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Adrenal Function in Women with Idiopathic Acne

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The adrenal secretion of androgens was examined in 9 women (ages 19–39 yr) with postadolescent idiopathic acne and compared to age and sex-matched normal controls. Plasma dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHAS), androstenedione (Δ^4-A), cortisol, 17-hydroxyprogesterone, 11-deoxycortisol, and testosterone were measured by radioimmunoassay in the basal state and during a 48 hr ACTH infusion. The mean plasma and time-integrated plasma levels of the 3 adrenal androgens in patients with acne were 15–25% higher than normal controls, but the groups were not significantly different ($p > .05$). The plasma testosterone values, on the other hand, were similar in both groups. In addition, cortisol, 11-deoxycortisol and 17-hydroxyprogesterone basal plasma values and responses to ACTH in patients with acne were similar to the normal control values. These findings suggest that adrenal androgen secretion is at most mildly elevated in patients with idiopathic acne and is unlikely to be the sole cause of acne since many patients without acne have similar hormone levels. Increased sensitivity of the sebaceous gland to androgens or increased local metabolism of androgen hormones in the skin to potent androgen metabolites may offer alternative mechanisms for the pathogenesis of this disorder.

Acne is an androgen dependent condition [1]. It may be present in the newborn (neonatal acne), probably in association with the androgen producing fetal adrenal gland or the functioning neonatal testis [2–4]. Later in life, acne usually develops around puberty, with facial comedones being seen as early as 5–8 yr. This coincides with the appearance of the adrenal zona reticularis and with increasing adrenal androgen secretion (adrenarche) [5,6]. Acne is also commonly seen in conditions associated with hyperandrogenism such as congenital adrenal hyperplasia, ovarian tumors, adrenal tumors, Cushing's disease, idiopathic hirsutism, and polycystic ovarian disease [7–13]. In these conditions plasma testosterone and adrenal androgen hormones or their urinary metabolites are usually elevated when compared to normal controls [7–13]. In children with a strong familial background of idiopathic acne, the androgen status has been examined by measuring basal 24 hr urinary excretion of testosterone, dehydroepiandrosterone, androsterone, etiocholanolone, and total 17-ketosteroids [14,15]. The incidence of acne in these children increases as urinary steroid excretion rises during adrenarche. Urinary testosterone excretion in the prepubertal children with acne is significantly greater than in age-matched controls, suggesting that hypersecretion of adrenal androgens may contribute to the pathogenesis of this disorder. These studies have led us to postulate that adrenal hyperandrogenism may also contribute to persistent idiopathic acne in adult women. We have tested this hypothesis by measuring plasma androgen levels basally and during maximal adrenal stimulation in women with uncomplicated (not associated with hirsutism or ovarian dysfunction) idiopathic acne and in age-matched controls.

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Abbreviations:
DHA: dehydroepiandrosterone
DHAS: dehydroepiandrosterone sulfate
THS: tetrahydro-compound S

MATERIALS AND METHODS

Subjects and Protocol

All subjects, 9 women with acne and 10 age- and sex-matched controls, were admitted to the Clinical Center of the National Institutes of Health for evaluation. The patients with acne (ages 19–39 yr, mean 24.3) had never received glucocorticoid therapy and had taken no medications for 6 weeks prior to the study except antibiotics. They were all menstruating regularly except one that had polymenorrhea. There was no hirsutism present in any of them according to the criteria of Ferriman and Gallwey [16] (scores <7 on all patients). The normal subjects (ages 19–24 yr, mean 20.5) had no evidence of any illness, including acne or hirsutism, by history, physical examination, and routine admission laboratory tests. All were menstruating regularly.

Both patients and normal control subjects received a standard 48 hr IV ACTH infusion (cosyntropin 80 U/day) [17]. Blood samples were collected before and during the infusion for steroid measurements. The ACTH infusions were administered without regard for the phase of the menstrual cycle. There was no significant difference between the proportion of patients and control subjects who received the ACTH infusion in the follicular versus the luteal phase.

Hormone Assays

Plasma dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHAS), androstenedione (Δ^4-A), cortisol, 11-deoxycortisol and 17-hydroxyprogesterone were measured by radioimmunoassay as previously described [18–20]. The detection limits for these assays are 25 ng/dl. 5 ug/dl, 15 ng/dl, 1 ug/dl, 40 ng/dl and 7 ng/dl, respectively.

Statistical Analysis

Unless otherwise stated, all data are presented as the mean ± SE. Comparisons were made using Student's *t*-test and the Mann-Whitney U test [21].

RESULTS

Cortisol, 11-deoxycortisol and 17-hydroxyprogesterone values in the basal state and during ACTH were similar in patients with acne and normal controls (Fig 1).

Adrenal androgen levels, including DHA, DHAS and Δ^4-A were slightly higher in patients with acne at all time points (Fig 2). However, *t*-test of the groups at each time point showed that the groups were not significantly different.

Plasma testosterone values were similar in acne patients and normal controls, both basally and during ACTH stimulation (Fig 2, *bottom panel*).

To compare adrenal steroid responses between acne patients and controls over the entire infusion, we calculated the time-integrated steroid response to ACTH for each patient (area under the curves, as presented in Fig 1 and 2) and compared the means of the 2 groups (Fig 3) using Student's *t*-test. None of these comparisons were significant ($p > 0.05$) although the DHA, DHAS and Δ^4-A values were 22, 15 and 25% higher in patients with acne. Furthermore, no significant differences were found when we compared the two groups using the nonparametic Mann-Whitney U test ($p > 0.05$). However, in 5 of 9

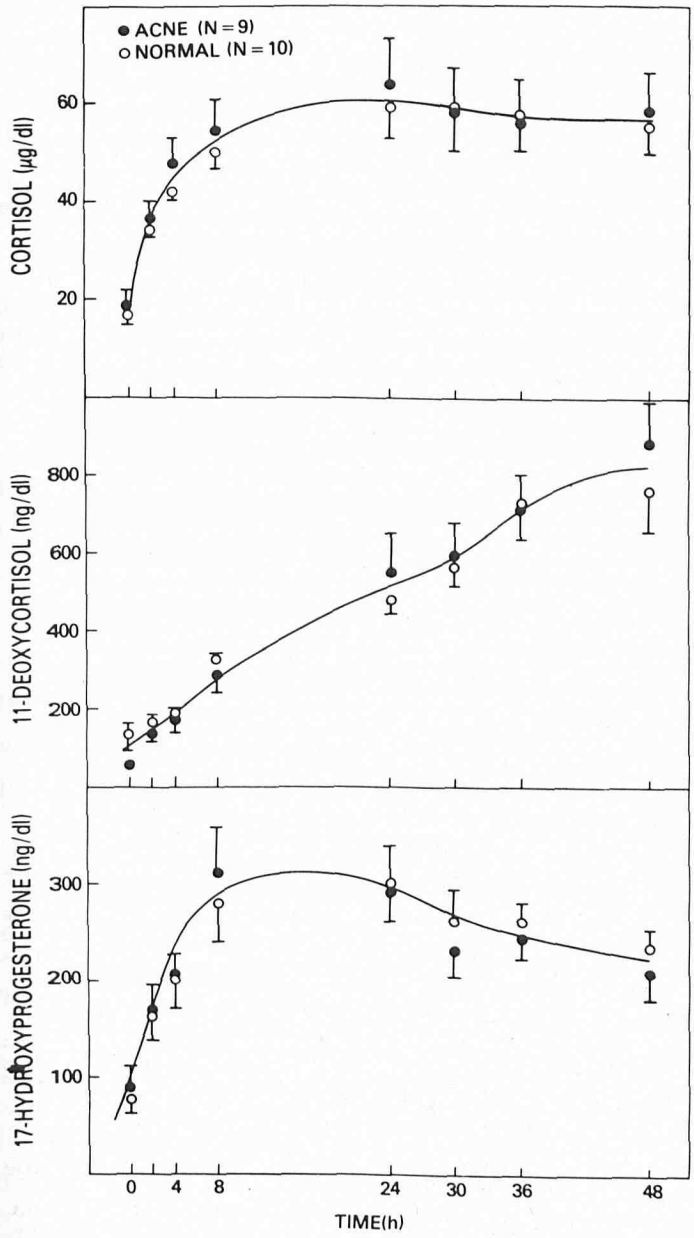

FIG 1. Plasma cortisol, 11-deoxycortisol and 17-hydroxyprogesterone during ACTH infusion in 9 patients with acne (●——●) and 10 normal controls (○——○).

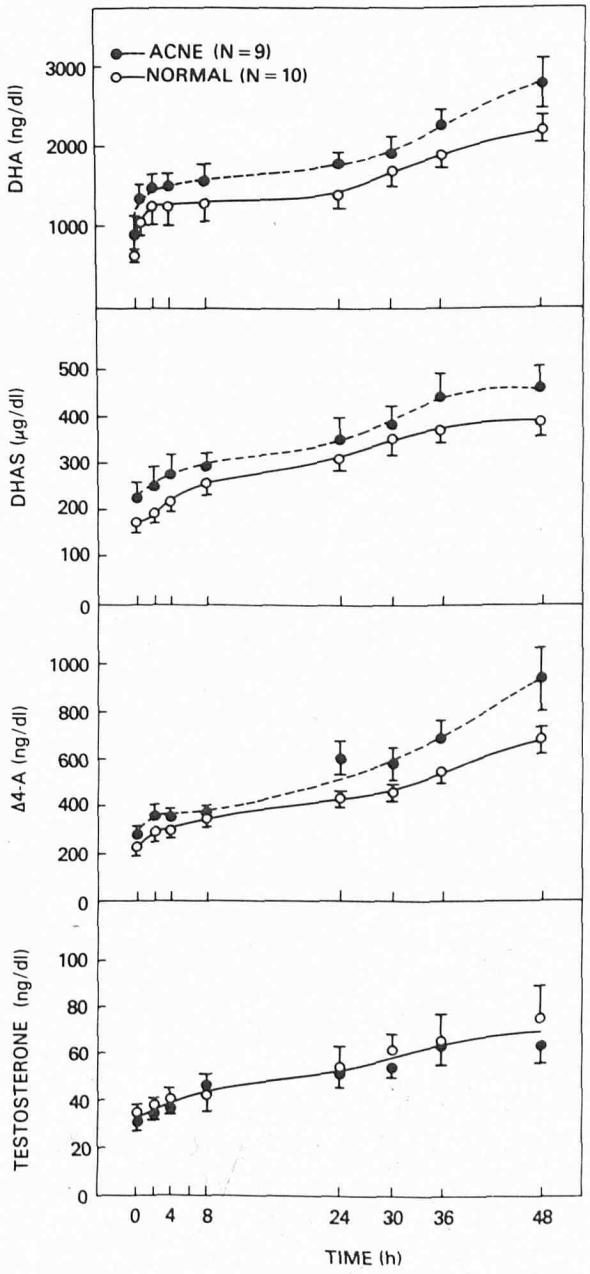

FIG 2. Plasma DHA, DHAS, Δ^4-A and testosterone during ACTH infusion in 9 patients with acne (●——●) and 10 normal controls (○——○).

patients with acne (ages 19–25) the time-integrated Δ^4-A values were above the 95% confidence limits for normals suggesting that examining a larger patient sample might show significantly although only slightly elevated plasma levels of Δ^4-androstenedione.

There was no correlation between the severity of acne as evaluated by the number of skin lesions and basal or time-integrated plasma androgen hormone values (data not shown).

DISCUSSION

These studies demonstrate that circulating adrenal androgens, testosterone and cortisol, both basally and after prolonged adrenal stimulation, are not significantly different between women with persistent acne and age-matched controls. Thus, although acne is an androgen dependent condition, its expression in women does not appear to be substantially related to increased circulating androgen levels.

Mild (late onset) congenital adrenal hyperplasia can be difficult to diagnose, and may require ACTH stimulation with measurement of plasma 17-hydroxyprogesterone or 11-deoxycortisol, or their urinary metabolites pregnanetriol and THS, to establish a diagnosis [22,23]. No patient in the acne group met the requirements for 21 or 11-hydroxylase deficiency. In contrast, in another study patients with severe, refractory, nodulocystic acne, had increased ACTH-stimulated urinary pregnanetriol and tetrahydro-compound S(THS) but normal 17-ketosteroids [8]. No mention of associated hirsutism and ovarian dysfunction (menstrual irregularities and infertility) was made. The same author later reported a group of women who had acne but who had presented to a gynecologist with a chief complaint other than acne. These patients also had increased ACTH-stimulated urinary pregnanetriol and THS [9]. This latter group clearly differs from our patient population, who presented to a dermatologist (G.L.P. and E.G.G.) with the sole complaint of acne. We suspect that this difference in patient selection may contribute to the different findings of our studies. Gynecologic disorders such as menstrual irregularity or hirsutism frequently are associated with high circulating androgen levels and acne as a related consequence of hyperandrogenism.

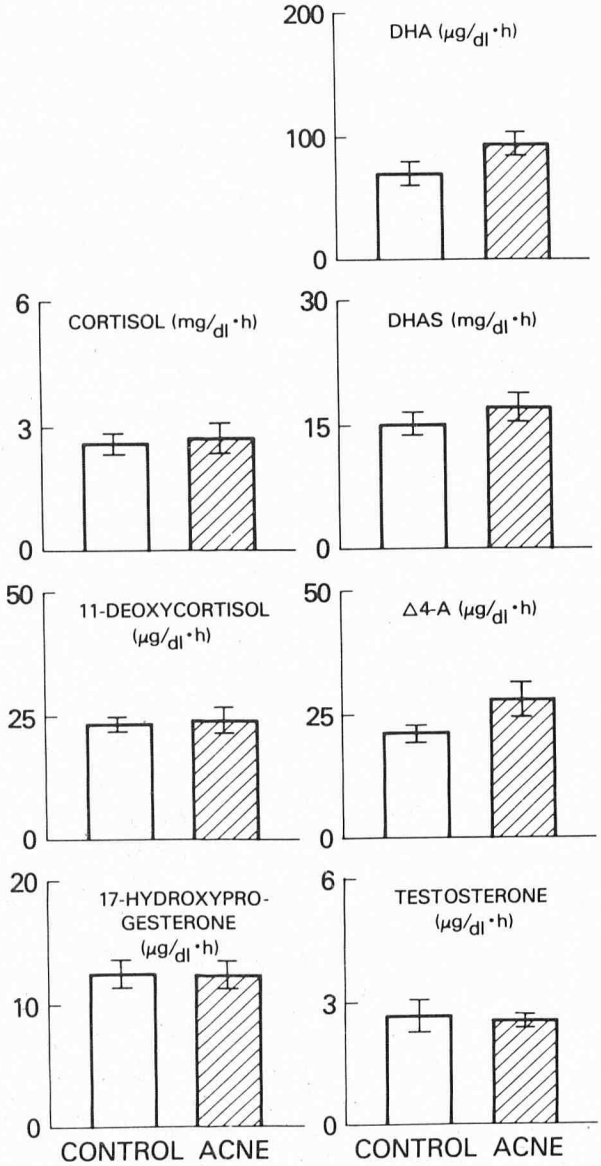

FIG 3. Comparison of time-integrated plasma steroid hormone values between patients with acne (*shaded bars*, mean ± SE, N = 9) and normal control subjects (*open bars*, N = 10). The time-integrated value for each patient was calculated from the area under the curve of steroid concentration vs. time for the 48 hr ACTH infusion.

Thus, although attenuated 21-hydroxylase and 11-hydroxylase deficiencies have been reported in this setting [8,9], we did not encounter these disorders in our patients with uncomplicated acne.

The various circulating androgens act on the sebaceous gland to stimulate sebum production either directly, as hormones, or as prohormones, which undergo local metabolism to form active metabolites. Human skin has been shown to convert testosterone to 5α-dihydrotestosterone (DHT) and other 5α-reduced steroids both *in vivo* and *in vitro* [24–27]. The sebaceous gland itself has a high 5α-reductase activity when tested *in vitro* by a micromethod [28]. On the other hand, circulating Δ^4-androstenedione is converted peripherally to testosterone [29]. Dehydroepiandrosterone may be converted peripherally to Δ^5-androstenediol [30], which itself may have intrinsic androgenic activity [31], and then to testosterone. However, there is little knowledge of the extent to which these conversions occur in the normal and abnormal sebaceous gland, and of their importance relative to plasma uptake as a source of local testosterone. Thus, our observation that circulating testosterone, DHA, DHAS and Δ^4-A in patients with acne were not significantly different from normal controls does not invalidate the hypothesis that altered local metabolism of these hormones may contribute to the pathogenesis of acne. In fact, increased 5α-reductase activity has been observed in the skin of patients with acne [32,33], as well as in other androgen dependent conditions, such as male pattern baldness and idiopathic hirsutism [34,35]. In addition, increased sensitivity of the sebaceous gland to androgens represents another potential but unproven mechanism for the pathogenesis of this disorder.

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Announcement

The Annual Clinically Oriented Symposium of the European Society for Dermatological Research (E.S.D.R.) will be held in Amsterdam, The Netherlands, January 31, to February 1, 1983. The theme of this meeting will be: "Brain and Skin." Abstracts should be submitted in English, typed double-spaced on A4-sized paper (five copies). The deadline for submission is October 1, 1982. Correspondence: Professor Rudi H. Cormane, M.D., Department of Dermatology, Academic Medical Center, Meibergdreef 9, NL-1105 AZ Amsterdam-Zuid-Oost, The Netherlands.