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Decreased adrenal sex steroid levels in the absence of glucocorticoid suppression in postmenopausal asthmatic women

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Background and aim: Reduction of serum sex steroid levels has been reported to occur after the administration of β -adrenergic medication. In that β -adrenergic blockade is a central pathophysiologic feature of asthma, this study was done to explore the possibility of hormonal alteration in asthma.

Methods: Sex steroids obtained from 22 postmenopausal asthmatic and 22 age-matched, postmenopausal, nonasthmatic women were assayed. No subject had received estrogens, progestins, or oral corticosteroids for 120 days before the study.

Results: Mean dehydroepiandrosterone sulfate (DHEAS; $p < 0.002$), dehydroepiandrosterone (DHEA; $p < 0.03$), estradiol ($p < 0.02$), and estrone ($p < 0.02$) levels were lower in asthmatic patients compared with nonasthmatic subjects. Results could not be accounted for by current medication. Patients with asthma demonstrated no decrease in 17-hydroxyprogesterone or cortisol compared with nonasthmatic subjects, limiting findings to the Δ^5 , and not the Δ^4 , steroidogenic pathway. In a second phase of the study, DHEAS was measured before and after 3 days of oral β -agonist stimulation in eight postmenopausal asthmatic women. Serum DHEAS concentration increased in eight of eight subjects, from a mean of 28.6 ± 19.9 $\mu\text{g/dl}$ (mean $\pm$ SD) to 40.7 ± 24.8 $\mu\text{g/dl}$ ($p = 0.002$). Serum cortisol concentration was unchanged.

Conclusion: The results indicate that postmenopausal asthmatic women have lower serum levels of adrenally derived sex steroids than their nonasthmatic peers and that this anomaly may be ameliorated by adrenergic stimulation. (*J ALLERGY CLIN IMMUNOL* 1996;97:1-8.)

Key words: Asthma, DHEAS, estrogen, sex steroids, adrenergic blockade

Decreased sex steroid levels have been reported in subjects taking β -adrenergic blocking medication.¹⁻⁴ This study was undertaken to explore the

possibility of hormonal alteration in patients with asthma, in whom β -adrenergic responsiveness is blunted.⁵

Dunn et al.⁶ have reported a decrease in dehydroepiandrosterone sulfate (DHEAS) levels in 40% of patients hospitalized for treatment of asthma. Although DHEAS was initially studied as

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Abbreviations used

CV:	Coefficient of variation
DHEA:	Dehydroepiandrosterone
DHEAS:	Dehydroepiandrosterone sulfate
IL:	Interleukin
RIA:	Radioimmunoassay

a parameter of therapeutically induced adrenocortical suppression, many subjects lacked a history of corticosteroid use. In a later study, 44% of asthmatic patients with low DHEAS levels were found to have normal cortisol increments after ACTH stimulation, reflecting differing control mechanisms for cortisol and DHEAS.⁷ Similarly, Feher et al.⁸ reported low serum levels and low urinary excretion of dehydroepiandrosterone (DHEA) and DHEAS in female patients with nonsteroid-dependent asthma.

In the first phase of the study, serum sex steroids obtained from postmenopausal asthmatic and nonasthmatic women were assayed and compared. In the second phase of this study, the effect of β -adrenergic stimulation on sex steroid levels in postmenopausal asthmatic women was assessed.

METHODS

In the initial phase of the study, subjects were 22 postmenopausal asthmatic women and 22 postmenopausal nonasthmatic women. History of cough, episodic shortness of breath, wheezing, excess bronchial mucus production, and documented improvement in peak expiratory flow rate or forced expiratory volume in 1 second of greater than 20% after the use of a bronchodilator constituted criteria for asthma. Nonasthmatic subjects denied history of chronic or recurrent cough, shortness of breath, excess sputum production, or wheezing. No subject was receiving or had received estrogen, progestins, or corticosteroids within 120 days before the study. Blood was drawn between the hours of 8:00 and 10:00 AM and immediately frozen.

In the second phase of the study, eight postmenopausal women known to have low sex steroid levels, were selected. No subject had received oral or subcutaneous β -agonist medication, estrogen, progestins, or corticosteroids within 120 days before the study. History of hypertension, cardiovascular disease, or adverse effects related to adrenergic medications were criteria for exclusion from this phase of the study. Subjects were instructed to maintain their current medication regimen during the study period, with the exception of inhaled adrenergic agents, which were to be used as needed, rather than regularly. Blood was drawn for DHEAS and cortisol assays between the hours of 8:00 and 10:00 AM on the day before and on the morning after the last

dose of oral, sustained-release albuterol (4.0 mg two times a day for 3 days) was administered and was immediately frozen. All study protocols were reviewed by the Providence Hospital Institutional Review Board, and all subjects entered the study after giving informed consent.

DHEA-SO₄, 17-hydroxyprogesterone, total testosterone, and cortisol levels were measured with solid-phase iodine 125 radioimmunoassay (RIA) kits (Diagnostic Products Corporation, Los Angeles, Calif.). The DHEA-SO₄ RIA was reported to have a 0.56% cross-reactivity with estrone-SO₄ and 0.30% cross-reactivity with androstosterone-SO₄. The 17-hydroxyprogesterone RIA was reported to have a 3.5% cross-reactivity with progesterone and 1.5% cross-reactivity with 11-deoxycortisol. The testosterone RIA was reported to have a 3.3% cross-reactivity with dehydrotestosterone and 0.5% cross-reactivity with androstenedione. Minimal detectable levels were 5.0 μ g/dl for DHEAS, 0.1 ng/ml for 17-OH progesterone, 0.1 ng/ml for testosterone, and 0.5 μ g/dl for cortisol.

Estradiol was measured with a double-antibody assay from Diagnostic Products Corporation. The estradiol RIA was reported to have a 12.5% cross-reactivity with estrone and a 0.235% cross-reactivity with estriol. The lowest detectable level for estradiol was 2.5 pg/ml.

Estrone was measured with a double-antibody RIA from Pantex (Santa Monica, Calif.), with standards of 1.25 to 640 pg/ml. All measured levels were above the lowest standard. Estrone was reported to have a 0.28% cross-reactivity with estradiol and 0.0068% cross-reactivity with estriol.

DHEA was measured with a double-antibody RIA from Diagnostic Systems Laboratories (Webster, Texas). DHEA was reported to have a 0.020% cross-reactivity with DHEAS and less than 1% cross-reactivity with other sex steroids. The lowest detectable level for DHEA was 0.10 ng/ml.

All samples were run in duplicate and in one assay for each hormone analyzed. Samples before and after β -agonist stimulation were run in a single assay. The coefficient of variation (CV) between duplicate samples was less than 5%. Diagnostic Products CON6 Immunoassay Tri-level Control levels 4, 5, and 6 were run with each assay. Their values were within 2 standard deviations of the expected means. The 0 standard was interspersed within each assay in order to determine the intraassay CV ($CV = SD \div \text{mean}$). Intraassay CVs were: 1.9% for DHEA-SO₄, 4.5% for 17-OH progesterone, 1.6% for total testosterone, 1.4% for estradiol, 3.7% for estrone, 3.1% for DHEA, and 2.8% for cortisol.

Results are expressed as means $\pm$ SD, unless otherwise noted. Data were analyzed by Student's *t* test, and in the second phase of the study, by paired *t* test. Estradiol levels below the lowest detectable value of 2.5 pg/ml were estimated to be 2.5 pg/ml for purposes of statistical assessment. Correlation between measured sex steroid levels and each subject's age was performed by regression analysis.

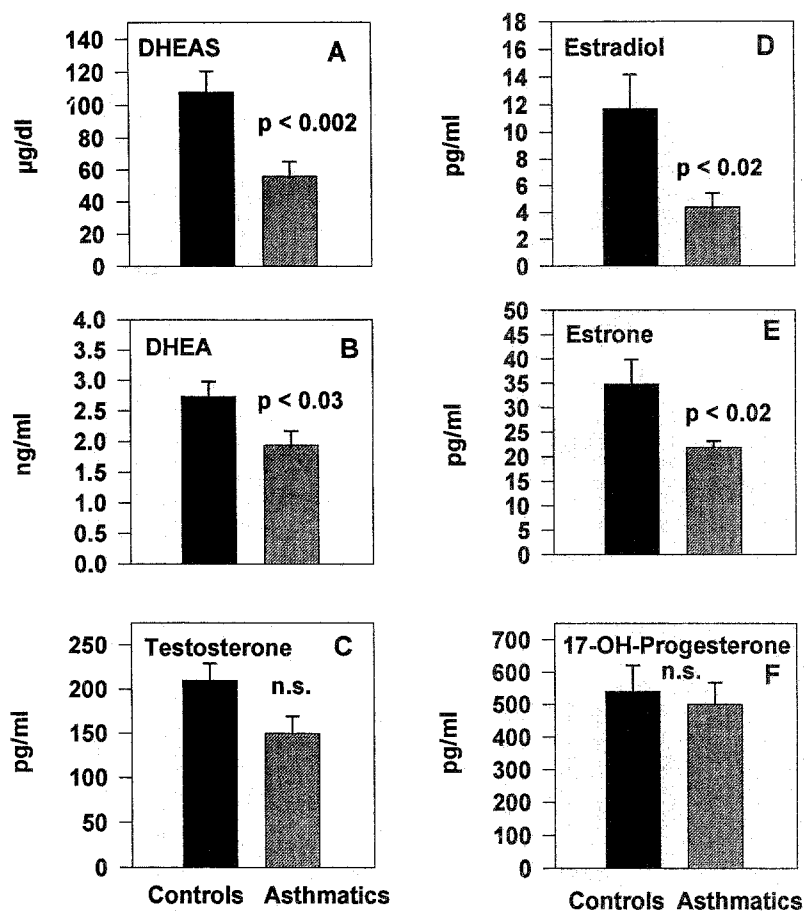


FIG. 1. Serum sex steroid concentration in 22 postmenopausal asthmatic women and 22 postmenopausal nonasthmatic women (mean $\pm$ SEM). *n.s.*, Not significant.

TABLE I. Sex steroid levels in 22 asthmatic and 22 nonasthmatic postmenopausal women

	Subjects		<i>t</i>	<i>p</i> Value
	Asthmatic	Nonasthmatic		
DHEAS (μ g/dl)	56.1 $\pm$ 43.0	108.0 $\pm$ 59.2	3.33	<0.002
DHEA (ng/dl)	1.93 $\pm$ 1.01	2.69 $\pm$ 1.16	2.31	<0.03
17 Hydroxyprogesterone (ng/ml)	0.50 $\pm$ 0.32	0.54 $\pm$ 0.38	0.38	NS
Testosterone (ng/ml)	0.16 $\pm$ 0.08	0.21 $\pm$ 0.09	1.95	NS
Estradiol* (pg/ml)	4.4 $\pm$ 3.2	11.7 $\pm$ 12.7	2.62	<0.02
Estrone (pg/ml)	21.54 $\pm$ 6.45	34.8 $\pm$ 22.8	2.63	<0.02

Values are expressed as means $\pm$ SD.

NS, Not significant.

*Calculated by estimating nondetectable values as 2.5 pg/ml (lower level of detectability).

RESULTS

Age

The mean age of 22 asthmatic subjects was 67.8 ± 7.7 years, and the mean age of 22 nonasthmatic control subjects was 64.5 ± 8.2 years ($p = 0.17$). No correlations between age and any of the measured sex steroid levels were found by regression analysis, in the entire study group, in patients with asthma, or in nonasthmatic subjects.

Sex steroid levels

Subjects' sex steroid data are presented in Table I and Figs. 1 and 2. Mean DHEAS levels were 56.1 ± 43.0 μ g/dl in asthmatic subjects and 108.0 ± 59.2 μ g/dl in nonasthmatic subjects ($p < 0.002$). Mean DHEA levels were 1.93 ± 1.01 ng/ml in asthmatic subjects and 2.69 ± 1.16 ng/ml in nonasthmatic subjects ($p < 0.03$). Mean estradiol levels were 4.48 ± 3.2 pg/ml in asthmatic subjects and $11.7 \pm$

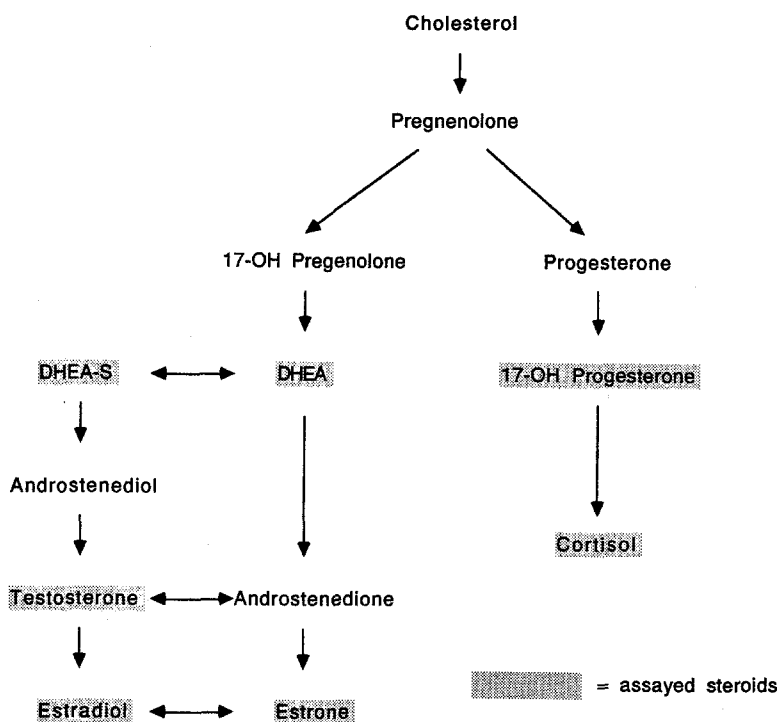


FIG. 2. General scheme of steroid synthesis indicating position of assayed steroids.

12.7 pg/ml in nonasthmatic subjects ($p < 0.02$). Mean estrone levels were 21.54 ± 6.54 pg/ml in asthmatic subjects and 34.8 ± 22.8 pg/ml in nonasthmatic subjects ($p < 0.02$). Mean testosterone levels were 0.16 ± 0.08 ng/ml in asthmatic subjects and 0.21 ± 0.09 ng/ml in nonasthmatic subjects ($t = 1.95$, $p = 0.06$, approaching but not reaching significance). Mean 17-hydroxyprogesterone levels were 0.50 ± 0.32 ng/ml in asthmatic subjects and 0.54 ± 0.38 ng/ml in nonasthmatic subjects ($p = \text{NS}$).

Cortisol assay

Mean serum cortisol concentrations were 15.01 ± 4.32 $\mu\text{g/dl}$ in asthmatic subjects and 17.40 ± 5.06 $\mu\text{g/dl}$ in nonasthmatic subjects ($p = \text{NS}$).

Effect of medications on sex steroid levels

Eighteen of 22 asthmatic subjects required medication (consisting of theophylline, inhaled β -agonist, and/or inhaled corticosteroid) at the time of study (Table II). DHEAS levels were significantly decreased in asthmatic subjects, regardless of whether they were using any single therapeutic agent, compared with nonasthmatic subjects. Mean DHEAS concentration was 54.4 ± 46.3 $\mu\text{g/dl}$ in 11 patients with asthma who were using all three medications, which was significantly de-

creased compared with nonasthmatic subjects and similar to the mean concentration of 55.0 ± 61.1 $\mu\text{g/dl}$ found in the small group of four subjects who were using no medication. 17-Hydroxyprogesterone levels were similar in all groups: asthmatic, nonasthmatic, and asthmatic receiving medication, and asthmatic not receiving medication. Estradiol, estrone, DHEA, and testosterone levels were significantly lower in asthmatic patients receiving medication, comprising larger groups, compared with nonasthmatic subjects. Statistical differences in sex hormones other than DHEAS were not found when smaller groups of patients with asthma not receiving medication were compared with nonasthmatic subjects. Testosterone and estradiol concentrations were numerically, but not statistically, higher; and estrone values were numerically similar when patients with asthma not taking medication were compared with those taking an individual medication or all three medications.

Response to adrenergic agonist treatment

Mean age of eight asthmatic women studied was 65.1 ± 9.9 years. Levels of serum DHEAS increased in eight of eight subjects after 3 days of oral albuterol administration (Table III). Mean DHEAS concentration was 28.58 ± 19.86 $\mu\text{g/dl}$ before and 40.68 ± 24.83 $\mu\text{g/dl}$ after oral albuterol administration ($p = 0.002$). Mean cortisol concen-

TABLE II. Effect of medication on serum sex steroid concentration in 22 postmenopausal asthmatic women

Asthma	Medication	No. of subjects	DHEAS (μg/dl)	DHEA (ng/ml)	17-Hydroxyprogesterone (ng/ml)	Testosterone (ng/ml)	Estradiol (pg/ml)	Estrone (pg/ml)
No		22	108.0 ± 59.2	2.69 ± 1.16	0.54 ± 0.38	0.21 ± 0.09	11.7 ± 12.7	34.8 ± 22.8
Yes	Theophylline	15	60.1 ± 43.1	1.96 ± 1.16	0.52 ± 0.38	0.14 ± 0.07	4.2 ± 2.1	20.8 ± 7.1
			<i>p</i> < 0.015			<i>p</i> < 0.02	<i>p</i> < 0.05	<i>p</i> < 0.05
Yes	No theophylline	7	47.4 ± 44.8	1.88 ± 0.64	0.47 ± 0.13	0.21 ± 0.09	4.2 ± 5.3	23.1 ± 5.0
			<i>p</i> = 0.02					
Yes	Inhaled β-agonist	16	56.4 ± 42.2	1.94 ± 1.12	0.50 ± 0.35	0.15 ± 0.07	4.0 ± 2.0	21.6 ± 6.5
			<i>p</i> < 0.01	<i>p</i> < 0.05		<i>p</i> < 0.03	<i>p</i> < 0.05	<i>p</i> < 0.05
Yes	No β-agonist	6	55.4 ± 49.2	1.95 ± 0.70	0.52 ± 0.25	0.19 ± 0.11	5.6 ± 5.8	21.4 ± 6.8
			<i>p</i> = 0.05					
Yes	Inhaled corticosteroid	13	51.7 ± 43.0	1.73 ± 0.83	0.51 ± 0.38	0.15 ± 0.07	3.7 ± 1.6	20.6 ± 6.2
			<i>p</i> < 0.002	<i>p</i> < 0.02		<i>p</i> < 0.03	<i>p</i> < 0.05	<i>p</i> < 0.05
Yes	No inhaled corticosteroid	9	62.4 ± 44.7	2.23 ± 1.20	0.49 ± 0.20	0.19 ± 0.09	5.5 ± 4.7	22.9 ± 6.9
			<i>p</i> < 0.05					
Yes	All medications*	11	54.4 ± 46.3	1.75 ± 0.91	0.52 ± 0.42	0.15 ± 0.08	3.2 ± 2.3	20.2 ± 6.7
			<i>p</i> < 0.015	<i>p</i> < 0.05		<i>p</i> = 0.05	<i>p</i> < 0.05	<i>p</i> < 0.05
Yes	No medication	4	55.0 ± 61.1	2.14 ± 0.75	0.48 ± 0.18	0.24 ± 0.10	5.8 ± 6.7	24.6 ± 6.0

All values are expressed as means ± SD, and *p* values are versus nonasthmatic subjects.

*Theophylline, inhaled β-agonist, and inhaled corticosteroid.

tration was 15.0 ± 5.0 μg/dl before and 15.39 ± 4.65 μg/dl after oral albuterol administration (*p* = NS).

DISCUSSION

This investigation followed a pilot study in which we assayed serum DHEAS, estradiol, and 17-OH progesterone obtained from 31 asthmatic women, both premenopausal and postmenopausal, and compared their values with those of 28 female nonasthmatic control subjects. DHEAS was found to be significantly lower, estradiol frequently undetectable, and 17-OH progesterone values similar, in postmenopausal asthmatic women compared with postmenopausal nonasthmatic women (Weinstein et al. Unpublished data). Hormonal differences between premenopausal asthmatic and nonasthmatic women were not as clearly dissimilar as differences in postmenopausal women in our pilot study, possibly because of wider age range, cyclic variations in hormonal levels, or ovarian hormonal contribution in premenopausal subjects, the latter being diminished in menopause.^{9,10} A postmenopausal cohort was therefore chosen for this study, both in an attempt to substantiate our findings and in consideration of the potential clinical importance of diminished estrogen levels in this population.

The results of this study concordantly demonstrate a decrease in serum DHEAS levels in post-

TABLE III. Serum DHEAS before and after oral albuterol administration

Subject	DHEAS (μg/dl)	
	Before administration	After administration
A. M.	47.6	60.2
J. R.	25.6	32.2
M. R.	24.4	34.3
B. W.	39.2	65.5
L. R.	62.9	79.9
R. A.	11	18.7
C. R.	7.7	10.6
L. W.	10.2	24
Mean*	28.6 ± 19.9	40.7 ± 24.8

Four milligrams of oral, sustained-release albuterol was administered twice daily for 3 days.

**p* = 0.002.

menopausal asthmatic women compared with postmenopausal nonasthmatic women (*p* < 0.002). DHEAS levels were decreased regardless of medication or lack thereof. DHEA levels were also lower in asthmatic subjects compared with nonasthmatic subjects (*p* < 0.03). The circulating half-life of DHEA is relatively short, and serum levels are contingent upon interconversion with DHEAS.¹¹ The finding of decreased DHEA is therefore corroborative of decreased DHEAS in patients with asthma.

In contrast to lower values for DHEAS and DHEA in asthmatic compared with nonasthmatic subjects, values for 17-OH progesterone and cortisol, representative of steroidal synthesis via the Δ^4 pathway and the pathway for corticosteroid production, were similar in asthmatic and nonasthmatic subjects. The absence of a decrease in both 17-OH progesterone and serum cortisol in asthmatic versus nonasthmatic subjects argues against corticosteroid-induced adrenal-pituitary suppression as an explanation for lowered DHEAS and DHEA levels in the patients with asthma studied.

The lower assay limit for estradiol was 2.5 pg/ml. Proportionately more patients with asthma (8 of 22) than nonasthmatic subjects (2 of 22) had levels below this limit. Estradiol was diminished in asthmatic subjects as determined by estimating undetectable values at the lower assay limit ($p < 0.02$). All estrone levels fell within the assay range, and mean estrone concentration was lower in patients with asthma ($p < 0.02$), corroborative of decreased estradiol. All but four asthmatic subjects required at least one medication at the time of study, and groups of unmedicated asthmatic subjects were consequently small. Both estradiol and estrone levels were found to be decreased in groups of medicated asthmatic subjects compared with nonasthmatic subjects. Although statistical significance was not achieved compared with nonasthmatic subjects, values for estrogens in the smaller groups of unmedicated asthmatic subjects were numerically similar to values for the larger groups of medicated asthmatic subjects and uniformly lower than those for nonasthmatic control groups. The reduced estrogen levels found in postmenopausal asthmatic women are likely secondary to reduction of adrenal DHEA-DHEAS substrate, the major precursor for postmenopausal sex steroid production.¹⁰ Testosterone was found to be marginally decreased in asthmatic subjects; the lack of correlation is likely related to ovarian testosterone production, which is known to persist after menopause.⁹

Although DHEA and DHEAS are major secretory products of the adrenal gland, information regarding their concentrations, regulation, and functional significance in health and disease has only recently been accumulating and is incomplete. Low levels have been postulated as predictive of decreased life expectancy and death caused by cardiovascular disease¹² and have been considered as a concomitant of chronic illness, infection, and stress.¹³ Decreased DHEAS and elevated cortisol levels have been reported in fetally distressed infants by Parker et al.¹⁴ and in term infants with

respiratory acidosis by Harlan et al.¹⁵ A similar divergence of adrenocortical response has been found in subjects with syphilis and in patients with burns.^{16, 17}

Interleukins appear to play a role in the regulation of sex steroid levels, as well as glucocorticoids, and merit attention as an explanation of our findings in patients with asthma. Interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor- α are known to stimulate adrenocorticotrophic hormone and glucocorticoid output.^{18, 19} IL-1 also causes diminished gonadotropin and sex steroid secretion.¹⁸ Reflecting the mechanistic complexity of these interactions, IL-1 reportedly inhibits luteinizing hormone-induced androgen release but stimulates basal androgen release in cultured rat Leydig cells.²⁰ Tumor necrosis factor- α is reported to differentially modulate estrogen and progesterone production in human granulosa cells²¹ and inhibit adrenocorticotrophic hormone-induced cortisol production in cultured fetal adrenal cells.²² Inhibition, by transforming growth factor- β , of basal and adrenocorticotrophic hormone-stimulated DHEAS and cortisol production, with greater inhibition of DHEAS, has been demonstrated in vitro in human fetal adrenal cells.^{23, 24}

Of many possible explanations for decreased sex steroid levels in asthma, anomalous sympathetic control of adrenal androgen production deserves consideration and is supported by our finding of a 42% increase in mean serum DHEAS in patients with asthma after a course of albuterol. β -Adrenergic blockade is a central pathophysiologic mechanism in asthma,⁵ and analogously, decreased sex hormone levels have been associated with β -adrenergic blocking medications.¹⁻⁴ Significant decreases in follicle-stimulating hormone, luteinizing hormone, testosterone, and estradiol have been reported in men with hypertension, 2 and 24 weeks after they began receiving atenolol.¹ Total and free testosterone levels were decreased in normal male volunteers who were given each of four β -blockers for 1-week periods,² and follicle-stimulating hormone, prolactin, and testosterone levels diminished after a single dose of acebutolol or propranolol.³ Catecholamines are known to exert a regulatory influence on secretion of many hormones,²⁵ and β_2 -adrenergic recognition sites that regulate ovarian²⁶ and testicular²⁷ androgen secretion have been identified.

An immunomodulatory role has been purported for DHEA. Low levels have been associated with rheumatoid arthritis^{28, 29} but not osteoarthritis.³⁰ In animal models, administration of DHEA or

DHEAS has been shown to prevent autoimmune hemolytic anemia³¹ and tumor development³² and to inhibit antibody formation and development of lupus.³³ DHEAS reportedly enhances the synthesis of IL-2 by helper T cells,³⁴ inhibits natural killer cell differentiation,³⁵ and inhibits production of tumor necrosis factor and toxicity secondary to endotoxin administration in mice.³⁶ Levels of DHEA and DHEAS decrease with age,³⁷ and the dysregulation of both lymphokine and antibody production associated with immune senescence have been reported to be ameliorated by DHEA.^{38, 39} Of particular interest with regard to osteoporosis, the elevation of IL-6 associated with aging can be reversed with DHEAS supplementation in rats.³⁹ IL-6 has been shown to enhance osteoclast development and bone resorption, and its elevation in oophorectomized mice can be reversed with estradiol.⁴⁰ The development of osteoporosis is of particular concern in patients with asthma, in whom corticosteroids and immobility have been traditionally considered major risk factors. Our findings suggest that postmenopausal asthmatic women may be at particularly increased risk because of diminution of both DHEAS and estrogen levels.

Determination of sex steroid levels in similar and other asthmatic populations, including premenopausal asthmatic women, is warranted to confirm and extend our findings and to relate them not only to the pathophysiology of asthma but also possibly to the development of allergy. β -Antagonists taken by nonatopic women during pregnancy have been reported to result in elevated cord blood IgE and a high incidence of allergy in offspring.⁴¹ In that maternal adrenal androgens provide a significant proportion of precursor for estrogen synthesis by the fetoplacental unit,⁴² β -antagonists may influence the fetal immune system through alteration of its hormonal milieu during development.

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