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The Use of Androgens in the Menopause and Other Gynecic Disorders

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Though estrogens and progesterone are essential ingredients in the biologic and psychologic development of a woman, androgens, too, play an important role. The use of testosterone in the management of gynecic disturbances has been frowned upon. Embedded in the minds of most clinicians is the notion that its use for such purposes is not only contraphysiologic but also antipharmacologic. Somehow the point has been obscured that testosterone is not necessarily a male sex hormone but a metabolic one, common to both man and woman. In fact, the production of androgens by the adrenal is equal in both sexes, and the ovary in reproductive life as well as postmenopausally is also a source of androgens.

Many physicians believe that testosterone is the opposite of estrogen and is antiestrogenic, the very antithesis of estrogen. In small but effective pharmacologic doses, testosterone does not alter normal endometrial development, does not cause atrophic changes of the vaginal mucosa, does not interfere with ripening of the cervical mucus, and rarely upsets normal cyclic menses. In the castrate monkey, both estrogen and testosterone will cause redness and turgescence of the perineum. Moreover, when simultaneously administered, these hormones do not neutralize one another, whereas progesterone will induce blanching and deturgescence.[12]

In the synthesis of ovarian steroids, progestogens, androgens, and estrogens occur in that order; thus the immediate precursors of estrogens are androgens. The ovary, in common with other steroid hormone–producing glands, converts acetate to cholesterol, the obligatory precursors of all steroids. Pregnenolone and progesterone are derived from cholesterol, and these form the substrate for androgen synthesis. The most potent androgen is testosterone followed in order of decreasing activity by Δ^4androstenedione and dehydroepiandrosterone. Testosterone, however, must be converted to dihy-

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drotestosterone before it is effective at the target gland level. Concentration of testosterone in plasma of women is about 1/20th that of men, but serum levels of Δ^4androstenedione and dehydroepiandrosterone are far higher in women than in men. A large fraction of testosterone in women is derived from Δ^4androstenedione in peripheral tissues.[32] Testosterone may in a very real sense be considered a weak estrogen. In the relative scarcity of endogenous estrogen, testosterone per se can bind to and activate the estrogen receptor with subsequent regulation of the expression of specific genes, which are generally considered estrogen responsive.[51] In fact, when testosterone is administered to women who have had ovariectomies, serum estrone and estradiol levels rise appreciably (Table 1).[25]

Are androgens merely intermediates in the biosynthesis of estrogens or actual secretory products of the ovary? In the polycystic ovary syndrome of Stein-Leventhal, the secretion of urinary androgens is markedly reduced after wedge resection of the ovaries.[21] The isolation of Δ^4androstenedione in pooled ovarian tissue was demonstrated by Zander.[52] Wedges resected from normal ovaries contained small quantities of Δ^4androstenedione but large amounts of 17αhydroxyprogesterone and Δ^4androstenedione after in-vivo stimulation with human pituitary follicle-stimulating hormone (FSH), whereas polycystic ovaries contained large quantities of Δ^4androstenedione and/or dehydroepiandrosterone without prior stimulation with gonadotropins.[36] High levels of Δ^4androstenedione were found in cystic fluid obtained from polycystic ovaries of Stein-Leventhal.[46] The major radioactively labeled steroids, Δ^4androstenedione, dehydroepiandrosterone, and testosterone, appear to be produced by the ovarian stroma.[29]

ANDROGEN PRODUCTION IN THE AGED WOMAN

The menopausal ovary loses it capability to aromatize sex steroids; the lack of conversion of Δ^4androstenedione to estrone, and testosterone to estradiol, results in elevated levels of serum androgens. Judd, Lucas, and Yen[33] reported the results of ovarian and peripheral vein blood values of androgens in menopausal women.

Table 1. *Serum Estrone and Estradiol (pg per ml) Levels After Administration of Testosterone**

	Patient M.S.		Patient F.F.	
	Estrone	*Estradiol*	*Estrone*	*Estradiol*
Before	74.00	23.80	38.70	31.62
After 2 days	104.30	55.31	45.52	22.24
After 4 days	94.36	61.35	51.87	41.36
After 6 days	100.54	59.53		

*Levels rose after injection of 100 mg of testosterone cypionate in two ovariectomized women.

The mean ovarian testosterone levels were 15-fold higher than in the antecubital vein, and Δ^4androstenedione levels were four to five times higher. Judd and co-workers concluded that ovarian Δ^4androstenedione and testosterone secretion is greater in postmenopausal than in premenopausal women.

A similar study was performed by Greenblatt and co-workers[23] following ovarian stimulation with 5000 IU of human chorionic gonadotropin (hCG) intravenously. The results presented in Table 2 indicate that levels of Δ^4androstenedione are much higher in ovarian vein blood (2.3 ± 0.28 ng per ml) of the menopausal woman than in normal women (1.72 ng per ml)). Peripheral vein (1.15 ± 0.17 ng per ml) and adrenal vein blood (1.72 ± 0.14 ng per ml) levels are also much lower than in ovarian vein blood. Testosterone values are also higher in the menopausal group and significantly higher than in postmenopausal peripheral and adrenal vein blood samples. Both Δ^4androstenedione and testosterone rose dramatically in patients studied 30 minutes after an intravenous injection of hCG; the former was much higher than the latter (Fig 1). When adrenocorticotropic hormone was administered intravenously to one normal woman and several menopausal women, ovarian and adrenal vein blood obtained by catheterization revealed good adrenal response of Δ^4androstenedione and testosterone but not estradiol (Fig 2).[23]

CLINICAL CONSIDERATIONS

The use of androgens in the management of disorders in women was first suggested by Demarest and Capitain[9] in Europe, and in the United States by Greenblatt.[15] Salmon[45] published a plea for their use in women. Controversy arose since it was claimed that androgens

Table 2. *Mean ± SE Values of Testosterone, Δ^4 Androstenedione, and Estradiol in Menopausal and Nonmenopausal Women**

	Peripheral	Adrenal	Ovarian
	Mean ± SE	Mean ± SE	Mean ± SE
Testosterone (ng/ml)			
Menopausal	0.53 0.06	0.85 0.11	0.91 0.13
Normal	0.28 0.4		0.87
Δ^4Androstenedione (ng/ml)			
Menopausal	1.09 0.10	1.85 0.15	2.12 0.17
Normal	1.47		1.72
Estradiol (pg/ml)			
Menopausal	21.26 2.18	21.44 1.92	30.52 2.49
Normal	41 ± 15 (follicular)		
	58 ± 11 (luteal)		83.1

*Values in 11 menopausal and 10 normal women. Note significantly higher values for Δ^4androstenedione and testosterone in ovarian vein than peripheral blood.

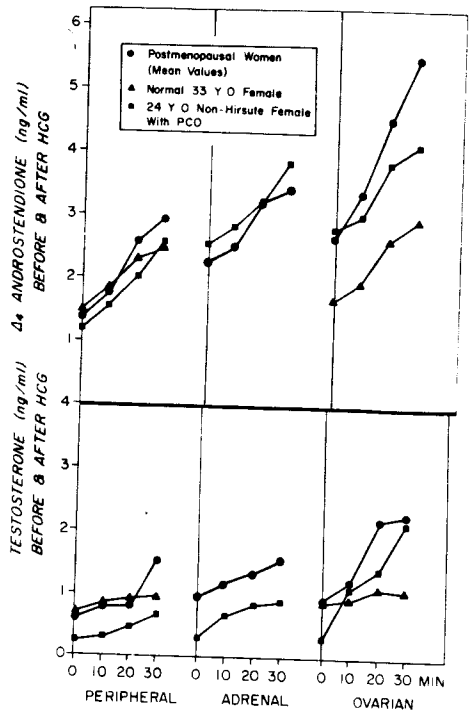

Figure 1. Following 5000 IU of hCG given intravenously the Δ^4 androstenedione and testosterone levels in ovarian vein blood increased considerably in menopausal women.

were contrasexual and ovary-negating and that there were no hypoandrogenic states to justify their use.[28] The editor of the *Journal of Clinical Endocrinology* asked this essayist to referee the gross difference in points of view as published by Salmon and Hamblen. The answer then was the same as it is now. In a letter to the editor, I stated that (1) androgens were not contrasexual; otherwise, we could not account for the appearance of the same androgens in the urine of men and women; (2) androgens, administered in nonvirilizing doses, were not ovary-negating since ovulatory menstrual cycles continue. Massive doses are contraphysiologic and ovary-negating, but large doses of estrogens also suppress ovarian activity; (3) hypoandrogenic states do exist in Addison's disease and in sexual infantilism due to hypopituitarism. Furthermore, hormones are used not only in deficit states but also as pharmacologic agents, just as cortisone is employed in the management of rheumatoid arthritis or adrenaline in an acute case of asthma.[16]

Menopausal Syndrome

None will dispute that estrogens will alleviate vasomotor symptoms such as the hot flash and night sweats. When estrogens

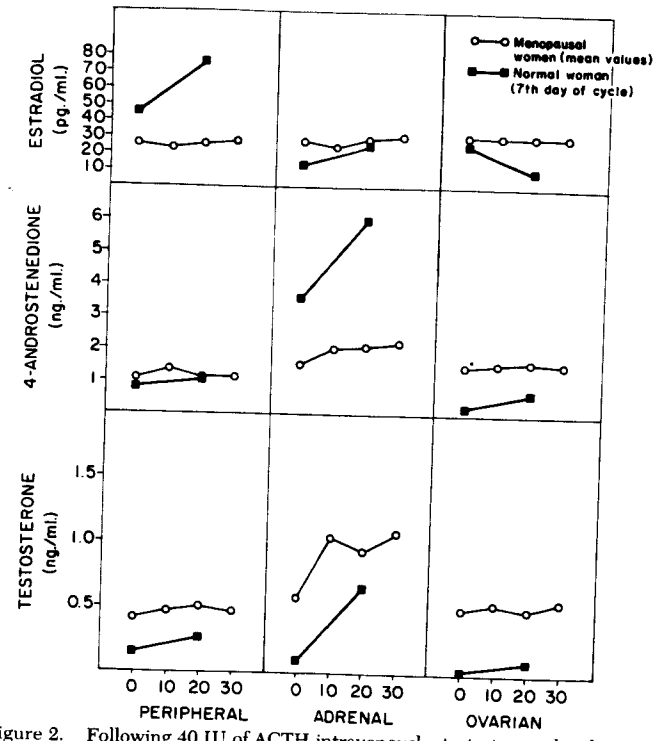

Figure 2. Following 40 IU of ACTH intravenously, testosterone levels rose sharply in the adrenal vein blood in both normal and menopausal women without a rise in peripheral or ovarian vein blood.

are contraindicated, androgens frequently yield relief, though progestogens may also do so. The latter, however, do not provide the same degree of well-being and vigor. When estrogens alone are less than effective, then the addition of an androgen frequently will prove satisfactory. A double-blind randomized study using an estrogen, an estrogen-androgen combination, an androgen, and a placebo revealed that alleviation of hot flashes occurred in 96 per cent on estrogen, 89 per cent on androgen-estrogen, 55 per cent on androgen, and 16 per cent on a placebo.[19] The estrogen-androgen preparation was preferred because not only were hot flashes relieved but also libido was greater than with the estrogen alone (Table 3).

Sexual Dysfunction

When dyspareunia adversely affects and dampens desire for sexual relations in menopausal women, the chief reason usually is vaginal dryness caused by atrophy of the mucosa. Estrogens adminis-

Table 3. *Increase in Libido of Menopausal Women on Androgens**

	Courses of Therapy		Percentage of Patients	
	Private	*Clinic*	*With Increased Libido*	*With No Improvement in Hot Flashes*
AE-1				
Diethylstilbestrol, 0.25 mg	67	21	12.3	3.1
AE-2				
Diethylstilbestrol, 0.25 mg				
Methyl testosterone, 5.0 mg	54	19	23.5	10.4
AE-3				
Methyl testosterone, 5.0 mg	44	19	42.0	23.6
AE-4				
Placebo	36	24	1.8	83.8

Increase in the libido occurred in 65.5 per cent of menopausal women on androgens in comparison to 13.3 on estrogens and 1.8 on a placebo in a double blind study. (*Modified from* Greenblatt et al: Evaluation of an androgen, an estrogen, an androgen-estrogen combination, and a placebo in the treatment of the menopause. J Clin Endocrinol 10:1547, 1950)

tered orally, parenterally, or locally by the use of estrogen creams are often quite satisfactory. When estrogens prove insufficient to restore lost sexual desire, when a trial with androgens is indicated.

Several reports in the literature on androgens in sexual dysfunction meet fairly rigid criteria. In the previously mentioned double-blind study, an increase in libidinous drive was experienced in 65 per cent of the women on androgen, 12.3 per cent on the estrogen only, and 1.8 per cent on the placebo (Table 3).[19] A study of 76 women who received pellet implants of 50 mg of estradiol, a combination of 50 mg of estradiol and 100 mg of testosterone, or a blank showed that only the women on the combination experienced a decided increase in sexual response and frequency of coitus.[48]

Sherwin and Gelfand[46] investigated the effects of intramuscular injections of estradiol valerate, testosterone enanthate, alone or in combination, and a placebo on the physical and psychologic symptoms in surgical menopause. The study was carried out prospectively, in a double-blind cross-over fashion. They concluded "although estrogen reliably relieves atrophic vaginitis and dyspareunia, it has no effect on sexual arousal, desire, or number of orgasms, but in women who received androgens or the combined androgen-estrogen drug, the mean level of sexual desire, the number of sexual fantasies, and the level of sexual arousal was greater than in those women who received the estrogen alone or the placebo."

Androgens are the hormones of choice in helping restore lost sex drive, although estrogens alone may help some women. Even progestogens are occasionally effective. In women with primary frigidity, sex counseling and the assistance of a psychologist to uncover a deep-seated complex may be needed; nonetheless, several trials with hormones may prove rewarding. In an open-ended study of intelligent and apparently well-adjusted women reporting loss of libido, a variety of hormones were tried, including estrogen, androgens, progestogens, and placebo. The response to androgens, especially when pellets of testosterone were employed (1 or 2 pellets of 75 mg of pure testosterone), was most gratifying. Figure 3 charts a typical response. In a series of depressed menopausal women who reported lost or low sexual drive, marked improvement or return of libido was noted in a good percentage following implantation of two pellets of estradiol (25 mg each). Actually, even better results were obtained when a testosterone pellet was added to the regimen. In this series, the low serum free and total tryptophan levels increased decidedly, confirming the findings of Aylward,[1] who found an increase in serum tryptophan after estrogen administration. Coincident with the lessening of depression, a good percentage of these women experienced a marked improvement in libido. The question remains whether the lifting of the depression or the hormones per se accounted for the beneficial sexual response (Table 4).[24]

Sexual libido is a complex phenomenon that can be studied only in the human. The state of one's health and psychogenic, anatomic, neurologic, and hormonal factors play important roles. Many sex therapists believe that most of the problems of sexual dysfunction are psychogenic and therefore could be treated by psychiatrists, psychologists, or sex counselors. This may be true for a small proportion of women, but it is good to remember that libido may be compared to a

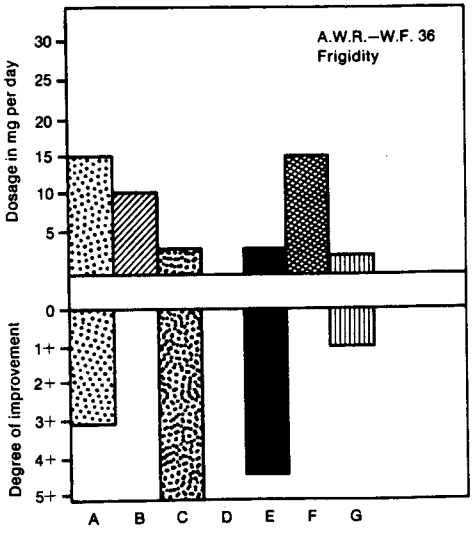

Figure 3. Comparative effects of various hormones on libido in a 36-year-old woman complaining of frigidity. *Top*, sequence of hormone dosages. *Bottom*, Responses (+ to 5+). A = methyltestosterone; B = placebo; C = testosterone by implantation; D = no therapy; E = testosterone propionate s.c.; F = progestogens; G = estrogens. (*From* Greenblatt RB, Leng J-J: Factors influencing sexual behavior. J Am Geriatr Soc 20:49, 1972; with permission).

Table 4. *Serum Tryptophan Values in Depressed Menopausal Women**

	FREE (4.2–6.0 μMOL/ML)		TOTAL (34.3–48.3 μMOL/ML)	
	Before	*After*	*Before*	*After*
Depressed	3.78 ± 0.02	4.78* ± 0.37	35.33 ± 0.67	41.33 ± 5.93
	n = 160	n = 104	n = 160	n = 104
Nondepressed	5.12 ± 0.34	5.79 ± 0.87	44.80 ± 5.93	45.10 ± 3.01
	n = 20	n = 20	n = 20	n = 20

*$P \leq 0.05$.

†Values rose following implantation of two pellets of estradiol (25 mg each). Depression lessened in 84.38 per cent and libido improved in 81.35 per cent. When a pellet of testosterone (75 mg) was added to the regimen of therapy, there was no further lessening of depression, but the intensity of libido increased.

test tube equation—there may be many factors but the androgenic component is essential. A beautiful woman with feminizing testes (androgen-resistant syndrome), as a rule, has little if any sexual libido.

The metabolic fate of testosterone involves conversion into estradiol and 5αhydroxytestosterone; one of the enzymes in the pathway of biosynthesis has aromatase activity (Fig. 4). The intracerebral administration of an aromatase blocker (andros 1,4,6,triene-3,17-dione) will inhibit masculine sex behavior in spite of presence of testosterone.[4] It appears that estradiol and 5αhydroxytestosterone are essential for expression of such behavior rather than the parent testosterone.[5]

OSTEOPOROSIS

Postmenopausal osteoporosis was described by Albright and colleagues in 1940.[2] They believed that loss of calcium and phosphate, the principal minerals of bone, resulted from the estrogen deficiency. In a retrospective study of 220 women with far-advanced osteoporosis followed for 1507 patient-years, Gordan, Picchi, and Roof[14] showed that estrogen replacement therapy reduced the fracture rate to 0.3 per 1000 women per year. Henneman and Wallach[30] reviewed the prolonged use of estrogens and androgens by Albright and concluded that the patient (man or woman) for the most part ceased losing height and stopped having fractures. Hernberg[31] used androgens and estrogen with satisfactory results. Davidson and co-workers[7] found that women with hip fractures had lower levels of free estrogen and testosterone than control subjects.

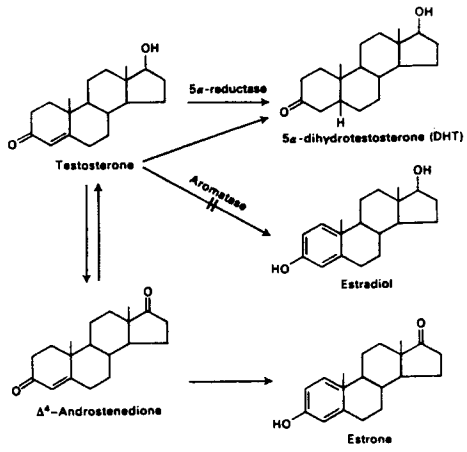

Figure 4. Testosterone is reduced to DHT (dihydrotestosterone, the active form of testosterone) through aromatization to estradiol. A blockade of aromatase activity will inhibit sexual behavior. Estradiol and dihydrotestosterone are essential for expression of sexual behavior. (*From* Christensen LW, Clemens LG: Blockade of testosterone-induced mounting behavior in in the male rat with intracranial application of the aromatization inhibitor, androst 1,4,6-triene-3,17-dione. Endocrinology 97:1545, 1975; with permission.)

Justification for the addition of androgens to the estrogen regimen may be found in a report by Lindsay and co-workers,[35] who showed that the more rapid bone loss in the early menopausal years was associated with low circulating levels of androstenedione and estrogen. Furthermore, they confirmed that steroid agents other than estrogens also prevent bone loss and showed that an anabolic agent (OD 14) was quite effective. Moreover, the addition of a progestational agent to an estrogen regimen, either in combination or sequentially, not only prevented bone decay but actually increased bone density.[41]

Osteoporosis, in most instances, is a preventable disease—provided hormonal therapy is instituted within 3 years of the menopause and continued as long as possible, along with an adequate intake of calcium and a moderate degree of activity (exercise). Actually, it is never too late to start hormonal therapy: even in advanced osteoporosis, further bone decay often may be prevented.

LICHEN PLANUS VEL ATROPHICUS

Invariably associated with thickening and whitening of the vulvar tegument and shriveling of the labia is an intense pruritus. This disorder, usually seen in aging women, may also occur in younger women with a marked estrogen deficiency. Other terms used to describe this condition are leukokraurosis, chronic atrophic dermatitis of the vulva, and kraurosis vulvae.

Little is known about the etiology of the syndrome. Some believe that the estrogen deficiency is associated with a nutritional factor. Swift[49] suspected that achlorhydria prevented proper vitamin

A absorption from the diet. Actually, in our own series of 18 cases, analysis of gastric juices revealed that only three had free hydrochloric acid; the others had low values for total hydrochloric acid.[20] Although the treatment of choice is an estrogen administered orally or parenterally along with the local use of hydrocortisone creams or their analogues, there are many reports on the effectiveness of local testosterone ointments, as recommended by Richardson and Williams.[44]

NOCTURIA AND INCONTINENCE

Disorders of micturition in women not due to infection, anatomic defects, cardiovascular-renal disease, or psychogenic disturbances may be the result of hormonal dysfunction. Nocturnal frequency of micturition is the most common urinary symptom in the elderly, and usually it is not associated with infection.[38] In a double-blind trial using estrogens and placebo in 29 incontinent patients, Walter and colleagues[50] found that symptomatic relief frequently occurred in the estrogen-treated group.

If estrogens are useful, why employ androgens? Androgens alone or in combination with estrogens may be used in those not responsive to estrogens alone. Furthermore, some women who require large dosages of estrogen may actually develop urinary frequency just as occurs early in pregnancy. Actually, testosterone was used for the alleviation of disorders of micturition in menopausal patients by Mocquot and Moricard as far back as 1936.[39] Androgens were also employed in an attempt to reduce the size of fibromyomata. Reduction in the size of massive uterine tumors failed to occur, but the nocturia was alleviated in the majority of women treated with testosterone pellets (Fig. 5).[17] Few reports have appeared to corroborate the beneficial action of androgens in the management of urinary problems. De Watteville[8] felt that in cases of slight stress incontinence transitory relief sometimes followed moderate doses of testosterone propionate (25 mg intramuscularly at 10- to 15-day intervals). Muellner and Hamilton[40] found that testosterone propionate administered to both men and women improved tonus of bladder musculature.

PRIMARY AND SECONDARY HYPOPITUITARISM

Women who develop destructive pituitary lesions (Simmonds' disease) or hypopituitarism as a result of postpartum pituitary necrosis (Sheehan's syndrome) will manifest varying signs and symptoms of multiglandular failure. Hormone replacement therapy with estrogens and progestogens, and thyroid hormone and corticoids when needed, will allow the patient to enjoy a modicum of

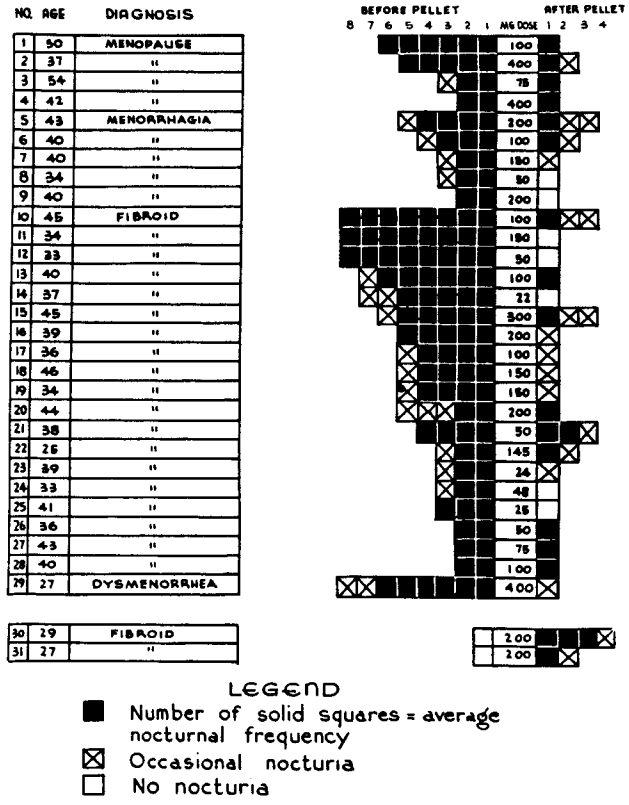

Figure 5. Influence of pellets of testosterone on nocturia. (*From* Greenblatt RB: Testosterone propionate pellet implantation in gynecic disorders. JAMA 121:11, 1943; with permission).

good health. But unless androgens are added to the regimen, sexual hair loss will not be restored, anemia usually remains unresponsive to iron, and vitality remains low. So, too, it is with young women with sexual infantilism resulting from hypopituitarism (Kallmann's syndrome), primary hypopituitarism, craniopharyngioma, chromophobe tumor and failure to menstruate or develop secondary sex characteristics (breast growth and pubic and axillary hair). Menses may be induced and breasts may grow after sequential treatment with estrogen and progestogen, but sexual hair will not appear unless an androgen is added to the regimen of therapy. If after the appearance of pubic and axillary hair a placebo replaces the androgen, sexual hair will regress (Figs. 6).[18] Androgens play a primary role in the maintenance of normal sexual hair.

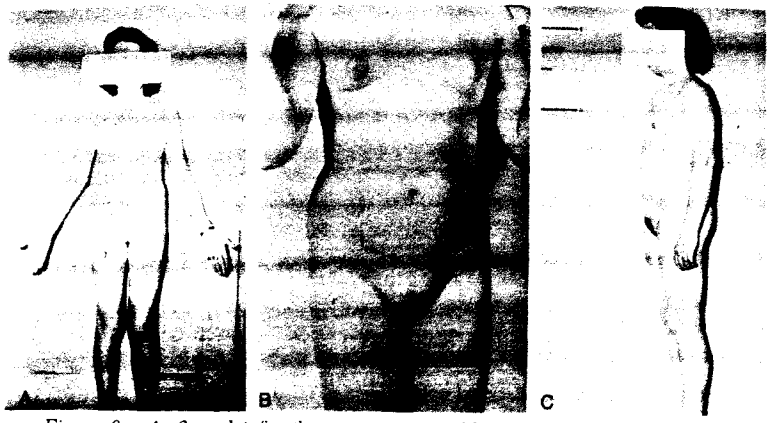

Figure 6. *A*, Sexual infantilism in a 23-year-old woman with hypopituitarism. *B*, Following 2 years of cyclic estrogen and progesterone therapy, breast development occurred, as did regular withdrawal menstrual bleeding, but no growth of sexual hair occurred. *C*, The addition of androgens to the regimen resulted in pubic hair, which regressed when a placebo was substituted. (*From* Greenblatt RB: Sexual infantilism in females. West J Surg 53:222, 1945; with permission).

PREMENSTRUAL SYNDROME

The current notion is that the onset of menopause will put an end to the misery experienced by the woman with premenstrual syndrome. The reverse is more likely to occur. Many such women are destined to suffer the agonies of a severe menopausal syndrome. The personality defects and the inability to cope continue with the changing hormonal status.

Ten to 20 per cent of women in their reproductive years seek medical aid because of cyclic bouts of nervousness, irritability, depression, and hostility often accompanied by bloating and breast tenderness. These signs and symptoms start between day 14 of the cycle and a few days before the expected menses. They usually disappear with the onset of the menstrual flow. The symptom complex usually appears only in ovulatory women, and for that reason faulty progesterone metabolism or an abnormal psychophysical response to progesterone has been suspected. In fact, Gillman[13] warned that progesterone administration might provoke the syndrome.

A dozen theories as to etiology have been offered since Frank first described the syndrome in 1931. Many therapeutic procedures, all with some measure of success, have been offered for its alleviation ranging from psychotherapy, vitamins, diuretics, hormones, tranquilizers, and placebos. Dalton[6] recommends massive doses of progesterone up to 2400 mg per day in the form of suppositories. Magos and Studd[36] suggest inhibiting ovulation by subcutaneous implantation of 100 mg of estradiol pellets at 6-month intervals. Unfortunately, characteristic symptoms of premenstrual syndrome may recur during the seven to 10 days of the progestogen therapy needed to induce orderly withdrawal periods. Barfield and co-workers[3] offered a comprehensive approach to treatment with a progestogen-diuretic-tranquilizer combination, but there is no standard form of treatment since the etiology remains an enigma.

If every modality of treatment fails, a trial of androgens is recommended[26]—such as injection of testosterone (50 mg of testosterone cypionate), or one or two pellets of pure testosterone implanted at 6-month intervals, or methyl testosterone, 2.5 to 5 mg administered orally for 10 to 14 days during the luteal phase.[11]

ENDOMETRIOSIS

In the past, endometriosis was managed either surgically, hormonally, or both. Earliest attempts to modify the pelvic discomfort common to women with endometriosis were by the use of androgens. Several publications attested to its value. Even Hamblen,[28] who had once opposed the use of androgens in gynecic disorders, finally reported on the beneficial use of methyl testosterone in endometriosis. For many years, my group employed two testosterone pellets implanted at 6-month intervals. At this dose level, menses as a rule continued, relief was frequently obtained, and masculinizing symptoms (hirsutism, acne) were rare or minimal. Later, Kistner[34] introduced continuously increasing doses of oral contraceptives to induce a pseudopregnancy. Many women were relieved of their discomfort by the prolonged period of amenorrhea. A good percentage of women, however, could not tolerate the large doses needed to prevent breakthrough uterine bleeding.

With the advent of danazol (an impeded androgen derived from 17-ethinyl testosterone), remarkable relief was attained in 50 to 70 per cent of women treated with a dosage deemed adequate for the particular case. Doses ranged from 100 to 800 mg per day in trials ranging from 3 to 9 months, depending on the severity of the complaints and the objective findings on pelvic examination or laparoscopy. In the larger doses, amenorrhea usually occurred; untoward reactions such as mild acne, hirsutism, weight gain, and many other trivial side effects were frequent.[10,22] The benefits outweighed the untoward effects.

FIBROCYSTIC BREAST DISEASE

Growth hormone, prolactin, insulin, corticoids, androgens, but particularly estrogens and progesterone influence breast growth and function. Fibrocystic breast disease is a common disorder of women. It begins during the early reproductive years as a consequence of histologic changes induced by the monthly ebb and flow of hor-

mones. Inappropriate physiologic responses result in mastodynia, mazoplasia, dysplasia, adenosis, fibromatous changes, and apocrine epithelial metaplasia. These are thought to be abnormal histologic changes rather than disease. However, women with gross breast cysts that occur mainly in the perimenopausal years often have papillary excrescences and ductal papillomas. These women are thought to be at four times greater risk of developing mammary cancer. It is therefore prudent to try to prevent the progression of fibrocystic breast disease. When danazol was first employed in the treatment of endometriosis, many women volunteered the information that breast pain and lumpiness frequently lessened or disappeared. Danazol (in doses varying from 50 to 400 mg per day) has proved quite effective.[42] When danazol is contraindicated because of untoward effects, then bromocriptine, progestogens, thyroid hormones, and even placebo may be tried.[43]

ADDISON'S DISEASE

Chronic adrenal cortical hypofunction, known as Addison's disease, was once a fatal disease. With the advent of cortisone therapy, patients may be kept in a good state of health. The adrenal cortex produces three distinct sets of hormones: the mineralocorticoids (aldosterone), the glucocorticoids (hydrocortisone), and gonadal steroids (androgens). While cortisone and its analogues alone may prove satisfactory in management of most cases, there remain those who also require salt-retaining corticoids such as Florinef or desoxycorticosterone to help maintain electrolyte and water balance and to normalize blood pressure. Because of the androgen deficit, the addition of testosterone to the treatment regimen has proved of value in restoring lost sexual hair, muscle mass, strength, and sexual drive.[20]

UNTOWARD EFFECTS

Large doses of testosterone will cause cessation of menses, induce regressive changes of the vaginal mucosa, and defeminize a woman, but only rarely on low pharmacologic doses. A small percentage of women will develop some hirsutism, mild acne, and, more rarely, voice changes or slight enlargement of the clitoris even on low dosages. If so, further androgen therapy should be discontinued; the untoward effects usually subside. In some cases, one quarter of a teaspoonful of a 1 per cent testosterone cream applied locally to the genital area may be used to advantage in those women highly sensitive to oral or parenteral testosterone. But even this modality is not without some untoward effects in the occasional case. Despite such untoward reactions, many women prefer to continue androgen medication because the benefits far outweigh the inconveniences. Whenever parenteral estrogens in combination with androgens are used in

women who have not had hysterectomies, cyclic 7- to-10 day courses of an oral progestogen are mandatory to assure regular withdrawal bleeding and reduce the risk of endometrial cancer. In those who are opposed to withdrawal periods, 1.25 mg of methyl testosterone or the equivalent and 0.625 mg of conjugated estrogens or the equivalent may be administered orally from Monday to Friday of each week. If breakthrough bleeding occurs on this regimen, then an endometrial biopsy is mandatory to rule out endometrial neoplasia.

In the United Kingdom, estrogen pellets are readily available, but in the United States their availability is limited to physicians who obtain, by application, IND (investigational new drug) status from the FDA. Testosterone pellets are available in the United States; no FDA permission is required.

Androgen dosage should be limited when used orally to 100 mg of methyl testosterone or 50 mg of fluoxymesterone per month; intramuscular injections of testosterone enanthate or cypionate to 50 mg every 3 to 4 weeks; or pellets of testosterone, 75 to 150 mg every 6 months. Table 5 lists available commercial preparations.

CONCLUSIONS

In the menopausal woman, anabolic androgens take on considerable importance. Perhaps their role, aside from being a source of estrogens through conversion, is to conterbalance the continuing catabolic effect of glucocorticoids, which do not, to any degree, di-

Table 5. *Clinical Experience with Androgens*

Oral
Methyl testosterone, 5–25 mg
Fluoxymesterone (Halotestin, Upjohn), 5–10 mg
Danazol (Danocrine, Winthrop), 50–200 mg
Injectables
Testosterone cypionate (Depotestosterone, Upjohn), 50 mg/ml
Testosterone enanthate, 50 mg/ml
Testosterone propionate, 25 mg/ml
Testosterone-estrogen combinations for parenteral use
Depotestadiol (Upjohn), 50 mg testosterone cypionate and 2 mg estradiol cypionate
Pellets
Testopel (Bartor Pharmacals), 75 mg
Oreton (Progynon Associates), 75 mg
Combination estrogen-androgen preparations for oral use
Premarin and methyl testosterone (Ayerst)
0.625 + 5 mg
1.25 + 10 mg
Estrone sulfate and methyl testosterone
1.25 + 2.5 mg (Estratest, Reid-Rowell)
0.625 + 1.25 mg (Estratest (HS), Reid-Rowell)
Topical use
1% Testosterone ointment (can be made up by the pharmacist)

minish with age. In the aging woman, signs of a forme fruste of a Cushing-like syndrome frequently become manifest, such as thinning of the skin (with loss of subcutaneous matrix, easy bruisability, petechial hemorrhages), loss of muscle mass (protein wasting), demineralization of bone (loss of bone mass, collapsed vertebrae, dowager hump), rising blood pressure, and impairment of carbohydrate metabolism. The addition of androgens to estrogen medication may serve to counteract the catabolic milieu of the postmenopausal period.

Androgens are psychotrophic drugs, participating in both physiologic and psychologic components of sexual behavior. They modulate the neurohumors of the brain and influence affective behavior. Androgens in nonvirilizing doses complement estrogens, are synergistic rather than contraphysiologic, and may be employed effectively by most women to whom the steroid has been administered alone or in combination with an estrogen. The menopausal women who has failed to experience the expected benefits of estrogen replacement therapy should be offered a trial of an estrogen-androgen combination. Androgens are helpful in many gynecologic and nongynecologic disorders. Their use has not been exploited fully.

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Nonoral Routes of Estrogen Administration

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There are about 40 million women in the United States who no longer have ovarian function and for whom hormone replacement may be appropriate. Recent estimates by the FDA indicate that only about 4 million women are currently using replacement therapy. Thus, approximately 90 per cent of American women who might benefit from replacement therapy have chosen not to use it. There are several explanations for this, including ignorance about its benefit, contraindications to its use, fear of its risk, development of side effects, and lack of menopausal symptoms. Thus, the challenge in this field is to develop methods that retain the benefits of hormone replacement while reducing or eliminating its side effects and risks.

ORAL ESTROGEN: RISK VERSUS BENEFIT

Estrogens, particularly those administered by mouth, have effects on the gastrointestinal system. These include the symptoms of nausea, vomiting, and abdominal bloating. Estrogens also affect hepatic proteins and lipid metabolism. They enhance the production of carrier proteins, such as sex hormone–binding globulin (SHBG), cortisol-binding globulin (CBG), thyroxine-binding globulin (TBG), transferrin, and ceruloplasmin. These changes do not represent a medical hazard but do alter the results of the clinical laboratory tests used to determine serum levels of the substances bound to these carrier proteins.

Estrogens do influence the hepatic synthesis of other proteins that have been incriminated in causing or contributing to the occurrence of certain disease processes. For example, hypertension may occur or be exacerbated in women receiving estrogen replacement therapy.[8] The elevation of blood pressure is usually reversible when

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