

Effects of Syphilis Infection on Adrenocortical Function in Men (43239)

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Abstract. It is becoming apparent that severe stress leads to a reduction in ¹⁹C-steroid production in the adrenals of humans. Based on the finding in a prior study of high levels of cortisol (F) and subnormal levels of dehydroepiandrosterone sulfate (DS) in umbilical cord serum of newborns having congenital syphilis, we sought to investigate adrenal function in adult men having syphilis infections. Diagnostic serum samples obtained from 30 men having untreated syphilis and sera from 30 normal men who were pair-matched with the syphilitic men for age and time of blood sampling were compared with respect to their concentrations of DS and F and the DS to F ratio. Serum levels of F (nmol/liter) were significantly higher in syphilitic men (322 ± 25) than in control men (226 ± 16), $P = 0.0018$. Serum DS levels ($\mu\text{mol/liter}$) were significantly reduced in syphilitic men (5.80 ± 0.80) compared with normal men (9.84 ± 0.94), $P = 0.0018$. Also, the DS to F ratio in syphilitic men was less than 50% than that of the control men, $P = 0.0001$. Men having advanced (secondary) syphilis had the greatest alteration in adrenocortical function. We hypothesize that the apparent divergence in adrenal production of DS compared with that of F probably is due to factors other than altered pituitary production of adrenocorticotrophic hormone, because patterns of adrenal DS and F production similar to those in syphilitic men have been observed by others to occur in conditions of excessive as well as subnormal pituitary adrenocorticotrophic hormone secretion.

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Whereas adrenal steroidogenesis classically has been considered to be broadly activated by various stressors, recent findings in humans have led to questions concerning the regulation of adrenal hormone production. Several years ago, evidence was provided for subnormal rates of adrenal androgen production in newborn infants of women having pregnancy complications that were considered to cause severe stress to the developing fetus (1, 2). We initially viewed these findings as paradoxical. Subsequently, however, we and others have found evidence for a similarly altered pattern of adrenal steroidogenesis in adults who are stressed due to severe trauma or life-threatening illness (3–8). Recently, it also was noted that infants who had congenital syphilis had significantly reduced plasma levels of dehydroepiandroste-

rone sulfate (DS) and increased levels of cortisol at birth when compared with age-matched noninfected infants (9). Interpretation of those results was difficult due to the complex, poorly understood nature of fetal adrenal regulation. Consequently, we sought to extend these studies in a less complicated endocrine setting by characterizing the effect of syphilis infection on adrenal steroidogenesis in man.

Materials and Methods

Samples of serum from 30 men having untreated syphilis were kindly provided by the Jefferson County Health Department, Birmingham, AL. Syphilis was diagnosed based on a positive Venereal Disease Research Laboratories or rapid plasma reagin test and physical findings. These samples, as supplied to us, were coded only as to the age of the subject, the time that the samples were drawn, and the disease stage (primary or secondary). Serum samples were drawn by us from normal healthy men who denied the presence of any sexually transmitted disease, after giving informed consent, to closely match the specimens from syphilitic men for age (± 2 years) and sampling time (± 30 min). The ages of the syphilitic men (range, 20–58 years; mean, 30.47 years) were similar to those of the control

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men (range, 20–59 years; mean, 30.43 years). All sera were kept frozen until assayed. These studies were approved by the Human Use Review Board of the University of Alabama at Birmingham.

DS and cortisol were quantified in diluted serum by direct radioimmunoassay procedures, as described previously (10, 11). Syphilitic sera and their respective control sera were analyzed in the same radioimmunoassay procedure. Data were analyzed by paired *t* test.

Results

As shown in Table I, men having syphilis had significantly lower serum levels of DS and significantly higher serum cortisol (F) levels than did normal men who were carefully matched for age and time of serum sampling. The DS to F ratio in men having syphilis was only about 50% that of normal adult men. Regardless of whether the serum samples were obtained in the morning (8–12 AM, 18 pairs) or afternoon (1–5 PM, 12 pairs), men having syphilis had lower serum DS, higher serum F, and lower DS to F ratios than did their control counterparts (data not shown).

When the men having syphilis were subdivided according to disease stage (Fig. 1), those having primary syphilis, as defined by the presence of chancroid lesion (*n* = 9), had hormone values that were slightly, although not significantly, different from their control subjects. On the other hand, men having more advanced, secondary syphilis, as defined by the presence of diffuse rash or palmar erythema (*n* = 21), had strikingly abnormal serum levels of DS and cortisol, and DS to F ratio.

Discussion

The regulation of adrenal steroid production in humans is now recognized to be much more complex than was once perceived. The pituitary peptide (ACTH) clearly is an important factor in adrenal steroidogenesis that can enhance adrenal production of both androgens and corticosteroids *in vivo* as well as *in vitro*. There are, however, numerous circumstances *in vivo* wherein the production of DS, the quantitatively major ¹⁹C-steroid of the human adrenal cortex, is inversely related to that of cortisol. Apart from the usual, though poorly understood, divergence that occurs with puberty (12) and aging (13), most reports of nonparallel changes in serum

levels of DS and cortisol have been noted to occur in fetuses (1, 2, 9) or adults (3–8) who have experienced extreme circumstances of stress.

In the study presented here, we provide evidence for infection-associated alterations of adrenal steroidogenesis in adult humans that are, although more subtle than those seen with trauma, suggestive of perhaps a mild form of the human stress response. Although statistically significant changes in the endocrine milieu of the entire group of men having syphilis were noted, the most striking shift in adrenal steroidogenesis, i.e., decreased DS and increased cortisol output, was observed in men with more advanced stages of syphilis. Perhaps analogous to the results of our study, men with advanced stages of human immunodeficiency virus infection (AIDS patients) have recently been found to have a more striking reduction in serum DS levels than did those who were infected but asymptomatic (14). Interestingly, there is no evidence for impaired adrenal androgen production (as judged from serum dehydroepiandrosterone levels) in prepubertal children infected with human immunodeficiency virus (15). Recall, however, that the major site of adrenal androgen production, apart from the fetal zone of the adrenal during intrauterine development, appears to be the zona reticularis, which is not morphologically (16) or biochemically (12) differentiated until after puberty. Thus, the specific inhibitory effect of infections or trauma on adrenal androgen production may only be evident when the adrenal is at a developmental state that is normally characterized by high rates of ¹⁹C steroid production.

The mechanism(s) responsible for increased cortisol production and decreased adrenal androgen secretion in humans subjected to various stressors is unclear. It is unlikely to be due solely to variations in pituitary ACTH production, because the same general pattern of adrenal androgen deficiency and relative hypercortisolism is observed with extreme stress due to trauma, presumably associated with increased ACTH secretion (5), as well as with human immunodeficiency virus infection in adults, which appears to be associated with lower than normal plasma ACTH levels (14). Because patients with syphilis are at high risk for other sexually transmitted diseases, we cannot rule out the possibility that adrenal function might have been affected by other coexisting disorders. Nevertheless, the degree of adrenal

Table I. Effect of Syphilis on Adrenal Function in Men^a

Group	<i>n</i>	DS (μ mol/liter)	Cortisol (nmol/liter)	DS/Cortisol ratio ^b
Syphilis	30	5.80 \pm 0.80	322 \pm 25	2.12 \pm 0.38
Control	30	9.84 \pm 0.94	226 \pm 16	5.16 \pm 0.55
<i>P</i>		0.0018	0.0018	0.0001

^a Data are presented as the mean \pm SE.

^b Computed as μ mol DS/liter \div nmol cortisol/liter \times 100.

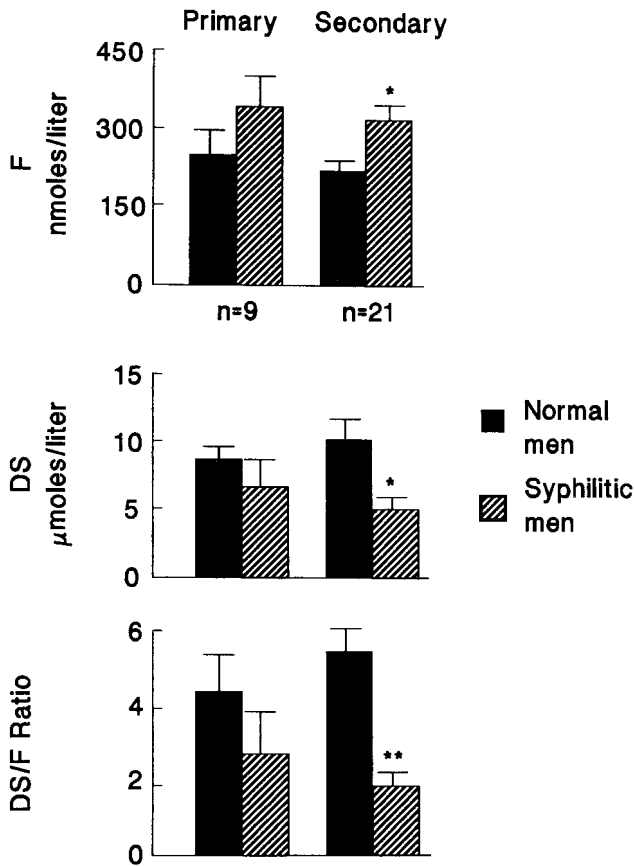


Figure 1. The effects of primary and secondary syphilis on adrenal steroid production in men. Data for syphilitic men were segregated according to disease stage and compared with data for their respective pair-matched control subjects by paired *t* test. The DS to F ratio was computed as $\mu\text{mol DS/liter} \div \text{nmol F/liter} \times 100$. Data are plotted as the mean \pm SE. **P* < 0.01 compared with control values; ***P* < 0.001 compared with control values.

dysfunction was clearly related to the stage of syphilis, being most abnormal in men in whom the infection had led to systemic responses. A frequent sequela of syphilis is anorexia, which has also been linked, by unknown mechanisms, to an increase in adrenal glucocorticoids but a decrease in adrenal androgens (7). It is tempting to speculate that the paradoxical pattern of adrenal steroidogenesis seen in various "stress" situations in humans might result from the direct actions of one or more cytokines (17–20) that are produced in such circumstances. Further study is, however, required before any linkage between cytokines and adrenal steroid production *in vivo* is established.

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