Some Biochemical and Clinical Aspects of the Action of Androgens and Estrogens*

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SUMMARY

The highlights of current biochemical endeavor and speculation about the sex hormones have been briefly reviewed. A résumé has also been given of their currently known clinical applications in the treatment of cancer.

A substantial effort has been made to elucidate the biochemical role of estrogens in the mammalian economy. Many interesting phenomena have been observed, and some areas have been clarified; but there has been no evidence of an inherent key role to explain the activity of estrogens. Indeed, Jensen (11) recently published a masterful review of the subject in which he offered a novel suggestion based on failure to find an adequate clue in the work which has been done to date.

From the many careful studies in which both "cold" and "hot" or isotope-labeled materials have been employed, it seems clear that estrogens arise from cholesterol by the route from 17-hydroxy-progesterone to testosterone and thence by removal of the angular methyl group on 10 and aromatization of ring A to the estrogens (7). Recent work has added numerous estrogen metabolites to our previously well recognized estrone, estradiol, and estriol (2).

We have seen that minute amounts of estrogen can act to transport hydrogen between a DPN and a TPN system (21). This does not appear to be a prerequisite for estrogenic activity, since some of the most potent estrogens lack this interesting biochemical property.

Extremely small amounts of estradiol-17β are fixed as such by the uterus of the castrate rat and appear to be responsible for the chain of events characteristic of estrogenic action on the uterus (12). Significantly, other tissues (e.g., liver), but not the uterus, metabolize the estrogen they fix.

The presence of the estradiol starts the uterus on the way to phospholipide, ribonucleic acid, and protein synthesis, and imbibition of water and the other building blocks of protoplasm (16). However, if the protein synthesis is arrested by means of puromycin, the entire process is stopped (17). Nevertheless, there does not appear to be a specific place in the mechanism, as we presently understand it, for the estrogen. It is encouraging to know that the estrogen-stimulated uterus makes protein and nucleic acids through the presently known enzymatic machinery, even though there seems to be no specific slot into which the estrogen can fit.

These considerations led Jensen (11) to his ingenious proposal that we have been looking in the wrong place for the biochemical role of estrogen by feeling that it has a positive effect as an inherent part of the mechanism. He envisions that estrogen-sensitive tissues, in the absence of estrogen, have an efficient shunt mechanism, such as adenosine triphosphatase, which drains off high-energy phosphate. The estrogen then acts to block this enzyme and make high-energy phosphate fuel available to the synthetic machinery already present in the cells; this accounts for the rapid action.

There is even less knowledge of the specific mode of action of androgens than of estrogens. Androgens are classically associated with nitrogen retention (14) which, in naturally occurring androgens, is found pari passu with the androgenic effects and is responsible for the larger stature and musculature of the male. The biochemical mechanism for carrying this out as yet lacks a recognized role for the steroid.

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It has been shown that, under the influence of androgen, protein is indeed synthesized, since there is increased incorporation of the isotopically labeled amino acid glycine into the tissue protein (5). This phenomenon, as expected, is accompanied by an increase in enzymes involved in protein synthesis (6).

When large amounts of testosterone were given, it was shown that enhancement of seminal vesicle protein synthesis is secondary to acceleration of soluble ribonucleic acid-amino complexes to microsomal ribonucleoprotein (2).

In recent years we have been using a different approach to the mode of action of the androgens. We have looked for the essential structure for any display of androgenic activity and have found that even the basic hydrocarbons 5α-androstane and Δ4-androstene have androgenic properties (19).

On the other hand, we have searched for compounds of substantially greater androgenicity in the belief that the presently known androgens may be only intermediates or metabolites of the real key compounds and that we are therefore looking at the wrong materials. We reasoned that such compounds could well be evanescent—produced locally and rapidly metabolized—and that therefore we should begin our search for compounds of enhanced local androgenicity and then attempt to protect the essential structural features and ascertain whether we then have systemic compounds of great activity.

The discovery of a structural change was recently reported (20) which fulfils the first portion of this, the introduction of a double bond in the 14, 15 position of testosterone. We are not prepared at present to discuss the protection of this structural feature from enzymatic destruction.

However, we will consider briefly our first complete success with this concept (18). Then we will discuss its implications in the whole picture of sexogenic hormone biochemistry.

Chart 1 illustrates that simple removal of the angular methyl group at position 10 of four steroids (the so-called 19-nor androgens) produces a consistent and significant increase in androgenicity when measured by local application on the chick comb. It is of interest that the increase is greater if we start with 17α-methylestrogen, so that we see the first evidence of protection of the locally more potent 19-nor structure.

When these same compounds are given parenterally, the well recognized decrease in androgenicity occurs (9). We illustrated this effect (Chart

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The introduction of a double bond in the 14, 15 position of testosterone leads to little change if the resultant compound is assayed by the parenteral route in rats (Chart 3). The local assay in chicks indicates a decrease in androgenicity. However, introduction of the 7α-methyl group into the 19-nor steroids (Chart 4) affords substantial protection of this function. We then have a compound of substantially greater androgenic potency when assayed parenterally in the rat. The local chick assay is not appreciably affected by the 7α-methyltestosterone, since this compound already has the enhanced local androgenicity. The most androgenic member of this series combines the protective influence of both 17α-methyl and the 7α-methyl (Chart 5). The resultant 7α,17α-dimethyl-19-nortestosterone is the most potent
androgen which we have ever seen in animals. As yet we have no data on clinical potency. The chemistry (3) and biology (15) of the 19-nor-7a-methyl androgens have recently been described by investigators at Upjohn, who also generously made this group of compounds available to us for study.

This series of observations is particularly cogent in view of the fact, as has already been mentioned, that estrogens arise in the body by removal of the C-10 angular methyl group, and the 19-nor androgens may therefore be obligatory intermediates and may well be produced in highly effective concentration and form at the site of action!

The favorable clinical application of hormonal
1 We wish to thank Dr. John C. Babcock of the Upjohn Company for the generous supply of 19-nor-7a-methyl androgens which was made available to us for study, and particularly for enough of 19-nor-7a-methyltestosterone acetate (U-15614, NSC-69948D) to enable us to undertake clinical studies in breast cancer patients.

Additional supplies, prepared by the Upjohn Company, have been made available through the courtesy of the Cancer Chemotherapy National Service Center, National Cancer Institute, Public Health Service.

![Chart 2](chart2.png)

**Chart 2.**—Androgenicity of 19-nor steroids: rat androgen assay, subcutaneous. Also tested: testosterone, Δ4-androstenedione

![Chart 3](chart3.png)

**Chart 3.**—Rat androgen assay, subcutaneous; chick androgen assay, local. Steroids tested: 7α-methyltestosterone, testosterone.
alteration against advancing cancer of the breast and prostate has no better explanation than have the biochemical effects. However, we are making progress which has been constantly stimulated by a series of hypotheses, none of which appears to be adequate for the complete answer, but most of which have stimulated clinical advances.

The usefulness of progestational agents in advanced cancer of the endometrium is well established (13). These agents were tried initially because of the concept that endometrial cancer is due to the prolonged unopposed overstimulation by estrogens (10). Progesterone was therefore selected as a physiologic corrective for this situation.

There is one interesting new observation which we hope will be confirmed (8). It has recently been reported that etiocholanolone, a urinary androgen metabolite which can produce steroid hyperprolactinemia, is capable of producing regression in advanced lymphomas. Use of corticoids in lymphomas and leukemias is based upon their physiologic role in the regulation of leukocytes. Corticoids are often of striking aid in such situations. Because of the difference in the sex inci-

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**Chart 4.**—Androgenicity of 19-nor steroids: rat androgen assay, subcutaneous; chick androgen assay, local

**Chart 5.**—Androgenicity of 19-nor steroids: rat androgen assay, subcutaneous; chick androgen assay, local
Evidence of bronchogenic carcinoma, sexogenic steroids have been tried in this condition but to date without success (23). Some steroids have passed the Cancer Chemotherapy National Service Center standard screen and are now being tried in a wide variety of tumors. We hope that evidence of their clinical effectiveness will soon be forthcoming.

The clinical improvement after castration or initial therapy with estrogens in advanced cancer of the prostate is well established. However, the favorable activity of hormonal therapy beyond this is still questionable. A double-blind study was used to compare a placebo medication with diethylstilbestrol in this situation, but no difference in response between the two groups was noted (1).

The objective response of advancing breast cancer to testosterone propionate can be considered typical of the pattern of the results of hormonal therapy. We now recognize two major factors which temper the rate of response: the menopausal age of the patient and the body system most importantly involved by the disease. Chart 6, which was based on the results of the Cooperative Breast Cancer Group, shows the interrelation of the two factors (4). Patients were categorized into the system of major involvement as local soft tissue, osseous, and visceral (including central nervous system), but when more than one system was involved, as is frequently the case, the patient was placed in the category with the worst prognosis (local, best; visceral, worst; and osseous, intermediate). Chart 6 clearly shows that for all three systems the response is proportionately better with increase in menopausal age. This curve is steepest for local disease and flattest for osseous.

The general response is best for local and least for visceral disease.

Although the complete data of the Cooperative Breast Cancer Group are not yet available, significantly increased survival associated with objective regression, as defined by the group, has been reported (4). Thus it appears that induction of objective regression of the tumor carries with it "a vacation from death" as well as enough subjective improvement to make the "vacation" generally a worth-while event.

Though many of our correlations and postulates have proved invalid as we have learned more about hormonal therapy of advanced breast cancer, one still requires further testing—namely, that the most potent androgens seem to be more effective than the less potent ones. This does not deny that we have found clinically effective non-androgenic steroids. However, we have previously been unable to test androgens more potent than testosterone, since none were known to exist. We have just reviewed a little of the biology of a series of 19-nor-7a-methyl androgens which are substantially more potent than testosterone. We have been fortunate in obtaining enough of the 19-nor-7a-methyltestosterone acetate (U-15614, NSC-69948D) to undertake clinical studies in cancer of the breast.1 Since our primary study is double-blinded with testosterone propionate, we do not yet know the results. However, we have treated a few patients in whom we know the therapy employed. They are receiving 10 mg. 3 times weekly instead of the 100 mg. of testosterone propionate which we use as standard therapy. The first of these has been treated long enough for evaluation. She is strongly virilized, and there has been good remission of the extensive osseous disease.
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