Borrower: WSM

Lending String: *ME6,CHS,MHT,OS2,SVH
Patron: Glaser, Rebecca-139367
Journal Title: Obstetrics and gynecology clinics of North America.
ISSN: 0889-8545
System: OCLC
PMID: 14091825

Volume: 14 Issue: 
Month/Year: 1987 Pages: 251-68

Article Author:

Article Title: Greenblatt; The use of androgens in the menopause and other gynecologic disorders

Imprint: Philadelphia ; W.B. Saunders, c1987-

ILLiad TN: 137280

ILL Number: 42545814

Location:
Odyssey: 206.107.42.197
ARIEL No
Ariel: Regular
Charge
Maxcost: 15.00FM

Shipping Address:
Fordham Health Sciences Library
Wright State University
3640 Colonel Glenn Highway
Dayton, OH 45435
Billing Address:
Fordham Health Sciences Library
Fax: 937-775-2232
Email: Barbara.Schaper@Wright.edu
Phone:
Notes:
Cyclical Disorders

Menopause and Other

The Use of Androgens in the

*Robert B. Greenblatt, M.D.*
droteosterone before it is effective at the target gland level. Concentration of testosterone in plasma of women is about 1/50th that of men, but serum levels of Δ¹androstenedione and dehydroepiandrosterone are far higher in women than in men. A large fraction of testosterone in women is derived from Δ¹androstenedione in peripheral tissues.Δ¹ Testosterone may be 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.Δ¹ In fact, when testosterone is administered to women who have had ovariectomies, serum estrone and estradiol levels rise appreciably (Table 1).Δ¹

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.Δ¹ The isolation of Δ¹androstenedione in pooled ovarian tissue was demonstrated by Zander.Δ¹ Wedges resected from normal ovaries contained small quantities of Δ¹androstenedione but large amounts of 17α-hydroxyprogesterone and Δ¹androstenedione after in-vivo stimulation with human pituitary follicle-stimulating hormone (FSH), whereas polycystic ovaries contained large quantities of Δ¹androstenedione and/or dehydroepiandrosterone without prior stimulation with gonadotropins.Δ¹ High levels of Δ¹androstenedione were found in cystic fluid obtained from polycystic ovaries of Stein-Leventhal.Δ¹ The major radioactively labeled steroids, Δ¹androstenedione, dehydroepiandrosterone, and testosterone, appear to be produced by the ovarian stroma.Δ¹

**ANDROGEN PRODUCTION IN THE AGED WOMAN**

The menopausal ovary loses it capability to aromatize sex steroids; the lack of conversion of Δ¹androstenedione to estrone, and testosterone to estradiol, results in elevated levels of serum androgens. Judd, Lucas, and YenΔ¹ reported the results of ovarian and peripheral vein blood values of androgens in menopausal women.

<table>
<thead>
<tr>
<th>Table 1. Serum Estrone and Estradiol (pg per ml) Levels After Administration of Testosterone*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT M.S.</strong></td>
</tr>
<tr>
<td>Before</td>
</tr>
<tr>
<td>After 2 days</td>
</tr>
<tr>
<td>After 4 days</td>
</tr>
<tr>
<td>After 6 days</td>
</tr>
<tr>
<td><strong>PATIENT F.F.</strong></td>
</tr>
<tr>
<td>Before</td>
</tr>
<tr>
<td>After 2 days</td>
</tr>
<tr>
<td>After 4 days</td>
</tr>
</tbody>
</table>

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

**USE OF ANDROGENS IN THE MENOPAUSE**

The mean ovarian testosterone levels were 15-fold higher than in the antecebulal vein, and Δ¹androstenedione levels were four to five times higher. Judd and co-workers concluded that ovarian Δ¹androstenedione and testosterone secretion is greater in postmenopausal than in premenopausal women. A similar study was performed by Greenblatt and co-workers following ovarian stimulation with 5000 IU of human chorionic gonadotropin (hCG) intravenously. The results presented in Table 2 indicate that levels of Δ¹androstenedione are much higher in ovarian vein blood (2.3 ± 0.28 ng per ml) of the menopausal woman than in normal women (1.72 ± 0.17 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 Δ¹androstenedione 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 adrenocorticotropin 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 Δ¹androstenedione and testosterone but not estradiol (Fig 2).Δ¹

**CLINICAL CONSIDERATIONS**

The use of androgens in the management of disorders in women was first suggested by Demarest and CapitaniΔ¹ in Europe, and in the United States by Greenblatt.Δ¹ SalmonΔ¹ published a plea for their use in women. Controversy arose since it was claimed that androgens

**Table 2. Mean ± SE Values of Testosterone, Δ¹ Androstenedione, and Estradiol in Menopausal and Nonmenopausal Women**

<table>
<thead>
<tr>
<th></th>
<th>Peripheral</th>
<th>Adrenal</th>
<th>Ovarian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TESTOSTERONE (ng/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal</td>
<td>0.53 ± 0.06</td>
<td>0.85 ± 0.11</td>
<td>0.91 ± 0.13</td>
</tr>
<tr>
<td>Normal</td>
<td>0.28 ± 0.4</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Δ¹Androstenedione</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal</td>
<td>1.09 ± 0.10</td>
<td>1.85 ± 0.15</td>
<td>2.12 ± 0.17</td>
</tr>
<tr>
<td>Normal</td>
<td>1.47</td>
<td>1.72</td>
<td></td>
</tr>
<tr>
<td><strong>ESTRADIOL (pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal</td>
<td>21.26 ± 2.18</td>
<td>21.44 ± 1.92</td>
<td>30.32 ± 2.49</td>
</tr>
<tr>
<td>Normal</td>
<td>41 ± 15 (follicular)</td>
<td>58 ± 11 (luteal)</td>
<td>83.1</td>
</tr>
</tbody>
</table>

*Values in 11 menopausal and 10 normal women. Note significantly higher values for Δ¹androstenedione and testosterone in ovarian vein than peripheral blood.
SEXUAL DISCRIMINATION

The problem was greater when the estrogen alone (Fig. 9). In the estrogen groups, the dose of the estrogen alone (Fig. 9) was greater than in the estrogen plus progesterone group, and this was expected, as the lower doses of estrogen were also used in the estrogen alone group. The estrogen plus progesterone group had lower levels of estrogen and progesterone, and the estrogen-only group had higher levels of both hormones. A double-blind, randomized study using estrogen only in the estrogen group was expected to provide the most accurate information about the effects of estrogen on the endometrium, as well as its effects on other reproductive organs. Therefore, when the estrogen dose was the same in both groups, estrogen alone was the choice of treatment. However, when estrogen was also used in the estrogen plus progesterone group, estrogen levels were lower, and this was expected to provide more accurate information about the effects of estrogen alone.

Figure 2: Comparison of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) levels post-ovulation.

Figure 3: Comparison of Estradiol levels pre- and post-ovulation.

Figure 4: Comparison of Testosterone levels pre- and post-ovulation.

Figure 5: Comparison of 4-androstenedione levels pre- and post-ovulation.

Figure 6: Comparison of Estradiol levels pre- and post-ovulation.

Figure 7: Comparison of Testosterone levels pre- and post-ovulation.

Figure 8: Comparison of 4-androstenedione levels pre- and post-ovulation.

Figure 9: Comparison of Estradiol levels pre- and post-ovulation.

Hypothalamic-pituitary activity in adrenal is decreased in female rats, as estrogen levels are lower. The ovaries are stimulated by estrogen, leading to decreased adrenal activity.
Table 3. Increase in Libido of Menopausal Women on Androgens*  

<table>
<thead>
<tr>
<th>COURSES OF THERAPY</th>
<th>PERCENTAGE OF PATIENTS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>With Increased Libido</td>
<td>With No Improvement in Hot Flashes</td>
</tr>
<tr>
<td></td>
<td>Private</td>
<td>Clinic</td>
<td>12.3</td>
</tr>
<tr>
<td>AE-1</td>
<td>67</td>
<td>21</td>
<td>12.3</td>
</tr>
<tr>
<td>Diethylstilbestrol, 0.25 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE-2</td>
<td>54</td>
<td>19</td>
<td>23.5</td>
</tr>
<tr>
<td>Diethylstilbestrol, 0.25 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE-3</td>
<td>44</td>
<td>19</td>
<td>12.6</td>
</tr>
<tr>
<td>Methyl testosterone, 5.0 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE-4</td>
<td>36</td>
<td>24</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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). 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 Gelfand48 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 estrone 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 deepseated complex may be needed; nonetheless, several trials with hor-
Table 4. Serotonin Tryptophan Values in Depressed Menopausal Women

<table>
<thead>
<tr>
<th></th>
<th>Free (4.2–6.0 μMOL/ML)</th>
<th>Total (34.3–48.3 μMOL/ML)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Depressed</td>
<td>3.75</td>
<td>4.75</td>
</tr>
<tr>
<td></td>
<td>± 0.02</td>
<td>± 0.37</td>
</tr>
<tr>
<td>n = 160</td>
<td>n = 104</td>
<td>n = 160</td>
</tr>
<tr>
<td>Nondepressed</td>
<td>5.12</td>
<td>5.79</td>
</tr>
<tr>
<td></td>
<td>± 0.34</td>
<td>± 0.87</td>
</tr>
<tr>
<td>n = 20</td>
<td>n = 20</td>
<td>n = 20</td>
</tr>
</tbody>
</table>

*P < 0.05

Values rose following implantation of two pellets of estradiol (20 mg each). Depression lessoned in 84.38% per cent and libido improved in 91.35% 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.

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

Osteoporosis

Postmenopausal osteoporosis was described by Albright and colleagues in 1940. 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 showed that estrogen replacement therapy reduced the fracture rate to 0.3 per 1000 women per year. Henneman and Wallach 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 used androgens and estrogen with satisfactory results. Davidson and co-workers found that women with hip fractures had lower levels of free estrogen and testosterone than control subjects.

USE OF ANDROGENS IN THE MENOPAUSE

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 the male rat with intracranial application of the aromatization inhibitor, androst 1,4,6-triene-3,17-dione. Endocrinology 97:1545, 1978, with permission.)

Justification for the addition of androgens to the estrogen regimen may be found in a report by Lindsay and co-workers, 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 anabolic agent (OD 14) was quite effective. Moreover, the addition of a progesterational to an estrogen regimen, either in combination or sequentially, not only prevented bone decay but actually increased bone density.

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 shrinking 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 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. 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.

**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. In a double-blind trial using estrogens and placebo in 29 incontinent patients, Walter and colleagues 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月末 and Morales as far back as 1936. Androgens were also employed in an attempt to reduce the size of fibroids. 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). Few reports have appeared to corroborate the beneficial action of androgens in the management of urinary problems. De Watteville 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 found that testosterone propionate administered to both men and women improved tonus of bladder muscularity.

**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 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, craniofaryngioma, 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). Androgens play a primary role in the maintenance of normal sexual hair.
Use of Androgens in the Menopause

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 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—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 3 mg administered orally for 10 to 14 days during the luteal phase.

Endometriosis

In the past, endometriosis was treated 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, 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 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. 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, mastalgia, 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 have papillary excrecescences 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. When danazol is contraindicated because of untoward effects, then bromocriptine, progestogens, thyroid hormones, and even placebo may be tried.43

ADDITION'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 deoxycorticosterone 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.40

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

USE OF ANDROGENS IN THE MENOPAUSE

women who have not had hysterectomies, cyclic 7- to-10 day courses of an oral progesterone 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 enanbate 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 counterbalance the continuing catabolic effect of glucocorticoids, which do not, to any degree, di-

<table>
<thead>
<tr>
<th>Table 5: Clinical Experience with Androgens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Injectable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Testosterone-estrogen combinations for parenteral use</td>
</tr>
<tr>
<td>Pellets</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Combination estrogen-androgen preparations for oral use</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Topical use</td>
</tr>
</tbody>
</table>
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 physiological and psychologic components of sexual behavior. They modulate the neurohormones of the brain and influence affective behavior. Androgens in nonvirilizing doses complement estrogens, are synergistic rather than contraprophysologic, and may be employed effectively by most women to whom the steroid has been administered alone or in combination with an estrogen. The menopausal woman 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.

REFERENCES

4. Baum MJ, Starr MS: Inhibition of sexual behavior by dopamine antagonist or serotonin agonist drugs in castrated male rats given estradiol or dihydrotestosterone. Pharmacol Biochem Behav 13:57, 1980
6. Dalton K: Sex hormone binding globulin concentrations in women with severe premenstrual syndrome. Postgrad Med 75:360, 1984
17. Greenblatt RB: Testosterone propionate pellet implantation in gynecologic disorders. JAMA 121:11, 1943
26. Greenblatt RB: Syndrome of major menstrual molimina with hypermenorrhoea allevi ated by testosterone propionate. JAMA 115:120, 1940
The Menopause

Marcelle I. Cedars, M.D.,* and Howard L. Judd, M.D.†

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 benefits, 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. The elevation of blood pressure is usually reversible when

---

*Fellow, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, California
†Professor, Department of Obstetrics and Gynecology, and Chief, Division of Reproductive Endocrinology, UCLA School of Medicine, Los Angeles, California