0021-972X/93/7606-1542$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 76, No. 6
Printed in U.S.A.

Differential Changes in Serum Concentrations of Androgens and Estrogens (in Relation with Cortisol) in Postmenopausal Women with Acute Illness*

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ABSTRACT

Previous studies of adrenal androgens and estrogens in critical illness were limited by measuring only selected sex steroids and by including men (who have confounding simultaneous changes in gonadal steroids). We evaluated relationships between changes in serum levels of cortisol (F), androgens, estrogens, and gonadotropins in 20 postmenopausal women with acute critical illness to determine if changes in adrenal androgens and estrogens paralleled gonadal axis suppression or adrenal stimulation.

Two patterns of changes in sex steroids were observed. Admission serum levels of androstenedione (Δ^4-A), estradiol, and estrone, like F, were increased compared to healthy controls ($P < 0.0001$). Δ^4-A and estrone then decreased toward normal by day 5 in parallel with cortisol ($r = 0.56$ and 0.60). In contrast, admission serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) were not elevated and testosterone (T) was decreased in our patients compared to controls ($P < 0.0005$) in parallel with serum gonadotropin levels. Serum levels of DHEA and T continued to decrease by day 5 in parallel with gonadotropins.

We conclude that in agonadal patients with acute critical illness, serum levels of DHEA-S and T are selectively decreased in relation to F, Δ^4-A, and estrogens. The decreased serum T levels suggest inhibition of 17β-OH-dehydrogenase and/or increased aromatization to estradiol. The marked increase in serum estrogen levels also suggests increased aromatization. The absence of increases in DHEA and DHEA-S suggest enhanced activity of 3β-hydroxysteroid dehydrogenase and/or inhibition of C17,20-lyase activity of P-450$_{c17}$. The clinical significance of this marked increase in the ratio of estrogens to androgens in acute illness requires further investigation. (*J Clin Endocrinol Metab* **76:** 1542–1547, 1993)

ALTHOUGH stress-induced adrenal activation was described more than 50 yr ago (1), the differential effects of stress on adrenal steroid pathways remain controversial. Increased serum estrogen and decreased testosterone (T) levels in critically ill men (2, 3) suggest generalized activation of adrenal pathways (producing increased estrogen precursors) with simultaneous gonadal suppression (2). In contrast, hyperreninemic hypoaldosteronism (4–6) and decreased or unchanged serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) levels (7–11) in severely ill patients suggest selective enhancement of cortisol (F) secretion during acute illness (7, 8). Further confusing this picture are reports of serum androstenedione (Δ^4-A) as unchanged (2, 9), increased (10, 11), or decreased (12) during critical illness. Thus, the composite pattern of changes in adrenal androgens and their estrogen derivatives in critical illness in relation to cortisol is not well defined. At least two factors may contribute to this conflicting data: 1) Serum concentrations of adrenal androgens (including T), estrogens, and F have not been evaluated simultaneously within a single study (2–12), and 2) studies have been conducted in men (7, 11, 12), or mixed populations of men and women (8–10), in whom simultaneous changes in serum levels of gonadal steroids confound evaluation.

We studied serum levels of adrenal androgens and their peripheral androgen and estrogen derivatives to determine if androgen levels decreased in parallel with reproductive axis suppression in acute illness whereas estrogen levels rose in parallel with activation of cortisol secretion. Postmenopausal women were studied to minimize interference from changes in gonadal steroids (13). Serum gonadotropin levels in these women reflect gonadal axis suppression even in the absence of gonadal function (14, 15).

Subjects and Methods

Patient population

Over a 17-month period (1/16/87–11/15/87 and 9/19/88–4/7/89) all postmenopausal women (age > 55 yr) admitted to the Special Care Units and Cardiac Intensive Care Units of Maine Medical Center were screened for entry into the study. Forty patients qualified for the study by not having the following factors known to affect the adrenal or reproductive axes independently from acute illness: 1) surgery during the first 5 days of hospitalization; 2) known intracranial disease or head trauma; 3) renal or hepatic failure (reflected by elevated serum concentrations of creatinine, bilirubin, aspartate aminotransferase, or alkaline phosphatase); 4) history of ethanol/drug abuse or calorie deprivation; 5) use of steroid hormone medications during the 2 months before admission or during the first 5 days of hospitalization; and 6) known hypothalamic-pituitary, thyroid, or adrenal disorders. Of these 40

Received August 3, 1992.
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* Presented in part at the AFCR National Meeting, Washington, DC, 1990.

women, 20 had sufficient serum sample volume on admission and on day 5 of hospitalization for multiple hormone measurements. This study was approved by the Institutional Review Board of Maine Medical Center.

The 20 study patients were aged 59–80 yr (mean 70.7 ± 1.6 SE). All patients were admitted with acute onset of disease, or acute exacerbation or complication of chronic disease. Diagnoses were based on data available at discharge and included acute myocardial infarction (n = 11), unstable angina (n = 2), respiratory illnesses (n = 3), congestive heart failure (n = 2), peripheral ischemia (n = 1), and sepsis (n = 1). Seven of these women had previously undergone bilateral oophorectomy. Sixteen of 20 patients survived hospitalization with a mean length of stay of 15.3 ± 2.0 days.

All day 5 samples were obtained between 0600 and 0900 h. Because critically ill patients do not have a diurnal variation of F (16), admission serum sampling was not limited to the early morning. To confirm the lack of diurnal variation of F, F was measured on paired morning (0430–0850 h) and evening (1620–2345 h) serum samples from 21 other critically ill patients not receiving glucocorticoids. The mean AM cortisol level (809.1 ± 143.5 nmol/L) was not different from the mean PM level (786.1 ± 99.3 nmol/L).

Normal subjects

One hundred and ten healthy postmenopausal women aged 56–78 yr served as a pool of controls for determination of serum hormone concentrations. Inclusion criteria were: 1) good general health; 2) no history of endocrine disorders or use of hormone medications within 3 months before blood sampling; 3) no weight change of greater than 10 pounds within the year before blood sampling; 4) no hospitalization within 1 yr or illness within 1 month of sampling; and 5) no history of depression or other psychiatric illness. Serum F levels were obtained between 0600 and 0900 h. The time of the day of other blood sampling was varied.

Protocol

Serum samples routinely obtained in these women at admission and on day 5 of hospitalization were immediately refrigerated, then transferred to storage at −15 C pending assay. Days 1 and 5 were selected to permit evaluation of changes in serum levels of these hormones as adrenal axis activation decreased during recovery. Hormones selected for monitoring are indicated in Fig. 1. Serum levels of F, DHEA-S, Δ^4-A, E_1, and E_2 were determined on both samples in 14 women and T in 10 women. Sufficient serum volume was available for determination of DHEA concentrations in both samples in 7 of these 14 women. Therefore, F and DHEA concentrations were determined in samples from days 1 and 5 in 6 additional women.

Statistics

Mean hormone values in patients at admission and day 5 were compared by Student's *t* test to mean values in healthy control subjects. In patients, correlations were evaluated between serum F and sex hormones on days 1 and 5. Finally, the differences between hormone values on days 1 and 5 (Δ) were calculated (day 5 − day 1). Correlations between changes (Δ) in F and sex hormones were then analyzed. All correlations were determined by linear regression analysis. *P* values of <0.05 were considered significant.

Assays

Serum LH and FSH concentrations were determined by double antibody RIAs as previously reported (17). Detection limits for LH and FSH were 0.8 U/L. Intra- and interassay coefficients of variation for both assays were less than 10%. Serum concentrations of T, Δ^4-A, DHEA, E_1, and E_2 were determined by RIA after extraction with cyclohexane and ethyl acetate, and purification over a celite column as previously described (18, 19). Serum DHEA-S concentrations were determined by a kit RIA assay (RSL I^{125}-double antibody). All samples from a given patient were analyzed in duplicate in a single assay.

Results

F and gonadotropins

Figure 2 demonstrates that serum F levels in our patients on admission and day 5 of hospitalization were higher than in healthy controls ($P < 0.001$). In contrast, serum gonadotropin levels were lower in patients than in healthy controls. Mean FSH was lower in patients than in controls, both at admission (day 1) and on day 5 ($P < 0.001$; Fig. 2). Similarly, mean LH on day 1 (34.1 IU/L ± 5.9 SE) and day 5 (24.6 ± 5.3 IU/L) were both lower than the mean control value (73.3 ± 6.5 IU/L; $P < 0.001$). Although serum F levels on day 5 suggested a trend toward control values with recovery ($P =$

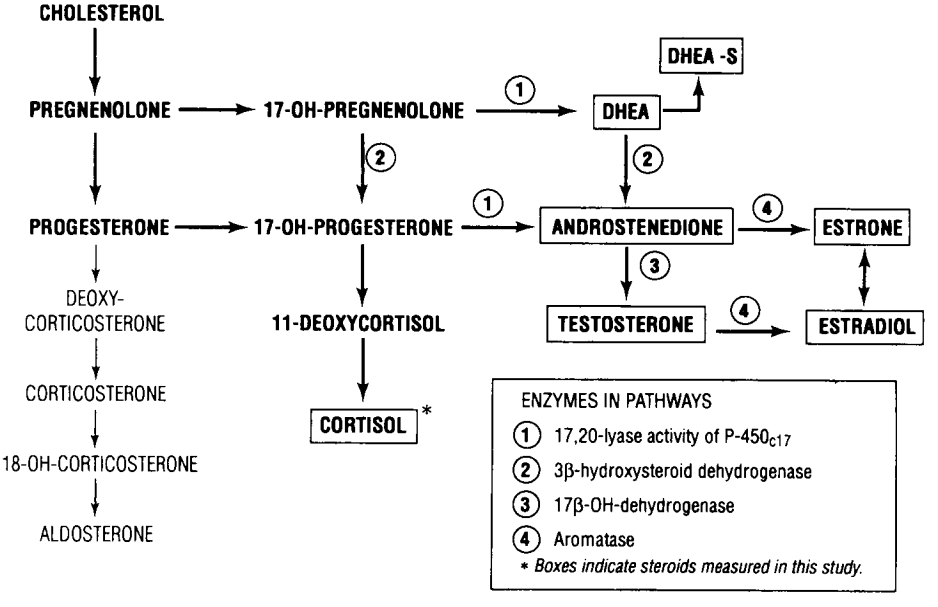

FIG. 1. Pathways of adrenal steroidogenesis. Enzymes relevant to this study are indicated. Conversions of Δ^4-A to T and E_1 and of T to E_2 occur chiefly in peripheral tissues.

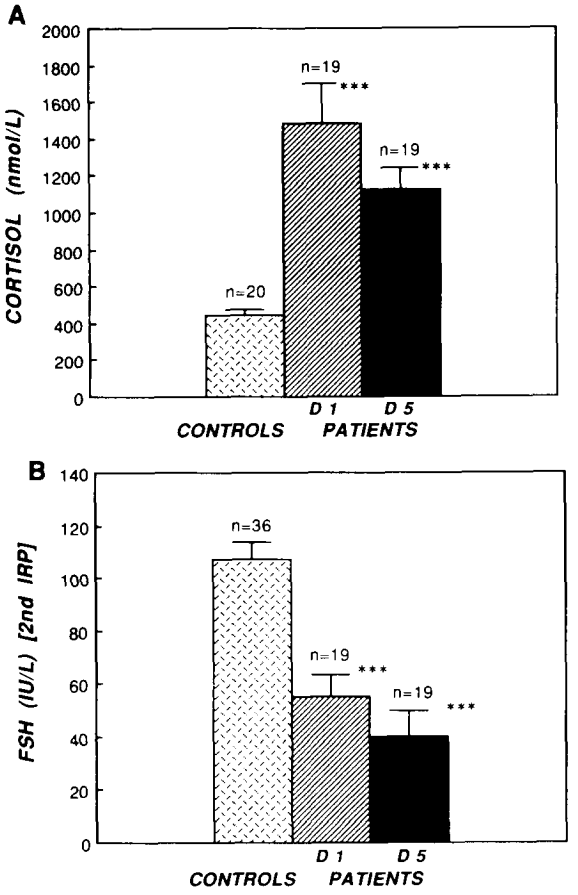

FIG. 2. Mean (±SE) serum concentrations of F and FSH in healthy control subjects and in postmenopausal patients at admission (D1) and on day 5 (D5) of hospitalization. ***, $P < 0.001$ *vs.* control.

0.16), serum gonadotropin levels suggested a trend toward further suppression below control values ($P = 0.05$ for both LH and FSH) (Fig. 2).

Estrogens and Δ^4-A

Similar to serum F but not to gonadotropin values, serum levels of E_1, E_2, and Δ^4-A were elevated above control values on both days 1 and 5 of hospitalization (Fig. 3). Mean patient serum E_1 at admission (281.9 ± 52.9 pmol/L) was 168% higher than the mean control E_1 (105.1 ± 7.4 pmol/L) with individual levels as high as 691.7 pmol/L (187.0 pg/mL). Mean patient serum E_2 (121.9 ± 10.3 pmol/L) demonstrated a lesser elevation of 105% over the mean control E_2 (59.5 ± 6.2 pmol/L) with individual levels as high as 201.9 pmol/L (55.0 pg/mL). Thus, the predominant increase in serum estrogen concentrations occurred with E_1. Also similar to the trend suggested by F levels, serum concentrations of E_1 ($P = 0.28$) and Δ^4-A ($P < 0.05$) returned towards control levels with recovery (Fig. 3).

T, DHEA, and DHEA-S

Similar to serum gonadotropin levels (but not to cortisol, estrogens, or Δ^4-A levels), serum T levels in patients were lower than control values on admission and tended (but not

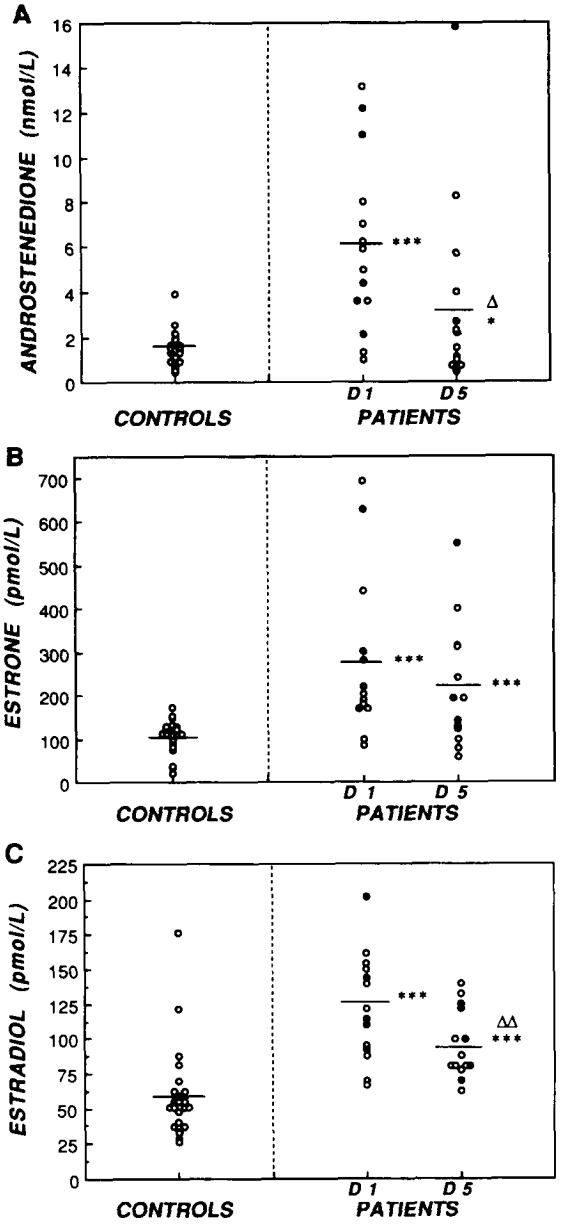

FIG. 3. Serum concentrations of Δ^4-A (A), E_1 (B), and E_2 (C) in healthy control subjects and in postmenopausal patients at admission (D1) and on day 5 (D5) of hospitalization. *Solid circles* indicate women with previous bilateral oophorectomy. *, $P < 0.05$ *vs.* control; ***, $P < 0.001$ *vs.* control; Δ, $P < 0.05$ *vs.* day 1; Δ $P < 0.01$ *vs.* D1.

significantly) to fall further during early recovery (Fig. 4). Serum levels of DHEA and DHEA-S were not different than control values at admission (Fig. 4). However, DHEA (with a shorter half-life than DHEA-S) demonstrated a decline below control values by day 5 (Fig. 4).

Correlations between changes in F and androgens or estrogens

Table 1 lists the correlation coefficients (r values) for serum levels of F and of sex steroids at admission or on day 5 of hospitalization. R values for changes (Δ) in serum levels of F and of sex steroids from admission to day 5 of hospitalization

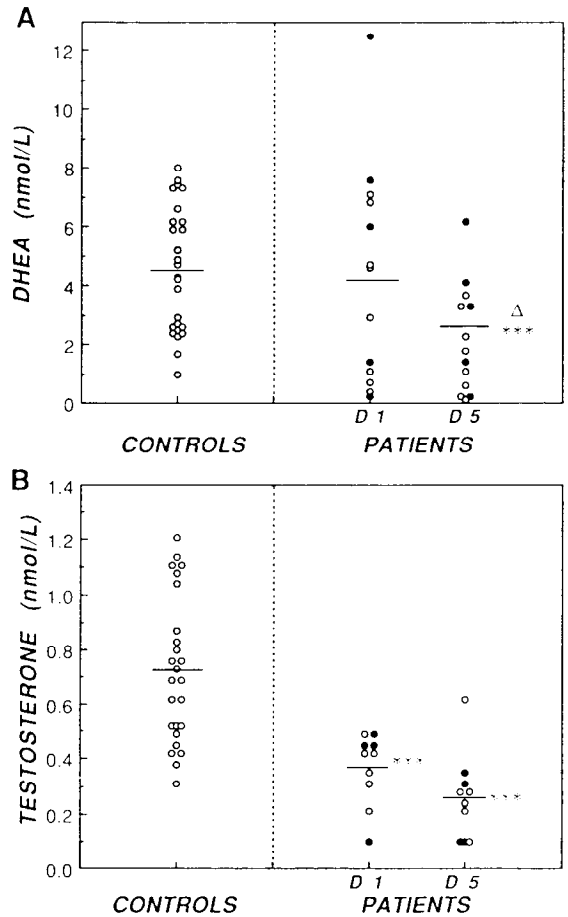

FIG. 4. Serum concentrations of DHEA (A) and T (B) in healthy control subjects and in postmenopausal patients at admission (D1) and on day 5 (D5) of hospitalization. *Solid circles* indicate women with previous bilateral oophorectomy. Mean DHEA-S values are listed in Table 1. ***, $P < 0.001$ *vs.* control; Δ, $P < 0.05$ *vs.* day 1.

TABLE 1. Correlation coefficients (r values) between serum levels of F and sex steroids

	E_1	E_2	Δ^4-A	DHEA	DHEA-S	T
Admission F	0.55	0.50	0.53	0.45	0.05	0.20
Day 5	0.83[a]	−0.02	0.71[b]	0.25	0.63[c]	0.38
1Δ(D1–D5) for F[d]	0.60[c]	0.28	0.56[c]	0.46	0.17	0.47

[a] $P < 0.001$ for correlation with F.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] Δ(D1–D5), Change in hormone values between admisson and day 5 of hospitalization.

are also listed. Correlations between F and Δ^4-A or E_1 were evident, but not between F and other sex steroids. The mean of r values for F and Δ^4-A or E_1 (0.63 ± 0.05 for all pairs of values) was significantly greater than the mean of r values for F and DHEA, DHEA-S or T (0.34 ± 0.06; $P < 0.005$), or for F and DHEA, DHEA-S, T or E_2 ((0.32 ± 0.06; $P < 0.005$). Figure 5A illustrates the strong correlations between changes in F and Δ^4-A from admission to day 5 of hospitalization. Changes in Δ^4-A and E_1 were also highly correlated (Fig. 5B). These results suggest that serum levels of F, Δ^4-A, and E_1 during critical illness are controlled in a coordinated fashion.

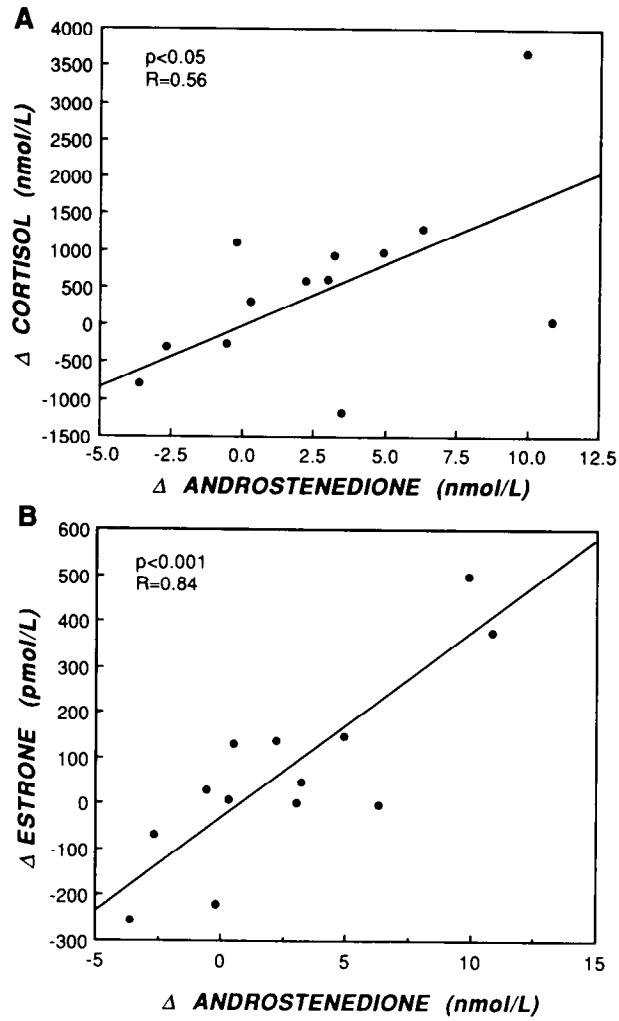

FIG. 5. Correlation between changes (Δ) in F and Δ^4-A (*upper panel*) and between Δ^4-A and E_1 (*lower panel*) between admission and day 5 of hospitalization.

Discussion

We evaluated serum concentrations of sex steroids in critically ill postmenopausal women in whom changes could be attributed to altered adrenal secretion or peripheral metabolism rather than altered gonadal function. Changes in sex steroids followed two general patterns. Serum levels of E_1 and E_2 and their precursor Δ^4-A rose in parallel with increased adrenal glucocorticoid output. In contrast, serum DHEA and DHEA-S levels were not elevated at admission, and serum levels of T, a more potent androgen, were decreased in parallel with serum gonadotropins. This dichotomy is further emphasized by differences in the temporal patterns of these changes. F, estrogens, and Δ^4-A were elevated at admission and fell toward control values as patients recovered. However, T and the gonadotropins (which were already decreased below control values at admission) tended to fall further below control values as the patients' recoveries began. Similarly, serum DHEA levels in patients fell below control levels as recovery occurred.

Previous studies of adrenal androgens and estrogens in

critical illness have yielded apparently conflicting data (2, 3, 7–11). These studies have all been conducted in men or mixed populations of men and women in whom simultaneous confounding changes in gonadal steroids occur. On one hand, decreased serum levels of DHEA and DHEA-S in critically ill men with increased serum F levels have suggested that adrenal androgen secretion is selectively suppressed in critical illness (7, 8). Serum Δ^4-A, T, and estrogen levels were not reported in these studies. On the other hand, increased serum E_1 and E_2 levels in men (2, 3) have suggested a generalized increased secretion of adrenal androgen precursors (2). However, Δ^4-A levels were not elevated and DHEA was not measured in these studies (2, 3). Additional studies confirmed a decrease in serum DHEA-S in critically ill men, but reported increased levels of Δ^4-A (10, 11). Because different studies measured different combinations of steroids in different patient populations, it is difficult to derive from these reports a composite picture of changes in adrenal androgens and their estrogen derivatives in relation to F in acute critical illness. Furthermore, because men with functioning testes were studied, changes in adrenal Δ^4-A were difficult to isolate from changes in gonadal Δ^4-A and data regarding T were not reported.

Our data suggest that both hypotheses advanced by previous reports are, in part, correct. The adrenal gland is generally stimulated to the extent that secretion of both F and one adrenal androgen (Δ^4-A) increase with accompanying increases in estrogens. However, the increase in serum Δ^4-A is not accompanied by increases in serum DHEA, DHEA-S, and T. Thus, secretion of some, but not all, adrenal androgens appear to be suppressed in acute critical illness. These changes occur rapidly with the onset of illness and are already evident at admission.

This pattern of contrasting sex steroid changes cannot be explained solely by enhanced ACTH stimulation, which produces simultaneous increases in F, DHEA, and Δ^4-A (20). ACTH probably does have a role in general androgen stimulation in critical illness. Higher serum levels of both DHEA and Δ^4-A are higher in patients with more severe illness and higher F levels compared to those with less severe illness (10). An additional factor increasing serum estrogen levels in illness may be increased aromatization as suggested by a previous study in women after (21). F enhancement of aromatization has been suggested by *in vitro* studies (22, 23), but not confirmed by *in vivo* studies (24, 25). However, neither ACTH stimulation nor increased aromatization can account for the differential changes in serum levels of DHEA, Δ^4-A, and T. Decreased serum T levels may be explained by decreased 17β-OH-dehydrogenase activity and/or increased aromatization. Our observation that E_1 increases to a greater degree than E_2 suggests that decreased 17β-OH-dehydrogenase activity rather than increased aromatization is the principle cause for the decline in serum T levels.

The contrast between changes in DHEA and Δ^4-A, which is not observed with ACTH administration alone, is more difficult to explain. A selective increase in 3β-hydroxysteroid dehydrogenase (converting DHEA to Δ^4-A) may account for this pattern of changes. 17-OH-pregnenolone levels have not been monitored in our study or other studies of critically ill patients to test this hypothesis. Alternatively, altered C17,20-lyase activity may be proposed. However, decreased production of DHEA secondary to decreased C17,20-lyase activity of P-450_{c17} would also be expected to produce decreased serum Δ^4-A levels. To support this hypothesis, different effects of the same enzyme in two pathways must be invoked (as occurs with decreased P-450_{c21} activity in the cortisol but not the aldosterone pathway in simple virilizing congenital adrenal hyperplasia) (26).

Other aspects of peripheral metabolism are unlikely to explain contrasting changes serum levels of sex steroids. Differential changes in clearance rates of DHEA and T *vs.* Δ^4-A, E_1, and E_2 are unlikely since similar pathways are shared by these hormones. Changes in hepatic function can also contribute to changing serum levels of sex steroids (27). In rats, hepatic vein ligation is accompanied by increased serum estrogen levels and decreased T levels (28). However, these observations are unlikely to extend to our patients who had no evidence of hepatic failure.

These data and previous studies suggest the following factors as a potential explanation for the pattern of changes we observed in adrenal androgens and their estrogen derivatives: 1) Increased ACTH stimulation of all adrenal steroid pathways; 2) Increased activity of 3β-hydroxysteroid dehydrogenase producing increased Δ^4-A and F levels and decreased DHEA levels (or, less likely, suppression of C17,20-lyase activity in the DHEA but not the Δ^4-A pathway); 3) Decreased 17β-OH-dehydrogenase activity producing decreased serum T levels. 4) Increased aromatization and increased availability of Δ^4-A producing increased serum concentrations of E_1 and, to a lesser degree, E_2. Although the pathophysiological mechanisms of these changes have not yet been defined, cytokines must be considered as possible mediators. Cytokines activate the adrenal axis through stimulation of CRH and ACTH secretion (29, 30) and, probably, through direct stimulation of glucocorticoid secretion (31). However, the effects on adrenal androgen secretion have not been reported. Data regarding cytokine effects on peripheral aromatase activity is also scarce. However, interleukens appear to enhance aromatase activity in breast tissue (32). These preliminary data suggest that cytokines may have an important role in patterns of adrenal reaction to illness.

Dissociations between F and adrenal androgen secretion, and/or between DHEA and Δ^4-A secretion, have also been reported in adrenarche (33, 34), exogenous glucocorticoid suppression (35), secondary hypoadrenalism (35), and anorexia nervosa (36). In adrenarche, increases in serum DHEA and DHEA-S are much more pronounced than increases in serum Δ^4-A levels (33, 34). Most studies report no increase in serum T during adrenarche (33, 34). Since some increase in Δ^4-A will result from increased availability of its precursor, DHEA, the predominant change in adrenal steroids at adrenarche appears to be increased production of DHEA. Our data demonstrates that in acute illness, inhibition of adrenal sex steroid secretion also preferentially affects DHEA (with a simultaneous effect on peripheral production and/or conversion of T). Thus, acute illness appears to reverse this adren-

archal change in adrenal androgen secretion. Mechanisms underlying the changes in adrenal androgen secretion in adrenarche have also not been defined. In addition, decreased adrenal and/or peripheral production of T in acute illness appears to complement pituitary-gonadal suppression occurring in acute illness (37) (which suggests regression of the increased androgen secretion of gonadarche).

The clinical significance of these differential changes of androgens and estrogens in critical illness is not yet defined. Whether these changes also occur with less severe illness is not yet known. Identification of clinical significance from this acute shift to a high estrogen to T ratio at the onset of illness requires further study.

Acknowledgments

We wish to thank Drs. Allan Pont and Douglas Thompson for their advice, Charlene Franz and Karen Goodale for precise technical work, Judy Barrington for artwork, and Gail O'Donnell for secretarial assistance.

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