A CASE OF ADRENAL VIRILISM PERSISTING UNCHANGED AFTER EXCISION OF BILATERAL ADRENOCORTICAL ADENOMA

BY

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Adrenal virilism can be defined as the group within the adrenogenital syndrome where the effect of the adrenocortical hyperfunction is mainly one of virilisation affecting women after puberty.

Numerous single cases of the adrenogenital syndrome have been reported in the course of time, and also many excellent synopses dealing with this syndrome have been published, in particular within recent years. A detailed account of it will, therefore, be omitted here, but reference may be made to text-books of endocrinology (see a. o. Goldzieher, 1939, Hoffman, 1945 and Nielsen, 1938-42) or some of the synopses mentioned above (Broster, Allen, Vines, Patterson, Greenwood, Marrian & Butler, 1938, Cahill, 1944, Cameron 1947, Dahl-Iversen & Hojensgaard, 1947 and Kenyon, 1944).

However, the present case of adrenal virilism seems worth publishing because of certain facts of particular interest observed in this patient.

1. An enormously high androgen and 17-ketosteroid excretion.
2. The favourable response of the facial hypertrichosis to
treatment with large intramuscular injections of oestradiol monobenzoate.

3. The unchanged persistence of the syndrome after excision of adenomas in both adrenals.

CASE HISTORY

Neurological Dept., Frederiksberg Hospital. Case 130/46. Divorced female worker in a box factory, born 1901.

Past history: No known cases of endocrine disturbances in the family. A sister has had psychogenic psychosis twice, but otherwise no cases of nervous or mental diseases in the family.

The patient had rheumatic fever ab. the age of 10 years with attending cardiac complication, but has had no cardiac symptoms since, and has always been of good health except for her present complaint.

The patient has from a child been rather hairy on her arms. The growth of hair was otherwise normal until the age of 20, when hairs began to grow on her upper lip and chin, and subsequently also on her cheeks. Some years later an abnormal growth of hair began to appear also on the breast, the remaining part of the body, and the extremities. The hypertrichosis increased steadily for 7 to 8 years and has since remained unchanged. About the age of 23 the patient began to grow bald. Ostensibly the loss of hair started after an accident when her hair had caught fire and some of it had been burnt away. The burning was inconsiderable, but after that she developed baldness of a typically male character, so that since the age of 29 she has had only a fringe of hair at the back of her head. If she did not remove the growth of hair on her face she would grow a beard like a man. She has applied epilation almost daily.

Almost simultaneously with the development of hypertrichosis the clitoris began to increase in size. It grew considerably in the course of a few years. The enlarged clitoris caused her no trouble during coitus, but affected her mentally. On the advice of her doctor she was, therefore, in April 1936,
Photo 1.
Before treatment.
(The pt. wears a wig — different in the two pictures).

Photo 2.
After Oeex treatment.

Photo 3 and 4.
Before treatment, but the same after treatment.
admitted to a surgical department, where the clitoris, 3 to 4 cm. long and ab. 1 cm. in transverse diameter, was extirpated. Her voice became deeper and coarser about the age of 20, but otherwise she has remarked no bodily changes.

Menses did not begin till about the age of 18. They have always been irregular, of 1 to 2 weeks’ duration with intervals of from one to several months. She has never been pregnant. After 1935 increasing metrorrhagia, on account of which amputation of the supravaginal part of the uterus in October 1936. The body of the uterus was orange-sized and fibromatous. Ovaries and internal genitals were perfectly normal. A few years after the amputation of the uterus she began to suffer from hot flushes, which occurred continually through 5 or 6 years.

The patient’s libido was always weak. She had not had sexual intercourse, nor been interested in erotic or sexual relations till about the age of 22, when she made her husband’s acquaintance. Was married from 1924 to 1928, but then divorced her husband, because he played her false. While married she had sexual intercourse with her husband, comparatively rarely, indeed, but she believed to have obtained a normal pleasure from it. After the divorce the patient led a continent life until 1937, when she met a man, with whom she lived for 2 years. Within this period she had sexual intercourse at intervals from weeks to months. She felt some pleasure at it, at least no resentment against it. Since then she has had sexual intercourse only a few times without actually obtaining any pleasure from it. She no longer feels a sexual desire. Except for this gradual loss of libido, which was always weak, she has undergone no changes in a sexual respect, more particularly she has never felt homosexual or other morbid inclinations.

Mentally the patient was originally quiet, even-tempered, and cheerful, but after the divorce in 1928 she became of a more melancholy disposition, and would often be in low spirits. Since about 1930 she has been suffering from an almost constant frontal headache, and since 1940 she has developed
an ever increasing feeling of tiredness, and has, moreover, been suffering from giddiness, of the kind one may feel on a deck. No change has occurred in her personality or her psyche, apart from that elicited by the depression.

Because of these symptoms the patient was in January 1945 admitted to the Neurological Dept., Frederiksberg Hospital, to which she was admitted 4 times in all until February 1946.

*Physical examination (on admission):*

Mentally: very emotional and sensitive with a vein of depression.

Her voice is rather deep, somewhat rough and hoarse. Her features are somewhat coarse and clumsy. There is pronounced acne. On the whole her complexion bears the stamp of the daily epilation (see photo 1). There is marked blepharoconjunctivitis. The skeletal structure and the distribution of fatty tissue are of the male type, and the mammae are highly atrophic (see photos 3 and 4). Height 169 cm., weight 60 kg.

Growth of hair: On the head there is found only a 3 to 4 cm. broad fringe of hair from the back of the head to both ears. The rest of the head is completely bald, without cicatricial changes in the skin (the patient wears a wig). The eyebrows are rather thick, growing together over the nose. Eyelashes normal. The growth of hair on the body is very thick and "shaggy", particularly so on breast and back, where the individual hairs reach a length of 5 and 3 cm. respectively (see photo 5). Axillary hairs normal. Pubes rather thick, but no particular hairiness along the linea alba, whereas the pubes are continuous with the growth of hair on abdomen and femora. The growth of hair round anus and genitals are of the male type. The growth of hair on the lower arms is very thick, and the hairs are up to 2 cm. long. The upper arms are less hairy. The femora likewise present a thick and up to 2 cm. long growth of hair, whereas that on the lower legs is less pronounced.

The medical and neurological examinations revealed nothing abnormal.
The eyes were likewise found to be normal, except for the blepharoconjunctivitis.

Ear and throat examination: The thyroid cartilage is strongly developed, of the male type, the angle between the laminae of the cartilage being 90° (the normal for women is 120°); otherwise nothing abnormal.

Gynaecological examination: Cicatrice after extirpation of clitoris, vagina normal, adnexa not palpable, movable uterus rest.

X-ray of skull: Pronounced digital impressions; no hyperostoses; sella normal. X-ray of kidneys and adrenals revealed normal conditions, normal pyelograms. X-ray of column: Light spondylosis deformans in the thoracolumbar part; otherwise nothing abnormal.

Electrocardiogram: Nothing definitely abnormal.

Glucose tolerance test (3 times): Fasting blood sugar normal, but the blood sugar level has not become quite normal after 3 hours; twice there was seen a rather considerable rise (maximally 202 and 182 mg. % respectively).
Basal metabolic rate: 134 to 122 %.

Blood pressure slightly increased, fluctuating between 175/110 and 150/80.

Serum protein determination (twice) showed normal values for total protein and albumin, while the globulin fraction was on the lower side of the normal.

Fractional cholesterol determination in serum (determined 3 times) revealed no definitely morbid conditions. Twice, however, there were found decidedly low values for total cholesterol.

Calcium, phosphorus, potassium, and sodium concentrations in serum normal. Serum phosphatase normal.

White and red blood corpuscles, index, differential counting, osmotic resistance, and capillary resistance normal.


Cerebrospinal fluid normal.

Hormone analysis on 24-hour urine: Excretion of gonadotrofine low (less than 5 R.U.). Oestrogen excretion normal (33 M. U.). Androgen excretion 602 C. U., and 17-ketosteroid excretion 286 mg. within 24 hours, in other words enormously increased (see later).

Summary of case history:

The patient is a woman, aged 44, who had been of normal health until the development of her present complaint about the age of 20, with almost universal hypertrichosis, masculine baldness, clitoris hypertrophy (extirpated 1936), irregular, but rather profuse menses (until amputation of the uterus 1936), a deeper voice, somewhat masculinized bodily type, and possibly decreasing libido. Except for this virilisation the patient presented no signs or symptoms of any kind. The signs of virilisation had become fully developed after 7 or 8 years and had persisted unchanged for 16 or 17 years, when I first saw the patient in 1945. Examination of the patient revealed, in addition to the virilisation, an enormously in-
creased androgen and 17-ketosteroid excretion, as well as a slightly increased basal metabolic rate, inconsiderable hypertension, and a somewhat lowered carbohydrate tolerance, but otherwise no unquestionably pathological features, neither on clinical nor on laboratory examinations.

On the basis of the above findings we judged the patient’s affection to have been caused by a hyperfunction of the adrenal cortex. This hyperfunction seemed to be due rather to hyperplasia than to a tumour, chiefly on account of the protracted course and of the fact that no tumour could be demonstrated.

Treatment and Course:

Having previously tried to treat hypertrichosis in women with oestrogens, though, indeed with a somewhat uncertain result, I started with submitting this patient to such treatment, because I regarded her as particularly fit for it on account of her large androgen production. I treated her exclusively by oestrogen (Ovex) injections of 50,000 I. B. U. each (i. e. 5 mg. oestradiol monobenzoate dissolved in oil).*

A total of 82 injections were given from April 9 to Oct. 16, 1945, at first 3 times weekly, and in the end once daily. The acne in the face had disappeared and the blepharitis been cured after 4 or 5 weeks (i. e. after 12 to 15 injections); but no effect was observed yet on the growth of hair. After well over 2 months, when ab. 30 injections had been given, the hypertrichosis began to respond to treatment, particularly so on face and neck, where the hairs grew lighter, scarcer, and easy to epilate. Also the hairs of the body seemed to sit more loosely. By the end of the course of treatment the effect on the hypertrichosis was evident on face and neck (see photo 2). Hairs did grow out here, indeed, but they were far smaller in number, much lighter, and much easier to epilate. While she had previously spent from 1 to 1½ hours daily with epilation she could now do with less than 5 minutes. The growth of

*) The Ovex applied was most kindly placed at my disposal by Lovens kemiske Fabrik, to which I bring my sincerest thanks.
hair on body and extremities had not decreased to any visible extent, but the individual hairs seemed to be looser.

The hypertrichosis on the face increased again after a pause of a few months in the Ovex treatment; but it never reached the former thickness. We now attempted X-ray on adrenals and pituitary body, prompted to this treatment among others by certain statements in the literature. A total of 1000 r distributed over 10 treatments were given first to each adrenal. Ab. 3 months later X-rays were applied to the pituitary body, 3 fields with a total of 300 r to each. No effect was observed, however, neither on the hypertrichosis nor on the other signs of the patient's virilisation.

The Ovex treatment was, therefore, resumed. Daily Ovex injections, a total of 24, were given from Jan. 28 to Febr. 21, 1946, after which the hypertrichosis on face and neck decreased, just like after the former Ovex treatment. After one month's pause in the treatment the hypertrichosis increased somewhat again. Hence Ovex was given from April 4 to July 1, 1946, about twice weekly, a total of 25 injections, and with the same favourable result as before.

After discontinuation of the treatment the growth of hair became a little thicker again. Since the patient suffered mentally under her affection, which must be supposed to be localized in the adrenals, either as hyperplasia or as a tumour, operation was decided on. In September 1946 the patient was, therefore, admitted to the Surgical Dept. C of the State Hospital (Prof. Dahl-Iversen). On Sept. 13, 1946 she was operated on in the left side. The left adrenal proved to have been transformed into a 15 × 11 × 8 cm. large tumour, in which there was found no normal adrenal tissue, except for a narrow strip at the anterior lower pole. The entire adrenal was excised. Well over 2 months after the operation the growth of hair on face and neck had become thinner again, perhaps a little more so than after the previous Ovex treatments, whereas the hypertrichosis on body and extremities was unchanged. After 4 or 5 months, however, the patient presented increasing hypertrichosis on neck and face. As she was still excreting large
amounts of androgens and 17-ketosteroids she was operated on in the right side on March 3, 1947. A fist-sized capsulated adrenal tumour was found, which peeled readily from the adrenal. The tumour, measuring $9 \times 9 \times 5$ cm., was excised. Microscopy of this tumour, as well as of that removed at the former operation, revealed a typical adrenocortical adenoma with no signs of malignancy. Both operations ran an uncomplicated course with no suggestion of adrenal insufficiency (Dahl-Iversen & Hojensgaard, 1947).

A few months after the latter operation a decrease was observed in the hypertrichosis on face and neck, corresponding almost to that seen after a thorough Ovex treatment. On body and extremities, on the other hand, the hypertrichosis persisted unchanged. However, after yet another month the hypertrichosis on neck and face was seen to have increased somewhat again. The Ovex treatment was, therefore, resumed with injections twice weekly, a total of 23, from June 13 to Sept. 11, 1947. The treatment had an excellent effect on the facial hypertrichosis, even somewhat better than previous treatments, but none on that of body and extremities.

The growth of hair on face and neck is now (Jan. 1948) very thin, the hairs are light and very loose. The patient manages with epilation once weekly, and still there are but few hairs. Her complexion is clear (almost as photo No. 2). The baldness is unchanged, and the remaining hypertrichosis as when I first saw the patient. Mammae, distribution of fatty tissue, and general habit are likewise unchanged.

The patient is in a depressed state of mind, very disappointed with the poor result of the operation, which she had hoped would have a great effect. She is very sensitive with inferiority complexes, very self-centred, and is always tormented by the idea that she is abnormal. Otherwise no mental changes. She feels as a woman, also sexually, but her libido has actually disappeared.

Table 1 summarizes the determinations of the output of 17-ketosteroids and of androgens.

The previously slightly increased blood pressure is now
Table 1.

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<th>1945</th>
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<td>July</td>
<td>252</td>
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<td>136</td>
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<td>Sept.</td>
<td>395</td>
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<td>Oct.</td>
<td>394</td>
<td>202</td>
<td>74</td>
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<td>100*</td>
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<td>Nov.</td>
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<td>212</td>
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<td>17-ketost. in mg/24 h.</td>
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<td>androgen in C. U./24 h.</td>
<td>602</td>
<td>150</td>
<td>120</td>
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<td>730</td>
<td>200</td>
<td>73</td>
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Excretion of 17-ketosteroids and androgens in the urine.*

The excretion of 17-ketosteroids, indicated in milligrams, was determined photometrically, except that marked *, which was prepared in a chemically pure form.

The excretion of androgens was determined biologically on capons and indicated in capon’s comb units (C. U.).

The figures in Table 1 indicate the average 24-hour excretion for 3 to 5 days. The 24-hour excretion was, however, often higher, once (July 8, 1945) even 582 mg. and 1360 C. U. respectively.

normal (about 120/80). There is no postural hypotension. The basal metabolic rate is likewise normal (107 %), and the glucose tolerance no longer definitely abnormal. These functions seem to have become normal after X-ray treatment of the pituitary body.

DISCUSSION

Androgen and 17-ketosteroid excretion.

The excretion of androgens as well as that of 17-keto-

*) The androgen excretion as well as that of 17-ketosteroids have most kindly been determined in Løvens kemiske Fabrik, for which I want to express my sincerest thanks to the factory and to M. Tonnesen, Dr. pharm., Director of the Biological Department. The androgens were determined biologically on capons, and the 17-ketosteroids photometrically according to Callow’s method (see also Jensen, C. C., Pedersen-Bjergaard, K. & Tonnesen, M.: Bibliot. f. læger, separate issue Dec., 1944).
steroids, followed throughout the course, varied a great deal, but the variations were generally parallel for the two substances (see Table). The Ovex treatment had no definite influence on the androgen and 17-ketosteroid excretion, whereas each excision of an adrenocortical adenoma elicited a marked fall in both, followed, however, by a prompt rise, though not to the original amounts. The excreted 17-ketosteroids, both before and after excision of the adenomas, have been prepared in a pure form in Lovens kemiske Fabrik. The last time, after the excision (12th to 18th of Sept., 1947), the 24-hour excretion of 17-ketosteroids amounted to ab. 100mg. In both cases the substance consisted of 60 to 80 % dehydro-androsterone, while the rest was a mixture of different 17-ketosteroids (Theil Nielsen, Pedersen-Bjergaard & Tonnesen, 1948). In other words the β-fraction (consisting chiefly of dehydro-androsterone) is greatly increased in proportion to the remaining 17-ketosteroids, the former constituting normally no more than 10 % of the entire amount of 17-ketosteroids (Salter, Cahen, Sappington & Sappington, 1946). The findings in the present patient seem to accord well with previous statements (Crooke & Callow, 1939, Friedgood, 1944 and Mason & Kepler, 1945), according to which in particular the dehydro-androsterone concentration in the urine is said to be increased in association with adrenocortical tumours, unlike what is the case in hyperplasia. However, these statements seem to deal chiefly with malignant tumours versus hyperplasia. Other writers (Salter, Cahen, Sappington & Sappington, 1946) have found the β-fraction considerably increased, both absolutely and relatively, in proportion to the α-fraction also in association with adrenocortical hyperplasia, though less pronounced so than with adrenocortical tumours.

The androgen and 17-ketosteroid excretions found in this patient are enormously high. Slot (1936), in a woman with malignant adrenal tumour, found an excretion of 2200 I. U. per litre of urine (biologically determined), which corresponds to nearly 440 C. U. or 220 mg. Slot's finding is stated (Cahill, 1944 and Goldzieher, 1939) to be the highest reported so far.
Crooke & Callow (1939) found an excretion of up to 850 mg. 17-ketosteroid per litre of urine in a girl, aged 6, with left adrenocortical carcinoma; but the highest 24-hour excretion was 288 mg. Westman (1941), on the other hand, has published a case of adrenocortical adenoma, where no less than 20,000 C. U. were found per litre of urine.

Determinations of the androgen and 17-ketosteroid concentrations in blood are as yet rather uncertain, but various methods have been suggested and applied by a number of investigators (Mc. Cullagh, Mc. Cullagh & Hicken, 1931, Mc. Cullagh & Osborn, 1938, Törnblom, 1946 and Zimmermann, 1944). In Lovens kemiske Fabrik experiments have been made with the object of finding a method fit for the purpose, but no reliable method has been found so far. The enormous excretion of androgens presented by this patient induced us to think that she might also have a high androgen concentration in the blood and thus be found particularly fit for experiments of determination of androgens in the blood. The biological method (the capon's comb method) was applied for the determination. However, despite repeated experiments and although up to ½ litre of blood was applied each time only very small amounts of androgens could be demonstrated, so small that they were demonstrable only by application on the capon's comb, but not by the injection method. The amount found did not exceed that present in the blood of adult men. This corresponds, however, to previous statements (Crooke & Callow, 1939 and Törnblom, 1946) of a normal serum 17-ketosteroid value despite large excretion in the urine, an observation which is suggestive of a low renal threshold value of these substances and a very prompt excretion. It likewise accords with the fact that the concentration of total cholesterol in the blood was not found increased in our patient.

Treatment. X-rays on adrenals and pituitary body have sometimes been applied with success in cases of the adrenogenital syndrome (Goldzieher, 1939, p. 723). X-ray treatment of the adrenals proved to have no effect whatever in the case of
our patient. This is only what might be expected, since inhibition of the adrenal function must be supposed to be obtainable only by administration of such large X-ray doses that the surrounding organs are damaged. X-rays on the pituitary body, on the other hand, seemed to reduce the blood pressure, the basal metabolic rate, and the glucose tolerance to normal values, but had no influence on the virilism. This it not to be wondered at, since the latter was due to adrenocortical tumours. An effect might perhaps have been expected, if the syndrome had been caused by adrenocortical hyperplasia, which may possibly be due to an increased production of a corticotrophic hormone.

Also oestrogen in large doses has been stated sometimes to have a favourable effect on the adrenogenital syndrome and to reduce the 17-ketosteroid excretion (Goldzieher, 1939 and Talbot et al., 1942). Our patient, however, presented no decrease of the androgen or the 17-ketosteroid excretion, despite prolonged treatment with large doses of oestrogen (Ovex). The Ovex treatment had a markedly inhibitory effect on the growth of hair in the patient's face, from which it could be kept away almost entirely, but no definite effect on the remaining hypertrichotic (virile) hairiness. The reason for this is unknown. It is, however, no doubt only a question of the quantity used, since a high dosage seemed to loosen the hairs on body and extremities, so it is not unlikely that an even higher dosage might have inhibited the growth of hair. The excretion, and therefore probably also the production, of androgens having remained unchanged during the Ovex treatment, the inhibitory effect of the latter on the facial hypertrichosis cannot have been due to a decrease in the androgen production, but must be supposed to have been caused by a direct antagonism between oestrogen and androgen (Leth Pedersen, 1947).

The oestrogen dose received by the patient was enormous. Within a scant 2½ years she was given 154 Ovex injections of 50,000 I.B.U. each (= 5 mg. oestradiol monobenzoate), or a total of 770 mg. After having got about 40 injections the patient developed oedema of feet and crura as well as petechiae in these areas, which, however, subsided shortly
after discontinuation of the treatment, not to recur despite renewed treatment with equally large doses as before. The treatment involved no other complications or troubles of any kind. If, however, the uterus had not been amputated, there would no doubt have been haemorrhage from this organ.

**Diagnosis.** It cannot be said for certain why excision of the two adrenocortical adenomas was not followed by recovery from the virilism, as we had expected. There is no clinical evidence to suggest that the syndrome should have been caused by a pituitary lesion (e.g. basophilic adenoma) in addition to the adrenocortical adenomas, nor that an ovarian tumour (ar-rhenoblastoma) should be present as well. The ovaries had also at previous laparotomy been seen to be normal. Moreover, the adrenogenital syndrome is never associated with such a large 17-ketosteroid excretion when caused by lesion in pituitary body or ovary.

Hence there can hardly be any doubt that the patient’s virilism is still due to adrenocortical hyperfunction. It seems unlikely that the remaining right adrenal, which seemed normal after excision of the adenoma, should have become so hypertrophic that it can be supposed alone to produce such large amounts of 17-ketosteroids. Also metastases seem an unlikely possibility, since the removed tumours showed no signs of malignancy.

Therefore, I believe the most reasonable explanation to be one of hyperplasia or small tumours in accessory adrenals or aberrant adrenocortical tissue, of very common occurrence, most often situated close to the adrenals, along the spermatic veins, in ligamentum latum, ovaries, or testes. Cases of virilisation due to tumours in such accessory adrenals or aberrant adrenocortical tissue have previously been reported (Cahill, 1944 and Østergaard, 1946); but cases of concurrence of tumours in both normal adrenals and tumours or hyperplasia in accessory adrenals have to my knowledge not been described in the literature.

It seems doubtful whether the fact that the greater part
of the excreted 17-ketosteroids in our patient consisted of dehydro-androsterone also after excision of the adrenal adenomas can justify one in concluding that it is still tumour tissue which is responsible for the 17-ketosteroid production. The theory of the relative increase of the $\beta$-fraction in association with adrenocortical tumours, unlike what is the case in hyperplasia, seems applicable, if at all, only where it is a question of differential diagnosis between malignant adrenal tumours and hyperplasia. In the present case, as mentioned above, the tumours were hardly malignant. Therefore, if tumours are responsible, they must be of a benign nature (adenomas), and as such they should probably be regarded as forming part of a universal adrenocortical hyperplasia. The 17-ketosteroid excretion in our patient seems, therefore, to go against the above theory.

**SUMMARY**

A case is reported (woman, now aged 46) with a history of pronounced adrenal virilism of ab. 25 years' duration. She excreted enormous amounts of androgens and 17-ketosteroids in the urine, and the greater part of the 17-ketosteroids proved to be dehydro-androsterone.

X-rays on adrenals and pituitary body had no effect on the virilisation. By administration of large doses of oestradiol monobenzoate as intramuscular injections (Ovex) it was possible to reduce the growth of hair on face and neck, while the treatment had no effect on the hypertrichosis on body and extremities. By operation first one adrenal was removed, which had been transformed into a large adenoma, and next a fairly large adenoma was excised from the other adrenal. But the virilism persisted unchanged, and the androgen and 17-ketosteroid excretion continued to be considerably increased.
The reason for the persisting virilism after excision of the adrenal adenomas is supposed to be the presence also of hyperplasia or tumours (adenomas) either in accessory adrenals or in aberrant adrenocortical tissue.

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