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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 and stated again in a recent discussion that this hormone should never be given to a woman suffering from a menopausal syndrome. Moreover, 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. Moreover, 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 who found that in occasional cases of ovarian agenesis, pubic hair growth was obtained only if testos-
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. Psychical: 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, concommitant 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 out-
weigh 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. Psychiatric asthenia and mild depression (mainly in premenopausal
and menopausal women)
3. Mild stress incontinence
4. Menopausal syndrome (especially in patients with fibroids, endo-
metriosis, or previous endometrial or breast cancer)
5. Dyspareunia due to atrophic vaginitis. Frigidity (mainly in pre-
menopausal 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 pa-
tients 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, with-
out 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 in-
dication did not warrant taking the risk. This difficulty is being over-
come by the development of the new synthetic steroids (e.g., norsteroids)
which seem to combine marked anabolic properties with reduced andro-
genicity.

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 andro-
gen, i.e., the increase in bladder tonus, first described by Muller and
Hamilton. It is the writer's experience that in cases of slight stress in-

CONTINENCE TRANSITORY RELIEF WILL SOMETIMES FOLLOW A TREATMENT WITH
MILD DOSES OF TESTOSTERONE (E.G., 25 MG. TESTOSTERONE PROPIONATE 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, es-
pecially 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 Rieck's disease). There is some evidence that these
disorders may be identified with precancerous states.

There is no definite proof that estrogens are cancerogenic; 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 admin-
istered to menopausal and postmenopausal women. In the writer's opin-
ion, 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 sensi-
tive to estrogen, shows no excessive response (less than 50 per cent corni-
fication and/or less than 65 per cent keratopynosis 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 men-
opause. Treatment with estrogens of symptoms due to spontaneous meno-
pause or therapeutic castration could stimulate recurrent or metastatic
growth of endometrial or mammary cancer tissue which may have pre-
served 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 estrone, first used by Demarest and Capitan 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 Lunenfeld21 (5 mg. methyl-testosterone and 0.01 mg. ethinylestradiol), Suenderhauf and Aeppli29 (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 propionate 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 Pondel.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, post-menopausal 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 Williams15 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.8 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,11 815 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 pro-
gestosterone-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 Bar-
field, excellent results are obtained with a combination of estrogens with
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 re-
duce 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 in-
hibit 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 re-
currence when the normal menstrual rhythm is resumed after stopping
the androgen treatment. This temporary "hormonal castration" is indi-
cated 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 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 fre-
quentely 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 be-
fore. 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 postmeno-
pausal 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 myo-
metomy remains, of course, the treatment of choice, and androgens will
be indicated mainly in premenopausal patients. In these, it may be possi-
bile 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 sup-
press 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, the
author shares the opinion of Carter et al., who place premenstrual ten-
sion 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 men-
strual 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 testos-
terone is the painful congestion of the breast. The same is true for the
painful swelling associated with the suppression of lactation after de-
ivery. If nursing is continued, lactation is not affected by the testos-

terone 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. 

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, nonpurerperal
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\(^1\) suggests 250
mg. of testosterone propionate per month during 2 to 3 months; and
Atkins,\(^2\) 400 mg. of testosterone propionate within 4 weeks. In all cases
in which definite morphologic change of the mammary gland is clinically

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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 be-

tween 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.\(^9\) Since the
beneficial effect persists for some time after the treatment has been dis-
continued, it is possible after a few months to stop the administration
either definitely 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 photog-
raphs, but even more impressive are the dramatic relief from pain and
the improvement in general condition, whether or not the lesions pro-
gress. 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 premeno-
pausal women in whom, therefore, androgens should be tried first. In
fact, the course of the disease is delayed in younger women by ovariec-
tomy. The high doses of androgen given for this condition (at least 300
mg. of testosterone propionate per week, for several months) will cer-
tainly suppress ovarian activity, but it seems likely that other mechan-
isms 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 unskilful 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]

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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 common-place in the practice of obstetrics and gynecology. Fränkel, 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 Aneel and Bounin 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 sow 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 progestasins 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