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TREATMENT OF SIMPLE HIRSUTISM, INCLUDING THE HIRSUTE TYPE OF STEIN-LEVENTHAL SYNDROME

BY

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The results of diminishing androgen production by steroid therapy or adrenal surgery, in patients with congenital adrenal hyperplasia and adrenal cortical tumour respectively, from the point of view of the hirsutism are variable. They may be dramatic, useful, or even disappointing (Hamilton and Shepardson, 1952; Blizzard and Wilkins, 1957; Heinbecker *et al.*, 1957; Prunty *et al.*, 1958).

In these patients there is usually a clear and major overproduction of adrenal ketosteroids. Occasionally in patients developing post-pubertal hirsutism there is an adrenal lesion similar to that seen in congenital adrenal hyperplasia (Brooks *et al.*, 1960). Such patients have been excluded from the present study. However, most patients suffering from post-pubertal hirsutism do not have these lesions. Many may be described as having simple hirsutism and some have the hirsute type of Stein-Leventhal syndrome with accompanying anovulatory menstrual cycles and sterility. In some of both of these groups abnormalities of adrenal ketosteroids may be demonstrated (Prunty *et al.*, 1958; Gallagher *et al.*, 1958; Brooks and Prunty, 1960).

The present paper concerns attempts at treatment of patients of these two latter types. The effect of prednisone, often combined with ethinyl oestradiol, on the hirsutism of these patients has been observed. While sometimes there is an undoubted favourable response, it must be stated at the outset that it is more often most disappointing. Hirsute patients with the Stein-Leventhal syndrome, the diagnosis being established as described previously (Prunty *et al.*, 1958), have more often been treated by ovarian wedge resection (Stein *et al.*, 1949), since this appears to be the treatment of choice for sterile married women.

Material and Methods

The patients studied included 21 of those described under the heading of simple hirsutism by Prunty *et al.* (1958) and three patients with the Stein-Leventhal syndrome having hirsutism. One of these three patients was included in the earlier paper under the heading of simple hirsutism. The presence of ovaries of the Stein-Leventhal type had been suspected, but at laparotomy they were found to be normal. Two years later she presented with a twisted ovarian cyst, at operation for which the ovaries were found to be typical of the Stein-Leventhal syndrome. Meanwhile she had irregular periods, but temperature records suggested she was ovulating during the few months immediately after the first laparotomy. All these patients were treated with steroids. Their approximate ages at onset of the hirsutism are given in Table I. The precise age at which it occurred is usually difficult to determine.

TABLE I.—Age at Onset of Hirsutism

Age in years	11-15	16-20	21-25	26-30	31-35
No. of patients	11	7	5	0	1

An additional seven patients with the Stein-Leventhal syndrome were subjected to ovarian wedge resection and not treated with steroids.

Twenty patients received 10 mg. of prednisone daily in divided doses; one received 30 mg., reduced to 20 mg.; one had 15 mg.; and one had 5 mg. In addition, 19 received ethinyl oestradiol in dosage between 0.05 and 0.3 mg. daily for three weeks in every four. Of these, 17 received either 0.1 or 0.2 mg. daily. The duration of steroid treatment varied from 4 to 39 months.

The urinary 17-ketosteroids were usually determined, often with two consecutive days' collection for each determination, to ensure that adequate suppression of 17-ketosteroids was maintained.

The assessment of changes in the hirsutism is not an easy matter. It is naturally most difficult, and undesirable, to prevent patients from removing their facial hair for a sufficient time to make an objective assessment of its rate of growth; the observer must therefore rely on patients' statements about frequency of removal. Bearing this difficulty in mind, patients in category 1 were said to have improved when there was a significant reduction in the frequency of the necessity for removal. This could sometimes be confirmed objectively. Patients who appeared to be certain that the hair, on their limbs particularly, was less virile were placed in category 2. All patients of category 1 also noted this feature. It was usual for all these patients to state that hair had become softer and lighter in colour. Patients in category 3 were those who received no benefit.

Results

Response of Hirsutism

Of the 24 patients on steroid treatment, six were classified in category 1, nine in category 2, and nine in category 3. There was one patient with the Stein-Leventhal syndrome in each category. In category 1 there was at least a doubling of the time intervals between shaving or electrolysis. The poorest response was from once daily to once in three days. The best response was a decrease of frequency of electrolysis from fortnightly to three-monthly intervals. This occurred after treatment for six months.

All patients in category 1 had had hirsuties for more than five years; four had urinary 17-ketosteroids initially exceeding 15 mg./day, two had levels less than these; three out of the four tested had abnormal responses to corticotrophin (Prunty *et al.*, 1958)—that is, the response ratio of ketogenic steroid/17-ketosteroid was less than 2/1.

In category 2 four were hirsute for less than five years, and five for longer; four had initial 17-ketosteroids above 15 mg./day and five less than this; seven responded abnormally to corticotrophin and one normally.

In category 3 four were hirsute for less than five years, five for longer; three had 17-ketosteroids above 15 mg./day and six less than this; two responded abnormally to corticotrophin and five normally.

The depression of 17-ketosteroid levels in these patients is shown in Table II: 11 out of 20 had levels below 3 mg./day.

TABLE II.—Relation of Response of Hirsutism to Degree of 17-Ketosteroid Suppression

		No. of Patients with 17-Ketosteroid mg./day		
		Less than 3	3-5	More than 5
Category 1	..	3	2	1
" 2	..	5	1	1
" 3	..	3	3	1

It is not possible to draw definite conclusions concerning the effect of added oestrogen therapy. Of the five patients who did not receive oestrogen four were given 10 mg. of prednisone daily, and one had 30 mg. reduced to 20 mg. Three of the four for whom 17-ketosteroid data were available showed a depression to less than 3 mg./day, and two of these were in category 1 and one in category 2; the fourth patient was in category 3. The fifth in this group, receiving high

Effect of prednisone, with and without additional ethinyl oestradiol, on suppression of urinary 17-ketosteroids in a patient with simple hirsutism.

B

steroid dosage, showed a depression of 17-ketosteroid to only 8 to 9 mg./day and was assigned to category 1.

The average doses of oestrogen were similar in all categories—0.12 mg./day for category 1, 0.11 mg. for category 2, and 0.14 mg. for category 3. The effect of oestrogen in one patient was studied carefully (see Fig.) It will be seen that there was a sudden decrease of 17-ketosteroid when oestrogen was added to treatment, and that a rebound occurred on withdrawal of the oestrogen.

Of the patients studied, three had a moderate degree of acne. All received oestrogen. There was significant improvement in this condition in two of these patients.

Patients with the Stein-Leventhal Syndrome

In our original series of hirsute patients there were nine with this syndrome. An additional patient can now be added for reasons described above. These 10 patients were subjected to ovarian wedge resection and in all of them menstrual periods returned to normal. From temperature records taken of seven all appeared to be ovulating. Six of the patients were trying to have babies and four succeeded in doing so within six months of operation. The operation did not appear to affect the hirsutism significantly.

Three patients have been mentioned above who received additional steroid therapy. Two of these began treatment after menstruation had returned to normal post-operatively, both receiving prednisone and oestrogen. In one the menstrual cycles remained regular, in the other they became slightly irregular. The third patient is the one mentioned above who was diagnosed later. Between operations she received prednisone only, and prior to wedge resection the periods remained quite irregular; subsequently they became regular and ovulatory.

Two of the patients with simple hirsutism became pregnant while on steroid therapy; one was receiving 0.2 mg. of ethinyl oestradiol, the other none.

Untoward Effects of Steroid Therapy

One patient developed mild hallucinatory symptoms which ceased when treatment was stopped. Three had some degree of menorrhagia while receiving ethinyl oestradiol, and this substance appeared to be associated with the development of migraine headaches in two others.

Discussion

There is no doubt that in the main the results of steroid therapy for hirsutism under the conditions of our observations were disappointing. This has been the experience of de Mowbray *et al.* (1959), who concluded that prednisone produced no striking improvement and that steroid therapy was not justifiable on the grounds of hirsutism alone. Others have been somewhat more enthusiastic (Perloff *et al.*, 1958), as have some observers using cortisone (see Jefferies and Levy, 1959). Our results have been variable and reminiscent of the disappointing responses seen in respect of the hirsutism in congenital adrenal hyperplasia. It is noteworthy, however, that it is often stated that the hair becomes softer and finer. This usually occurred with our patients, many of whom felt that it was a worth-while result, but in a few cases the improvement was certainly more striking than this. The less encouraging results of de Mowbray *et al.* (1959) may have been due to a

lesser 17-ketosteroid depression or a shorter time of treatment, together with a smaller number of patients.

The fact that some response was obtained, presumably by suppression of adrenal androgen production, supports the view that there is some abnormality in adrenal secretion in these patients (Brooks and Prunty, 1960). The 17-ketosteroids were well suppressed in nearly all patients, but even in spite of this many showed little or no improvement. There is a hint from the results that the response was best in those patients who responded abnormally to corticotrophin.

The effect of added oestrogen in the hirsutism could not be determined and we do not have the impression that under our conditions it was important. Nevertheless it is of theoretical interest that we have observed some synergism with prednisone on 17-ketosteroid depression, though this was relatively small. This effect has also been observed by Armstrong (1955) on combining stilboestrol and cortisone and by ourselves in the congenital type of adrenal hyperplasia (Brooks *et al.*, 1960).

The unfavourable results of ovarian wedge resection in the Stein-Leventhal syndrome on the accompanying hirsutism seems to be a frequent experience (Perloff *et al.*, 1958) though some observers have claimed to find favourable changes (Leventhal and Cohen, 1951). The fact that four out of six patients who were trying to become pregnant after wedge resection did so is in keeping with the 60% occurrence of this result observed by others (see Bailey, 1959).

Summary and Conclusion

The effects of prednisone therapy, usually 10 mg./day and usually combined with ethinyl oestradiol treatment, have been observed in 21 patients with simple hirsutism and three with the hirsute type of Stein-Leventhal syndrome. In six there appeared to be significant improvement, which was much more doubtful in a further nine.

In 10 Stein-Leventhal patients ovarian wedge resection was carried out by our colleagues. The results are discussed. Four out of six patients attempting to become pregnant did so within six months of operation.

In conclusion, while steroid therapy may benefit the occasional patient to a noticeable degree when a reasonably low dosage level is used, we do not feel that it is sufficiently beneficial to justify its use routinely. It is not yet possible to predict whether any particular individual will respond, and the problem of relapse on cessation of treatment also arises.

We are indebted to our several colleagues in the department of obstetrics and gynaecology who kindly performed the ovarian wedge resections.

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SOME EXPERIENCES WITH A NEW ANABOLIC STEROID (METHANDROSTENOLONE)

BY

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Considerable advances have been made in separating the androgenic from the anabolic effects of substances related to testosterone in recent years. Whereas in men there is no real advantage in having an anabolic hormone which is relatively non-virilizing, this is of great practical importance in therapy for women and for children of both sexes.

The development of these new steroids and their applications has been reviewed (Foss, 1959a, 1959b) with preliminary mention of 1-dehydro-17 α -methyl-testosterone.

Chemical Composition

Methandrostenolone (1-dehydro-17 α -methyltestosterone; "dianabol") has the following structural formula, which is compared with that of methyltestosterone. Unlike methyltestosterone, there is double-bonding in the first benzene ring with loss of two atoms of hydrogen from carbons 1 and 2.