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ANDROGEN THERAPY IN GYNECOLOGY

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MORE THAN 20 YEARS AGO, androgens were added to the therapeutic armamentarium of the gynecologist. Since then, male hormones have been used extensively for women suffering from various gynecologic disorders, and a great number of papers have been published on this subject. Nevertheless, no unanimity has yet been reached on the real value of this so-called paradoxical hormonal therapy, and an endocrinologist as competent as Hamblen has condemned indiscriminate use of androgens[8] and stated again in a recent discussion that this hormone should never be given to a woman suffering from a menopausal syndrome.[9] Furthermore, there is today an increasing tendency to use, instead of testosterone, new synthetic steroids which apparently have more pronounced anabolic effects with less marked virilizing properties. Therefore, it may be useful to discuss the rationale for the use of testosterone and its esters in women and to report personal impressions on the results obtained in a gynecologic office practice even though this experience cannot be based on sound statistical material.

In our opinion, the term "paradoxical hormone therapy" is not very adequate, for it is now well known that considerable amounts of androgenic substances are present in any healthy woman, and that these substances are the product of the physiologic metabolism of steroids from the adrenal cortex. There is good evidence that androgens are secreted by the ovaries of birds during the breeding season and also by the ovaries of some species of mammals. However, it has so far not been proved that detectable amounts of testosterone are produced by the ovary in the normal woman (no fluctuation of urinary androgens after castration or during the menstrual cycle).

Androgens are regularly found in the female organism, but nothing definite is known as yet on their possible physiologic role. The only author we can quote in this connection is Wilkins[23] who found that in occasional cases of ovarian agenesis, pubic hair growth was obtained only if testos-

terone was added to the estrogen treatment. According to the experimental findings of Gaarenstrom and de Jongh,[4] testosterone plays a definite role in the induction of ovulation in rats, but no clinical or experimental evidence for a similar role in the woman has yet been reported.

EFFECTS OF ANDROGEN THERAPY

The effects of androgen administration on the female genital organs have been extensively studied in laboratory animals, and these experiments are thoroughly discussed in several excellent and complete reports, e.g., Wenner,[22] Carter, Cohen, and Shorr,[2] Dorfman and Shipley.[3] The action of pathologic amounts of androgens in women becomes evident in cases in which the secretion of these steroids by the adrenals or the ovary is increased (adrenogenital syndrome, adrenocortical-like ovarian tumor, arrhenoblastoma, occasional cases of Stein-Leventhal syndrome). Amenorrhea, acne, hypertrichosis, and lowering of the voice are the most striking signs of such an androgenic virilization. The various effects of testosterone and its esters on the female organism, which have been observed in clinical studies and in animal experiments, may be classified in 4 groups (*see Table 1*).

The therapeutic possibilities of androgens in women are based a) on the inhibition or modification of the effects of estrogens on their target organs and b) their general effects on metabolism and psychic condition. In fact, numerous reports in the medical literature leave no doubt that successful treatment of various gynecologic disorders by androgens is possible. It is equally true, however, that many physicians hesitate to prescribe testosterone for women, because they fear untoward side effects, especially virilization, which is related to its proliferative action on its proper target organs (Table 1, Part III). This complication is very real, but it is not an insurmountable obstacle to androgen therapy in women, provided that certain clinical correlations are not neglected.

The degree of virilization depends, of course, upon the total amount of testosterone given. A prolonged continuous treatment with small doses is, however, more likely to produce the effect than higher doses given either for a short period or intermittently. Moreover, the range in individual susceptibility is rather wide, and, just as in the fields of bio-assay and pharmacology, it is not possible to define a "minimal effective dose."

Acne

The various signs of virilization generally appear in a definite order. Acne is one of the earliest symptoms, but does not develop in all patients.

Table 1. Effects of Androgens on the Female

I. Antiestrogenic action	
a. Direct action: Inhibition of the estrogenic effects on the target organs (endometrium, myometrium, cervix, vagina, mammary gland).	
b. Indirect action: Inhibition of the gonadotrophin secretion by the pituitary gland with subsequent diminution of the estrogen secretion by the ovary.	
II. Progesterone-like action	
Modification of estrogen effects on the target organs (endometrium, myometrium, cervix, vagina, mammary gland).	
III. Proliferative action	
a. Synergistic with estrogens: vulva (clitoris, especially); vagina; nipples.	
b. Specific: hirsutism, larynx, tubular epithelium of the kidney, sebaceous glands.	
IV. General effects	
a. Metabolic:	Retention of nitrogen, and possibly creatine
	Increased protein synthesis
	Retention of phosphorus and drop of serum acid-phosphatase
	Retention of calcium and increased osteosynthesis
	Retention of chloride, potassium, and sodium and secondary retention of water.
b. Psychic:	Increased feeling of well-being and energy; antidepressive, especially in menopausal and postmenopausal patients.

It is due to a hypersecretion of the sebaceous glands and a hyperproliferation of their epithelium, but other factors, in addition to these direct testosterone effects, seem to intervene.

Hirsutism

Hirsutism, starting in the face and extending to the arms and legs and finally to the trunk, is another early sign. There is wide genetic and racial variation in normal pilosity, and the "nuisance value" of additional hair growth produced by androgen administration varies accordingly.

Alopecia

Similar considerations apply to the loss of hair, which may lead to induction of baldness, but this is usually a later and less typical symptom.

Voice Changes

Voice changes, varying from slight huskiness to a male pitch, come late in the order of appearance. They are due to a hyperemia followed by a thickening of the vocal cords, and, contrary to the other symptoms discussed so far, the latter morphologic change may not be reversible by discontinuing the administration of the male hormone. It should be noted that even the reversible signs may take months to disappear.

Enlargement of the Clitoris

Similar considerations apply to the androgen effect on the clitoris. Small doses may lead to hyperemia causing increased sensitivity which sometimes is registered as uneasiness and burning. Higher doses and prolonged treatment (over 300 mg. of testosterone propionate monthly, according to Salmon[17]) may induce hypertrophy which will persist for a long time after cessation of treatment.

Breast Changes

Diminution in size and flaccidity of the breasts is a common manifestation, and this effect may be undesirable in some patients.

Other Side Effects

Other side effects must be attributed to interference with general metabolism or mental outlook (Table 1, Part IV). The severe clinical signs of hypercalcemia will occur only at the high dosage used in cancer therapy, whereas a gain in weight due to water retention and protein synthesis has frequently to be reckoned with. An increase or excess of mental energy may take the form of insomnia, irritability, or even aggressiveness.

On the other hand, many of the side effects discussed can be counteracted effectively by an adequate, concomitant treatment: acne, by local treatment of the skin; hirsutism, by cosmetic measures such as bleaching or depilations; vulval irritation, by ointments; gain in weight, by restriction of salt and calories in the diet and by saluretics; irritability, by sedatives or tranquilizers.

It has already been stated that intermittent dosage will minimize the hazards of these side effects. Moreover, complete cessation of treatment at their first appearance certainly will minimize any lasting damage. It is, however, only fair to inform the patient at the start that she may expect these effects to occur. Thus she herself will be able to recognize the

early symptoms of masculinization and the other side effects, and to decide at any time whether the beneficial effects of the treatment outweigh its disadvantages.

THERAPEUTIC INDICATIONS

Turning now to the discussion of therapeutic indications, androgen treatment may be useful for these conditions:

1. Osteoporosis or general debilitated condition
2. Psychic asthenia and mild depression (mainly in premenopausal and menopausal women)
3. Mild stress incontinence
4. Menopausal syndrome (especially in patients with fibroids, endometriosis, or previous endometrial or breast cancer)
5. Dyspareunia due to atrophic vaginitis. Frigidity (mainly in premenopausal or menopausal patients)
6. Functional uterine bleeding
7. Endometriosis
8. Uterine fibroids
9. Dysmenorrhea
10. Premenstrual pelvic congestion and premenstrual tension
11. Suppression of lactation or painful postpartum congestion of the breasts. Mastalgia and benign mastopathia (adenofibrosis, non-puerperal lactating mamma, cystic disease)
12. Generalised breast cancer (mainly bone metastasis and for patients in the younger age group).

It should first be emphasized that the metabolic action of testosterone and the gain in weight it produces, far from always being undesirable, is one of the main reasons why the physician prescribes the male hormone to patients in a debilitated condition or suffering from osteoporosis, without any sexual disorder. Until recently, the usefulness of this anabolic, symptomatic treatment was compromised by the risk of masculinization. Other measures of treatment were available, and the urgency of the indication did not warrant taking the risk. This difficulty is being overcome by the development of the new synthetic steroids (e.g., norsteroids) which seem to combine marked anabolic properties with reduced androgenicity.

It remains to be seen, however, whether these new compounds have the same antidepressive and stimulating properties as testosterone.

The same is true for another peculiar and specific effect of this androgen, i.e., the increase in bladder tonus, first described by Muellner and Hamilton. It is the writer's experience that in cases of slight stress incontinence transitory relief will sometimes follow a treatment with moderate doses of testosterone (e.g., 25 mg. testosterone proprionate intramuscularly 2 to 3 times per month).

Menopausal Syndrome

Historically, the earliest indication for the use of androgens in women was the menopausal syndrome, and it probably still is one of the main indications. Many of the symptoms of the menopausal syndrome are undoubtedly due to the cessation of ovarian function. Therefore, the logical therapy is replacement of the lacking ovarian hormones, and the administration of estrogen has indeed proved to be the most effective treatment. It abolishes rapidly the classical menopausal symptoms, especially hot flashes and sweating. However, the doses needed will, in some patients, produce pelvic congestion, uterine bleeding, and painful swelling of the breasts. Prolonged administration, even of small doses, carries the risk of pathologic epithelial proliferation in the endometrium (cystic glandular hyperplasia) and in the mammary gland (adenofibrosis and formation of cysts, or Reclus' disease). There is some evidence that these disorders may be identified with precancerous states.

There is no definite proof that estrogens are cancerigenic; but there is ample experimental evidence, supported by some clinical observations, that cancer develops more easily if the endometrial or mammary tissue is maintained by estrogens in a state of excessive proliferation. For this reason, there is a widespread feeling that estrogens should not be administered to menopausal and postmenopausal women. In the writer's opinion, estrogens may be given in most cases without risk provided that the dosage is intermittent (e.g., oral daily administration during 20 days of each month) and that the vaginal epithelium, which is particularly sensitive to estrogen, shows no excessive response (less than 50 per cent cornification and/or less than 65 per cent karyopyknosis in the superficial cells of the vaginal smear).

There are, however, conditions which definitely preclude the use of estrogens.

1. Patients previously treated for cancer of the breast or the corpus uteri, unless the tumor has developed more than 5 years after the menopause. Treatment with estrogens of symptoms due to spontaneous menopause or therapeutic castration could stimulate recurrent or metastatic growth of endometrial or mammary cancer tissue which may have preserved its responsiveness to this hormone.
2. Patients with uterine fibroids or endometriosis. Cessation of ovarian function in the menopause or after castration removes the proliferative

stimulus, and the symptoms of these disorders will disappear. If the concomitant menopausal syndrome were treated with estrogens, these symptoms would reappear.

In these 2 groups, testosterone may usefully replace the contra-indicated estrogen treatment, even though the male hormone, in a dosage which avoids untoward side effects, cannot be expected to bring full relief from menopausal complaints in all cases.

The simultaneous administration of testosterone and estrogen, first used by Demarest and Capitain in 1937, has rapidly gained widespread recognition. In a carefully designed clinical study, Greenblatt *et al.*[5] have demonstrated beyond doubt the superiority of the combined treatment (5 mg. methyl-testosterone and 0.25 mg. stilbestrol) over each of the single treatments and a placebo, and similar results have been reported by others including de Watteville and Lunenfeld[21] (5 mg. methyl-testosterone and 0.01 mg. ethinylestradiol), Suenderhauf and Aeppli[19] (25 mg. testosterone propionate and 1 mg. estradiol dipropionate). This superiority stems from an advantageous combination of synergistic and antagonistic effects. Complete relief of menopausal symptoms is obtained with lower dosage of the components, thus avoiding the undesirable side effects of each hormone. The improvement in general condition and mental outlook is particularly striking, and the present author has noticed occasionally that the combined preparation may be habit-forming. It should not be overlooked that the ultimate aim of any treatment of the menopausal syndrome is the progressive adjustment of the patient to a new endocrine equilibrium with no need for further hormone treatment.

Estrogen and androgen synergize each other also in their effect on the vagina and the vulva. The atrophic vaginal epithelium is stimulated by testosterone alone. Moderate doses (5 × 25 mg. testosterone proprionate in 10 days) produce proliferation of the intermediate and superficial cell layers with abundant glycogen deposition, and a characteristic aspect of the vaginal smear, which has been described in detail by Pundel.[14] The combination of androgen with estrogen enhances the proliferation and desquamation of the vaginal epithelium, while the estrogen effect of cornification and karyopyknosis in the superficial cell layer is inhibited. These changes favor the development of the Doederlein bacilli, thus increasing the acidity of the vaginal secretion and improving the self defense of the vagina against pathologic germs. As a consequence, postmenopausal dyspareunia due to the dryness and inflammation of the mucous membrane is cured by testosterone and, even more efficiently, by the combined treatment. Richardson and Williams[15] report the disappearance of dyspareunia in cases of kraurosis vulvae and a noticeable regression of the skin lesions after local treatment with a testosterone propionate ointment.

The hyperemia of the vulva and clitoris which occurs following the administration of these hormones, singly or in combination, increases the sensitivity and improves the response of the female partner during intercourse. The administration of testosterone to menopausal women led to the discovery of its specific enhancing effect on the sex drive.[7] Since then clinical experience has shown that the male hormone augments or complements the effects of other drugs in the treatment of frigidity. It should be emphasized, however, that this disorder, especially in younger women, is often of psychic rather than endocrine origin, and therefore psychotherapy may be indicated.

Functional Uterine Bleeding

Another gynecologic disorder frequently treated with androgens is functional uterine bleeding. Here, the use of male hormone derives from its direct and indirect anti-estrogenic action (Table 1, Part I). The androgen-induced inhibition of gonadotrophic secretion by the pituitary gland has been clearly established in numerous animal experiments.[3] In menopausal women, the increased urinary output of pituitary gonadotrophin is reduced significantly or even completely suppressed by an intensive treatment with androgens (Laroche *et al.*,[10] 15 to 20 × 25-50 mg. testosterone propionate within 35-60 days; Salmon,[17] 815 mg. testosterone propionate within 27 days). The suppression of ovarian function, observed as a consequence of this pituitary inhibition, can be reversed either by the simultaneous administration of gonadotrophin, or by discontinuing the androgen treatment.

In women the menstrual cycle is completely suppressed by 150 mg. testosterone or more per week throughout the entire cycle.[2] If androgens are given to women or experimental animals during the first phase of the cycle, corpus luteum formation does not occur, whereas post-ovulatory administration does not interfere with luteal function. The changes in menstrual rhythm frequently observed during testosterone administration probably reflect changes in the pituitary-gonadal relationship (shortened cycle after moderate dosage, delayed menstruation after higher doses starting earlier in the cycle).

The direct anti-estrogenic action of testosterone at the level of the target organs has been demonstrated by the simultaneous administration of both hormones to castrated animals or women. In the uterus and the breast, the estrogen-induced proliferation is inhibited by adequate

amounts of the male hormone. Smaller doses seem to exert a slight progesterone-like effect on the estrogen-primed endometrium.

Although many authors have reported that arrest of flow is obtained with testosterone in functional uterine bleeding from a hyperplastic endometrium, the writer feels that the same result can be achieved in a more physiologic way by the administration of estrogens combined with increasing amounts of progesterone. According to Greenblatt and Barfield,[6] excellent results are obtained with a combination of estrogens with testosterone and progesterone. Testosterone has proved to be very effective in the prevention of *recurrent* functional bleeding. Doses between 300 and 1000 mg. per month produce marked regressive changes in the endometrium, and consequently a sharp reduction in menstrual flow or even temporary amenorrhea. This latter effect may be desirable in cases of recurrent cystic glandular hyperplasia in that it will frequently reduce the menstrual flow without major changes in menstrual rhythm or endometrial histology; it seems likely that testosterone modifies the development of the coiled arteries. Several authors have confirmed that the beneficial effect of higher doses often persists for several months after the treatment has been discontinued.

Although the usefulness of testosterone in functional uterine bleeding is established, the new synthetic oral gestagens may prove to be superior.

Endometriosis

In cases of endometriosis, testosterone, even in moderate doses, will inhibit the proliferation of the aberrant tissue, thus relieving the pain in a high proportion of patients. Prolonged treatment with higher doses may lead to complete atrophy of the implanted endometrium without recurrence when the normal menstrual rhythm is resumed after stopping the androgen treatment.[2] This temporary "hormonal castration" is indicated when surgical removal of the growth is not feasible or not complete. However, recent experiments which contradict the foregoing clinical findings should be mentioned here. Indeed, Scott and Wharton[18] did not observe histologic changes in endometriosis that was surgically produced in Rhesus monkeys after treatment with 6 mg. of testosterone in aqueous suspension, twice a week during 6 to 27 months.

Uterine Fibroids

It has been observed that abnormal uterine bleeding may be treated successfully with androgens even in the presence of uterine fibroids. This may be attributed partly to the effect on the endometrium which has already been discussed, since this condition seems to be associated frequently with a hyperplastic mucous membrane. On the other hand, there is no doubt that androgens inhibit the further growth of fibroids a) by removing the estrogen stimulus through "hormonal castration," and b) by counteracting the estrogen effect at the level of the myometrium, the mechanism of the anti-estrogenic effect being the same as discussed before. The prevention of estrogen-induced fibroids in castrated guinea pigs by simultaneous administration of testosterone (Lipschutz *et al.*, 1939, v. Wattenwyl, 1944) demonstrates the local effect. The postmenopausal regression of fibroids may be anticipated not only by radiological castration, but also by "hormonal castration" with high androgen doses, and sometimes a patient, if properly advised, may prefer a certain degree of virilization to the menopausal syndrome following irradiation, or to the hazards of surgical removal of the fibroids. Hysterectomy or myomectomy remains, of course, the treatment of choice, and androgens will be indicated mainly in premenopausal patients. In these, it may be possible to keep the fibroid growth under control until the onset of natural menopause, without having to prolong or to intensify the androgen treatment unduly.

If the patient belongs to a younger age group and provided that the fibromatous uterus does not exceed a certain size, a treatment with 50 to 150 mg. of testosterone per month during several months will frequently suppress the premenstrual pain and reduce the abnormal menstrual flow, and these beneficial effects will usually outlast the treatment by many months. If the fibroids produce dysmenorrhea, this symptom is likely to disappear with the others.

Dysmenorrhea

Dysmenorrhea in general has been extensively treated with androgens, and the literature abounds in favorable reports on a great variety of effective dosages. The author, judging from his own experience, finds himself unable to share this widespread enthusiasm. It should be noted that the etiology of the disorder is manifold; it is unlikely that all cases would respond to the same treatment. As far as hormones are concerned, the writer gives his preference to estrogens which have proved effective mainly in cases of uterine hypoplasia, even in doses which do not suppress ovulation and in spite of the association of progesterone.

Premenstrual Tension

Premenstrual tension is another gynecologic disorder frequently and successfully treated with testosterone. The beneficial effect of moderate or even small doses (15-75 mg. per month) cannot be denied, but the

mechanism of action is not clearly understood. It should be emphasized that the term "premenstrual tension" covers various combinations of numerous symptoms, and that the syndrome cannot be simply equated to an excess of estrogen, as originally suggested by Frank (1931). Although luteal deficiency with relative hyperestrogenism has been noted,[13] the author shares the opinion of Carter *et al.*[2] who place premenstrual tension in the same category as the menopausal syndrome. These authors report successful treatment with estrogens, and, in the experience of the present writer, substitution therapy with estrogens followed by estrogens plus progesterone has given good results in selected cases. Frequently, any hormone treatment will disturb the patient by affecting the menstrual rhythm, and it should not be overlooked that often a symptomatic treatment with tranquilizers and diuretics will bring satisfactory relief.

Painful Congestion of the Breast

In premenstrual tension, the symptom most readily relieved by testosterone is the painful congestion of the breast. The same is true for the painful swelling associated with the suppression of lactation after de livery. If nursing is continued, lactation is not affected by the testosterone treatment which, nevertheless, will bring relief from the painful engorgement. While the effectiveness of estrogens in arresting lactation is well established, their administration will frequently induce or increase hemorrhagic lochia. For this reason, it seems preferable to prescribe, as the author does, a combined treatment, e.g., 5 mg. estradiol dipropionate and 25 mg. testosterone propionate once or twice daily for 3 days, or another similar preparation.[16]

Organic Mastopathy

Breast development depends on the secretory activity of the ovary in addition to direct pituitary stimulation. Therefore, the treatment of functional mastalgia or organic mastopathy (adenofibrosis, nonpuerperal mammary secretion, Reclus' disease) with androgens is again based on the anti-estrogenic and pituitary-inhibiting effect already fully discussed in the sections on uterine functional bleeding and fibroids. Although a stimulating effect of androgens on the mammary gland has been reported in animal experiments, clinical observations often show not only relief of pain, but also regression of abnormally developed mammary tissue when testosterone is given in rather large dosage. Loeser[11] suggests 250 mg. of testosterone propionate per month during 2 to 3 months; and Atkins,[1] 400 mg. of testosterone propionate within 4 weeks. In all cases in which definite morphologic change of the mammary gland is clinically

evident, biopsy or, even better, partial resection of the mammary gland with immediate histologic examination is preferred for the following reasons: 1) The relief obtained by androgen treatment may be only temporary, 2) clinical mastopathy may turn out to be a pre-cancerous condition (Schimmelbusch's disease), 3) the differential diagnosis between benign mastopathy and early cancer may be difficult or impossible. If the morphologic changes are not very marked or if there is only mastalgia, arrest of the pathological development and relief from pain may be obtained with relatively small doses of androgen, (e.g., 75 to 175 mg. testosterone propionate per month for 1 to 4 months.[20] Since the beneficial effect persists for some time after the treatment has been discontinued, it is possible after a few months to stop the administration either definitively or at least for a period of several months.

Breast Cancer

Whereas all the indications for administration of androgens discussed so far are in competition with other therapeutic possibilities, there is one indication for which it is generally agreed that there is no alternative to androgen treatment and that the risk of side effects carries no weight, i.e., generalization of breast cancer with bone metastases. The occasional regeneration of destroyed bone tissue is well established by x-ray photographs, but even more impressive are the dramatic relief from pain and the improvement in general condition, whether or not the lesions progress. In patients far beyond the menopausal age or suffering from soft-tissue metastases, estrogen treatment seems to be superior. On the other hand, this hormone may stimulate the growth of the tumor in premenopausal women in whom, therefore, androgens should be tried first. In fact, the course of the disease is delayed in younger women by ovariectomy. The high doses of androgen given for this condition (at least 300 mg. of testosterone proprionate per week, for several months) will certainly suppress ovarian activity, but it seems likely that other mechanisms contribute to the beneficial effect of androgens, since these effects are produced also in postmenopausal patients. Whatever the mechanism of the hormonal treatment, the result is not a destruction of the tumor, but only relief from symptoms, temporary arrest of the growth, and delay of the final, fatal outcome. It is hoped that the development of new antimitotic drugs will permit an effective chemotherapy for cancer to add to, or replace treatment by surgery and irradiation.

SUMMARY

Summing up this discussion on the treatment of various gynecologic

disorders with androgens, the following points, which are valid for any treatment with testosterone, must be emphasized: 1) The main effects of the male hormone in the female stem a) from its direct inhibitory action on the gonadotrophic function of the pituitary gland and the subsequent inhibition of ovarian secretion; 2) from the inhibition of the estrogen effects at the level of the target organs. These effects seem to be closely linked with the androgenic potency of the hormone and they are much more difficult to obtain by administration of one of the new synthetic steroids with anabolic or progestational properties.

2) Pathologic morphologic changes in the uterus or the breasts follow at least partly prolonged androgen treatment. The high dosage necessary carries, however, the definite risk of untoward side effects, especially troublesome virilization.

3) If the treatment is discontinued before the side effects have attained a marked degree and before the androgens have led to a distinct hypertrophy of the specific target organs (clitoris, larynx), the side effects will regress slowly after cessation of treatment and finally disappear completely after a few weeks or months.

4) Many functional disorders may be successfully treated by an intermittent administration of small or moderate doses of androgens without any noticeable side effects. The beneficial effect of such a treatment may last for a prolonged period of time after cessation of the hormone administration.

5) It seems probable that oral synthetic gestagens will prove superior to androgens in the treatment of functional uterine bleeding and perhaps of small fibroids.

6) In past cases when androgens have been prescribed for their effects on the general metabolism, they may now be replaced by the new synthetic steroids with increased anabolic, and diminished masculinizing, properties.

The author feels that he cannot do better than quote in conclusion the sentences with which Carter, Cohen and Shorr close their fine paper on the use of androgens in women and which are still pertinent: "Finally, it would be unfair to ignore the opinion which has been vigorously expressed that androgens have no legitimate place in the treatment of women because they are unphysiological for this sex (Hamblen, 1941, 1942). This criticism, which overlooks the participation of androgens in the normal hormonal economy of women, stems in large measure from an understandable anxiety over the possible induction of permanent virilization through their unskillful use. However, such undesirable consequences need not follow, except under special circumstances, if these

agents are intelligently employed and the necessary precautions observed for their prevention—reservations which apply to any potent therapeutic agent."[2]

REFERENCES

1. Atkins, H. J. B. Treatment of chronic mastitis. *Lancet 2*:411, 1940.
2. Carter, A. C., Cohen, E. J. A., and Shorr, E. The use of androgens in women. *Vitamins & Hormones 5*:317, 1947.
3. Dorfman, R. J., and Shipley, R. A. Androgens. New York, Wiley, 1956.
4. Gaarenstrom, J. H., and de Jongh, S. E. Contribution to the knowledge of the influences of gonadotropic and sex hormones on the gonads of rats. New York-Amsterdam, Elsevier, 1946.
5. Greenblatt, R. B., Barfield, W. E., Garner, J. F., Calk, G. H., and Harrod, J. I. Evaluation of an estrogen, androgen, estrogen-androgen mixture, and a placebo in treatment of the menopause. *J. Clin. Endocrinol. 12*:10, 1950.
6. Greenblatt, R. B., and Barfield, W. E. Hormonal control of functional uterine bleeding. *Am. J. Obst. & Gynec. 63*:1, 1952.
7. Greenblatt, R. B., and Scarpa-Smith, C. J. Nymphomania in postmenopausal women. *J. Am. Geriatrics Soc. 7*:339, 1959; *Excerpta Med. III, 14*:91, No. 393.
8. Hamblen, E. C. Androgenic therapy of women. *South M. J. 50*:743, 1957.
9. Hamblen, E. C. The effect of estrogens in the menopause. Trans-atlantic Telephone Symposium, Excerpta Medica Foundation, 1959.
10. Laroche, G., Simonnet, H., and Bompard, E. Influence des sels de testostérone sur l'émination urinaire des principes gonadotropes. *Compt. rend Soc. Biol. 129*:953, 1938.
11. Loeser, A. A. L'hormone mâle en gynécologie et dans le cancer du sein chez la femme. *Praxis* No. 13, 1949.
12. Master, W. H., and Megallon, D. T. Androgen administration in postmenopausal women. *J. Clin. Endocrinol. 10*:348, 1950.
13. Morton, J. H. Premenstrual tension. *Am. J. Obst. & Gynec. 60*:343, 1950.
14. Pundel, J. P. Les frottis androgéniques. *Bull. Soc. Roy. Belge Gyn. Obst. 25*:34, 1955.
15. Richardson, A. C., and Williams, G. A. Topical androgenic hormones in vulvar kraurosis-leukoplakia syndrome. *Am. J. Obst. & Gynec. 76*:791, 1958.
16. Rodenberg, Th. A., and Simon, H. J. Suppression of lactation. *Obst. & Gynec. 15*:522, 1950.
17. Salmon, U. J. Rationale for androgen therapy in gynecology. *J. Clin. Endocrinol. 1*:162, 1941.
18. Scott, R. B., and Wharton, H. R. The effect of testosterone on experimental endometriosis in Rhesus monkey. *Am. J. Obst. & Gynec. 78*:1020, 1959.
19. Suenderhauf, H., and Aeppli, H. Behandlung klimakterischer Ausfall-

erscheinungen mit einer Kombination von Orocyclin und Perandren. *Schweiz. Med. Wschr. 82*:589, 1952.

20. Taylor, H. C., Jr. Endocrine aspects of chronic mastitis; further report on rates of estrogen excretion and results of hormone therapy. *Surg. Gynec. & Obstet. 74*:326, 1942.
21. de Watteville, H., and Lunenfeld, B. Effets cliniques et cytologiques d'un traitement combiné par les oestrogénes et androgènes dans le syndrome ménopausique. *Schweiz. Med. Wschr. 83*:14, 1953.
22. Wenner, R. Der Wirkungsmechanismus des androgenen Hormons auf den weiblichen Organismus und dessen therapeutische Anwendung in der Frauenheilkunde. *Schweiz. Med. Wschr. 81*:1001, 1951.
23. Wilkins, L. *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence.* Springfield, Ill., Thomas, 1950.
24. Witschi, E., and Fugo, N. W. Response of sex characters of adult female starling to synthetic hormone. *Proc. Soc. Exptl. Biol. Med. 45*:10, 1940.

THE USE OF PROGESTATIONAL AGENTS IN OBSTETRICS AND GYNECOLOGY

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Although the corpus luteum was first described almost 300 years ago by the Dutch anatomist Regner de Graaf, widespread clinical application of its secretion, progesterone, has only recently become commonplace in the practice of obstetrics and gynecology. Fraenkel, in 1910, had proved to the satisfaction of his doubting confreres that the fate of the embryo depended upon the functional integrity of the corpus luteum; about the same time Ancel and Bouin demonstrated that the typical progestational changes in the endometrium were produced by the endocrine activity of this same structure. Since the treatment of recurrent abortion and dysfunctional uterine bleeding are still major problems confronting the practitioner in 1960, these historical observations form the background for the therapeutic schemes outlined in this chapter.

After Corner and Allen isolated a crystalline hormone from the corpora lutea of sows in 1929, progress was rapid. The structural formula was soon determined and Wintersteiner produced the hormone from an inert steroid of known composition in 1934. This hormone, called *progesterone* (L. *pro,* in favor of + *gestatio,* from *gestare,* to bear) may be looked upon biochemically as a "flat" molecule with an anterior surface, a posterior surface, and a ketone (=0) group at each end. (*See Fig. 1.*) The progesterone nucleus is a saturated derivative composed of 3 six-membered carbon rings (A, B, C) and a five-membered ring (D): cyclopentanophenanthrene. Since the progestins to be discussed are substituted progesterones or variants of testosterone, it should be noted that substituents on the anterior surface of the molecule are referred to as "beta" positions whereas those on the posterior surface are designated "alpha" positions.

METABOLISM

There is considerable evidence suggesting that both cholesterol and