CHAPTER 20

ENDOCRINE TREATMENT OF MALE AND FEMALE TRANSSEXUALISM

Christian Hamburger, M.D.

The aim of the endocrine treatment of male and female transsexualism is dual: suppression of the existing sexual characteristics and development and maintenance of the opposite gender's phenotype.

Suppression of the sexual characteristics can be obtained by surgical castration, but the effect is highly dependent on the age at which it is carried out. If the operation is done before puberty, the external sex organs remain infantile, and the secondary sexual characters do not develop. The closure of the epiphyseal growth zones is retarded and results in eunuchoid appearance with above normal body height and long extremities. The pigmentation of the skin is scanty and there is a tendency to obesity. The sexual libido is low and erections, ejaculations, or menses do not appear.

Ablation of the gonads in adult persons is not followed by marked changes of the phenotype. The metabolism may be diminished, but obesity develops only in a few percent of the cases. A serious complication is the appearance of "sex hormone withdrawal symptoms," well known from the female climacteric. The sexual libido diminishes but does not necessarily disappear completely. The growth of beard continues in castrated men, the voice does not change, and the effect on the growth of body hairs is usually not marked. The erective and ejaculatory powers decrease more or less gradually but do not always disappear completely. Ovariectomy is promptly followed by amenorrhea. While the effect on the size of the mammary glands is uncertain, a real involution of the tissue is seldom observed. Because the sex hormones possess anabolic effects on protein and calcium metabolism, osteoporosis is a frequent and serious complication of gonadectomy.

Long-term administration of male sex hormone to men and female sex hormones to women results in inactivation and, later on, in marked

atrophy of the sex glands. This condition is called "hormonal castration." Spermatogenesis and endogenous production of testis hormone are arrested. However, the suppression of the sex hormone is compensated, or usually overcompensated, by the exogenous hormone administration, and no inhibition of the secondary sex organs occurs. In women, the effects of continuous administration of female sex hormones will be confined to inhibition of ovulation and of menstruation.

Administration of sex hormones belonging to the other sex (heterologous or paradoxical hormone therapy) also results in "hormonal castration." This phenomenon was originally thought to be due to a sex hormone antagonism in the organism. However, Moore and Price (1932) in their classical publication proved that such sex hormone antagonism does not exist. The injuries to the gonads following administration of either sex hormone into either sex, were interpreted as the result of an inhibition of the activity of the hypophysis, that is, a suppression of what are now called gonadotropic hormones. Besides the hormonal castration, paradoxical sex hormone administration is accompanied by feminization in the male and masculinization in the female.

Chemistry and Metabolism of Sex Hormones

The sex hormones comprise the male hormone (testosterone) and two female hormones (estradiol and progesterone). Testosterone is produced in the male gonad; both female hormones are produced in the ovary. Testosterone is a virilizing hormone, responsible for the development and maintenance of the male sexual features, and estradiol and progesterone are feminizing hormones acting on the female sexual characters. This is the usual brief and clear-cut conception. It is, however, superficial and insufficient. It is important to realize that the sex hormones are certainly not sex specific. Testosterone is normally found in the female organism, and female sex hormones occur in men. Furthermore, the biosynthesis of sex hormones is not confined to the gonads, the adrenal cortex being an important source. The sex hormones share their masculinizing and feminizing effects with many other substances normally found in the organism, that is, precursors and metabolites of testosterone, estradiol, and progesterone.

All substances, whether precursors, hormones proper, or metabolites, that have the same biological actions as testosterone are called androgenic substances, those similar to estradiol are estrogenic substances, and progesterone-like substances are designated as gestagens, progestins, or progestational substances.

Chemically, the sex hormones and the adrenocortical hormones belong to the steroids. The mother substance in the organism is cholesterol, and the presence or absence of certain specific enzymes in the cells of the various organs determine what the end-result of a long

chain of metabolic conversions of cholesterol will be. The molecular structure of the steroid hormones, their precursors, and their metabolic breakdown products are known and they can be prepared synthetically. The pure compounds appear as white crystals. Most of them are insoluble in water but more or less soluble in oil and lipid solvents, such as ether and benzene.

Androgenic Substances

Testosterone (17β-hydroxy-androst-4-en-3-one) is produced by the Leydig cells in the interstitial testicular tissue. By means of new and highly sensitive analytical methods (isotope methods, gas chromatography), testosterone can be determined in the plasma of both sexes in minute amounts (in adult men: about 0.75 μg. per 100 ml.; in women: 0.04–0.10 μg. per 100 ml.). In women, the hormone is partly synthesized in cells in the hilus of the ovary, and an adrenocortical production is likely to occur in both sexes. A small fraction of testosterone is excreted as such in the urine, but the main part is converted to androsterone (3α-hydroxy-5α-androstan-17-one) which is an androgenic substance, and to etiocholanolone (3α-hydroxy-5β-androstan-17-one) which is hormonally inactive. Both of these metabolites are 17-ketosteroids, and they can be measured quantitatively by a rather simple chemical analysis (the Zimmermann reaction). The total amount of 17-ketosteroids originates from corticosteroids and from testosterone. In normal adult males about sixty percent of the 17-ketosteroids are adrenocortical metabolites, and in normal adult women most of the 17-ketosteroids are of adrenocortical origin. Following surgical castration, the 17-ketosteroid excretion decreases by about forty percent, that is, to the normal female level. A few milligrams of 17-ketosteroids are excreted per twenty-four hours in urine in children. The excretion increases during puberty and reaches a maximum at about twenty-five years in both sexes. Exogenous administration of testosterone is accompanied by an increased excretion of 17-ketosteroids. On the average, thirty percent of the intramuscularly applied testosterone is recovered as 17-ketosteroids.

Estrogenic Substances

One of the female sex hormones, 17β-estradiol (estra-1,3,5(10)-triene-3,17β-diol) is synthesized by the theca cells of the ovarian follicles. It circulates in minute amounts in the blood and is excreted in the urine partly unchanged and partly as the related metabolites estrone (3-hydroxy-estra-1,3,5 (10)-trien-17-one) and estriol (estra-1,3,5 (10)-triene-3,16α,17β-triol).

17β-estradiol and its metabolites are present in blood and urine of normal men, and estrone can be isolated from adrenocortical tissue.

Estrogenic substances are found in small quantities in urine from prepuberal children. The amount increases during puberty in either sex. In normal women the excretion (and the production) varies rhythmically in relation to the menstrual cycle. There are usually two peaks, the larger one at mid-cycle and the smaller one around the twenty-fourth day of the cycle. In the male the daily excretion is rather constant and does not decrease at advancing age. In post-menopausal women the excretion diminishes markedly and quite abruptly. With exogenous administration of estradiol, about twenty-five percent is recovered from the urine as estrogenic substances. When the activity of the gonads is stimulated by the administration of gonadotropic hormones, the urinary excretion of estrogens increases markedly in either sex. Testosterone is to some extent converted to, and excreted as, estrogens in normal men and women.

Progesterone

The other female sex hormone, progesterone (pregn-4-en-3,20-dione), is synthesized by the thecalutein cells of the corpus luteum. The hormone is also produced by the adrenal cortex and circulates in minute amounts in the blood of men and women. Progesterone is converted in the liver to pregnanediol (5β-pregnane-3α,20α-diol) and excreted as such in the urine. The urinary excretion of pregnanediol amounts to less than one milligram per day in normal men and in women during menstruation and in the follicular stage of the cycle. The excretion increases during the luteal stage of the cycle to three to ten milligrams per day on the average.

Gonadotropic Hormones

When the hypophysis is removed before puberty, the gonads remain infantile and secondary accessory sex organs are not developed. In the adult organism, hypophysectomy is accompanied by a rapid atrophy of the gonads and of the accessory organs, and the production of gonadal hormones is diminished. The effects of hypophysectomy can be repaired by hypophyseal transplantation or by injection of hypophyseal extracts. In immature animals, hypophyseal extracts induce precocious puberty by activation of the gonads: they contain gonad-stimulating or gonadotropic hormones (gonadotropins).

Gonadotropins can be extracted from hypophyses of animals and human beings. Although the biochemists have not yet succeeded in preparing completely pure gonadotropins, we know that these are polypeptides and their amino-acid composition is not far from being deciphered. Numerous biological experiments and, in particular, recent physicochemical investigations have shown that there are two distinct gonadotropic hormones in the extracts of the anterior lobe of the

hypophysis. One of them stimulates the development of the ovarian follicles and the tubular epithelium of the testis. It is called the follicle stimulating hormone (FSH). The other hormone stimulates the formation of corpora lutea in the ovary and the interstitial tissue with the Leydig cells in the testis. It is designated either luteinizing hormone (LH) or the interstitial cell stimulating hormone (ICSH).

The gonadotropic hormones are excreted in the urine. The excretion is insignificant before puberty. In the adult woman in the menstruating age, the excretion varies cyclically, and usually there is a peak of the LH excretion at the fourteenth to sixteenth day of the cycle at the time of ovulation. After the menopause, gonadotropin production and excretion increase rapidly. In males the excretion increases gradually from the age of forty years, but it does not reach the same high values as in aging and old women.

Regulation of the Sex Hormone Production

The biosynthesis of estradiol and progesterone in the ovaries and of testosterone in the Leydig cells is stimulated by the gonadotropic hormones. On the other hand, the sex hormones inhibit the release of gonadotropins from the hypophysis (negative feedback mechanism). A marked decrease of the sex hormones, for example, caused by ovariectomy or orchidectomy, is followed by an increased production of gonadotropins. In this automatic regulation, the central nervous system is involved.

The hypophysis is connected through the hypophyseal stalk with hypothalamic nerve centers on the base of the brain. Furthermore, there is a vascular connection in the stalk between hypophysis and brain through a special portal vessel system. So-called "neurosecretory material" has been found in the hypothalamic centers, and special "neurohormones" have been isolated from these centers. Numerous experiments involving transsection of the hypophyseal stalk, electrolytic destruction of hypothalamic centers, and local application of sex hormones in the hypothalamus have shown that there is a hypothalamic secretion of substances (polypeptides) that stimulate the release of hormones from the anterior lobe of the hypophysis, the gonadotropic hormones. These substances are called "releasing factors." Thus there are three links in the regulatory mechanism: FSH- and LH(ICSH)-releasing factors induce the release of both gonadotropins; these stimulate the secretion of sex hormones in the gonads; and the sex hormones inhibit the secretion of hypothalamic "releasing factors."

The negative feedback effect is common for the sex hormones, but their activity differs markedly per weight unit. Estradiol is most active, testosterone must be given in rather large quantities, and the effect of progesterone is variable, depending on the mode of administration, on the size of the doses, and on the time. Many details in the regulatory

mechanism need further clarification, but in broad outline this hypothalamo-hypophyseal-gonadal interaction explains the supposed antagonism between the male and female sex hormones. In the male organism, estradiol inhibits the release of gonadotropins resulting in testicular atrophy; in the female organism, testosterone has the same effect upon gonadotropin release, and atrophic changes in the ovaries appear. These facts are basic to the endocrine treatment of transsexualism.

Biological Effects of Sex Hormones

The gonadotropic hormones have a primary effect on the gonads. FSH stimulates the growth of the ovarian follicles, and LH the transformation of the ripe follicles into corpora lutea. Ovulation is probably induced by a sudden increase of LH secretion. FSH stimulates the spermatogenic tubules, and LH (ICSH) the Leydig cells in the interstitial tissue. This applies to animal experiments; in man, the gonadotropic regulation of the testicular functions may be more intricate.

In connection with structural changes in the gonads, the gonadotropins stimulate the biosynthesis of the gonadal hormones, and all the many extragonadal effects of the gonadotropins are caused by the sex hormones.

Effects of Female Sex Hormones in Women

Estrogenic hormones stimulate the female accessory sex organs such as salpinges, uterus, vagina, and mammary glands. They act on hypothalamic functions and on the metabolism of proteins, calcium, and water, and probably also on hair growth and the skin.

The effects of progesterone are closely linked up with the actions of estradiol, and these hormones act in many respects synergistically. Estradiol and progesterone regulate the menstruation processes. Under the influence of estradiol, the endometrium comes to the proliferative stage until the time of ovulation. Then secretory changes appear in the endometrium as the progesterone production increases. When the amount of progesterone decreases subsequent to degenerative changes in the corpus luteum, the superficial layers of the endometrium break down and are removed during the bleeding. Both hormones act on the cervical mucus: estradiol makes it liquid and translucent, progesterone increases its viscosity. The vaginal epithelium changes cyclically concurrently with the variations in estradiol and progesterone secretion. In the mammary glands, estradiol acts primarily on the duct system and progesterone on the alveolar growth.

Increased endogenous production of estrogens in girls before puberty results in precocious puberty with menstrual bleedings, development of mammary glands and of pubic hair. In women past the climacteric,

cyclical treatment with estrogens and gestagens is accompanied by withdrawal bleedings of normal menstrual character.

Effects of Female Sex Hormones in Men

Increased endogenous formation of estrogens in the male organism (by estrogen-producing tumors of the testis or adrenal cortex) or exogenous administration of estrogens elicits dramatic changes. At the center of these changes is primary gonadotropin inhibition with secondary testis atrophy and inactivation.

Added to these "negative" testosterone-withdrawal symptoms are the specific effects of estrogens on the rudimentary female sex structures. Gynecomastia develops gradually, and the breasts can increase to the size normally found in a girl in her late teens. The nipple and areola grow and get pigmented. The connective tissues in prostate and seminal vesicles increase, and certain embryologic female elements in the prostate (for example, the utriculus) show hyperplastic or metaplastic epithelial transformations. These changes in the accessory sex organs do not usually give clinical symptoms. The general metabolic effects are the same as in women. By long-continued estrogen influence, the distribution of subcutaneous fat can be changed in a feminine direction and the muscular strength diminishes. The influence of estrogens on the hair growth is extremely complex. The growth of beard rarely decreases, and usually the other masculine hairiness (chest, linea alba, etc.) can remain unchanged or diminish gradually. The growth of hair on the scalp seems to be stimulated by estrogens. In men with high temples new growth of hair has been observed in the bald triangle. Larynx, vocal cords, and the voice are not changed in the adult male. It is hardly possible to state whether or not estrogens have specific psychic effects in men. The whole situation is complicated, and it is impossible to untangle what is due to testosterone deficit (hormonal castration), what to the somatic feminization, and what to psychosocial reactions.

Progesterone has only slight effects in the male organism. The body temperature increases slightly, and drowsiness has been observed following high dosage (some steroids possess an anaesthetic effect). It has been maintained that long-term administration of progesterone can give irreversible arrest of spermatogenesis, and also that progesterone can increase the sexual potency. However, these observations need confirmation.

Effects of Testosterone in Men

In a normally developed adult man with a normal production of male hormone, a surplus of testosterone can hardly have any effects on the accessory sex organs and characters. If sufficient doses of testosterone are given continuously for some months, the number of sperms decreases

and complete aspermia can occur. The mechanism of this process is still obscure. Hypothalamic dysfunction with an abnormal ratio of FSH to LH may play a part, or estradiol formed by enzymatic conversion of testosterone could influence the spermatogenesis. Before puberty and in adult men with certain syndromes of hypogenitalism, the virilizing effects of testosterone are marked.

Effects of Testosterone in Women

The effects of androgens in women are well known both from observations in cases of increased endogenous production and from exogenous administration. In congenital adrenocortical hyperplasia, the abnormal androgen production sets in early in the fetal life and results in various degrees of masculinization of the genital organs. There is a marked masculine hairiness, menstruation does not occur, and the mammary glands remain undeveloped. In cases of androgen-producing adrenocortical tumors in adult women, menstruation is suppressed and virilizing symptoms appear, such as masculine hairiness, deep voice, acne, baldness, hypertrophy of the clitoris, and a change in intensity of the sexual libido, in some instances with a homosexual direction. Similar virilizing symptoms are known as side effects of testosterone administration to women with menopausal disturbances or with metastases after mammary carcinoma.

PREPARATIONS AND MODES OF ADMINISTRATION

Androgens

The naturally occurring male sex hormone, testosterone, can be given intramuscularly in oily solution. It is, however, readily absorbed and eliminated. The absorption and elimination can be retarded by combining testosterone with various fatty acids, for example, propionic acid and isobutyric acid. These esters can be injected with longer intervals than the free testosterone. There is some proportionality between the length of the fatty acid side chain and the duration of action. Testosterone enanthate has been claimed to be effective for about four weeks after a single intramuscular injection in oily solution. However, by determinations of 17-ketosteroids in the urine, it can be demonstrated that most of the preparation is excreted in the course of the first week. Testosterone and its esters can be applied in solid form either as intramuscularly implanted tablets or as intramuscular injection of microcrystals suspended in an aqueous medium. From the surface of the tablets or crystals there is a slow absorption, and if sufficient amounts of testosterone isobutyrate crystals are given, increased content of 17-ketosteroids can be found in the urine up to fifteen days after the injection.

Oral administration of testosterone and its esters is out of the question,

because the hormone is inactivated in the liver after absorption from the small intestine to the portal vessels. An artificial synthetic compound 17α-methyltestosterone is orally active, but in some patients it has side effects such as nausea or even jaundice due to damage of the liver.

Free testosterone is readily absorbed by the rectal mucosa in the region of the inferior hemorrhoidal vein plexus. In this way varying amounts of the hormone do not have to pass the liver and thus escape inactivation. Testosterone can therefore be administered in the form of rectally applied suppositories (Hamburger, 1964). The base of modern suppositories is neutral glycerine esters of saturated fatty acids, and they are devoid of local irritation. When testosterone suppositories are applied for eight hours (preferably overnight), the absorption is maximal.

Estrogens

The naturally occurring 17β-estradiol and estrone, given exogenously, are active by the oral route of administration. Estradiol monobenzoate is soluble in oil, and if injected intramuscularly twice a week, a satisfactory clinical effect is obtained. Estradiol esters can be injected as microcrystals in aqueous suspension with a markedly prolonged action (one month or more). Numerous artificial compounds with estrogenic activity have been synthesized for oral administration. Widely used is diethylstilbestrol (trans-3,4-bis(4-hydroxyphenyl)hexane-3), a compound that does not belong to the steroids. Closely related substances are dienestrol (3,4-bis(4-hydroxyphenyl)-hexadiene-2,4) and hexestrol (3,4-bis(hydroxyphenyl)hexane). 17α-ethinylestradiol is highly active by oral administration, but like the stilbestrol preparations it is not free from side effects (nausea). Mestranol (17α-ethinylestradiol-3-methyl-ether) is the estrogenic component of many of the orally active contraceptive steroids.

Estrogenic hormones are absorbed through the skin when applied in ointments or alcoholic solutions. Local application on the skin over the mammary glands has in some instances induced the growth of the glands (experiments with unilateral application).

Estradiol is absorbed by the rectal mucosa, and administration of the hormone in the form of suppositories may have some advantages in particular in combination with progesterone (see below).

Gestagens

Naturally occurring progesterone is insoluble in water. Oily solutions can be prepared with maximally 25 mg. per ml. When given intramuscularly large quantities of oil must be injected, and there is a risk of producing oil cysts. Furthermore, the hormone is absorbed and eliminated rapidly, and frequent injections are necessary. Long-acting esters cannot be prepared, because progesterone is a diketone (it

has no HO-groups). Progesterone can be administered as microcrystals in aqueous suspensions. The absorption from the crystals is, however, only slightly delayed as compared to oil solutions, and pains, reddening, and infiltrations on the site of injection are often unpleasant complications to this form of administration. Human tissues do not tolerate progesterone in solid state, and tablet implantations had to be given up because the tablets were often extruded. Oral administration of progesterone is only moderately effective, and the best mode of application of genuine progesterone is the rectal administration of suppositories.

In order to obtain orally active gestagens, pharmaceutical laboratories have synthesized numerous steroid compounds. Many of them have high progestational effects when given as tablets, but quite a lot of them have also estrogenic or androgenic properties. In contradistinction to genuine progesterone, most of the artificial gestagens have side effects (nausea, etc.).

17α-hydroxyprogesterone caproate has a rather long-lasting effect when injected intramuscularly in oily solution, but in accordance with the fact that it is an ester of 17α-hydroxyprogesterone, which is a precursor of testosterone, it has androgenic properties.

Hormonal Treatment of Transsexuals

Male Patients

The treatment consists almost exclusively in the administration of estrogenic preparations in doses sufficient to induce hormonal castration and feminization. In view of the fact that it is a long-term or life-long treatment, it is important to use the most lenient mode of administration. Intramuscular injections can be avoided or may be confined to the initial stages of the treatment, and oral administration ought to be the method of choice. It is recommended to try preparations of the diethylstilbestrol type or 17α-ethinylestradiol at first and continue, if they are tolerated well. Should the patients be nauseated or complain of other side effects, tablets containing genuine estrogens (for example, estrone) should be tried, and there are quite a lot of such preparations on the market. The possibility of giving sufficient amounts of estradiol in the form of suppositories should also be considered. In the long run it may be safer to use "Nature's own hormones" (for example, 17β-estradiol or estrone) than artificial compounds.

As to the dosage of estrogens, it is hardly possible to generalize. There is, however, no doubt that the time factor is of the greatest importance. Demasculinization and feminization cannot be precipitated by giving excessively high doses. The estrogenic hormones stimulate cell divisions in specific hormone-sensitive tissues, but millions and millions of cell divisions must have taken place, before the growth of the tissue is visible. As emphasized by Benjamin (1966), unphysiologically high doses

should be avoided, because they can disturb the interactions of endocrine glands. It is known from animal experiments that estrogens can inhibit the secretion of growth hormone by the hypophysis, and it is likely that thyroid and adrenocortical functions may also be affected.

An objective measure of gonadotropin inhibition can be obtained by following the daily excretion of 17-ketosteroids. Hamburger and Sprechler (1951) determined the twenty-four-hour excretion of 17-ketosteroids and reducing corticosteroids for half a year during estrogen administration to a twenty-four-year-old male transsexual. One hundred eighty-five specimens of twenty-four-hour urines were examined for 17-ketosteroids. Estradiol monobenzoate in oily solution was given intramuscularly and ethinylestradiol tablets orally. Treatment and results are shown in Figure 1.

It is apparent that inhibition of testosterone secretion begins immediately after an intramuscular injection. The 17-ketosteroids were depressed to the castrate level already on the day following the injection. Subnormal values were found for altogether twelve days. Ten injections of estradiol monobenzoate (5 mg. each) given over eleven days depressed the 17-ketosteroids for about twenty-six days. By long-term oral administration of ethinylestradiol it was found that a daily dose of 100–200μg. inhibited the 17-ketosteroids to the castrate level, and that as small a dose as 50 μg. per day was sufficient to maintain the low value. By discontinuation of the estrogen administration, at a time when the hormonal castration had been maintained for about half a year, the 17-ketosteroids remained at a low level for eight days and increased gradually, reaching the pretreatment level on the twenty-sixth day after the last hormone administration. Figure 1 also shows that the estrogens had no effect on the excretion of corticosteroids. In other words, the gonadotropin secretion was inhibited, but the corticotropin secretion was not.

During the periods of decreased 17-ketosteroid excretion, the testes diminished in size and were soft and flabby. The erective power and sexual libido were also markedly impaired. Increased pigmentation of the nipples and of the skin in the genital region occurred towards the end of the treatment, together with some gynecomastia. No untoward effects were noticed. After discontinuation of the estrogen administration, the size and consistency of the testes returned to normal in the course of three to four weeks, and erections and ejaculations reappeared.

Usually there is no reason to carry out such hormone analyses in order to find the suitable dosage. It should be sufficient to follow the progressive demasculinization and feminization clinically. As a rough approximation and general guidance for the dosage, it may be permissible to set forth this statement: Irrespective of preparation and mode of administration, the daily dose of estrogen should not be much different from that recommended on the label for treatment of menopausal

disturbances or amenorrhea; initially somewhat higher doses, and when the desired effects are apparent, somewhat lower doses.

Benjamin (1966) recommends combining estrogen treatment with progesterone or various synthetic gestagens. It is likely that such combined therapy will favor the induction of gynecomastia, as both hormones are necessary for the normal harmonious development of the mammary glands.

It is strongly recommended that the estrogen-induced castration should always be maintained for at least half a year in connection with careful somatic and psychiatric observations, before surgical castration and other irreversible interventions are carried out.

The attempts at feminization have better chances of being successful in patients having a neutral or not pronounced masculine appearance. If the patient presents a black and vigorous growth of beard, deep voice, excessive hairiness on trunk and limbs, strong muscles and prominent veins, it is very unlikely that the estrogen treatment will give a harmonious result. In such extreme cases it may possibly be wise to try to persuade the patient to abstain from any endocrine treatment unless the psychologic disposition makes such persuasion out of the question.

Female Patients

As mentioned before, the inhibitory effect of testosterone on the gonadotropin secretion is weaker than that of estrogens, and in order to induce defeminization massive doses of testosterone preparations must be given. As to the induction of virilization, the sensitivity varies individually. Some normal women, in particular the dark type, are very sensitive to testosterone, and less than 100 milligrams per month can induce growth of facial hairs and deepening of the voice. By long-term administration a marked hypertrichosis can appear, the skeletal muscles develop, and the clitoris often increases markedly in size and appears as a small hypospadiac penis.

The defeminizing effects of androgens are confined to two organs, the ovaries and the mammary glands. One could expect some regression of the breasts, and it may happen in a few cases, but all investigators agree that the effect of even large doses of testosterone is so uncertain that plastic surgery to decrease the size of the breasts is almost always, if not always, necessary.

The androgen-induced suppression of the ovaries will result in diminished or completely suppressed secretion of estradiol and progesterone, and the clinical manifestation will be the cessation of menstruation. As to the ability of testosterone preparations to induce amenorrhea, there seem to be somewhat divergent experiences. Benjamin (1966) maintains that weekly injections of 100 to 150 mg. of a long-acting testosterone ester usually stops menstruation, and that the amenorrhea can be preserved by monthly injections of 150 to 200 mg.

He emphasizes great individual differences, however. Vogt (1968) found that 250 mg. of testosterone enanthate injected every fortnight could not maintain amenorrhea consistently; in three of his five cases the ovarian function had to be suppressed by X-ray treatments and one of his patients was surgically castrated.

As to the choice of preparation and the mode of administration, it is unanimously agreed that the orally active 17α-methyltestosterone should not be used. The amounts of the preparation required to obtain the desired effects would have to be so large that the therapy would be dangerous to the liver. Intramuscular injections of aqueous suspensions of testosterone isobutyrate crystals have been used, but most investigators prefer oily solutions of long-acting testosterone esters. The solubility of these compounds is so high in oil that only small quantities of oil solutions need to be injected. The intramuscular injections are of course not very troublesome, but they can be avoided completely by the administration of suppositories containing free testosterone (50, 100, or 200 mg. per suppository to be applied overnight). This mode of application has so many advantages that it deserves large-scale trial. The preliminary experience by Vogt (1968) and by the author (unpublished) is promising.

Some untoward effects of the long-term androgen therapy should be mentioned, namely, attacks of acne and increase of the sexual libido. In some instances, the acnosis is transitory and usually it is moderate and need only local treatment. The libido increase (probably associated with enlargement of the clitoris) may be construed as undersirable and may be so troublesome that the androgen treatment must be discontinued. Benjamin (1966) has made the interesting observation that small doses of progesterone added to the testosterone can occasionally counteract the increase of libido.

The endocrine treatment of transsexual women has in a few instances been supplemented by plastic surgery on the external genital organs, but achievement of cosmetically and functionally adequate results has to date been limited.

Summary

The aim of the endocrine treatment of transsexual patients in either sex is dual: suppression of the existing sexual features (hormonal castration) and development and maintenance of sexual features belonging to the other sex "paradoxical hormone therapy." The sex hormones proper are steroids (testosterone, estradiol and progesterone) and together with many of their precursors and metabolites are divided into three groups: androgens, estrogens and gestagens. The sex hormones are not strictly sex specific.

Male and female sex hormones are normally found in both sexes, and their production is not limited to the sex glands. The gonadotropic

hormones are proteins and not sex specific; they stimulate the development and function of testes and ovaries. The complicated interaction between hypothalamic brain centers, the hypophysis, and the sex glands constitutes the physiological background for the hormonal treatment of transsexualism. With very few exceptions, the sex hormones used therapeutically are synthetic compounds; some of them are identical with the naturally occurring hormones, but most of them deviate chemically more or less from the natural hormones. The preparations can be administered orally in the form of tablets or linguets, intramuscularly in oily solution, or as aqueous suspensions of microcrystals, and rectally in the form of suppositories.

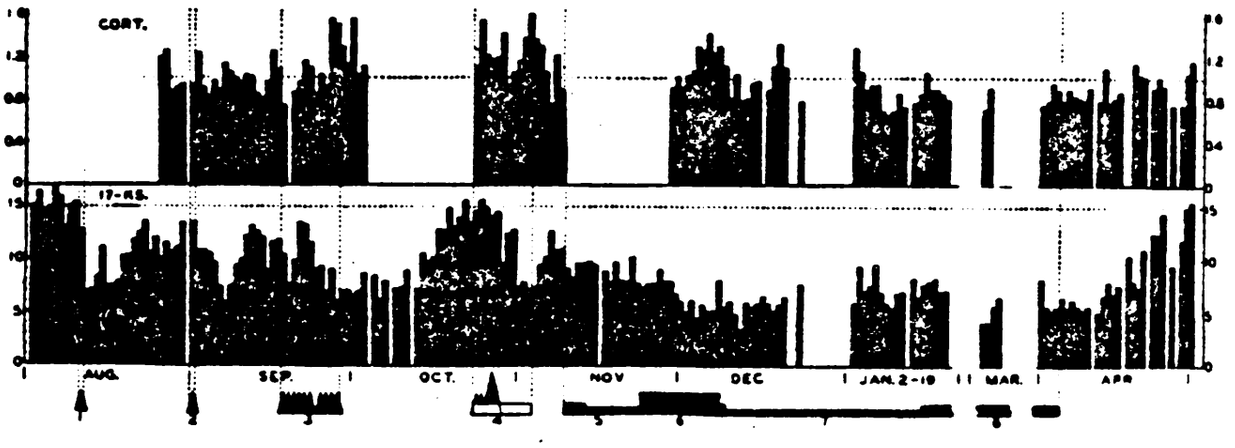

FIGURE 1. Urinary excretion (mg./24hr) of corticosteroids (CORT.) and 17-ketosteroids (17-KS.) in a twenty-four-year-old male transsexual during administration of estrogens:

1) Intramuscular injection of 15 mg. estradiol monobenzoate.
2) Intramuscular injection of 15 mg. estradiol monobenzoate.
3) Daily intramuscular injection of 5 mg. estradiol monobenzoate.
4) 300 mg. pregnenolone daily orally + 100 mg. intramuscularly for the first five days; the black wedge indicates the injection of 15 mg. estradiol monobenzoate.
5) Oral administration of 17α-ethinylestradiol, 0.10 and 0.06 mg. per day.
6) Oral administration of 17α-ethinylestradiol, 0.20 mg. per day.
7) Oral administration of 17α-ethinylestradiol, 0.05 mg. per day.
8) Oral administration of 17α-ethinylestradiol, 0.01 mg. per day, from January 15th to April 4th, 1951.

APPENDIX TO CHAPTER 20

For the Practicing Physician: Suggestions and Guidelines For the Management of Transsexuals

Harry Benjamin, M.D.

As a matter of principle, I feel that it is always wise to point out to the male transsexual how much trouble, how many risks, and how many difficulties he will save for himself if he succeeds in accepting himself in the role of his anatomical sex, possibly with the help of some form of psychotherapy, and/or hormonal treatment. In this way he would avoid an expensive major operation, with the results always being uncertain. The same applies analogously to the female transsexual.

Such advice, however, is rarely accepted by the patient, and surgical sex reassignment is insisted upon. Endocrine therapy would then be the immediate method of choice in order to provide emotional relief and gain time for more mature consideration.

Endocrine Treatment of Male Transsexuals

Many patients can be physically feminized and sufficiently benefited in their emotional life by oral medication only. According to my clinical experience, one tablet of Estinyl® (ethinyl estradiol) 0.5 mg. daily after meals may be used to begin with. Alternatively, Estinyl® 0.05 mg. three times a day after meals may be used, with one Provera® (medroxyprogesterone acetate) 10 mg. daily, or, if weight increase is desired, one or two Enovid® (norethynodril with mestranol) 10 mg. daily. Modification with other doses or steroids may be made according to response, judged after four to six weeks. Diethylstilbestrol (enseals) in the dosage suitable for transsexual feminization could, according to recent observations on aging men with cancer of the prostate, endanger the cardiovascular system through water retention. A salt-poor diet or an occasional diuretic may, therefore, be advisable under all prolonged steroid medication.

If synthetic estrogens are not tolerated, one to two Premarin® (conjugated estrogens—equine) tablets, 2.5 mg. each, daily, could be substituted, possibly with one Provera® 10 mg. or one Enovid® 10 mg. added daily or on alternating days.

If the patient is cooperative, an interruption of all endocrine treatment for two to three weeks every two to three months may be a beneficial precaution against undesired side-effects. The use of very large doses should be discouraged, as they may suppress pituitary function and have the opposite effect of the desired one (breast development).

If injections are required for psychological reasons or for lack of response to oral medication alone, a preparation like Delestrogen® (estradiol valerate) 30 to 40 mg. mixed with Delalutin® (hydroxyprogesterone caproate) 30 to 60 mg. or a similar progesterone is suggested every two weeks. Oral medication, as above or in reduced amounts, can be given at the same time. After fifteen to twenty injections, it may be well to discontinue injections and to maintain the patient on tablets only for about six months.

After a sex-reassignment operation, oral estrogen medication should be continued, to prevent castration symptoms, and to aid further feminization. Approximately one half or even less of the preoperative dose may be found sufficient, and occasional interruptions may be tried.

Liver function tests are recommended before estrogen therapy is started, especially if there is a history of hepatitis. Tests would best be repeated from time to time according to the intensity of the treatment. In addition to liver dysfunction, a history of thrombophlebitis, pulmonary embolism, or malignancy would be generally a contraindication to treatment or at least require a greatly reduced dosage.

Individualization is required. Schedules as above-described have given good results, but further research through clinical observation with different estrogen preparations and dosages is to be encouraged.[1]

[1] On the basis of a conservative theoretical position, namely that the hormonal treatment of the male transsexual should be as close as possible to that employed in standard replacement therapy, Dr. Claude Migeon prefers low dosages of both estrogenic and progestinic drugs. Thus, a possible combination therapy would be: diethylstilbestrol (enseals) 0.5 or 1.0 mg. twice daily plus Provera® 2.5 or 5 mg. twice daily. In place of diethylstilbestrol, Estinyl® 0.05 or 0.1 mg. twice daily might be substituted, or Premarin® 0.625 or 1.25 mg. twice daily. Before gonadectomy, the treatment would be every day for a minimum of four to eight months. Following surgery, treatment would be cyclic, for the first three weeks of each month, missing the fourth week.

An alternative to the foregoing combination of estrogen plus progestin taken separately would be a commercial product combining the two, for example, Enovid E® (norethynodrel 2.5 mg. and mestranol 0.15 mg.) or, in a larger dose, Enovid E® (norethynodrel 9.85 mg. and mestranol 0.15 mg.) one tablet a day for the first three weeks of each month.

If the patient prefers not to accommodate to a daily oral therapy, but to an intramuscular one instead, then the following could be prescribed: Delestrogen® (estradiol valerate) 10–20 mg. plus Depo-Provera® (medroxyprogesterone acetate) 50–100 mg. every two weeks. Instead of Delestrogen®, Depo-®estradiol

Endocrine Treatment of Female Transsexuals

In treating the female transsexual,[2] similar suggestions are to be made regarding surgical procedures as in the male. Before the surgery, androgen by injection is usually required in sufficiently large doses to suppress menstruation, to encourage some hair growth on face and body, possibly to lower the voice, and to accomplish a slight shrinkage of breast tissue. These changes can improve greatly the emotional state of the patient.

The dosage of androgen is subject to great individual differences; for instance, a weekly intramuscular injection of 200 of 250 mg. Delatestryl® (testosterone enanthate) may be necessary in the beginning, but can be reduced after menstruation has ceased.

It is wise to warn the patient that androgen treatment could produce temporary acne, as well as edema.

I have found oral androgen medication, including methyl testosterone, mostly unsatisfactory except for maintenance after a total hysterectomy and mastectomy. Buccal Oreton® propionate (testosterone propionate) or a similar preparation is to be preferred to methyl testosterone.

---

cypionate 2–5 mg. every two weeks might be substituted. After four to eight months of biweekly parenteral therapy, the same dosages could be given once every four weeks.

If in the preoperative state, the above dosages prove insufficiently effective after four to six weeks, then Dr. Migeon recommends that the dosage could be doubled or tripled. Otherwise, the rule is to use the smallest dosage that will give the desired clinical results.

[2] See also Chapter 26 by Randell.

TRANSSEXUALISM AND SEX REASSIGNMENT

Richard Green, M.D.,
and John Money, Ph.D., Editors

THE JOHNS HOPKINS UNIVERSITY PRESS, BALTIMORE

Manufactured in the United States of America

The Johns Hopkins University Press, Baltimore, Maryland 21218
The Johns Hopkins University Press Ltd., London

Originally published, 1969
Second printing, 1975

Library of Congress Catalog Card Number 69-15761
ISBN 0-8018-1038-8

CONTENTS