952).

Here in Denmark similar results were obtained in the treatment of a 14-year old girl suffering from pseudohermaphroditism (Andersen et al., 1952). Recently the treatment of 4 patients was reported from Sweden (Bergstrand, 1954).

Wilkins and collaborators (Wilkins et al., 1952) explain the effect of cortisone in the adrenogenital syndrome as an inhibition of the secretion of ACTH by the hypophysis. In this way the stimulation of the adrenal cortex is diminished which results in a decreased production of androgenic active substances. Later the inhibitory effect of these substances on the secretion of gonadotrophic hormone by the hypophysis ceases and an increased production of this hormone follows causing a natural stimulation of the gonads.
Some investigators (i.e. Kelle et al., 1953) have found an increased level of ACTH and a decreased level of 17-hydroxycorticoids in the blood of these patients. Following the administration of cortisone the blood level of ACTH decreased. A decreased ability of the adrenal cortex to elaborate glucocorticoids was suggested as the primary failure: The normal inhibition of the hypophysis is diminished resulting in the secretion of larger amounts of ACTH which in turn stimulates the adrenal cortex to elaborate larger amounts of other steroids than glucocorticoids (steroids with androgen activity and their precursors).

Assuming the theory outlined here, one should expect to find symptoms of adrenal cortical insufficiency in cases of stress situations in these patients. That is, however, only seldom seen. The pathogenesis is most likely much more complicated. There seems, however, to be a failure in one or more stages of the steroid synthesis in the adrenal cortex, especially in the further synthesis of 17-hydroxyprogesterone (Bongiovanni et al., 1954). Alterations in the steroid metabolism especially an increased utilization or break down of the glucocorticoids or a conversion of them into androgenic active steroids would also be able to bring about the symptoms and the pathophysiological findings of the adrenogenital syndrome.

In our opinion this essentially seems to be a disorder of the normal equilibrium between the two groups of steroids (glucocorticoids and androgenic steroids from the adrenal cortex). Only in this way is it possible to explain cases with a normal or a slightly raised excretion of glucocorticoids simultaneously with a higher excretion of 17-KS.

The problem is still unsolved. Further investigations on the steroids metabolism are necessary before final conclusions can be drawn.

CASE REPORTS

Four patients with congenital adrenal hyperplasia (two boys with macrogenitosomia praecox and two sisters with pseudohermaphroditism) were treated with cortisone for 9 to 15 months.

1) (958/52) male born 21/8-45. No siblings. No cases of endocrine disorders in the family. Rather big external genitals were observed shortly after birth. During the first years of life his growth was faster than normal, and from the age of 4 years pubic hairs appeared. At the age of 7 years his height was 149 cm., epiphysial fusion had begun, and the macrogenitosomia had advanced considerably; the testicles were of normal consistency, but only about 1½ X 1½ cm., which was in contrast to the somatic development. The child had never had symptoms of adrenal insufficiency.

2) (131/53) male born 29/7-42. No siblings. No cases of endocrine disorders in the family. The penis was rather big from birth. From the age of 7 years growth was greater than normal. At the age of 8½ years pubic hair appeared and shortly afterwards axillary hair. First time in clinic 9 years old. The left testis was then situated
in the scrotal sack and measured $1\frac{1}{2} \times 3$ cm., the right testis was felt in the groin and measured $1\frac{1}{2} \times 1\frac{1}{2}$ cm.

With regard to patient no. 1, the small size of the testes indicates that the macrogenitosomia is not caused by an androgenic hormonal production from these glands (testicular tumour, constitutional precocious puberty or precocious puberty caused by a cerebral lesion in the hypothalamic region). The size of the left testis in patient no. 2 is above the normal for his age, but this is possibly compensatory to the displaced and too small right testis. The large size of the left testis might also be caused by ectopic adrenal tissue.

X-ray examination of the skull and sella turcica, intravenous pyelography, ophthalmoscopy, determination of the field of vision, neurological and electroencephalographic examinations gave normal results in both patients. Bone age was 15 years in patient no. 1 when he was 7 years old and 14 years in patient no. 2 when he was 10 years old. Samples of 24-hours urine have been investigated for gonadotrophic hormones, which were not demonstrated and for oestrogenic hormones, which were found in

![Fig. 1.](image)

**Fig. 1.**

Case 1. Excretion of 17-KS and corticoids before and during 14 months of treatment with cortisone. The average excretion of 17-KS increased during the 3 years before treatment from about 15 mg./24 hours to about 30 mg./24 hours. The excretion of corticoids immediately before treatment was about 1 mg./24 hours. Normal values of 17-KS excretion were attained after one week of treatment with daily intramuscular injections and maintained with 75 mg. intramuscularly twice weekly. A temporary rise was seen before the maintenance dose was fixed and during cessation of therapy in connection with an acute appendicitis.
Case 2. Excretion of 17-KS and corticoids before and during 11 months of treatment with cortisone. The average excretion of 17-KS before treatment was about 13 mg./24 hours and of corticoids about 1 mg./24 hours. Normal values of 17-KS excretion were attained after one week of treatment with 50 mg. cortisone daily given intramuscularly and were maintained with 75 mg. given intramuscularly twice weekly. A slight elevation in the excretion of corticoids was seen in about 14 days after the beginning of treatment.

In patient no. 2 the possibility of constitutional precocious puberty was considered because of the rather big left testis and because of the only moderately elevated excretion of 17-KS. This was, however, above the excretion expected for his biological age and above the excretion we have seen in cases of constitutional precocious puberty in boys. In addition we have in a patient with constitutional precocious puberty, only seen a slight and rather late decrease in the excretion of 17-KS after treatment with cortisone (Fig. 3). As mentioned by Wilkins (1952) this may be used in the differential diagnosis between constitutional precocious puberty in boys and macrogenitosomia caused by congenital adrenal hyperplasia.

3) (919/52) female born 19/12-47. No. 3 of 4 children. She has two normal brothers. A sister has pseudohermaphroditism (our patient no. 4). No other cases of endocrine
disorders or abnormal genital development in the family. As far as we know, the delivery was at term, but the birth weight was only 2250 gm. and the length 49 cm. Hypertrophy of the clitoris was noticed at birth, and from the age of two years pubic and axillary hair appeared. The growth was advanced above normal from birth, so that at 5 years of age she was 14 cm. taller than girls of the same age. The family did not react to these symptoms, however, and the patient was first examined at the age of 5 years, when her sister was admitted to hospital on account of her genital malformation. On admission hypertrophy of the clitoris and pubic and axillary hair were noticed, but otherwise she had no hypertrichosis. She was a stocky build and muscular. There was no development of the mammary glands and she had not menstruated. Apart from the hypertrophic clitoris there was no malformation of the genitals.

4) (918/52) female born 29/12-49. Sister to patient no. 3. Born 4 weeks before time. Birth weight 2500 gm., length 50 cm. During the first months of life she had periods of diarrhoea and vomiting (insufficiency of the adrenals?). When the patient was 2½ years old malformation of the genitals was noticed and she was admitted to hospital. A hypertrophic clitoris and coalescence of the labia minora, which were separated by operation, were found. No pubic or axillary hair were found. She was 5 cm. above the average height.

In both sisters the same roentgenological and clinical investigations as in the first

Fig. 3.

The excretion of 17-KS and corticoids in a patient with constitutional precocious puberty before, during administration of 50 mg. of cortisone daily given intramuscularly for 10 days and 14 days after cessation of treatment. Only a slight depression in the excretion of 17-KS was seen compared with the effect seen in patients with congenital adrenal hyperplasia. No alterations were found in the excretion of corticoids.
two patients were made and gave normal results. The bone age in patient no. 3 was 7 years, when she was 5 years old, and in patient no. 4 5 years, when she was 3 years old. In 24-hours urines no gonadotrophic hormones were demonstrated, and oestrogenic hormones were only found in small amounts. The excretion of 17-KS and corticoids

**Fig. 4.**

Case 3. Excretion of 17-KS and corticoids before treatment, during 6 months of treatment with cortisone and 8 months without therapy. Before treatment the average excretion of 17-KS was about 14 mg./24 hours and of corticoids about 0.4 mg./24 hours. After one week of treatment with 50 mg. cortisone daily given intramuscularly, normal excretion of 17-KS was attained and with few exceptions maintained with 75 mg. given intramuscularly twice weekly. One month after cessation of therapy a slight rise was seen, but the excretion did not exceed 1/3 of the pretreatment level during the following 7 months. Excretion of corticoids rose slightly after the beginning of therapy and continued on this level with exception of two periods in which extremely high values were reached; one of these occurred during the therapy and the other after cessation of treatment – see text.
Case 4. Excretion of 17-KS and corticoids before treatment, during 6 months of treatment with cortisone and 7 months without therapy. Before treatment the excretion of 17-KS was about 3–4 mg./24 hours and of corticoids about 0.2–0.3 mg./24 hours. After one week of treatment with 25 mg. of cortisone daily intramuscularly the excretion of 17-KS was normalized and continued within normal values during the period of treatment (maintenance dose 25 mg. twice weekly) as well as during 7 months after the cessation of treatment. The excretion of corticoids increased slightly immediately after treatment and continued on this level with the exception of two periods as in case 3 (see text).

is shown in Figs. 4 and 5. In both, the excretion of 17-KS was considerably increased, while the excretion of corticoids was only slightly elevated. The clinical examinations, the familiar relationship of the girls and the result of the cortisone treatment demonstrate that the patients have a congenital adrenal cortical hyperplasia.

**DOSAGE OF CORTISONE**

The treatment with cortisone was initiated and continued with doses given by Wilkins et al., 1952. The treatment was started with a daily intramuscular injection, in the first 3 patients, of 50 mg. daily for 8–15 days, in patient no. 4 of 25 mg. daily for 7 days. Afterwards the doses for the first 3 patients were
75 mg. intramuscularly twice a week corresponding to about 20 mg. a day, and in patient no. 4 25 mg. twice a week corresponding to about 7 mg. a day. The patients were later treated successfully with cortisone given orally in daily doses two to three times those mentioned above.

THE ADRENAL HORMONAL RESPONSE TO THERAPY AND TO DISCONTINUATION OF THERAPY

In all 4 patients there was an immediate decrease in the excretion of 17-KS to values normal for the age of the patients. The values, however, varied somewhat in the first few weeks.

The excretion of corticoids which in the first 2 patients was elevated before treatment decreased only slightly in case no. 1 and to about normal values in case no. 2, while it increased slightly in the last 2 patients where it was only slightly raised before treatment.

In patient no. 1 the treatment was discontinued after about 2 months as the child developed an acute appendicitis. The patient was operated on in another hospital. The appendix was gangrenous but within perforation. In the peritoneum some purulent effusion was found. There were no symptoms of adrenal failure in connection with the operation. The wound healed normally but an intraabdominal abscess developed, which had to be incised. Associated with the appendicitis and discontinuation of the cortisone treatment there was an increase of the steroid excretion almost to pretreatment levels, and it became normalized as before after resumption of therapy. The treatment was followed for 14 months and the further course was uneventful. Whether or not the seriousness of the appendicitis has any connection with the treatment with cortisone or its sudden cessation is a subject for discussion but we are of the opinion, that the cortisone treatment ought to be continued in such conditions.

In patient no. 2 the treatment has lasted for 11 months and the steroid excretion has continued at normal values.

In patient no. 3 and 4 a considerable but temporary increase in the excretion of corticoids was found after treatment for 4 months. In patient no. 3 no signs of disease could be found but she reacted violently during this period to the injections and got nocturnal enuresis. Patient no. 4 had shortly after the increased excretion of corticoids an acute tonsillitis. There was no simultaneous increased excretion of 17-KS in any of the patients.

In order to estimate the extent of the depression of the adrenals, treatment was discontinued in both these patients after 6 and 7 months respectively. In both cases a transitory but considerable increase in the corticoid excretion without a corresponding increase in the 17-KS excretion was observed 1 1/2 to 2
months later. Patient no. 3 did not present anything remarkable, while patient no. 4 at the same period had two upper-respiratory infections.

In order to elucidate the problem concerning the variations in the corticoid excretion in the two last mentioned patients the following possibilities were considered. The amount of corticoids excretion originates partly from the corticoids elaborated in the adrenal cortex and partly from the cortisone administered. The last mentioned source is in all probability sufficient to explain the increased excretion seen in all the cases immediately after the beginning of treatment.

The further increased excretion later on during the treatment of the two last-mentioned patients is more difficult to explain. There seem to be two possibilities: 1) a less complete utilization of the cortisone administered combined with a larger excretion. 2) an increased endogenous production of corticoids due to stress. Patient no. 3 became quite afraid of the injections, and no. 4 developed a tonsillitis. Previous investigations have shown that in children the variations in the excretion of urinary corticoids are much more sensitive indicator of stress than are the 17-KS (*Sprechler & Vesterdal, 1953*) which might explain why the last mentioned group of steroids were not increased in those two cases.

Some time after the discontinuation of the treatment an increase of the corticoids was noticed again. In case no. 4 the simultaneously occurring infection is likely to be the stimulus. In case no. 3 no stress seemed to be present. Treatment with cortisone during a long period produces an atrophy of the adrenal cortex and the experiences with long-term treatment indicate that there is a prolonged interval after the discontinuation of the treatment before a normal size and state of the adrenal cortex is re-established. It is reasonable to assume that this normal equilibrium will not be established abruptly without fluctuations. Consequently it is possible to find elevated as well as decreased values. Studies on the corticoid excretion following surgery reveal that such fluctuations around the period of equilibrium actually occur.

**RESULTS OF TREATMENT**

In all patients we have found an inhibition of the adrenal cortex which has been maintained with such very small doses of cortisone, that side-effects have not occurred. In the 2 boys the development of secondary sexual characteristics has been prevented. In both some growth of the testicular glands has been noticed, a phenomenon which has also been observed by others (*Wilkins et al., 1952; Wilkins & José, 1954*). This may be caused by an increased secretion of hypophysial gonadotrophic hormones since the hypophysis is inhibited to a lesser extent by adrenal androgens. A corresponding phenomenon was found in
patient no. 3 in whom an early development of the mammary glands and a slight pigmentation of the areola occurred after three months of treatment. In this patient virilization has been prevented and in patient no. 4 the treatment has prevented virilization.

The adrenocortical inhibition obtained in the two last patients has continued for a remarkably long time after cessation of therapy.

5 months after discontinuance the excretion of 17-KS had not exceeded 1/3 of pre-treatment levels in patient no. 3 and in patient no. 4 in whom the therapy was started in an early age, it had not exceeded normal values. This first occurred after 12 months without therapy.

**SUMMARY**

Case reports are given on 4 patients with adrenogenital syndrome caused by adrenal cortical hyperplasia: 2 boys and 2 girls (sisters). They have been treated with cortisone for 9 to 15 months.

In all the patients a satisfactory inhibiting effect on the adrenal cortical function was obtained. In 2 patients the therapy was discontinued after 6 and 7 months. Five months after cessation the excretion of 17-KS had not exceeded 1/3 of pre-treatment levels in a 6 years old girl, and in a 4 years old girl it first exceeded normal values after 12 months without therapy. In 2 patients temporary but considerable elevations were seen in the excretion of corticoids without a simultaneous corresponding increase in 17-KS excretion during the treatment and for a couple of months after cessation of treatment. This is explained as a reaction to stress and it is pointed out that this corresponds to the normal reaction to stress in children. The possibility, that the oscillations in steroid excretion after discontinuance of cortisone therapy may be explained as a temporary imbalance in the hypophyseal-adrenal cortical relationship, is suggested.

The pathogenesis of the disease is discussed. A disturbance in the balance between the production of androgenic steroids and the glucocorticoids in the adrenal cortex may be essential, or it may be a disturbance in the cortical steroid synthesis or metabolism. Presumably cortisone acts by inhibiting the hypophyseal ACTH-secretion.

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