

Klinefelter's Syndrome: Historical Background and Development *

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ABSTRACT: When described more than 40 years ago, Klinefelter's syndrome (small testes, sterility, increased excretion of follicle-stimulating hormone, and usually gynecomastia) was thought to be an endocrine disorder. A second testicular hormone was postulated but has never been isolated. During the ensuing years, the syndrome has been found to be a chromosomal disorder, in which there is an extra X chromosome in 80% of the patients. The disorder occurs once in 500 to 1,000 male births and is best diagnosed by a buccal smear. When there is androgen deficiency, it is treated with testosterone. Gynecomastia is treated surgically because of the potential danger of malignancy or for cosmetic reasons.

IT WAS CUSTOMARY during the time that Dr. War-field Longcope was Professor of Medicine at the Johns Hopkins Medical School for the incoming resident in medicine to spend the year before his residency doing research at another

institution. I chose to do this in endocrinology at the Massachusetts General Hospital. It was difficult to find money for such a purpose at that time, and I learned later that my cousin and mentor, Dr. Walter Baetjer, had given the money for me to have that year in Boston.

I first worked under Dr. Howard Means, measuring oxygen consumption of adrenal gland slices in the Warburg apparatus, but I was so unsuccessful at it, breaking most of the apparatus,

*Read before the Section on Medicine, Southern Medical Association, 79th Annual Scientific Assembly, Orlando, Fla., Nov 17-20, 1985.

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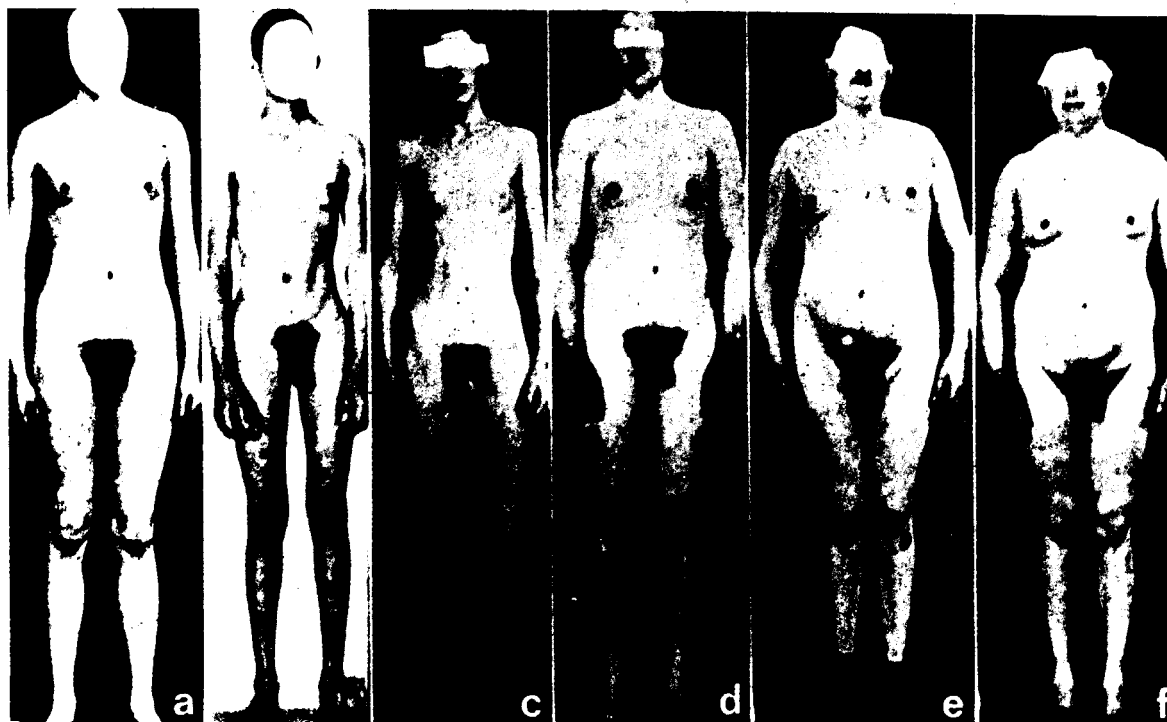


FIGURE 1. Six of original nine patients with Klinefelter's syndrome. Notice masculine body configurations and relatively normal development of accessory sex organs, except for breasts.

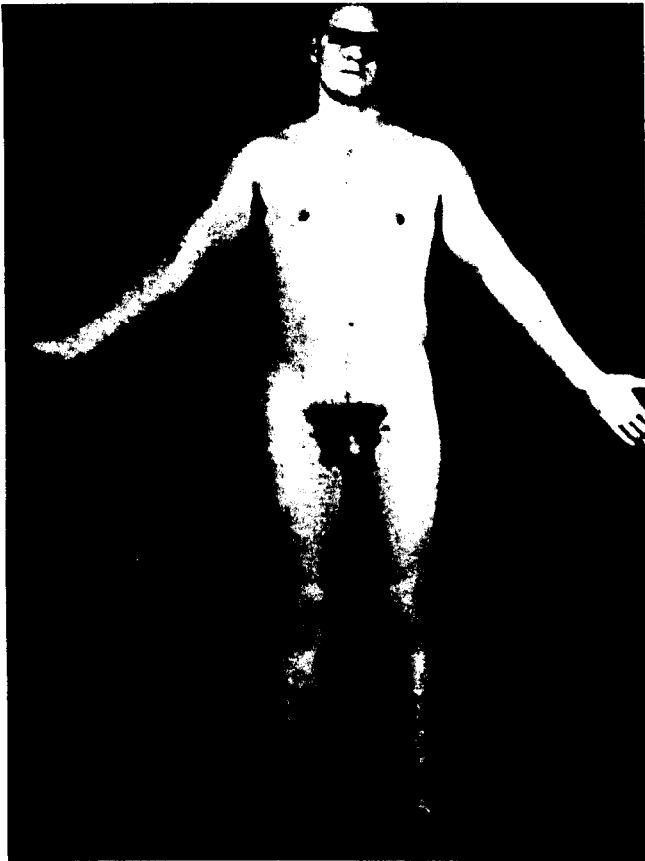


FIGURE 2. XXY patient with normal androgen function.

that in September, I asked Dr. Means if I might work with Dr. Fuller Albright, since I primarily wanted to learn some clinical endocrinology. Dr. Albright was the most outstanding clinical endocrinologist in the world, and Dr. Means readily agreed.

Albright's Saturday morning clinics were famous throughout the Massachusetts General Hospital. At the first one I attended, I saw a tall black boy named George Bland who had gynecomastia and very small testes (1.0 to 1.5 cm in length). When I asked Dr. Albright what this was all about, he said he did not know but that he would be happy for me to work on it. During the rest of the year, we found eight other patients with this same condition and reported the series at the endocrine meetings in 1942. Dr. Albright was charitable enough to let me put my name first on the paper that was published later in 1942 in the *Journal of Clinical Endocrinology*. The title, "A Syndrome Characterized by Gynecomastia, Aspermatogenesis Without Aleydigism, and Increased Excretion of Follicle-Stimulating Hormone," was so long that the syndrome came to be known by my name. though it was really just another of Dr. Albright's diseases. Albright had more ideas in a day than most people have in a lifetime, and it was a great pleasure and privilege to work with him. Not only did he have great ideas and theories, but if someone came up with a fact that blasted his current theory, he soon had another one!

Figure 1 shows six of the original nine patients. These patients tend to be tall, with normal secondary sex characteristics; most have normal sexual function. Figure 2 emphasizes that these patients often have an entirely normal appearance save for their small testes, and I am sure many escape detection because the testes are often not examined in a general physical examination. Figure 3 illustrates the gynecomastia of several of this group. Figure 4, a photomicrograph from a testicular

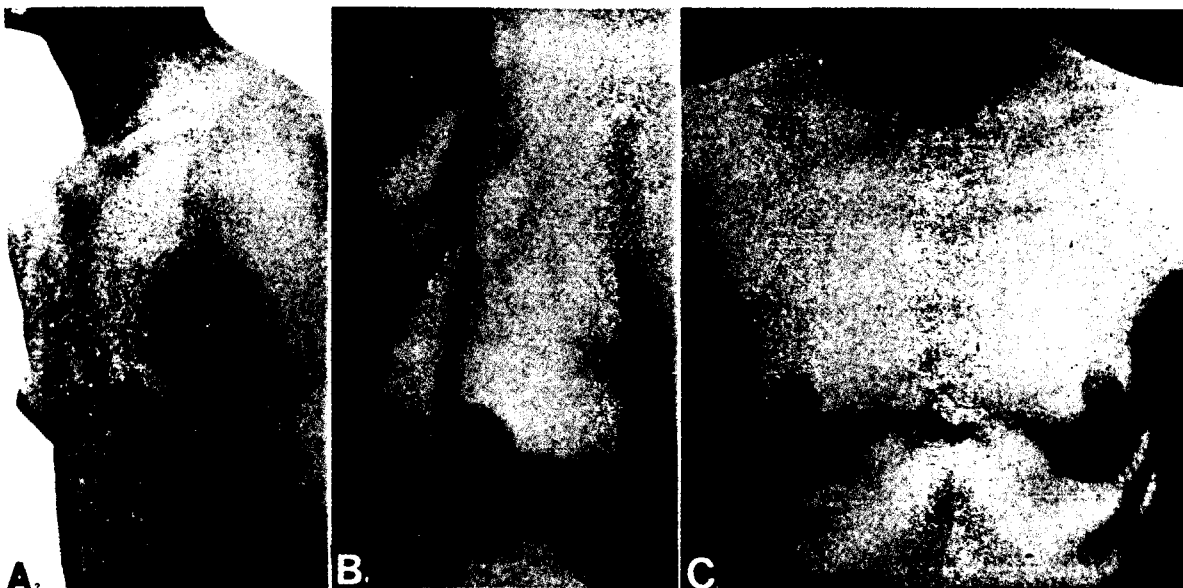


FIGURE 3. Bilateral gynecomastia in three patients shown in Figure 1.

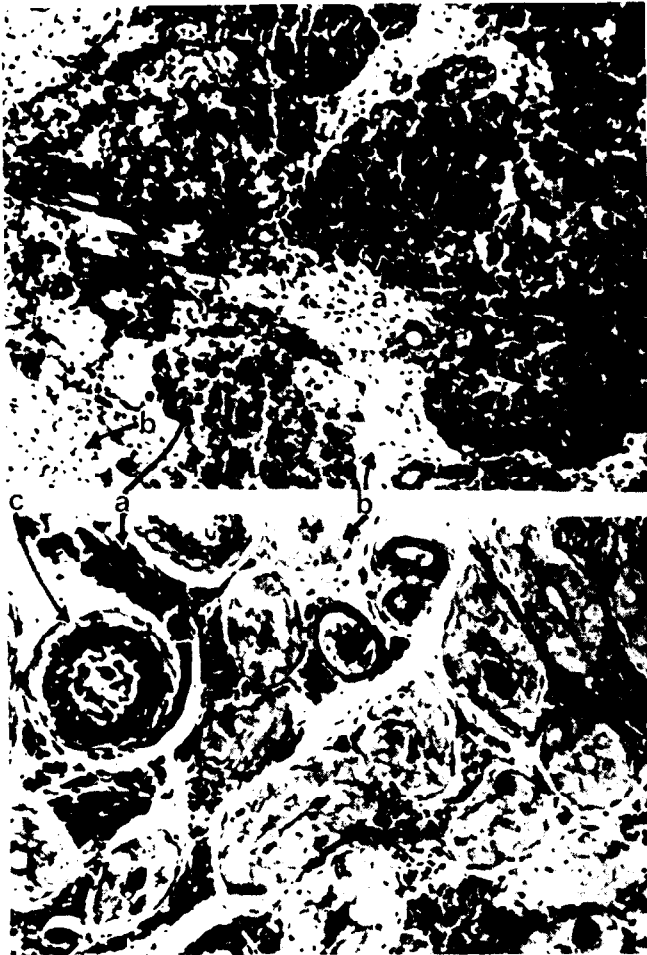


FIGURE 4. Testicular biopsy. (a indicates Leydig cells; b, completely hyalinized tubules; c, partially hyalinized tubules. Leydig cells (a) almost suggest adenoma formation.) (H & E. original magnification $\times 200$)

biopsy, shows the atrophy and hyalinization of the seminiferous tubules with preservation of the Leydig or interstitial cells.

A few years after the syndrome was described, Heller and Nelson² reported that the gynecomastia was not a necessary part of the syndrome, though it occurred in about 75% of the patients. The hallmarks of the syndrome, therefore, are small testes, sterility, and increased excretion of follicle-stimulating hormone.

We thought that this syndrome, which occurs in about one in 500 to 1,000 male births, indicated there was a second testicular hormone, analogous to estrogen in the female. Figure 5 shows diagrammatically the hormone relationships we thought existed. The solid and cross-hatched lines indicate presence of hormones; broken lines indicate absence. Stimulating influences are indicated by solid arrows, and inhibiting influences by open arrows.

There is a good deal of evidence from both animal and human studies to show that a second

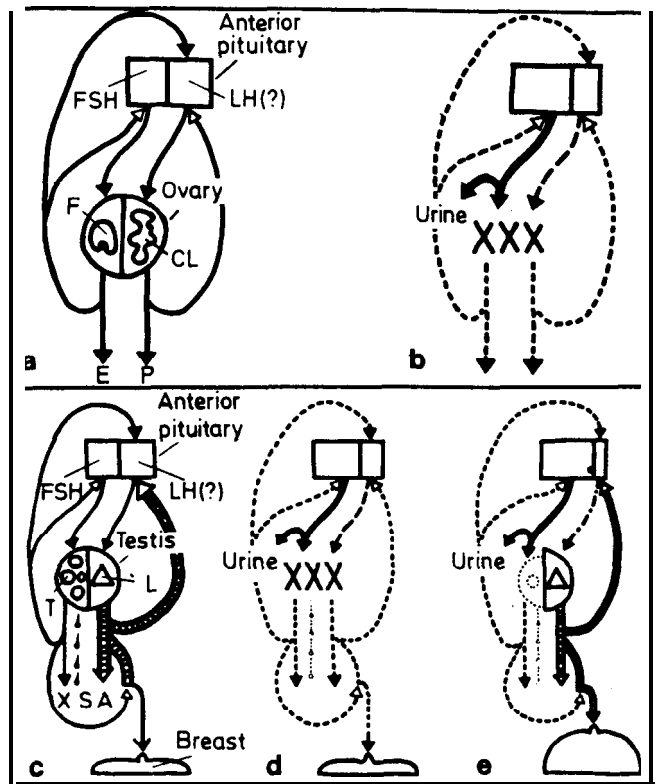


FIGURE 5. (Top) Schematic drawing of hormonal patterns in normal female (A) and female after gonadectomy (B). (Bottom) Schematic drawing of hormonal pattern in normal male (A), male after gonadectomy (B), and male with Klinefelter's syndrome (C).

testicular hormone exists. In the male castrate, testosterone does not control hot flashes, whereas estrogen does. In this syndrome, estrogen decreases the urinary FSH excretion much more readily than testosterone. In animals, testosterone fails to correct all the hypophyseal changes after castration. This second testicular hormone has been labeled inhibin. Despite a great deal of work, it has never been isolated, but we know that it is not a steroid.

We thought the gynecomastia was caused by the action of testosterone on the breast in the absence of this second testicular hormone. Figure 6 is a photomicrograph showing the difference in the appearance of the gynecomastia in this syndrome from estrogen-induced gynecomastia, shown on the right. In the latter there is more glandular tissue, and in the former, more periacinar fibrous tissue.

Fourteen years after the original description of the syndrome, two groups independently discovered that the buccal mucosal cells of these patients contained an extra chromatin mass (Fig 7), or were chromatin positive.^{3,4} A few years later, Jacobs and Strong⁵ found that these chromatin-positive patients had 47 chromosomes,

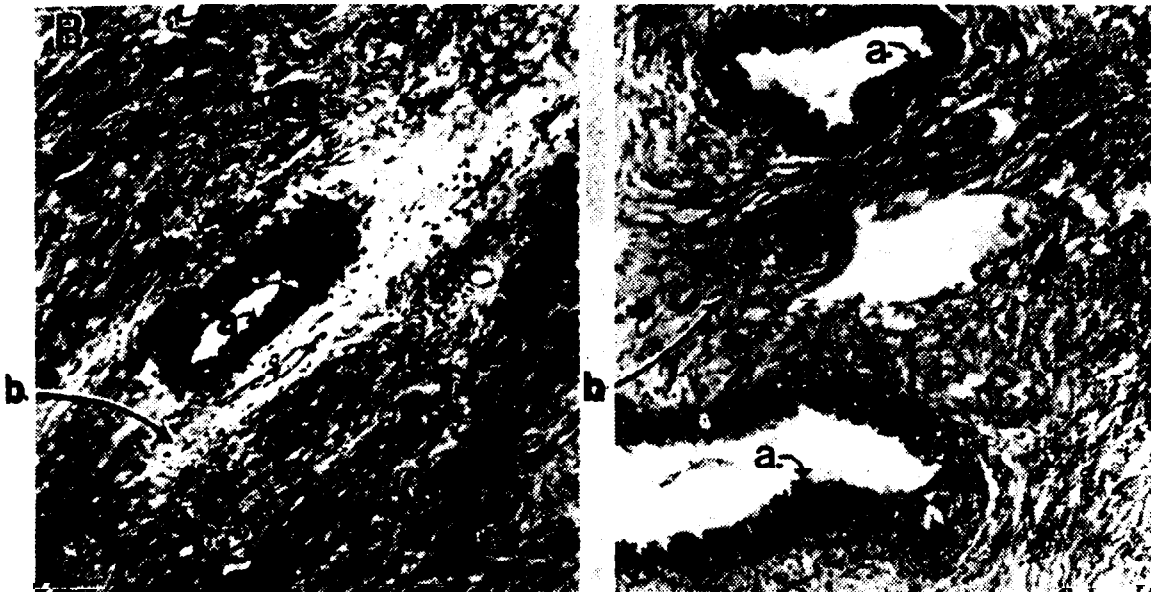


FIGURE 6. (Left) Breast tissue in Klinefelter's syndrome, with only moderate ductal hyperplasia (a), with marked proliferation of the periductal connective tissue (b). (Right) Breast tissue in estrogen-induced gynecomastia; ductal hyperplasia (a) is more marked, and periductal connective tissue (b) is less dense

with an extra X chromosome, and were XXY. The extra X chromosome results from either meiotic nondisjunction, in which a chromosome pair fails to separate during meiosis, or from anaphase lag. Anaphase lag might result in a gamete lacking a sex chromosome; a chromosome lags and is not incorporated in the new cell in the next stage of mitosis (anaphase). Such anaphase lag could account for the largest minority karyotypes, the mosaics XY/XXY and XX/XXY. Eighty percent of these patients have positive sex chromatin, and their karyotypes may vary widely, with many mosaics (Fig 8).

The syndrome in patients with positive chromatin in the buccal mucosa should probably be called Klinefelter's disease. Although these patients have positive female sex chromatin, they are phenotypic males and should never be considered otherwise. The other 20%, whose testes are not small, have XY chromosomes and should be studied further to determine etiology. These patients often have no complaints, and the condition is discovered in the course of a general physical examination. Sterility and gynecomastia are the most common complaints. It is thought that 5% to 10% of sterile males have this condition. When this disorder is suspected, a buccal smear is the first test to request. If the cells are chromatin positive, the diagnosis is made; testicular biopsy and karyotyping are not necessary. If the buccal mucosa is chromatin negative, further studies are indicated.

The extra X chromosome in these men has stimulated much interest, but its function, if any,

has not been determined. Systemic lupus erythematosus, a disorder more common in female patients, has been frequently reported in this syndrome, but the association is not statistically significant. The association with leukemia may also be coincidental. Leg ulcers, osteoporosis, and taurodontism occur with greater frequency in these patients than in control subjects, and dermatoglyphic studies have shown characteristic abnormalities.

Extensive studies of these patients during adolescence have shown that they may have different personality traits, which can be helped greatly with proper counseling of the parents as

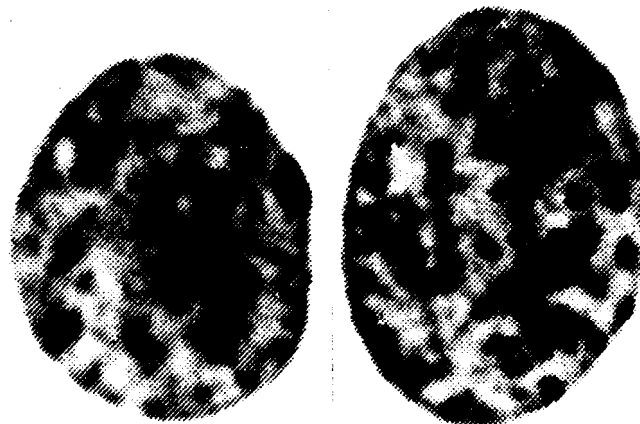


FIGURE 7. Photomicrograph of female cell on left, showing sex chromatin just under the nuclear membrane. Male cell on right shows absence of this chromatin mass. (Original magnification $\times 2,000$)

XXY, XXXY, XXXXY, XXYY, XX/
XXY, XY/XXY, XY/XXXXY, XXXY/
XXXXY, XxY/Xx/XY,²⁷ xxxn?, XX-
Y / x x , XXY/XY, XXY/XYY, XXY/
XXXXY, XXX/XXXXY, XXXXY/XXX-
XXY/XXX, XX(Y), XXXXY/XX-
XXY/XXX, XO/XY/XXY, YO/XY/X-
XY, XO/XX/XY/XXY/XXXXY, XY/
XXY/XXxY, XY/XXY/XXXXY, x x /
XY/XxY, XX/XY/XXY.²⁸

FIGURE 8. Mosaic chromosomal patterns found in Klinefelter's syndrome.

well as the patient.⁶ In most patients, however, the condition is not diagnosed until early adult life, when counseling may be less rewarding. Mental deficiency, manic depressive psychoses, and schizophrenia seem not to occur more commonly in this syndrome than in controls; most of these patients work regularly, and lead normal lives except for their inability to procreate.

There is no treatment for the sterility. The gynecomastia should be treated by excision of the tissue with preservation of the nipple. This should be done not only for cosmetic reasons but because cancer of the breast is about '20 times as frequent in this condition as in normal men.⁷ If hypogonadism is present, treatment with injected testosterone is effective. There is some evidence to suggest that treatment with testosterone in adolescence helps to correct some of the personality abnormalities that these patients show.

References

1. Klinefelter HF, Reifenstein EC, Albright F: Syndrome characterized by gynecomastia, aspermatogenesis without aleydigism, and increased excretion of follicle-stimulating hormone. *J Clin Endocrinol* 2:615-627, 1942
2. Heller CC, Nelson WO: Hyalinization of the seminiferous tubules associated with normal or failing Leydig-cell function. discussion of relationship to eunuchoidism, gynecomastia, elevated gonadotropin, depressed 17-ketosteroids and estrogens. *J Clin Endocrinol* 5:1-12, 1945
3. Bradbury JT, Bunge RG, Boccabella RA: Chromatin test in Klinefelter's syndrome. *J Clin Endocrinol* 16:689, 1956
4. Reis P, Johnson SG, Mosbeck J: Letter to the Editor. *Lancet* 1:962, 1956
5. Jacobs PA, Strong JA: A case of human intersexuality having a possible XXY sex-determining mechanism *Nature* 183:302-303, 1959
6. Nielsen J, Sorensen K: The importance of early diagnosis of Klinefelter's syndrome. *Klinefelter's Syndrome* Bandmann HJ, Breit R, Perwein E (eds). Heidelberg, Springer-Verlag, 1984, pp 170-187
7. Cole EW: Klinefelter's syndrome and breast cancer. *Johns Hopkins Med J* 138:105-108, 1976