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Study of the use of estrogenic hormones in the treatment of the male pseudohermaphrodie

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A STUDY OF THE USE OF ESTROGENIC HORMONES IN THE TREATMENT OF THE MALE PSEUDOHERMAPHRODITE

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CONTENTS

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The proper diagnosis of sex in cases of psuedohermaphroditism has been a problem that presents many difficulties. Nelson (31) and others have developed techniques which are quite satisfactory for the diagnosis of genetic sex by study of the chromatin patterns in cells. It has been observed that cells of genetic females have characteristic clumps near the nuclear membrane, whereas cells of genetic males do not have such clumps. This knowledge would make the problem very simple if one needed only to consider the genetic sex; however, in cases of "intersex" patients there are several other factors that must be considered. Morris (27) has suggested three criteria to be evaluated before assignment of sex in patients in whom there is question as to true sex: (1) general anatomic appearance of the external genitalia, (2) histological status of the gonads, and (3) somatic sex chromosomal pattern. The general anatomic appearance should be considered with regard to the ease with which the

external genitalia can be made, by plastic reconstruction, to appear and function normally, or as near normally as possible, for the sex of assignment. The histological status of the gonads is of importance because it gives a suggestion as to the probable future endocrinological function, and therefore, to the probable type of secondary sex characteristics that will be developed. The somatic sex chromosomal pattern is helpful because it gives accurately the genetic sex of the individual and therefore would be helpful in predicting the probable hormonal response of the target organs. Wilkins, et al (41) have suggested the following classification of "intersex" patients:

A. Congenital Adrenal Hyperplasia

B. Intersexes

1. True Hermaphrodite

2. Psuedohermaphrodite

a. Male

1. External genitalia male or ambiguous

2. External genitalia female

b. Female

According to their study most of these patients

develop female secondary sex characteristics at puberty except for those with congenital adrenal hyperplasia who will not be considered here. They state that male pseudohermaphrodites often have estrogenic hormone production at puberty, causing feminization. Our purpose here is to consider a reasonable means of treatment for those male pseudohermaphrodites whose sex of diagnosis and rearing has been female; and who, at puberty, undergo masculinization because of androgenic activity of undescended testicles.

There are distinct psychological implications in such patients that must be considered if our treatment of them is to be reasonable. Wilkins, et al (41) suggest that it is rarely, if ever, advisable to consider changing a patient's sex after age 18 months to 2 years. Kiefer (16) has defined sex as, "the overall state of body and mind by which the individual conforms to the male or female standards of normality in .... sex-determining factors." Money, Hampson and Hampson (24) stated, "It has (erroneously) been widely assumed that gonadal

structure would determine sexual outlook and desires", even though external appearance and secondary sexual appearance were the opposite. They also suggested (26) that the sex of assignment and rearing is more reliable in determining the psychological sex of an individual than are chromosomal sex, gonadal sex, hormonal sex, internal sex, or ambiguous external morphology. From their study of 105 hermaphroditic patients over a period of 5 years with special regard to sexual psychology, they suggested that the dividing age for possible satisfactory change of sex psychologically is 27 months. According to their findings the child deciphers sexual identity from many factors including the personal nouns and pronouns used by others in addressing him, modes of behavior directed toward him and expected from him by others, type of hair cut, style of dress, items of personal adornment, and the appearance of the external genitalia. Because of the early age at which sexual identity is formed, most writers have agreed that diagnosis and assignment of sex should be made very early in all cases of "intersex" patients. It is the opinion of most writers that the configuration of the external genitalia and the

ease with which the external genitalia can be altered by plastic procedures to resemble and function like those of the sex of assignment should be the most important single criterion to be considered in the assignment of sex.

It is evident, however, that if sex diagnosis be based on this factor, there will be cases, at puberty, whose endocrinological sex, and therefore, their secondary sex characteristics will be different from their sex of assignment and rearing. This introduces the problem of changing the secondary sex characteristics to more nearly correspond with those "normal" for their sex of rearing, or of subjecting these individuals to the psychological trauma of being morphologically different from their peers at an age when conformity is the first law of happiness; or, thirdly, of subjecting them to the psychological and social trauma of changing sex identity at an age when such a change is all but impossible. Theoretically this may be accomplished by a gonadectomy to remove the unwanted hormones, followed by substitution therepy using hormones compatible with

the sex of rearing. The remainder of our discussion will be related to the problems involved in such a substitution therepy in male pseudohermaphrodites, with particular reference to the effect of estrogen on breast tissue.

It was noted as early as the turn of the century that there is a correlation between ovarian activity and the development of the mamary gland. Burrows (1) quoted the work of Halban in 1905 who noted such a correlation in human patients, the work of Heape in 1906 who noted an increase in size of the mammary gland in the proestrum and the work of Marshall in 1910 who noted the formation of corpra lutea accompanied by different events than those of the proestrum. Ingleby (14) in 1942 reported a study of six young girls at autopsy in which she examined the breasts by means of specially prepared serial sections and correlated her findings with the status of ovarian development. These girls had been apparently normal until the development of a sudden illness and death. All had begun to show increase in breast size typical of pubertal changes. She

noted that the connective tissue in their breasts was always well developed. Most interesting of her findings were those on three of the girls, all age 13. Two of them had never menstruated. In one of these the breasts showed only ductal proliferation with club shaped swelling of the terminal ducts. In the other there was no history of menstruation but one of the ovaries was scarred as if from a ruptured follicle. In this case some of the areas of breast showed beginning acinar development. In the third girl who had menstruated for 9 months, all stages of breast development up to the adult type were present. In studying the effects of hormones upon the breast one might reasonably make an arbitrary division between their effects upon the various component tissues that comprise the breast.

It has been noted (35) that the nulliparous breast is composed mostly of fat tissue and stroma with little parenchyma. Burrows (1) has cited the work of Folley with castrate male goats treated with stilbesterol in which there was hypertrophy of the udder. His work, however, was inconclusive as to

whether this increase in stroma was a primary effect of stilbesterol or whether it was secondary to proliferation of the ducts. Ingleby (14) by her technique of serial sections has studied the changes occuring in the stroma during the menstrual cycle and found that "in the normal (human) female the periductal connective tissue becomes looser and undergoes mucoid degeneration in the second half of the cycle when the epithelial cells proliferate and swell." Gardner (3) in his work with mice noted that large doses of folliculin benzoate caused overgrowth of connective tissues.

It is postulated that estrogen causes growth of the nipples. Nelson (30) states that in males and spayed females of all species tested estrogen induces growth of the nipples. Burrows (1) states that it has been shown that there is an increase in the number of mitotic figures in the epidermis of the nipple under estrogen therepy. He further noted that estrogen administration to pregnant rats causes males to be born with nipples whereas normal male rats are born without nipples.

Pigmentation of the areola is another function attributed to estrogen. According to the work of Burrows (1) estrogen causes hyperemia of the nipple and increases permeability of the capillary walls so that non diffusable substances present in the blood stream will more easily pass through the capillary walls.

The chief effect of estrogen on the breast is on the parenchyma of the breast. Haagensen (12) has suggested three types of changes in the breast: (1) Growth and involution, (2) cyclical changes associated with menstruation, and (3) milk secretion. Animal studies have shown that estrogenic hormones administered alone in castrate animals cause proliferation of the ducts with extension and ramification and with occasional development of a few lobules of alveolar tissue. (1) Numerous other similar studies have been made with castrate animals reaching similar conclusions. Burrows (1) suggests, "There is reason to believe that estrogens need the co-operation of progestin, androgen, or some other accessory factor to produce the full development of acini and alveolar

lobules in the breast; and discrepencies in the results obtained with estrogen alone may depend upon the presence or absence of the accessory factor, whether derived from the gonad, adrenal, or elsewhere." Lyons and McGinty (19) demonstrated a greater growth of mammary tissue in immature male rabbits by using a combination of progesterone and estrogen than they were able to obtain using estrogen alone. They noted that there was an optimum dose of progesterone above which inhibition of estrogenic activity occurs. Selye (38) suggests that there is an indirect action of estrogen, and that its effect is mediated through the anterior lobe of the pituitary, which, in response to the increased levels of estrogen produces a mamogenic hormone. The mamogenic hormone then is responsible for development of the mammary gland. He bases this hypothesis on his own work and the work of others such as Gomez and Turner (5, 6, 7, and 8) who have experimented with hypophysectomized animals. It has been noted in these animals that whereas estrogen ordinarily causes mammary hypertrophy, estrogen administration after hypophysectomy fails to produce any increase in the mammary gland size.

It was also noted that after hypophysectomy the administration of both pituitary extract and estrogen causes mammary hypertrophy. It is necessary that the pituitary extract be given early in the post-operative period if mammary growth is to be achieved. Gomez et al (7) experimented with hypophysectomized guinea pigs who were treated with pituitary extract from rats which had been previously treated with large doses of theelin. In these cases the guinea pigs had hypertrophy of their mammary tissue, whereas in controls treated with pituitary extract from normal rats there was no such growth. Others have failed to reproduce his results. (1) In another publication Gomez and Turner (6) suggest that the failure of hypophysectomized animals to respond to estrogen may reflect a deficiency of other hormones such as the adrenocorticoids, thyroid, and the general growth factor of the pituitary rather than a specific mamogenic hormone. This view has been supported by several other workers. (1, 37, 39) Ingleby (14) studied human breasts by a serial section technique and found that prior to the menarche in pubertal

girls when presumably the chief sex hormonal influence would be estrogenic, and in adults during the estrogenic phase of the ovarian cycle there is a growth of the ductal tissue. By a process of proliferation of certain cells outward there is elongation of the ducts. The onset of menses indicates progesterone stimulation from leutean follicle formation. Ingleby found that with the onset of menses and in the progesterone phase of the ovarian cycle there was acinar development and lubule formation. In both animal experiments and in the human most workers have found that estrogen causes elongation of the ducts and breast enlargement, and that progesterone causes acinar and lobular formation. Most writers who have worked with the two hormones have concluded that there is greater hypertrophy of the mammary gland with a properly balanced combination of estrogen and progesterone than there is with estrogen alone. In an attempt to disprove the "mamogen" theory several workers have applied estrogen ointment directly to the breast and have found that it causes an increase in breast size. (39) MacBryde

(20) presented a study in which he worked with three hypogonadal women who lacked mammary development. He first treated them with 150,000 to 350,000 I. U. of estradiol benzoate weekly by subcutaneous injection and noted active mammary growth whereas there had been no previously visible or palpable breast tissue. After cessation of treatment there was regression to approximately the previous condition. Corpus luteum extract was tried with no effect. When 1 I. U. progesterone was combined with 20,000 to 50,000 I. U. estrogen daily he noted a greater breast growth than previously when estrogen had been used alone. He also noted that the regression following omission of treatment was less rapid after the combination of hormones than with estrogen alone. He also used local inunction with an ointment prepared using anhydrous wool fat and petrolatum with 5,000 I.U. estradiol benzoate per gram. This ointment was applied over an area 10 cm. in diameter with the nipple as the center using 5 gm of the ointment daily. The ointment was used unilaterally and an ointment prepared similarly but without the estrogen was used on the other

breast as a control. He evaluated the effect by using caliper measurements of the horizontal, vertical, and depth dimensions of the breast and areolar measurement. It was found that asymmetrical application of the estrogenic ointment caused asymmetric breast enlargement in all three patients.

There is an important question that has not as yet been answered completely. Namely, what differences exist, if any are present, between the effect of estrogen on the genetic female breast and that of the genetic male. It is suggested, however, by several writers that there is a distinct difference of response. Sanner has said, (35) "Sex is genetically determined, (therefore) the behavior of each body cell is conditioned by the sex of the individual, and therefore a greater growth response to estrogen occurs in young females, though a degree of enlargement of the male breast may be obtained under experimental conditions." Gynecomastia has been observed in otherwise normal males from skin contamination in stilbesterol workers. (2) In these patients breast development resembled that seen in adolescent girls. Selye (38)

stated, "Gynecomastia may develop in castrated, more easily, or in non-castrated men (with estrogen administration), in the latter due to suppression of the pituitary gonadotropic activity." In speaking of hormonal therapy for the intersex patient Wilkins (41) stated, "It must be remembered.....that the intersexuality may involve the maleness or femaleness of the end organs and determine the nature of the response to hormonal stimulation."

Case Summary: W. B. age 17

This 17 year old white "girl" entered UNH 6-12-57 because of question as to true sex. At birth this patient was thought to be female. There was no enlargement of the clitoris, and the labia appeared to be normal. The patient always had a husky voice and seemed to prefer masculine sports, but participated very little because she was quite thin. At age 8 or 9 years a lump had appeared in the right groin which was thought to be a hernia. It was excised and repaired at that time by the family physician and no report was made to the parents as to the tissue diagnosis.

After this her voice gradually deepened, she began to develop masculine type musculature, and the clitoris began to enlarge. At age 13 years another lump appeared in the left groin and persisted to the date of admission. She had no history of menses or of breast enlargement. Past history and systemic review were non contributory. Family history revealed that she had a sister who had no uterus since birth. She also had three brothers and another sister who were all normal.

Physical examination revealed a well nourished and well developed white girl with a deep masculine voice and a masculine physique with well developed muscles. Her height was 5' 6½" and her weight was 144 pounds. She had a female type of hair distribution and the skin was of normal appearance. The thyroid was not palpable. The breasts were small and atrophic resembling those of an early pubertal female. The heart and lungs were within normal limits. The abdomen was flat and muscular. There was an appendectomy and a right inguinal scar. The

liver tip was palpable on deep inspiration but no other masses were palpable. There was a mass 1 x 1.5 inches in the left inguinal canal which could be brought down into the left labia majora. Labia minora were apparently absent. The clitoris was enlarged to about 2 inches in length and resembled a small penis. The vaginal orifice was quite small and about 2 cm. in depth. Neither uterus or prostate were palpable on rectal examination, but there was a sense of fullness in the cul-de-sac and a palpable line in the midline anteriorly in the rectum.

Laboratory studies: 6-12-57 -- Chest x-ray was within normal limits; 6-13-57 -- CBC Hgb 15.3, Wbc 11,900 with seg 57, staff 8, eos 2, lympho 28, monos 5; ESR-2; PCV-48; serology - negative; urinary 17 - ketosteriods 29.5 mgm/24 hr., urinary 17 - hydroxysteriods 15.5 mgm/24 hr. 6-14-57 -- urinary 17 ketosteroids 32.8 mgm/24 hr., urinary 17 - hydroxysteroids 16.3 mgm/24 hr.; 6-19-57 urinalysis - straw, clear, sp. g. 1.006, pH 7.5, Wbc 1-2, albumin negative, sugar negative, acetone negative; 6-24-57 IVP and KUB within

normal limits, CBC - Hgb 13.4, Wbc 10, 400 with seg 63, staff 10, lympho 16, eos 4, monos 7; 7-31-57 -- urinalysis - straw, slightly cloudy, sp. g. 1.019, pH 4.5, albumin slight trace, sugar negative, acetone negative, Wbc 8-10, casts - occasional fine, moderate mucous threads.

Hospital course: Blood smear examination on 6-19-57 was not conclusive, but was suggestive of male type cell chromatin. Psychiatric evaluation was obtained which indicated that the patient fitted the female psycho-sexual pattern. Cystoscopy and endoscopy showed a normal urethra and bladder. On 7-16-57 after careful evaluation the patient was taken to the operating room where the mass was removed from the left groin and a hernia was repaired, the phallus was excised, and an artificial vagina was constructed using a split thickness skin graft from the thigh. On 8-3-57 the patient was dismissed on stilbesterol 1 mgm daily in an attempt to produce breast development. Follow up photographs taken after therapy show moderate breast enlargement.

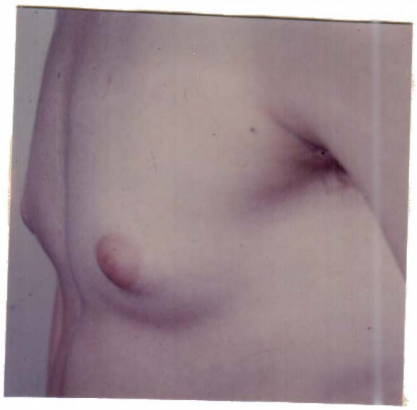

Fig. 1: W.B. before therepy

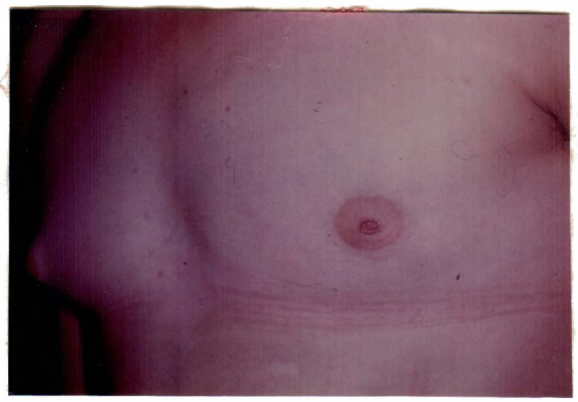

Fig. 2: W.B. after therepy with stilbesterol 1 mgm. daily

Male pseudohermaphroditism in which the external genitalia at birth resemble the female type, and which at adolesence undergo masculinization present a problem of therapy. Psychologically it is unwise to attempt to change sex identity in an individual after the age of two and one-half years, yet there is psychological trauma because of the difference between secondary sex characteristics and sex identity. A case has been presented in which gonadectomy, phallusectomy, and artificial vaginal construction were performed after which the patient was placed on stilbesterol therapy of 1 mgm daily with a moderate increase in size of the breasts. This seems to be a rational form of treatment in such

cases. It is possible, however, as suggested by several workers that slightly more gratifying results might be obtained with a combination of estrogen and progesterone therapy.

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