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Plasma Androgens in Women with Acne Vulgaris

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We have studied a group of young adult women of mean age 23.8 ± 6.5 (SD) years with only acne (A, n = 46), only hirsutism (H, n = 10), and acne plus hirsutism (A+H, n = 19) who sought dermatologic care. We measured the androgens, total and free testosterone (T), free 17β-hydroxysteroids (17-β), dehydroepiandrosterone sulfate (DS), and the androgen precursors 17α-hydroxypregnenolone (17-Preg) and 17α-hydroxyprogesterone (17-Prog), as well as testosterone-estrogen binding globulin in all patients. Plasma hormone levels of the patients were compared to those of 23 controls of mean age 25.6 ± 6.6 years who had neither acne nor hirsutism. Mean levels of all hormones measured, except 17-Preg, were elevated in the women with acne. Fifty-two percent of Group A, 60% of Group H, and 63% of Group A+H patients had at least one abnormal hormone level. The most frequently elevated plasma androgens in all the women with acne were: free T 25%, free 17-β 23%, and DS 19%. Total T was high in only 12%. Elevations of plasma androgens were present in some women who did not have hirsutism or irregular menses. Identification of endocrine abnormalities in women with acne may potentially offer an opportunity for hormonal therapy.

Acne vulgaris is a disorder of sebaceous follicles. It is well known that androgens stimulate the pilosebaceous unit; however, the clinical role of circulating plasma androgens in the pathogenesis of acne has seldom been documented. With the advent of new techniques for measuring free plasma androgens, elevations of androgens have been found in a large percentage of hirsute women [1]. Until recently [2,3], most hyperandrogenemia in women with acne has been detected during evaluation of hirsutism or menstrual disorders. In this study we have measured plasma androgens and their precursors in 75 women of mean age 23.8 ± 6.5 (SD) years who came to a dermatology clinic for acne and/or hirsutism. We measured the androgens, total testosterone (total T), free testosterone (free T), free 17β-hydroxysteroids (free 17-β), dehydroepiandrosterone sulfate (DS), and the androgen precursors 17α-hydroxypregnenolone (17-Preg) and 17α-hydroxyprogesterone (17-Prog), as well as testosterone-estrogen binding globulin (TEBG), and compared levels in the patients to those in control, age-matched women who had no significant acne or hirsutism. We have found a significant incidence of hyperandrogenemia in women with acne vulgaris.

MATERIALS AND METHODS

Patients

Seventy-five women of mean age 23.8 ± 6.5 (SD) years came to the Dermatology Clinic at the Yale New Haven Hospital Medical Center

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Abbreviations:
17-β: 17β-hydroxysteroids
CAH: congenital adrenal hyperplasia
D: dehydroepiandrosterone
DHT: dihydrotestosterone
DS: dehydroepiandrosterone sulfate
F: follicular
L: luteal
17-Preg: 17α-hydroxypregnenolone
17-Prog: 17α-hydroxyprogesterone
T: testosterone
TEBG: testosterone-estrogen binding globulin

for evaluation and treatment of acne vulgaris or hirsutism. The control group consisted of 23 female volunteers of mean age 25.6 ± 6.6 years whom we examined and found not to have significant acne or hirsutism. The mean ages of the patients and controls were not statistically different.

The 75 patients were divided into 3 groups (Table I). *Group A*, n = 46, were patients with only acne. *Group H*, n = 10, were patients with only hirsutism. *Group A+H*, n = 19, were patients who had both acne and hirsutism. A total of 65 patients had acne and a total of 29 had hirsutism. Medical and menstrual histories were obtained on all patients and controls. Follicular and luteal phases were ascertained by history, follicular being within 14 days of onset of menses. No patients were taking oral contraceptives or glucocorticoids. Acne was scored on a scale of 1–4 based on the presence of comedones, papules, pustules, or cysts present on the face, back, and chest [4]. The presence of more than 10 comedones, papules, pustules, or any cysts was considered significant acne. Most patients had moderate acne. Hirsutism was scored on a scale of 1–4 and recorded on preprinted diagrams outlining each of 9 anatomic sites [1]. Hirsutism was defined in this study as a total score of greater than 6. Each patient donated a single, random 30-ml sample of blood which was drawn into a heparinized tube, and the separated plasma was stored at −20°C until assayed. Written informed consent was obtained from all patients, and these studies were approved by the Yale University School of Medicine Human Investigation Committee.

Hormone Measurements

Hormone assays were performed in the Pediatric Endocrine Laboratory of the University of Chicago. Plasma total T, free T, free 17-β (a group measurement including testosterone, dihydrotestosterone (DHT), androstenediol, and androstanediol), DS, 17-Preg, 17-Prog, and TEBG were measured by radioimmunoassay and competitive protein binding methods as previously described [5,6].

Data Analysis

The upper limit of normal for each androgen was defined as 2 SD above the mean value of the 23 control women. Mean values for each hormone in each clinical group were compared to the appropriate control using Student's *t*-test adjusted where necessary to account for unequal variance among groups. In cases where there was not a normal distribution within a group, the nonparametric 2-group Wilcoxon Rank Sum test was utilized. Calculations were made on the CLINFO computer of the Yale University Clinical Research Center.

RESULTS

Mean Levels of Plasma Androgens (Fig 1)

The mean level of at least 1 hormone was elevated in every study group. In the 46 patients with only acne, (Group A) or the 65 patients with acne ± hirsutism, all steroids measured except 17-Preg were significantly elevated compared to controls. Of the 46 women with only acne (Group A), mean levels of total T (43.1 ± 16.0, $p < 0.05$), free T (7.9 ± 3.4, $p < 0.002$), free 17-β (44.0 ± 16.9, $p < 0.05$), and DS (204.5 ± 102.5, $p < 0.05$) were elevated. These data were similar to those found in all 65 women who had acne.

Individual Abnormalities of Plasma Androgens (Fig 1)

Total T was elevated in 13% of Group A, 30% of Group H, and 11% of Group A+H. In contrast, free T was elevated in approximately twice as many patients: 24% of Group A, 50% of Group H, 26% of Group A+H. Fig 2 illustrates that 13 of the 75 women studied had an elevated free T without any abnormality of total T. Of the 13 women, 9 had TEBG levels less than 31 nmol/l (the lowest value observed in the control group), and the other 4 had levels less than 37 nmol/l.

Fifteen percent of Group A had abnormal 17-β. Free 17-βs were more frequently elevated in the hirsute patients—high in 30% of Group H and 34.5% of all 29 hirsute patients. DS was elevated in 12/65 (18.5%) of the women with acne.

Follicular phase levels of 17-Prog were high in 4/13 (31%) of the acne only patients, 2/3 (67%) of the hirsute only patients, and 4/10 (40%) of the patients with both acne and hirsutism. Luteal phase levels of 17-Prog were rarely elevated. 17-Preg had a wide scatter even in control subjects and was not often abnormal in the patients. There was no statistical difference between follicular and luteal levels of any hormones other than 17-Prog measured in this study.

The most frequently abnormal androgen was free T which was elevated in 16/65 (24.6%) of acne patients. Free 17-β was elevated in 14/65 (23%) and DS was elevated in 12/65 (18.5%). Of the 65 women with acne, measurement of free T alone showed that 25% of the patients were hyperandrogenic; addition of DS raised the ascertainment to 33%, and addition of free 17-β raised it to 43%. There were 11/65 (17%) of patients who had abnormalities only of the androgen precursors 17-Preg and 17-Prog.

If one considers the lower limit of normal of TEBG to be 2 SD below the mean (TEBG = 17 nmol/l) then there were very few patients with low TEBG levels. However, if the cutoff for normal is set at the observed range of the normal controls (TEBG < 31 nmol/l) then 14/46 acne only patients (30.4%) and 22/65 acne and hirsutism patients (33.8%) had significantly low levels of plasma TEBG.

Overall, more than half of the patients had at least 1 abnormal steroid hormone (Table I). The number of plasma abnormalities per patient varied: 16 women had 1 abnormality, 13 had 2 abnormalities, 9 had 3 abnormalities, and 4 had 4 abnormalities. Of the latter 4 women, 1 had acne, 1 had hirsutism, and 2 had both. Two of them had irregular menses. There was no increased incidence of elevated plasma hormone levels in patients with a history of menstrual irregularities. Of the 65 women with acne, 21 patients had irregular menses and 13 (62%) of them had abnormal levels; but 44 patients had normal menses and 23 (52%) of them also had high hormone levels. The difference between the two groups was not significant. There was a similar distribution in the group with acne only and in the whole group. There was no significant correlation of androgen levels with age, severity of acne, or severity of hirsutism as determined by linear regression analysis.

TABLE I. *Women with acne and/or hirsutism who have one or more abnormal plasma steroid hormones*

Group	No. of patients	Percentage of patients
I. Acne only (A)	24/46	52.2
II. Hirsutism only (H)	6/10	60.0
III. Acne + hirsutism (A + H)	12/19	63.2
IV. All patients	42/75	56.0
V. All hirsutism (± acne)	18/29	62.1
VI. All acne (± hirsutism)	36/65	55.4

DISCUSSION

The ability of androgens to stimulate sebaceous glands is well known, but the importance of circulating plasma androgens (such as T, 17-β, and DS) and precursor substrates (such as 17-Preg and 17-Prog) in the pathogenesis of acne vulgaris has not been well substantiated. The advent of specific and sensitive radioimmunoassays for free and multiple androgens and their precursors permits a new evaluation of the significance of elevated plasma androgens in acne. We have found that more than half of a group of young adult women whose primary complaint was acne had elevated androgens or androgen precursors. Hyperandrogenemia in these patients was diagnosed on the basis of measurement of DS, free plasma testosterone, and other 17β-hydroxysteroids.

In the past no consistent abnormalities of urinary 17 ketosteroids or testosterone have been found in patients with acne [2,7–10]. Elevated urinary 5α-androstanediol was reported in 10 women with acne [11]. Plasma levels of total T have been reported to be both normal [9,11,12,13] and elevated [2,14,15,*]

* Marynick SP, Chakmakjian ZH, McCaffree D, Herndon JH Jr: Severe cystic acne: a spectrum of treatable endocrinopathies. Abstract 457, presented at the 1981 Annual Meeting of the Endocrine Society in Cincinnati, Ohio.

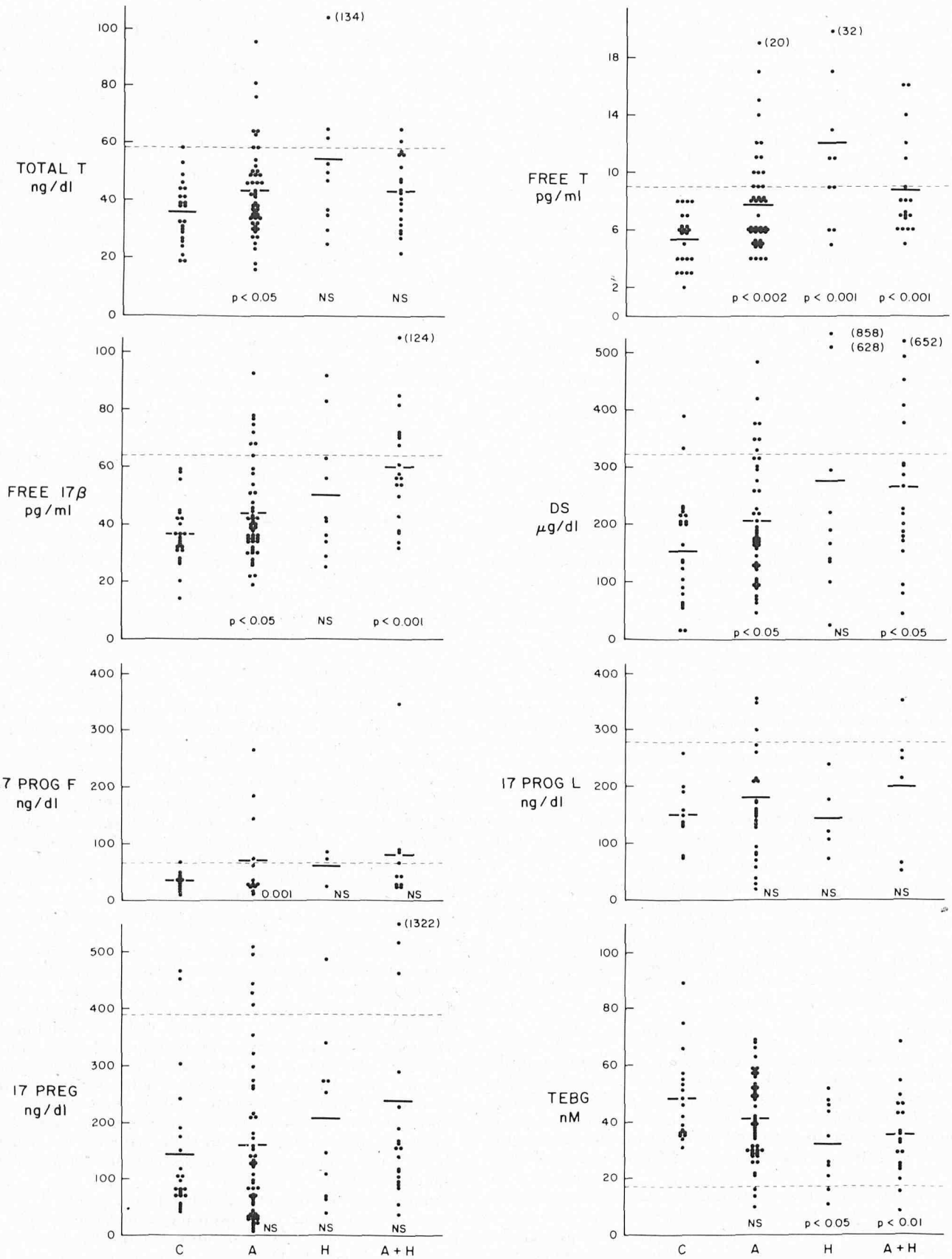

FIG 1. Plasma levels of the androgens, total testosterone (*total T*), free testosterone (*free T*), free 17β-hydroxysteroids (*free 17β*), and dehydroepiandrosterone sulfate (*DS*); the androgen precursors 17α-hydroxyprogesterone (*17-Prog*) in follicular (*F*) and luteal (*L*) phases of the menstrual cycle, and 17α-hydroxypregnenolone (*17 Preg*); and testosterone-estrogen binding globulin (*TEBG*) in 23 control women (*C*), 46 women with acne (*A*), 10 women with hirsutism (*H*), and 19 women with acne and hirsutism (*A+H*). *Dashed line* indicates limit of normal, *bar* indicates mean, and *p* values relate the mean levels of patients to the controls. Mean levels of all steroid hormones except 17 Preg are elevated in acne patients.

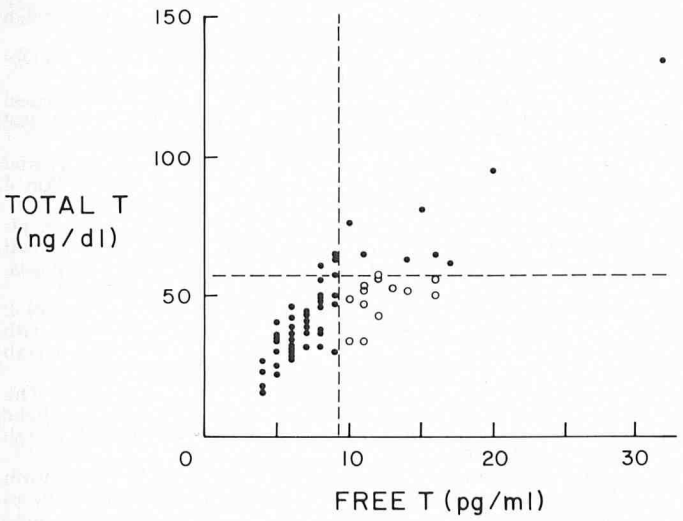

FIG 2. Plasma free testosterone (*free T*) and total testosterone (*total T*) in 75 women with acne and/or hirsutism. *Dashed lines* indicate upper limit of normal. *Open circles* represent 13 patients with normal levels of total T and elevated levels of free T. These women had TEBG levels less than 37 nmol/l. Androgen abnormalities would not have been detected if only T had been measured in these 13 women.

in patients with acne. In most studies where T was elevated, patients were ascertained because of gynecologic complaints or severe refractory cystic acne. There have been few studies of plasma free T in patients with acne. Lawrence et al [16] found 46% of women with severe acne and 89% with acne and hirsutism had elevated "derived" free T levels. Walker et al found no elevation of free T in 18 females with acne [17]. Free 17-β was found to be high when studied in a few females with acne [18]. Androstenedione has not been useful [15]. Recently there have been reports of elevated dehydroepiandrosterone (D) and DS in patients with refractory acne or gynecologic abnormalities [15,17,*] TEBG has been found to be both low [13,16,17] and normal [18,*] in women who had acne and were hyperandrogenic.

We found that more than 40% of our patients had elevated plasma androgens and more than half had at least 1 abnormal plasma hormone value when androgen precursors were included. We compared our patients to a group of women who were selected because they had neither acne nor hirsutism. The use of a nonselected "control" population in which individuals with acne are not excluded may result in significantly higher "control" values for androgens and underdetection of patients with hyperandrogenemia. Thus it is difficult to interpret previous studies in which the control group was not selected.

We found that free T was elevated in twice as many patients as total T. In 13 women free T was high when total T was normal. Their hormone abnormality would have been missed if only total T were measured. Most of these 13 had TEBG levels lower than the observed range of the control women to account for the discrepancy. Overall, a quarter of the women with acne had high plasma free T. T circulates bound primarily to TEBG, but only the free or unbound fraction seems to be biologically active. Low TEBG increases the fraction of T that is free and thus explains why total T may be unremarkable when free T is elevated. Similarly, measurements of free 17-β increased the ascertainment of hyperandrogenemia.

Our findings of high androgens in acne are similar to findings in studies of hirsutism [1,19]. In our study we found that a significant number of women who had acne without hirsutism also had abnormal androgens. The absence of hirsutism in women with acne does not therefore assure normal androgen levels. This discrepancy may be accounted for by individual sensitivity to stimulation of hair growth or by the duration of hyperandrogenemia.

Thirty-eight percent (10/26) of our patients had elevated levels of 17-Prog in the follicular (F) phase of the menstrual cycle. Luteal (L) phase levels were not different from controls. The patients with high 17-Prog (F) may have partial blocks in adrenal 21-hydroxylase, the most common form of congenital adrenal hyperplasia (CAH) as 17-Prog is the immediate substrate for 21-hydroxylase. Another possible explanation is that 17-Prog may be of ovarian origin, and its elevation in the F phase of the menstrual cycle may be related to the well-known cyclic flare of acne which occurs in the second half of the menstrual cycle. It is possible that sebaceous glands stimulated in the F phase with 17-Prog, progesterone, or more androgenic metabolites [20] may induce acne lesions in the ensuing L phase of the menstrual cycle. Further studies of hormone profiles at various times in the menstrual cycle are needed to test this hypothesis.

The source of abnormal plasma androgens in these women is unknown. Androgens are not only secreted by the adrenal and the ovary but are produced from precursor hormones by metabolism in the skin [21]. In this manner high circulating levels of weakly androgenic precursors may be locally metabolized to more potent androgens. Testosterone is derived from the adrenal, ovary, and from the conversion of precursors in locations such as fat, liver, and skin. DS is a good marker for adrenal androgen production as it is normally produced primarily in the adrenal [21]. Nineteen percent of our patients had elevated levels of DS. Patients with complete forms of CAH may develop acne when they are in poor control. Recently, mild CAH (also called partial, late onset, adult, or acquired CAH) with mild defects in 11- or 21-hydroxylase [22–28] or 3β-hydroxysteroid dehydrogenase [29,30] have been identified in women with evidence of high androgens such as menstrual dysfunction, hirsutism, and acne. Although only a small fraction of patients who come to a dermatologist because of acne may have mild CAH, the disorder is so amenable to treatment with low doses of glucocorticoids that it is worthwhile to identify them. ACTH stimulation tests or empirical trials of glucocorticoid suppression may be warranted in patients with high levels of DS.

We found that patients with acne and a "normal" menstrual history could also be hyperandrogenic, illustrating that occult ovarian or adrenal dysfunction may be present. Until now it had been assumed that end organ metabolism of androgens accounted entirely for the clinical expressions of acne and hirsutism. Documentation of this hypothesis has been difficult [31–33]. Our findings of elevated plasma androgens emphasize, in addition, that a hormonal basis of acne is frequent. Such cases may be amenable to hormone therapy.

In conclusion, we have demonstrated that there are abnormalities of plasma androgens in a significant number of adult women with acne vulgaris. Our patients represent a selected population because of persistence or appearance of acne in the third and fourth decades. Most of our patients were young women in their twenties and thirties; we do not have information on plasma androgens in adolescents with acne. Although acne alone was the reason that most of the women entered this study, one-third of them had menstrual irregularities and one-third were hirsute. We would emphasize, however, that half of the acne patients who had normal menstrual histories had elevated plasma androgens, and that patients with acne alone (A) had an incidence of elevated androgens similar to those with acne plus hirsutism (A+H). Measurements of plasma free T (and other free androgens such as 17-β) as well as DS in women with late onset or persistent acne may identify endocrine abnormalities potentially amenable to hormonal treatment.

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