

## AN ANTIANDROGEN IN ACNE AND IDIOPATHIC HIRSUTISM\*

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The pilosebaceous apparatus is a target organ under androgen influence. Acne and hirsutism are found to occur in clinical situations associated with excessive androgen secretion. In several instances, however, no androgen excess can be demonstrated in patients with acne and hirsutism within the limitations of our present knowledge and techniques. It has been suggested that in these situations the possibility of increased end organ sensitivity to androgens be given serious consideration (1). The long search for an agent that could neutralize this effect culminated in a detailed study of 17 $\alpha$ -methyl-B-nortestosterone (Fig. 1). This synthetic compound was reported to have antiandrogenic properties in rats and mice by Saunders et al (2). Studies done in our laboratory on experimental animals confirmed this antiandrogenic activity and indicated that it also possessed weak antigonadotropic and possibly weak androgenic properties (3). Competition for receptor sites at the target organ level is thought to be its mechanism of action as an antiandrogen. In the human, 17 $\alpha$ -methyl-B-nortestosterone was found effective in the management of acne and hirsutism and the results were reported in earlier papers (4, 5). Quantitative data were obtained using facial hair collection or sebum analysis in a limited number of patients. In the majority of cases the main criterion used for improvement in acne was the disappearance of existing lesions and marked lessening of new eruptions. Improvement in hirsutism was judged in general by decrease in hair growth and the frequency of shaving.

The purpose of this paper is to present the results obtained in 55 patients after the withdrawal of the drug. The study is largely confined to young women and only two males. The use of 17 $\alpha$ -methyl-B-nortestosterone in the male may be limited by the finding by Caplan (6) of gynecomastia in 12 of 13 cases, although

this complication was not observed in our 2 cases. While Caplan did not observe any real improvement of acne, an excellent response was obtained in our 2 male patients. The improved condition during therapy as compared to the return of the pretreatment status some weeks or months after discontinuation of the drug, seemed to lend weight to the efficacy of the antiandrogenic agent.

### MATERIAL AND METHODS

17 $\alpha$ -methyl-B-nortestosterone<sup>1</sup> was administered orally to 55 patients (53 females and 2 males) in daily doses ranging from 50 to 600 mg for periods of 1 to 22 months, beginning with a 50 mg dose and increasing by increments of 50-100 mg. While on this regimen, no other forms of medication were administered. Complete blood counts, urinalysis, coagulation time, SGOT, SGPT, BUN, alkaline phosphatase and serum creatinine were performed in all the patients at various intervals of time in order to study hepatic, renal and hemopoietic function during treatment. In several patients the estimation of 17 ketosteroids, 17 ketogenic steroids and steroid fractionations were carried out. The results were reported earlier (5).

### RESULTS

The effect of the administration of this compound on acne and hirsutism is shown in Table I. Although the total number of patients was 55, most of the patients had a combination of acne and hirsutism, thus giving a total of 75 points of study. Although the criterion of improvement was based on subjective judgement, nonetheless the results were quite obvious. Beneficial results were observed in 26 of 35 patients with acne (74.3%). Lessening of hirsutism was noted in 21 of the 40 patients studied (52.5%). The best effects were achieved with dosages ranging from 200 to 400 mg/day. Improvement in acne frequently was noted within a short time of one or more weeks. The more severe cases of acne showed the greatest improvement, while the diminution of hirsutism was more gradual and not related to the degree of hypertrichosis.

<sup>1</sup>17 $\alpha$ -methyl-B-nortestosterone used in this study was supplied by the Smith Kline & French Laboratories, Philadelphia, Pa.

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The interpretation of the results shown in Table I could be subject to two major criticisms. Firstly, the observations in Table I were subjective in many instances for want of distinct criteria for the quantitative evaluation of acne and hirsutism. Secondly, a double blind study for the efficacy of the drug would have been of great value. We had hoped to carry out a double blind study with 17 $\alpha$ -methyl-B-nortestosterone during the second phase of our clinical trials but the drug was withdrawn from clinical trials pending further animal experimentation. In the absence of a double blind study to evaluate the efficacy of 17 $\alpha$ -methyl-B-nortestosterone, it may be helpful to mention that the use of oral contraceptives has been tried extensively by many investigators for the management of acne (7-10). In a study with the classical contraceptive pill and the sequential form of the pill in our clinic, done under the same conditions as with 17 $\alpha$ -methyl-B-nortestosterone, the improvement in acne was noted to be 50% in cases with the classical and 46.8% with the sequential form (11). The beneficial outcome with 17 $\alpha$ -methyl-B-nortestosterone was found to be 74.3%. The comparison of the effect of this agent with those of oral contraceptive pills, offers in a measure additional confirmation to its efficacy.

Further confirmation of its efficacy was obtained by follow up studies after termination of therapy at varying intervals ranging from a few months to two years. The regressive changes noted on therapy were in almost every instance confined to the period of therapy and a short interval thereafter. Recurrence took place in all the patients with acne and in most of those with hirsutism (Table II).

The clinical laboratory tests were within

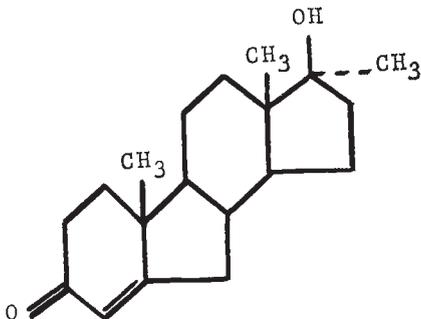


FIG. 1. Formula of 17 $\alpha$ -methyl-B-nortestosterone

TABLE I

Results under treatment with 17 $\alpha$ -methyl-B-nortestosterone

	No. of cases	Doubtful beneficial effects or no change	Improvement
ACNE	35	9	26
HIRSUTISM	40	19	21
TOTAL	75	28	47

TABLE II

Results after discontinuation of the treatment with 17 $\alpha$ -methyl-B-nortestosterone

	No. of cases	No change	Reappearance of symptoms
ACNE	26	-	26
HIRSUTISM	21	8	13
TOTAL	47	8	39

range of normal. Of interest was the uniform increase in urinary 17 ketosteroids. Interference of the drug in the routine method of Dreker *et al.* (12) for total ketosteroids was shown to be responsible for this effect (5). Tolerance for the age and absence of evident toxicity permitted its use for prolonged periods of time.

#### CONCLUSIONS

The introduction of an antiandrogen into our therapeutic armamentarium is a goal long sought. This agent, 17 $\alpha$ -methyl-B-nortestosterone was the first such preparation assayed clinically. The relative absence of untoward reactions and the lack of derangement in the other endocrine systems were features of this drug. We can conclude that the rational management of the manifestations of increased sensitivity to endogenous androgens is through the administration of an antiandrogen. The excellent results obtained, though temporary, offer promise to the long time approach of the treatment of acne and idiopathic hirsutism. It is hoped that continued search for the ideal antiandrogen will continue.

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