Drug Treatment of Disease

MALE SEX HORMONES

BY

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Androgens for Therapeutic Use

The true male hormone, secreted by the Leydig cells of the testis, is *testosterone*. It is inactive when given by mouth; its effect is very transient if given by injection; and indeed it is useful as a therapeutic agent only when implanted in the form of 100-mg. pellets, which remain effective for about six months. Pellet implantation should be undertaken only with full aseptic technique. Though the procedure is simple it constitutes a minor operation, and therefore does not commend itself to the busy practitioner.

Androgens have three main properties. They promote the development of male secondary sex characters, they are "anti-oestrogenic," and they are anabolic.

The objectives in developing suitable derivatives of testosterone for therapeutic use are therefore to produce preparations that will promote male secondary sex characters and that are reasonably long-acting if given by injection or effective when administered orally; to find compounds that are "anti-oestrogenic" without giving rise to undesirable virilizing effects; and to elaborate substances which are principally anabolic rather than androgenic.

Esterification is the usual method of prolonging the activity of parenterally administered steroid compounds, and for many years *testosterone propionate* was the preparation employed for intramuscular injection. It remains effective for two to four days and should be given twice a week to maintain a constant action.

Though testosterone is practically inactive when given by mouth, the 17-methyl compound, *methyltestosterone*, is an efficient oral androgen. When given in the form of tablets to be swallowed, its absorption from the intestine and its passage via the portal circulation through the liver results in only a small proportion of the active principle eventually reaching the systemic circulation, so that this is an extravagant way of producing an androgenic effect. Methyltestosterone has therefore been prepared in the form of flat tablets which can be placed beneath the tongue or between the lip and the gum and slowly dissolved to allow the active principle to be absorbed directly into the submucous systemic vessels. Though administration of methyltestosterone is a wasteful method of producing purely androgenic effects, it is a convenient means of procuring "anti-oestrogenic" effects in various gynaecological conditions. Here dosage must be kept low to avoid virilizing side-effects, and fortunately low doses are usually effective in achieving "anti-oestrogenic" results. When used for such indications, therefore, the sublingual route would seem to be of little advantage.

NEW ANDROGEN COMPOUNDS

Long-acting Esters

A number of esters have been studied. These include *testosterone phenylpropionate* ("Tes.P.P."), which in doses of 50 mg. remains active for up to two weeks.

Testosterone oenanthate ("primoteston depot") is about twice as potent as testosterone propionate, and an injection of 250 mg. remains effective for three to four weeks. Finally, a combination of esters of varying duration of activity is marketed under the trade name of "sustanon" in two doses, 100 mg. and 250 mg. The lower-dose ampoule contains 20 mg. of testosterone propionate, which comes into action immediately, its effect being taken over by 40 mg. of testosterone phenylpropionate for another week or ten days, when *testosterone isocaproate* (40 mg.) reaches its peak and remains effective for about another week. The 250 mg.-dose ampoule contains 30 mg. of the propionate, 60 mg. each of the phenylpropionate and isocaproate, and, in addition, 100 mg. of *testosterone decanoate*, which reaches its peak in two weeks and continues to be active for another two weeks. The lower-dose preparation should therefore be injected every two weeks and the higher-dose preparation every four weeks.

Another method of prolonging activity is to suspend the ester in solution in the form of microcrystals, and such a preparation is *testosterone isobutyrate* ("perandren M crystals") which is available in 50-mg. doses.

Orally Active Androgens

The tendency in recent times has been to search not for more potent orally active androgens than methyltestosterone, but for substances with either powerful anti-oestrogenic or anabolic action which are at the same time weak androgens, so that they may be administered to women without fear of producing masculinizing side-effects. Two such compounds that have been available for some time are *methylandrostenediol* ("protandren," "stenediol") and *methylandrostanolone* ("androstanolone," "anabolex"). When given in relatively small doses, such as 10 or 25 mg. daily, side-effects are seldom produced, but when high doses are employed, as in cases of inoperable carcinoma of the breast, virilization may occur. Another compound that has had a certain vogue among psychiatrists is the characteristic excretory product of adrenal androgens—namely, *dehydroepiandrosterone* ("diandrone").

The most recently introduced compounds are derivatives of 19-nortestosterone. Some are purely progestogenic, though their name suggests that they should be androgens. It should be remembered, however, that the orally active substitute for progesterone, ethisterone, is actually ethinyltestosterone. Two of these nortestosterone compounds are given for their relatively potent anabolic activity with little, if any, androgenic action. These are 19-nortestosterone *phenylpropionate* ("durabolin") and *ethyl-nortestosterone*, or norethandrolone ("nilevar"). Both may be given by injection, durabolin in 25-mg. doses once a week, nilevar in 25- or 50-mg. doses daily or in tablet form in doses of 30 to 50 mg.

Another new preparation is a halogenated testosterone compound, *fluoro-hydroxy-methyl-testosterone*, fluoxymesterone ("ultandren," "halotestin"), which is said to be five times as potent as

methyltestosterone both as an androgen and as an anabolic agent. It is supplied in 1-mg. and 5-mg. tablets.

Yet another recent preparation is *methandrostenolone* ("dianabol"), which is claimed to be a powerful, orally effective, non-virilizing anabolic agent to be given initially in daily doses of 15 or 20 mg., the maintenance dose being 5 or 10 mg.

Androgen Combinations

These are combinations of androgen with either oestrogen or progestogen. The former are advocated for use in treating menopausal symptoms, and each tablet consists of *methyltestosterone* 3 mg. and 0.01 mg. *ethinyloestradiol*. However, these combinations should be used with caution. Hirsutism can develop as the result of their prolonged and continuous use, especially when more than 3 tablets daily are prescribed. Another combination of androgen and oestrogen is *testosterone oenanthate* 65 mg. and *oestradiol valerianate* 4 mg. In this case the oestrogen is designed to counteract the possible virilizing effects of the long-acting androgen.

A combination of *methyltestosterone* 5 mg. and *ethisterone* 15 mg. has been prepared for use in menorrhagia.

INDICATIONS FOR ANDROGEN THERAPY

Replacement Therapy

Men suffering from gross androgenic deficiency leading to eunuchoidism, adult male castrates, and men showing evidence of pituitary failure owing to a chromophobe adenoma or craniopharyngioma may require androgen replacement therapy for the rest of their lives. In such circumstances it would seem logical to choose the most long-acting mode of administration, and this is pellet implantation. Six 100-mg. pellets of testosterone remain effective for six months.

If facilities for pellet implantation are not available, long-acting testosterone esters should be prescribed so that injections need be given as seldom as possible. Oral androgen therapy can be equally effective, but it is an extravagant way of giving androgens for life.

Anti-oestrogenic Therapy

Androgens may act in certain cases of functional menstrual disorders, such as menorrhagia and the premenstrual syndrome, either by directly antagonizing the effects of oestrogens or else by minimizing the results of oestrogen-progesterone imbalance during the post-ovulatory phase of the menstrual cycle. On the other hand the androgens may act by suppressing pituitary gonadotrophic stimulation of oestrogen production by the ovary. Fortunately the dose of androgen required in the treatment of these disorders of the menstrual cycle is low, and excellent results are usually obtained by giving 10 mg. of methyltestosterone daily by mouth either for the premenstrual fortnight or continuously for two months, with at least a month's interval between successive courses. It is seldom that such treatment leads to undesirable androgenic side-effects such as acne or facial hirsutism. From the point of view of side-effects there is no point therefore in abandoning the well-established therapeutic regime of giving methyltestosterone. It appears, however, that the new and potent oral progestogens are much more effective than progesterone or ethisterone were in restoring the oestrogen-progesterone balance, and it is likely therefore

Structural formulae of androgens in therapeutic use.

that nortestosterone compounds such as *norethisterone* ("primolut N") will replace androgens for these conditions.

The mode of action of androgens in arresting the progress of inoperable breast cancer is still not completely understood. Until recently it was considered necessary to administer high doses of androgens to bring about these results. Even methylandrostenediol and methylandrostanolone were apt to produce virilizing side-effects when given in the large doses needed. There are reports, however, that the new nortestosterone preparations do not give rise to masculinizing manifestations but are effective both in halting the malignant process and also in regenerating bone in the osseous metastases which often accompany the carcinomatous process. This may be due to the anabolic rather than the anti-oestrogenic effect of the drug.

Anabolic Therapy

Androgens are the most potent therapeutic agents at present available for laying down protein in the tissues, especially skeletal muscle and the matrix of bone. Men suffering from deficiency of androgen—eunuchoids and castrates—complain as much of muscular weakness as of lack of secondary sex characters and impotence. Androgenic deficiency secondary to pituitary failure due to such pituitary tumours as craniopharyngioma or chromophobe adenoma results in loss of protein and a negative nitrogen balance. Cushing's syndrome, in which protein is extracted from muscle and bone to be converted to glycogen, leads to osteoporosis and muscular atrophy. Senile osteoporosis is due to lack of oestrogen, which stimulates osteoblasts to lay down calcium and phosphorus in the bone, and to lack of androgen, which is responsible for building up the matrix of the bone upon which the calcium and phosphate are deposited.

The anabolic action of androgens and the osteoblastic activity of oestrogens are therefore beneficial in these conditions. Until recently this was provided by giving a combination of methyltestosterone and an oestrogen such as ethinyloestradiol or stilboestrol. The new potent nortestosterone compounds and other anabolic agents are likely to be more effective than methyltestosterone with less risk of producing virilizing side-effects.

Conclusion

Androgens are administered mainly for three purposes: to provide replacement therapy, to counteract the effect of prolonged or excessive oestrogen influence in certain functional menstrual disorders, and to encourage protein anabolism.

For replacement therapy the most long-acting and economical preparation should be selected. Implantation of testosterone pellets is probably the best way of satisfying these criteria, but the inconvenience of implanting the pellets is a great disadvantage. Long-acting testosterone esters which can be injected weekly (testosterone phenylpropionate), fortnightly (testosterone oenanthate), or monthly (sustanon) are therefore likely to take the place of implants for this purpose.

Androgen therapy in gynaecology is still effectively undertaken by giving methyltestosterone in 10-mg. doses daily. The new 19-nortestosterone compounds, which are powerful oral progestogens, are likely to replace methyltestosterone because they are capable of producing a more physiological remedy by restoring the normal

oestrogen-progestogen ratio instead of providing an "anti-oestrogen."

The potent anabolic properties of certain of the new 19-nortestosterone and other compounds may prove valuable in the treatment of osteoporosis and cancer of the breast with osseous metastases.

BOYS WHO COMMIT SEXUAL MISDEMEANOURS

BY

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If not the medical profession, at least many members of the public are apt to think that juvenile sexual delinquency is at least as serious as and probably more dangerous than most other forms of misdemeanour. My experience in dealing with a small number of boys responsible for such misconduct has engendered a degree of optimism with regard to the probable outcome if their cases are handled imaginatively.

Doshay (1943) studied 256 juvenile sex offenders who had been treated at the New York City Children's Court clinics between June, 1928, and June, 1934. None of the 108 of them who had no convictions for offences other than sexual had been known to commit a sex offence in later years, whereas of the remaining 148, who had as children committed other offences as well as sexual ones, only eight were known to commit violations of the sexual code in later life, and the 10 sexual offences committed by these eight were of a comparatively mild nature.

Mannheim (1948) found that the number of sexual offences was very small. In medical literature, however, there seems to be a dearth of contributions specifically dealing with juvenile sexual delinquency, and this justifies the writing of the present paper based, as unfortunately it is, on a small number of cases.

I think that sexual misbehaviour arises to quite a large extent from the need for expression of natural feeling among boys whose lack of self-confidence precludes them from asking from girls a reciprocal expression of instinctive urges in a culture the taboos of which block too many of the avenues to expression of these urges both in childhood and in adolescence. The other situation that seems to me to be of special importance is that some young people are unable to exercise the restraint that official society says that they should, and it is possible that some of these children may be less guilty of want of self-control than are the adults who judge them.

Cases of Indecent Assault

A 16-year-old boy in a country district had sexually assaulted a girl not far from his home. In addition to being brought before the juvenile court he was thrashed by his father, but the local policeman told the probation officer that the boy's father had, in his time, behaved similarly, but by ordinary standards his home was not unsatisfactory. The boy was of low average intelligence, and in interview he seemed to be reasonably adjusted to his environment and did not display any psychological abnormality. He had been referred by the magistrates, and I reported to them that I did not think that the punishment he had had at the hands of his father had been misplaced, and that I felt probation would meet his emotional and educative requirements. A year and nine months later the probation officer