Fig. 1. Appearance of the patient described at 13 years of age prior to any medication.
SPONTANEOUS PUBERTAL BREAST GROWTH IN A CASTRATED PATIENT WITH THE SYNDROME OF TESTICULAR FEMINIZATION

The changes in the endocrine system that occur at the time of puberty are not completely understood. Development of secondary sexual characteristics is due chiefly to the secretion of gonadal steroids, but the role of the increased adrenal androgen secretion, as well as the possibility of a significant increase in sensitivity to exogenous testosterone at the time of puberty, remains obscure.

In an attempt to learn more about the non-gonadal physiological mechanisms involved in normal pubertal development, this paper describes a patient with the syndrome of testicular feminization who had been castrated in early childhood but went on to develop breasts at puberty.

CASE REPORT

M.A. (YNHH 67-80-45), a white girl, was born on 5/8/57 weighing 7 pounds, 2 ounces and measuring 19½ inches. Pregnancy and delivery were normal.

At 13 months of age, a right inguinal hernia was discovered. During repair at 18 months of age, the hernia sac was found to contain a gonad which at the time was thought to be an ovary and reinserted into the abdomen. Three days later the baby developed an acute and painful left inguinal mass. Biopsy of this mass demonstrated testicular tissue. The incision was extended and the abdomen opened for pelvic exploration. No uterus or tubes were found. Only the aforementioned gonads, now defined as testes, were present. Since there was no enlargement of the clitoris, and the labia, hymen, and vagina seemed to be normal for an 18-month old girl, the diagnosis of male pseudohermaphroditism was made and both gonads removed. Pathological examination confirmed that both gonads were normal prepubertal testes. A buccal smear was chromatin negative.

Subsequently, the child has done well; she was seen for the first time at the Yale-New Haven Hospital at 11 years of age. A delightful young girl, she was 5'2" tall and weighed 124 lbs. Her school work was good and her
behavior was in every way that of a normal girl. She was discharged without medication and asked to return the following year for evaluation as to possible therapy.

When next seen at 13 years of age the patient had developed adolescent sized breasts (Fig. 1). The left breast was somewhat larger than the right, but there was bilateral glandular tissue. The areolae were immature. There was no axillary or pubic hair but a few vulvar hairs were noted. The labia were slightly atrophic and prepubertal; the clitoris was normal. The vagina was one inch deep and poorly epithelialized; no pelvic organs were palpated on rectal examination. A vaginal smear revealed 15% cornified cells, 85% intermediate cells, and no basal cells. A chromosomal study performed at this time revealed a 44 XY pattern. The possibility of prior ingestion of any preparation containing estrogens was carefully discussed and ruled out.

No member of this family has had a comparable condition. The patient has one brother and two post-pubertal sisters, both of whom have developed normally and are having menstrual periods. There are no relatives with a history of infertility and none with anything indicative of sexual abnormality.

Because of the rarity of finding breast development in a castrated indi-

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**Table 1. Pituitary And Adrenal Responses To The Administration Of Exogenous Hormones In A Patient With Feminizing Testicular Syndrome**

|                  | 17KS (mg/24 hr.) | 17OHCS (mg/24 hr.) | Estrogens (µg/24 hr.) | FSH (µg/ml.) | LH (µg/ml.) |
|------------------|-----------------|--------------------|---------------------|--------------|--------------|
| Normal basal values for a 13 year old girl | 2.6* | 4.3 ± 1.5** | 10-30† | 0.10± | 0.02± |
| Basal values for patient MA | 5.9 | 2.7 | 120 | 3.8 | .25 |
| Basal values for patient ACTH (40 U IV in 8 hours) | 29 | 27 | 49.3 | 4.3 | - |
| Basal values for patient Stilbestrol (2 mg PO qd × 4d) | 12 | 7.8 | 19.6 | 1.1 | .13 |
| Basal values for patient Testosterone Propionate (25 mg IM qd × 4d) | 25 | 5.4 | 21.5 | 1.4 | .09 |
| Basal values for patient Fluoxymestrone (25 mg PO q 12 hr × 4d) | 14 | 4.5 | 17.0 | 2.4 | .22 |
| Basal values for patient Dexamethasone (2 mg PO qd × 4d) | 4.1 | 0.7 | 15.2 | - | .32 |
| Basal values for patient Dihydrotestosterone Acetate (25 mg IM qd × 4d) | 12 | 2.7 | 24.7 | 3.3 | .33 |

* Talbot, et al.17
** Wilkins8
† Kase8
‡ Lee, et al.20
individual, she was admitted for evaluation. Initial determinations of hemoglobin, hematocrit, white cell count and differential, blood glucose, BUN, serum electrolytes and urinalysis were all normal.

Endocrine studies: The urinary excretion of 17 ketosteroids (17KS) were 5.9 mg/24 hrs. and of hydroxycorticoids (170HCS) (as Porter Silber chromogens) 2.7 mg/24 hrs. Total estrogens in urine as assayed by a fluorescence method were 20 μg/24 hrs. Estradiol in blood was assayed by a competitive binding system employing uterine cytosol protein as a binder and by an immunoassay utilizing anti-estradiol antibodies.

Both methods for the measurement of estradiol in blood yielded very low values. No estradiol was detected by use of anti-estradiol antibodies (limit of sensitivity 10 pcg/ml.) and the immunoassay measured 4 pcg/ml. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) in blood were assayed by radioimmunoassay in triplicate. FSH in blood was 3.8 μg/ml. (LER-907) and LH was .25 μg/ml. (LER-907). One milligram of LER 907 equals 20 international units of FSH and 48 international units of LH (Bioassay, second IRP). Normal values in our laboratory for menstruating women in the follicular phase (mean ± S.D.) : LH, 0.12 ± .04 μg/ml. and FSH, 0.47 ± 0.13 μg/ml. (reference for both—LER 907). The LH values are not elevated to the same extent as the FSH values.

After discharge, the patient was treated with methylestosterone 20 mg. q.d. for six weeks. No increased hair growth, acne, or other androgenic effects accompanied this treatment. Subsequently, the patient received Stilbesterol 0.5 mg. q.d. and further breast growth ensued.

DISCUSSION

The observation that exogenous androgen would not masculinize patients with the syndrome of testicular feminization led Wilkins to suggest that the basic lesion in this disease was peripheral insensitivity to androgen. Confirmatory evidence is that the testes of these patients produced normal amounts of testosterone both in vivo and in vitro. Recently it was determined that the skin and other target organs in those patients lacked the ability to convert testosterone into 5α-dihydrotestosterone, which is presumed to be one of the active metabolites of the hormone.

The diagnosis of testicular feminization is not easily made before puberty. Some male pseudohermaphrodites will develop full-blown virilization at puberty. In the absence of a family history, the diagnosis was made by demonstrating over a sufficient period of time clinical unresponsiveness to methylestosterone.

Despite castration in early childhood, this patient developed breasts. Two
similar patients who were castrated in childhood and observed throughout puberty did not develop breasts, but it is not certain that the male pseudohermaphrodites reported by Giusti had the syndrome of testicular feminization.

The production of endogenous estrogen by this patient was minimal as judged by her serum values. Metabolite excretion was in the low normal range but this value was probably misleadingly high. Other phenolic substances interfere with the assay and its specificity is questionable in the range of low values.

The serum concentration of estradiol in this patient, though far less than that found in normal males (around 30 pcg/ml.), was still enough to induce breast growth in the presence of androgen insensitivity. This phenomenon emphasizes the anti-estrogenic effect of androgens in mammary growth. The large breasts so commonly observed in such patients, when the diagnosis is made after puberty, (when the testes, as well as the adrenals, contribute to the estrogen pool), probably have a similar meaning. The physiological inhibition of the estrogen effect by androgens is also suggested by the fact that 17 α-methyl-β-nor testosterone, a nonestrogenic antiandrogen, has been reported to have induced gynecomastia in 12 out of 13 males.

SUMMARY

A patient is evaluated with the syndrome of testicular feminization who showed breast development at the time of puberty despite castration in early childhood. The finding of low blood concentration of estradiol (4 pcg/ml.) is consistent with the contention that mammary tissue develops despite low estrogen levels because of the unresponsiveness to androgen characteristic of testicular feminization. That thelarche occurred at a normal age despite castration in infancy suggests that modifications in steroid production pattern, or peripheral sensitivity, or both, occur at puberty independently of the presence of gonads.

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