HORMONE PATTERN IN PHARMACOLOGICALLY FEMINIZED MALE TRANSSEXUALS IN THE CALIFORNIA STATE PRISON SYSTEM

L.J. Valenta, MD, PhD, A.N. Elias, MD, and E.S. Domurat, MD
Irvine, California

The hormonal profile of 40 transsexual inmates from a pool of 86 inmates in the California State prison system was studied before and after therapy with feminizing hormones. Clinical and social data were obtained on all 86 inmates; the incidence of human immunodeficiency virus (HIV) seropositivity was examined in 76 of the 86 individuals.

Despite similar degrees of feminization in all 40 individuals in whom hormonal studies were performed, variable suppression of serum testosterone concentrations was present. Based on their testosterone concentrations while on feminizing hormone therapy, the transsexual inmates could be divided into three groups. In Group I (the "suppressed" group), the serum testosterone concentrations were markedly depressed (<10 ng/dL); in Group II (the "nonsuppressed" group), the values of testosterone were normal (446 to 1072 ng/dL); and in Group III (the "intermediate" group), the testosterone values were between those of the suppressed group and the nonsuppressed group. We speculate that feminizing hormone therapy may induce the development of a state of target hormone resistance to testosterone that results in similar degrees of feminization independent of the circulating concentrations of testosterone.

The incidence of HIV seropositivity (3/76) was considerably less than anticipated based on previous studies in populations at high risk for developing the acquired immunodeficiency syndrome. (*J Natl Med Assoc.* 1992;84:241-250.)

Key words • transsexuals • hormone therapy • feminization

In preparation for surgical male-to-female sex reversal, estrogens or progesterone are administered to accomplish feminization. Only limited data are available on blood hormone levels in such a population under estrogen/progestogen treatment.[1,2] The present study reports on sex hormone blood levels in 40 noncastrated males treated chronically with estrogens and medroxyprogesterone. The 40 individuals represent a population drawn from a total of 86 male transsexuals, all of whom were inmates of the California State prison system.

Since male transsexuals are often homosexuals, and as such represent a high-risk group for acquired immunodeficiency syndrome (AIDS), we felt it was also of interest to determine the incidence and manifestations of AIDS in this particular population.

MATERIALS AND METHODS

Eighty-six transsexuals who were inmates of the California Medical Facility (CMF) were studied. The term "transsexual" used in this report describes an effeminate male intent on assuming the female pheno-

From the Patton State Hospital, Department of Mental Health, State of California, Patton, and the University of California at Irvine, Irvine, California. Requests for reprints should be addressed to Dr Alan N. Elias, Division of Endocrinology & Metabolism, University of California at Irvine, Medical Center, 101 City Drive S, Orange, CA 92668.

type initially by hormonal therapy and ultimately by surgical means. The individuals studied were not always transvestites; they represented the total transsexual population of the California State prison system who were treated with female sex hormones as of the end of 1987, because all such inmates were transferred statewide to CMF. According to prison policy at the time of study, inmates who presented proof of being treated with estrogens or progestogens prior to incarceration continued to receive treatment while in prison. All studies were performed after informed consent was obtained by one of the investigators (LJV).

None of the males included in this study had been castrated, and all of them were known to have functioning testes as evidenced by male pubertal development and history of prior androgenization. All of them were found to have normal-sized penises and possessed both testicles in the scrotum.

Hormonal treatment consisted of daily single-dose, oral administration of conjugated estrogens (Premarin, Wyeth-Ayerst, Philadelphia, Pennsylvania) 2.5 mg, ethinyl estradiol (Estinyl, Schering Corp, Kenilworth, New Jersey) 0.5 mg, and medroxyprogesterone (Provera, Upjohn Co, Kalamazoo, Michigan) 10 mg.

Clinical evaluation, including a history and physical examination, was performed in all 86 inmates. Forty of these inmates consented to have their blood drawn for endocrinological evaluation, and hormonal data were obtained in these individuals. All blood samples were obtained at approximately 8:00 am in fasting individuals. The hormonal profile was consistent in different groups of individuals and was reproducible in cases where repeated studies were obtained. This makes unlikely that hormones released cyclically had a major impact on the results of the present study. Specific radioimmunoassays of the following hormones in serum were performed: total estrogens (E), progesterone (P), testosterone (T) and free testosterone (FT), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), and growth hormone (GH). Complete blood count and blood chemistry were also obtained, and peripheral leukocytes were used for chromosome analysis. All measurements were performed in a specialized commercial laboratory using kits produced by ICN (Costa Mesa, California). The intra/interassay variations expressed as percent were: E, 6/6; P, 5/7; T, 4/7; LH, 5/6; FSH, 7/6; GH, 5/8; PRL, 4/8. Free testosterone was measured by dialysis in Nichols Laboratories (San Juan Capistrano, California).

In all individuals, hormone therapy was discontinued at the beginning of 1988 after it was decided that treatment was not beneficial to the inmates' general health and could increase the risk of hypertension, hyperlipoproteinemia, and thromboembolic disease. In 27 inmates, serum hormone levels were measured subsequently at least once and as many as four times, at intervals reported below. In one case, a gonadotropin-releasing hormone test was performed with intravenous (IV) administration of 100 μg GnRH (Factrel, Wyeth-Ayerst, Philadelphia, Pennsylvania) and measurements of testosterone and gonadotropins (LH and FSH) were made before the injection and then at 15-minute intervals for 2 hours thereafter.

Seventy-six inmates agreed to be tested for AIDS. Human immunodeficiency virus (HIV) antibodies were detected by both ELISA and immunofluorescence techniques (Western blot). The test was performed by the Department of Health Services in the San Francisco, California area.

RESULTS

Demographic Data

The racial distribution was as follows: 26 whites, 47 blacks, and 13 Hispanics. The average age (mean ± standard deviation [SD]) was 29 ± 6 years (range: 19 to 49). Most of the inmates came from large metropolitan areas.

Historical Data

The historical data were obtained by the same investigator (LJV) in a one-on-one interview using a standard questionnaire. The individuals were sexually active for a mean duration of 15 ± 6 years with a range of 5 to 30 years. At the time of the study, 9% of the transsexuals reported less than one intercourse per month, 39% had between 1 and 6 intercourses per month, 25% reported 6 to 12 per month, and 27% reported more than 12 per month, ie, more than 3 intercourses per week. More than 62% characterized their libido as "low to nonexistent," while 21% and 17% characterized their libido as "average" to "above average," respectively.

None of the transsexuals on hormone therapy reported experiencing penile erections sufficiently tumescent to accomplish active intercourse. As a result, all of them played a passive, "receiver" role in the sexual act. The majority (77%) preferred anal intercourse, 21% performed anal and oral sex equally, and only a few individuals exclusively preferred oral sex. Almost one third of the inmates in the study admitted that they swallowed semen during oral sex.

About 40% of the individuals denied the presence of any orgasm. About one third claimed to feel "mental"

excitement, and others (20%) reported experiencing some physical sign of excitement such as a limp erection or urethral discharge equivalent to a minimal ejaculation.

Almost 60% of the inmates in the series claimed to have the same sexual partner for several consecutive years and to have "lived-in" with their partners. Some of them insisted that they only had two to three sexual partners in their lifetimes. About 30% admitted to having between 10 and 100 sexual partners a year, and 10% reported that they had more than 100 partners a year. Approximately 60% denied promiscuity. About 40% confessed to promiscuous sexuality for at least some time during their lives, and most of these individuals habitually walked the streets offering sex for money. At least one third of the inmates went through the experience of being raped. Only 11% admitted involvement in group sex orgies. Twenty percent gave a positive history of syphilis and about the same number also gave a positive history of hepatitis.

Other Risk Factors for AIDS

These transsexuals had other AIDS risk factors besides homosexuality. Nearly one half admitted to intravenous drug abuse. Three individuals had known past sexual contact with established AIDS patients. Two received frequent blood transfusions. At least 46 individuals exhibited multiple tattoos. Eight of 71 transsexuals examined by the same examiner were found to have substantial persistent generalized lymphadenopathy and 16 demonstrated "nonspecific" lymphadenopathy.

Almost 80% of the transsexuals took the HIV antibody test within the year prior to the study. The test was positive in only three individuals. Two of the three remained free of any manifestations of AIDS. One individual, who took the female sex hormones intermittently and inconsistently and who also was a heavy drug user, developed heroin-related nephropathy and end-stage renal disease, which required maintenance hemodialysis. While being followed for his kidney disease, and when he was off hormone therapy, he converted from HIV-antibody negative to positive within a year, and died of disseminated infection with *Mycobacterium avium/intracellulare* infection.

Hormonal Therapy

The average age ($\pm$ SD) of the inmates at the time they started hormone therapy was 21 ± 5 years (range: 12 to 41). The individuals were taking the hormone for 1 to 21 years, with a mean duration of therapy ($\pm$ SD) of 7.3 ± 4.7 years. The hormone therapy might have been intermittent prior to their incarceration, but all received estrogen and progestogen consistently during their stay in prison, which was for at least 6 months prior to the present study.

Feminization was assessed on a scale of 1 to 3. A grade of 1 represented gynecomastia (Marshall-Tanner stage 2 to 3)[3] as the only discernible estrogen effect; a grade of 2 represented gynecomastia stage 4, mild accentuation of the hips and abdomen by fat deposition; and a grade of 3 represented gynecomastia stage 4 to 5 with female-type fat and body hair distribution and a high-pitched voice. According to this scoring system, 2 to 3+ feminization was demonstrated by three fourths of the transsexuals. However, all the remaining individuals demonstrated at least grade 1 feminization.

The degree of feminization did not always correlate with loss of androgenization. Androgenization was characterized mainly by male facial and body hair, the need for shaving, the frequency of shaving, muscularity, deep voice and size of the testicles. Androgenization was also classified on a scale of 1 to 3. A grade of 1 represented soft testicles <2.5 cm in their longest dimension, absence of the male escutcheon and chest hair, absence of facial hair, and decreased muscle mass and strength; grade 2 represented soft testicles <3 cm in diameter, the need for shaving less than once per week, sparse hair above the xiphoid, and limited amount of pubic hair growing in the midline toward the umbilicus and not extending to the thighs; grade 3 represented testicles still relatively soft and measuring 3.5 cm in their longest dimension, the need for shaving more often than once per week but less often than daily, and near-normal male body hair distribution. According to this scale, 1+ androgenization was demonstrated by 63% of the males who had soft testicles <2.5 cm in the longest dimension, no need or reduced frequency of shaving, and decreased muscularity. They demonstrated variable degrees of feminization, mostly 2 to 3+. Only about 8% of the individuals showed both near-normal androgenization and relatively poor feminization. The remaining individuals were in between these two extremes of androgenization and feminization.

Of the 86 inmates, 28 started hormone therapy before the age of 20 and had taken medication for 3 to 17 years (mean $\pm$ SD, 9.7 ± 5 years). Almost all these individuals were very poorly androgenized; most of them had never shaved regularly and their voices were high-pitched. However, there was no clear correlation between their lack of androgenization and their feminization. A subgroup of six individuals started the hormone therapy before the age of 14. The timing of their puberty was

normal and despite poor androgenization, they all had normal-sized penises.

The remaining 58 inmates who started their therapy after the age of 20 had taken hormones for 1 to 17 years (6.5 ± 4 years). Twenty of these individuals demonstrated 2 to 3+ androgenization. The 3 to 5 years duration of therapy in these subjects correlated better with increasing feminization than with suppressed androgenization. The feminization progressed through the stages of Tanner's pubertal thelarche to female type of body fat distribution. In parallel, there was variable reduction of body and facial hair and a reduction in muscularity. A natural high-pitched voice was present only in males who started hormonal therapy early in their lives. Thus, the loss of androgenization was most dramatic in those individuals who started the estrogen and progestogen therapy early in life, while the extent of feminization depended primarily on the duration of therapy.

The estrogen and progestogen therapy caused a number of side effects in a majority of the transsexuals. Only eight individuals in the series claimed that they were totally free of side effects. Aside from erectile impotence reported by all inmates on therapy, the most frequent symptoms were weight gain and soreness of the breasts, which occurred in 62 and 66 males, respectively, in the series of 86 individuals. The next most frequent symptom, which affected 32 inmates, consisted of emotional instability or "moodiness." Nausea and vomiting at the start of therapy was reported by 14, while depression was experienced by 12. Edema, constipation or diarrhea, and weight loss were each reported by three to five inmates.

Withdrawal of therapy was also associated with adverse symptoms in 60 of the 86 transsexuals. Rebound androgenization, hot flashes, moodiness, and irritability or depression were the most frequent complaints, followed by headaches, sweats, weight loss, anorexia, tiredness, feeling "ill," paresthesias, seizure, constipation/diarrhea, and skin changes. Androgenization evidenced by return of penile erections and progressive return of male body hair pattern usually occurred after several weeks of sustained therapy withdrawal.

Other Clinical Data

Sixteen of the 86 inmates were mildly to moderately hypertensive with a maximum systolic blood pressure of 130 to 160 mm Hg and a diastolic blood pressure of 90 to 100 mm Hg.

Twenty-two patients gave a history of hepatitis; at least 15 of these males had abnormal liver function tests, and four had positive hepatitis B soluble antigen.

Twenty-six patients admitted to past venereal disease and at least 10 of them demonstrated positive syphilis serology.

Serum lipoproteins were measured in 40 individuals after a 14-hour overnight fast. Hyperlipoproteinemia was detected in seven of them. Three suffered from hypercholesterolemia (type IIA hyperlipoproteinemia) and three from combined hypercholesterolemia and hypertriglyceridemia (type IV hyperlipoproteinemia). One patient demonstrated type V hyperlipoproteinemia.

Nonspecific Hormonal Tests

In 40 individuals, measurements of serum prolactin and growth hormone were obtained. Prolactin was elevated in 12 cases; the values varied between 20 and 160 ng/mL (normal value: 2 to 15 ng/mL), while the mean $\pm$ SD was 39 ± 37 ng/mL. Growth hormone was detectable in all cases. In three cases, it was above the upper limit of normal (10 ng/mL): 16, 19, and 24 ng/mL.

Serum thyroxine (T_4), triiodothyronine (T_3), and cortisol were measured in a few cases and were found to be invariably elevated. Elevation of serum thyroid hormone and cortisol via the effect of estrogen increasing the binding by respective hormone-binding globulins (ie, cortisol-binding globulin and thyroid-hormone binding globulin) is well established and was not the subject of the present investigation.

Chromosome analysis on peripheral leukocytes was obtained in 28 individuals. The analyses demonstrated 46 X-Y pattern in all cases.

Following discontinuation of the estrogen/progestogen regimen, the prolactin level, when previously elevated, progressively decreased over several weeks. However, in six individuals it remained elevated. Testing of growth hormone was not repeated off therapy. Computed tomographic (CT) scans of the pituitary were obtained when prolactin elevation persisted for periods as long as 15 weeks off therapy. In three individuals, the prolactin levels had remained elevated when last measured, but CT scans had been normal in all such instances. In one patient with persistent prolactin elevation at 9 weeks, normalization occurred after an additional 7 weeks off therapy.

Sex Hormone Studies

As outlined above, serum testosterone, estrogen and progesterone, luteinizing hormone, and follicle-stimulating hormone were measured in 40 individuals. In 24 of these individuals, serum free testosterone was also obtained. In 27 cases, the studies were repeated after hormonal therapy had been discontinued.

TABLE. SERUM CONCENTRATIONS OF TOTAL TESTOSTERONE (T), FREE TESTOSTERONE (FT), ESTROGEN (E), LUTEINIZING HORMONE (LH) AND FOLLICLE-STIMULATING HORMONE (FSH) IN 40 MALE TRANSSEXUALS*

	T (ng/dL)	FT (pg/mL)	E (pg/mL)	LH (mIU/mL)	FSH (mIU/mL)
Group I Suppressed N = 17	12.8 ± 5.8 (<10-34)	0.6 ± 0.1 (0.5-0.8)	433.5 ± 310.3 (66->1000)	0.4 ± 0.3 (0.3-1.3)	0.5 ± 0.5 (0.3-1.9)
Group II Nonsuppressed N = 15	747.1 ± 196.7 (446-1072)	36.7 ± 16.3 (13.5-80.2)	131.2 ± 44.6 (56-246)	9.1 ± 6.5 (2.4-27.6)	16.5 ± 15.6 (2.4-63.5)
Group III Intermediate N = 8	146.3 ± 111.9 (60-358)	† (6.1-9.3)	244.1 ± 293.5 (67->1000)	5.8 ± 4.2 (1.4-14)	5.5 ± 3.6 (1.3-13.9)
Normal values	360-990	10-40	40-100	1-10	1-14

*Values given as means ± standard deviation.
†Mean FT not reported because of small sample size (3 individuals)

According to the pattern of hormone levels, the patients could be differentiated into three groups (Table).

Group I is described as "suppressed"; 17 of the 40 inmates fell into this group. In Group I, serum testosterone was either unmeasurable (ie, <10 ng/dL; normal: 360 to 990 ng/dL) or markedly decreased (ie, <35 ng/dL), and free testosterone was also markedly decreased down to a range of 0.5 to 0.8 pg/mL (normal: 10 to 40 pg/mL). In these individuals, both luteinizing hormone and follicle-stimulation hormone were generally below the normal range or at the lower limit of normal (Table).

Group II is described as "nonsuppressed" and consisted of 15 transsexuals. In these individuals, male gonadal steroid measurements were perfectly normal. Testosterone and free testosterone concentrations ranged from 446 to 1072 ng/dL and 13 to 80 pg/mL, respectively. The serum gonadotropins were also normal or moderately elevated in six and nine of the 15 patients, respectively. Both luteinizing hormone and follicle-stimulating hormone were above normal limits in five cases; luteinizing hormone alone was elevated in one individual, and follicle-stimulating hormone alone was higher than normal in three individuals.

Group III is described as "intermediate" between Groups I and II and consisted of eight individuals. Serum testosterone in these transsexuals was below the normal range. Free testosterone was measured in three cases—it was normal in one case and below normal in the other two. Serum gonadotropins in this group were normal; however, in two individuals the luteinizing hormone alone was slightly elevated in the presence of normal follicle-stimulating hormone concentrations.

Although the hormonal patterns in the above three groups were quite distinctive, they correlated poorly with any other observed variable. In other words, there was no apparent relationship between an individual's hormonal pattern and his degree of androgenization or feminization, his age when therapy was started, or his duration of treatment. Although the total serum estrogen was highest in the suppressed group and lowest in the nonsuppressed group (Table), individual values between groups overlapped. Serum progesterone was slightly elevated to a comparable level in all groups.

Hormone Therapy Withdrawal

Estrogen and progestogen medication was discontinued abruptly in all transsexuals. Of the 40 in whom blood hormone studies were performed while they were on hormone therapy, 27 had subsequent hormonal studies when they were off treatment. This follow-up was accomplished in eight of the nonsuppressed group, 14 of the suppressed group, and 5 of the intermediate group. These additional measurements were performed up to 24 weeks following discontinuation of therapy.

In the nonsuppressed group, repeat studies were obtained 1 to 9 weeks after medication withdrawal (average time: 4 weeks). The final total serum testosterone level (mean ± SD) in these individuals was 779 ± 186 ng/dL, which was not different from the starting value (Table) obtained while the transsexuals were on hormone therapy; the range of values was 467 to 1056 ng/dL. The serum gonadotropin levels also remained essentially unchanged when comparing results obtained off therapy to those obtained while on therapy: luteinizing hormone

(mean ± SD) off treatment was 8.7 ± 4.5 mIU/mL (range: 4.9 to 15.1) and follicle-stimulating hormone was 16.5 ± 17.6 (range: 1.3 to 54.8). Thus, the only appreciable change in measured hormone pattern was a decrease in estrogen (Table).

In the suppressed group, with unmeasurable testosterone while on hormone therapy, serum testosterone after therapy discontinuation normalized on final measurement in 10 of 14 individuals, with their values ranging from 399 to 1225 ng/dL, with a mean ± SD of 738 ± 308 ng/dL. The earliest normalization of serum testosterone was observed at 4 weeks after discontinuation of treatment; in some cases, however, suppressed values posttherapy persisted for up to 10 weeks before normalization ultimately occurred.

In four individuals in the suppressed group, low testosterone (values: 11, 99, 153, and 358 ng/dL) was still present when last measured, which was 4 to 7 weeks, and in one extreme case, 24 weeks following discontinuation of hormone therapy.

As described above, the suppressed group demonstrated the hormonal pattern of hypogonadotropic hypogonadism, with markedly low luteinizing hormone and follicle-stimulating hormone values while on therapy. Off therapy, however, the serum gonadotropin levels became generally normal or slightly elevated when first measured, which in some cases was as early as 4 weeks after the discontinuation of therapy. Such a rise in gonadotropins invariably preceded normalization of serum testosterone (even by as much as 10 weeks) and was also observed in cases where the serum testosterone subsequently remained low. In an extreme case, for example, serum testosterone was still low (153 ng/dL) 24 weeks after discontinuing therapy. Prior to that point in time, the values of testosterone, luteinizing hormone, and follicle-stimulating hormone were 10, 0.2, and 0.2, respectively, during hormone treatment; 7 weeks after discontinuing hormone therapy, the levels were 141, 29, and 43, respectively; and after another 3 weeks the levels were 153, 30, and 42, respectively.

Serum gonadotropins when last measured in the members of the suppressed group ranged from 3.5 and 29 mIU/mL for luteinizing hormone, and from 2.5 and 53 mIU/ml for follicle-stimulation hormone. The respective means ± SD were 15 ± 7 and 30 ± 16 mIU/mL.

One patient in the suppressed group with delayed normalization of serum testosterone consented to the gonadotropin-releasing hormone stimulation test. At the time the test was performed, serum testosterone had already increased to 399 ng/dL, and baseline luteinizing hormone and follicle-stimulating hormone were 7 and 2.4 mIU/mL, respectively. The results of the stimulation test for luteinizing hormone/follicle-stimulating hormone/testosterone were 7/2.4/399, respectively, at time 0 minutes, and 19/4.7/534, 27.6/5.9/441, 30.3/7.1/477, 23.7/5.8/454, and 15.5/5.8/515 at 15-minute intervals thereafter, which was consistent with a normal response.

In five members of the intermediate group, final serum testosterone concentrations after being off therapy for 3 to 9 weeks were normal; the mean ± SD of the values was 853 ± 211 ng/dL (range: 512 to 1046). A suppressed value was noticed in one individual at 5 weeks posttherapy, but this value normalized at 8 weeks posttherapy.

There was a marked increase in serum gonadotropins after hormonal therapy discontinuation in all intermediate group cases, even though the gonadotropin levels during therapy in this group were normal (Table). Serum luteinizing hormone (mean ± SD) increased from the initial 5.8 ± 4.2 mIU/mL (on therapy) to 13 ± 5 mIU/mL (off therapy) and follicle-stimulating hormone (mean ± SD) from 5.5 ± 3.6 mIU/mL to 20 ± 9 mIU/mL while on and off therapy, respectively.

In almost all treated transsexuals, serum estrogen was elevated to as high as >1000 pg/mL; in all of these individuals, there was a progressive decrease in the serum estrogen level after discontinuation of the therapy. No large differences in serum estrogen were observed between the three groups of transsexuals. Serum progesterone measurements showed varied results. The levels were normal in some individuals and slightly elevated in others. Measuring progesterone levels after the discontinuation of therapy was not accomplished.

DISCUSSION

Male transsexuals represent a special class of individuals, often homosexuals, who are said to have a "flawed" or "ambiguous" gender identity.[4]

In the present series of transsexuals, all 28 individuals tested for chromosomal pattern were normal males, and by history, all 86 individuals developed as males at the time of puberty. Even individuals in whom full androgenization (such as male facial and body hair, muscularity, and deepening of the voice) was prevented by early pubertal initiation of hormone therapy had normal-sized penises. Since penile growth depends on dihydrotestosterone rather than on testosterone,[5] even low blood levels of testosterone at the time of puberty are apparently sufficient to generate adequate local amounts of dihydrotestosterone and effect maturation

of the male external genitalia.

While lack of androgenization appeared to depend on the age of the individual at the start of hormone therapy, the presence of feminization appeared to be related more to the duration of therapy. Treatment that was started prepubertally, or at least before the age of 20, produced the most dramatic lack of androgenization.

The estrogen and progestogen treatments resulted in a number of physical, psychological, and biochemical abnormalities that were reversible to a variable degree. In regard specifically to sexual function among these patients, they reported loss of libido, decreased sexual activity, and erectile impotence. The erectile impotence was reversible within several weeks following discontinuation of hormone therapy.

Mild to moderate hypertension was reversible at least in one third of the 16 individuals who were affected. No data are available on the reversibility of hyperlipoproteinemia that was identified in seven of 40 individuals.

Hyperprolactinemia was identified in 12 of 40 transsexuals and was reversible upon the discontinuation of the treatment in all but three individuals. Normalization of the prolactin blood level occurred between 3 and 7 weeks after the discontinuation of therapy in most instances. In one case with persistent prolactin elevation at 9 weeks, normalization was observed when prolactin was measured at 16 weeks. None of the patients was noticed to have galactorrhea. Computed tomography or magnetic resonance imaging scans were normal in all cases with persistent hyperprolactinemia.

Serum growth hormone was detectable in all transsexuals and was clearly elevated in three individuals. The levels off treatment were not obtained.

Increased serum growth hormone and prolactin are well-recognized effects of estrogen administration.[6-10] The present study contributes information on the relative frequency of such increases in male patients and on the reversibilty of the prolactin elevation.

Because of erectile impotence, many transsexuals are "receivers" or "passive" homosexuals. About 40% of the series claimed that they previously lived with a single sexual partner in a stable relationship. However, this reported self-image may have been a prevarication, in at least some, because on repeated questioning a significant number admitted promiscuity at certain periods in their lives ("walking the streets" and competing with female prostitutes).

Besides homosexuality and sexual promiscuity with high incidence of anal intercourse, other risk factors for AIDS were present in our patients, namely IV drug abuse, prior sexual exposure to AIDS patients, and multiple blood transfusions. About 80% of the series were tested for HIV antibodies. Three of 69 tested were HIV-antibody positive, but only one of these developed overt disease with disseminated *Mycobacterium avium/intracellulare* infection. The other two patients remained asymptomatic although one was found to have significant persistent generalized lymphadenopathy, which was present in an additional five patients who tested negative and in two who refused to take the HIV antibody test.

Given the frequent and exclusive anal-receptive intercourse in the observed population, high prevalence (more than 50%) of IV drug addiction, and taking into account the data on New York City and San Francisco cohorts,[11,12] the expected incidence of HIV seropositivity is between 50% and 70%.[13-15] Notwithstanding the limited sample size, the actual incidence in the present study is strikingly lower than anticipated.

In contrast to the AIDS epidemiology of the African continent, that of Western countries, including the United States, is sex dependent with a substantially lower prevalence of seropositivity in females[16] compared with males. This study suggests that at least one possibility for the difference in sexual dependence observed, at least in this country, is related to hormonal factors. Steroid hormones, and notably progesterone among all sex steroids, are known immunomodulators.[17] Because of the crucial role of immunological mechanisms in HIV infection, sex steroids could be "protective" by positively influencing patients' resistance to HIV with respect to both acquiring seropositivity and manifesting the disease. Parenthetically, one of the authors had the opportunity to observe a terminally ill patient with AIDS (unrelated to the present series) who had disseminated infections. During a 3-month course of estrogen and progestogen therapy, this patient demonstrated marked clinical improvement with a 15-pound weight gain, increased strength and ambulatory ability, improved gastrointestinal symptoms, and facilitation of the healing of herpes simplex virus II genital lesions. This overall clinical improvement suggests that sex hormone therapy may have some value in the management of AIDS, albeit merely of a supportive or palliative nature.

In the study population, hormones of the gonadal axis demonstrated quite distinct serum profiles. Serum estrogen levels were above the normal male range in virtually all patients. In most patients, estrogen was grossly elevated; in some cases, the elevation exceeded 1000 pg/mL (normal up to 110 pg/mL), which is the

upper limit of the proportionality of the assay. The assay was performed using materials produced by ICN. According to information from the manufacturer, the estrogen antiserum in the assay does not crossreact with conjugated estrogens or ethinyl estradiol. The estradiol may represent residual 17β-estradiol esters, which may have been taken by the inmates prior to incarceration. These injections raise the level of 17β-estradiol for 24 to 36 months after the last injection. Alternatively, the possibility that at least a certain fraction of Premarin or ethinyl estradiol administered may have been converted in vivo into measurable estrogen metabolites for the crossreactivity to occur must also be considered. That the serum estrogen level upon repeated measurement decreased progressively after discontinuation of therapy also indicates that the initial elevated estrogen concentration was due to exogenous and not endogenous hormone. The observations indicate compliance of the transsexual inmates with estrogen therapy. It was beyond the scope of this study to establish the true nature of the crossreactivity of the exogenous estrogen in the laboratory assay.

In both sexes, testosterone, estrogen, and progestogens all exhibit negative feedback control of pituitary gonadotropin secretion.[18-23] In the male, excess estrogen has been shown to cause hypogonadotropic hypogonadism.[24-26] A similar condition was also present in the majority of patients in the present series. The reversibility of the hypogonadotropic hypogonadism upon discontinuation of the hormone therapy confirms the functional as opposed to an organic cause of the hypogonadism.

It was surprising, though, to discover a group of patients in this study with perfectly normal serum testosterone and free testosterone, and nonsuppressed or even slightly elevated concentrations of gonadotropins. This was not observed by Futterweit et al[27] who reported invariably low levels of testosterone in transsexuals on estrogen treatment. Their study was different, however, in that only short treatment time periods were involved, and the patient sample was relatively small. The first logical explanation of this finding would be noncompliance with the medication.

In reality, there are several factors that would make noncompliance unlikely. First, the nonsuppressed individuals as a group were feminized to a degree that was comparable to that of other suppressed groups of patients. Second, they were poorly androgenized to a degree that was comparable to that of the other groups. Third, they demonstrated elevated serum estrogen that progressively declined when the treatment was discontinued. Since withdrawal of hormone therapy does not result in immediate recovery of the serum testosterone and gonadotropins concentrations to normal (vide infra), it is unlikely that normal testosterone values in these patients were due to "skipping" the medication a few times. In addition, these patients reported rebound androgenization symptoms when off the feminizing hormone therapy. Another argument in favor of the true existence of the nonsuppressed group was the presence of an intermediate group of patients with partial sex hormone suppression (vide infra). Finally, all medications were dispensed to the prisoners individually by a registered nurse who was instructed to witness that the patient did in fact take his medication. Patients were specifically observed for "pocketing" the medication inside their mouths.

In addition to being feminized, these nonsuppressed transsexuals were poorly androgenized relative to the other patient groups. In the presence of normal serum testosterone concentrations, poor androgenization suggests target organ resistance, probably at the receptor or postreceptor level. Since these individuals were well androgenized prior to their starting feminizing hormones, the hormonal resistance was logically related to estrogen and progestogen, possibly through their competitive interaction with testosterone at the receptor level or through affecting testosterone intermediary metabolism.

In addition to putative receptor-level mechanisms, differences in intermediary metabolism may also explain differential responses to the suppressive effect of sex steroids on gonadotropins. Interference of estrogen and progestogens with testosterone action would then also be responsible for the observed abnormalities of gonadotropin feedback, through the receptor or intermediary metabolism mechanisms. Although testosterone, estrogen, and progesterone are known to have suppressive effects on pituitary gonadotropins, they may exert such suppressive effects only after being metabolized to other entities such as dihydrotestosterone or α-androstane 3β-ol in the case of testosterone[23] or to catecholestrogens in the case of estrogen.[28] The presence of male subpopulations who manifest different suppressive effects of estrogen on gonadotropins might then be due to differences in efficiency and substrate specificity of the enzymatic systems involved in the conversion to these suppressive metabolites.[29]

In the intermediate group, serum testosterone was subnormal but not totally suppressed, and the gonadotropins were normal but inappropriately low for the levels of testosterone. Apparently, the gonadotropins

were prevented from becoming appropriately elevated by the estrogen and progestogen combination therapy. But why serum testosterone was low in the face of normal gonadotropin levels remains uncertain. One possible explanation is that estrogen inhibits a number of testicular enzymes, particularly 17α-hydroxylase, 17,20-lyase (desmolase), and Δ^5–3β-hydroxysteroid dehydrogenase activities,[30-37] and thereby impair the ability of the testis to synthesize adequate amounts of testosterone in response to endogenous luteinizing hormone or to exogenous human chorionic gonadotropin.[38] It has also been shown that chronic therapy with estrogen results in a reduction in the number of luteinizing hormone or human chorionic gonadotropin receptors in the testes, thereby rendering the gonad refractory to luteinizing hormone/human chorionic gonadotropin stimulation.[39]

Discontinuation of estrogen and progestogen therapy resulted in progressive normalization of low serum testosterone, where present, in most of the transsexuals in this study. Such normalization was invariably preceeded by an increase in serum luteinizing hormone and follicle-stimulating hormone concentrations that occurred over several weeks. High post-castration levels were never achieved. The normalization in serum testosterone was preceded by an increase of gonadotropins by 4 to 10 weeks. Therefore, in analogy to the recovery of the adrenocortical system after chronic hormonal suppression,[40] the recovery of the male gonadal axis also proceeds first through recovery of the hypothalamic-pituitary system before moving on to restoration of normal testosterone secretion. The required duration of recovery of the axis appears to vary among individuals, and in the present study, it ranged from 4 weeks to more than 24 weeks. In one individual, serum testosterone levels remained subnormal after 24 weeks off therapy.

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