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# Chapter 44

## Klinefelter's Syndrome

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### INTRODUCTION

Klinefelter's syndrome was originally described by Harry Klinefelter, Jr., et al. in 1942 as a unique form of **hypergonadotrophic hypogonadism** (1). Later Heller and Nelson (2) expanded the characteristics of the syndrome to include variable degrees of Leydig cell dysfunction. In 1956 Plunkett and Barr (3) demonstrated that patients with Klinefelter's syndrome exhibited a chromatin-positive buccal smear pattern. This indicated that an abnormality in X chromosomes was involved. However, it was not until 1959, when Jacobs and Strong (4) showed that the chromosomal pattern in these patients was XXY, that a clear understanding of the **pathogenesis** was gained. Klinefelter's syndrome is now well recognized as a common form of primary testicular failure caused by the presence of supernumerary X chromosome(s). Moreover, since the original description of the classic **XXY** disorders, multiple variant forms of the syndrome have been noted (Table 44-1). The existence of these variant forms indicates that, in addition to nondisjunction of maternal or paternal chromosomes, the disorder may **also arise from zygotic nondisjunction** in the affected subjects. Recent **evidence** from multiple family members with this disorder in which the mother was XXX/XX has also given rise to a third proposed etiology, i.e., the passage of 2 XX chromosomes that originally developed from nondisjunction of a parental **zygote** (5).

Another common form of primary testicular failure (incidence, 1:9,000) is the XX male syndrome (6,7). This entity may be considered to be a variant of **Klinefelter's** syndrome, because most of the subjects have been demonstrated to have a portion of Y chromosome translocated to one of the X chromosomes. The XX **gonadal** dysgenesis syndrome is of further importance in that animal models are available for study, whereas models for the classic form of Klinefelter's syndrome are rare. The differences in individual aspects of **XXY** and **XX** disorders are discussed later in this chapter (Genetic and Epidemiologic Evidence; also see Table 44-1).

From a phenotypic standpoint, men with Klinefelter's syndrome have a polymorphic appearance. The usual manifestations include a mildly **nesthenic** body habitus, height >184 cm, somewhat small head circumference, bilateral **gynecomastia**, a female **escutcheon**, normal-appearing penis, and small, **firm testes** <9 ml in volume following puberty (8-12). Distribution of facial hair is quite variable, with enough hair growth present: on the upper lip for a **moustache** but limited mandibular hair growth. There also may be "cross-hatching" wrinkles over the malar region in older patients

with Klinefelter's syndrome, as is typical of hypogonadism in general. One important physical characteristic that has been shown to differentiate Klinefelter's syndrome clearly from other forms of prepubertal androgen deficiency syndromes is the lack of a classic eunuchoidal body **habitus** (13). In Klinefelter's syndrome the upper segment to lower segment ratios are < 1; however, unlike eunuchoidal proportions, the **arm span** is not greater than the height. As has been previously indicated, different individuals with **Klinefelter's** syndrome may present with variable degrees of expression. Another variable is the effect of age in the same individual. Gabrielove et al. (14) have shown that as patients with Klinefelter's syndrome age, Leydig cell function decreases and the individuals are more clearly hypogonadal.

Klinefelter's syndrome is also expressed in the central nervous system. For example, many of the patients have impaired intellectual function with or without psychiatric disease (15,16). Nonbiased studies do demonstrate decreased performance on the verbal portion of the IQ test and an associated delay in reading abilities (16,17). On the whole, the psychosocial problems are mild. Because many studies were performed with biased methods of sample selection, the issue as to whether social problems are characteristic of the XXY genotype with associated decreased I.Q. or secondary **co androgen deficiency** is unresolved (see Table 44-2) (18-21).

Garson et al. (9) noted in a prospective study that the only clinical finding characteristic of Klinefelter's syndrome found on screening physical examinations performed during routine hospital admissions was the presence of small, firm testes. Therefore, although many physical, developmental, and associated medical difficulties have been noted with increased frequency in Klinefelter's syndrome, the clinical findings related to these associated entities are not specific.

### CLINICAL EVALUATION OF THE GENETIC INFORMATION

Because boys with Klinefelter's syndrome are physically normal prior to puberty and seemingly proceed through puberty at a time similar to that of their nonaffected peers, affected children are not detected unless they have participated in genetic screening programs or screening programs for learning disabilities. Thus treatment information about Klinefelter's syndrome is not given until the patients are detected and treated when they reach adulthood. The few fragmentary studies that have reported cases of Klinefelter's syndrome

TABLE 44-1. KLINEFELTER'S SYNDROME: KARYOTYPE AND CLINICAL AND LABORATORY FEATURES OF CLASSIC AND VARIANT FORMS

Classic Form XXY	Variant Forms		
	"XX" Group: XX	"XY" Groups: XXY, XXXYY; XX <sub>i</sub> (Y <sub>p</sub> )Y/XY; X <sub>i</sub> (X <sub>p</sub> )Y	Mosaicisms: XXY/Xx; XXY/XY; XXY/YYY; XXY/XXYY; XX <sub>i</sub> (X <sub>p</sub> )Y/XY; Y <sub>i</sub> (X <sub>p</sub> )Y; 46XX/47,XX,+Y(q12-1qter)
<p><b>Prepubertal:</b> No definite decrease in germinal cells, no hyalinization, no fibrosis of tubular membranes, but testes often smaller than those of age-matched controls</p> <p><b>Cryptorchidism:</b> Incidence not increased</p> <p><b>Subnormal intelligence</b> (varying degrees—usually mild)</p> <p><b>Bone abnormalities,</b> not consistent</p> <p><b>Buccal smear.</b> One sex chromatin (Barr) body</p>	<p>This type is <b>very</b> uncommon. Patients <b>possess</b> the same features of the syndrome, except that they may be somewhat shorter in height</p> <p>The key laboratory findings to explain the male phenotype and testes is the presence of the transposed testis-determining portion of a Y chromosome onto one of the X chromosomes</p>	<p>Not common. Clinical and laboratory features similar to those seen in classic form except for the following: (1) more <b>severe</b> degree of <b>mental</b> retardation; (2) tendency to be tall, e.g., <b>over 6 ft</b>; (3) increased incidence of (a) "antisocial" <b>behavior</b> and (b) varicose veins</p>	<p>Mosaicisms: XXXY/XY; XXXY/XXY; XXXY/XXYY; XXXY/XXXXY; XXXY/XXXXY/XXY</p> <p><b>Poly X + Y Chromosomal Groups</b></p> <p>Mosaicisms: XXXY/XY; XXXY/XXY; XXXY/XXY/XY; XXXY/XXXXY; XXXY/XXXXY/XXY</p> <p><b>Poly X + Y Disorders:</b> XXXY; XXXYY; XXXXY; XXX<sub>i</sub>(X<sub>p</sub>)Y; X<sub>i</sub>(X<sub>p</sub>)Y; XX,invY(p + q-); XXq - Y</p> <p>Clinical and pathologic features of mosaicism vary. In patients with sex chromosomal mosaicism, <b>spermatogenesis</b> may be active and <b>sperm</b> present in the ejaculate. Thus the testes may be <b>virtually</b> normal in size. This is particularly true when the normal stem cell line (XY) is present in the testis. Patients with other forms of mosaicism usually demonstrate testicular damage that extends to that observed in the classic form</p>
			<p><b>Prepubertal:</b> Definite decrease in immature <b>germinal cells</b>, with hypoplastic tubules and increased connective <b>tissue stroma</b></p> <p><b>Cryptorchidism:</b> Increased incidence</p> <p><b>Subnormal intelligence</b> (severe)</p> <p><b>Bone abnormalities:</b> Radioulnar synostosis and other abnormalities of the elbow</p> <p><b>Buccal smear:</b> 2 <b>sex chromatin</b> bodies in XXXY and XXXYY; 3 <b>sex chromatin</b> bodies in XXXY</p>

early in childhood present conflicting opinions as to the usefulness of early treatment (22). On the one hand, early identification and treatment of the mild learning disability may avoid social problems arising from peer identification as being abnormal and may improve the support structure of the individual (23). Other investigators, on the other hand, maintain that because the identification of Klinefelter's syndrome will not prevent the dysfunction in spermatogenesis, verbal problems, or associated physical complications, such identification is not helpful (24,25). This latter pessimistic conclusion does not appear to be justified, since recent long-term treatment data show significant benefit of androgen therapy even when treatment is begun in the adult (26).

Another important point on this issue concerns the symptoms of androgen deficiency. In this case early diagnosis should be important for treatment early in puberty and later for subsequent maintenance of muscle mass and strength in the postpubertal period (see Androgen Therapy, below).

**GENETIC AND EPIDEMIOLOGIC EVIDENCE**

**Disease Definition**

Klinefelter's syndrome was described in 1942 and is a form of hypergonadotrophic hypogonadism caused by supernu-

merary X-chromosomal material. However, it was not until Jacobs and Strong (4) demonstrated the presence of the extra X chromosome in 1959 that the term **XXY gonadal dysgenesis** was applied. Then a further twist was given to the syndrome with results from sensitive and specific radioimmunoassays for measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (27). It became apparent that many men with Klinefelter's syndrome were not strictly hypogonadal from the standpoint of **low serum testosterone levels. Indeed, many patients** had serum testosterone levels well within the normal adult male range but still exhibited the classic **XXY karyotype**. In these men gonadotrophin levels were also invariably elevated (Table 44-3). The reason for the discrepancy between serum testosterone levels and the gonadotrophin titers is not entirely clear. Therefore, the specific characteristic of the testicular abnormality in Klinefelter's syndrome should be defined as seminiferous tubule failure associated with **Leydig cell dysfunction**. The mechanisms resulting in this form of the syndrome are addressed in the discussion of **pathophysiology**.

In spite of this change from the original definition of the syndrome, Klinefelter's syndrome is still considered the most common cause of primary male hypogonadism. Typically patients with Klinefelter's syndrome are identified after the affected individual is past the age of puberty (28). The disease is commonly detected during an evaluation for infertility or complaints related to other manifestations of **hypogonadism** (29,30). Occasionally, these patients present earlier with complaints of inadequate androgenization. They may be diagnosed when they have other associated medical problems or on routine physical examination. Klinefelter's **syndrome** in young males is also part of the differential diagnosis for psychosocial problems (31). In addition, these patients may be identified by associated physical and developmental abnormalities such as taurodontism, learning dis-

Table 44-2. INTELLIGENCE TEST SCORES IN XXY AND CONTROL BOYS (AGED 7 YEARS)

	Verbal IQ (Mean ± S.D.)	Performance IQ (Mean ± S.D.)	Full-Scale IQ (Mean ± S.D.)
XXY (n = 12)	96.5 ± 11.4	97.0 ± 9.1	96.3 ± 10.3
XY (n = 12)	106.9 ± 14.2	101.0 ± 10.7	104.7 ± 12.3
	P < 0.02	N.S.	N.S.

From Bancroft et al. (21).

**TABLE 44-3.** TESTOSTERONE, LUTEINIZING HORMONE (LH), AND FOLLICLE-STIMULATING HORMONE (FSH) LEVELS IN KLINEFELTER'S SYNDROME PATIENTS

	Serum Testosterone (ng/ml; N = 26)	Serum LH (mIU/ml; N = 26)	Urine FSH (IU/24 hr urine; N = 16)
Range	0.4-8.8	17->128	56-205
Mean	2.8	49	102
Normal	3.1-12.0	5.8-17	X8-20

abilities, undescended testes, and early behavioral problems. As has been previously noted, the most characteristic clinical finding of patients with Klinefelter's syndrome is the presence of small, firm testes, and the most characteristic histologic finding in these testes is the duplicated thickened basal membrane and severe sclerosis and hyalinization of the seminiferous tubular lamina propria (Fig. 44-1)(9).

The incidence of Klinefelter's syndrome in neonatal and general population studies using buccal "smears" to detect the supernumerary X chromosomes is 0.21% with a range of 0.15%-0.24% (32-35). Because the incidence for both age groups is similar and because an excess of XXY metaphase plates by karyotype has not been found in spontaneous abortions, it would appear that the extra X chromosome probably does not confer the same lethal effect on the conceptus as does a 45,XO or 45,YO sex chromosomal arrangement (see Chapter 45).

Subsets in the general population may show a clustering of patients with Klinefelter's syndrome. For example, an increased incidence of 0.45%-2.38% may be encountered if the population groups are mentally retarded, or an incidence of 4% may be found in populations in which testicular biopsy has been performed for male infertility (29,30,36,37). Caution should be used, however, when screening populations for Klinefelter's syndrome. For example, even though the buccal "smear" is properly obtained and processed and is specific in detecting the extra X chromosome, mosaic forms of the syndrome may be overlooked. Furthermore, most laboratory results indicate that up to 10% Barr body positivity may be considered normal. In this instance, they are taking into account the presence of folded cells or debris that may prompt false-positive readings for Barr bodies, particularly by observers with little experience. Thus, if laboratory workers do not have in depth experience and rely on this methodology, they will miss some true chromatin-"positive" slides and will underestimate the incidence of the XXY karyotype in a population study or overlook the diagnosis in individuals. In addition, false-positive readings may lead to an incorrect diagnosis.

No racial difference has been reported in terms of prevalence, but most population studies have emanated from northern European countries. The few studies that have come out of Asian countries, however, show the prevalence to be essentially the same as that in European countries (10). Although many individual cases have been reported in the black population, no extensive prevalence studies have been performed in this racial group.

### Hypogonadism and Infertility

The most characteristic histologic findings in the small [testes of subjects with Klinefelter's syndrome are thickened basement membrane, severe sclerosis, and hyalinization of

the seminiferous tubular lamina propria (Fig. 44-1). Even in those patients with the mosaic form of the syndrome in which spermatogenesis may be present in the biopsy specimen, the Sertoli cells are abnormal to light and electron microscopic examinations (38-43). The nuclei are round without typical indentations. The cytoplasm has fewer organelles such as mitochondria and rough endoplasmic reticulum. Careful microscopic studies have shown that despite the "clumping" and adenomatous appearance of the Leydig cells, their actual number is decreased when compared with normal testes. Furthermore, the Leydig cells demonstrate marked vacuolization and an increased ratio of smooth to rough endoplasmic reticulum as well as abnormal mitochondria (44,45).

The reason why the extra X chromosome should cause these abnormalities is not known. Because of the other associated connective tissue abnormalities in Klinefelter's syndrome patients, the basement membrane, which is necessary for subsequent germ cell development, may be the site of the primary pathologic abnormality. Recent evidence indicates that "feedback signals" exist between seminiferous tubules and Leydig cells (46-48). Thus in these patients the Leydig cells may lack appropriate "cross-talk" between other testicular elements and not function normally.

It is of interest that the results of the few testicular biopsies performed prior to puberty have indicated either normal testes or early evidence of germ cell loss (8,22,49). If there are abnormalities in the testes prior to puberty, they are not reflected in the function of the hypothalamic-pituitary-gonadal axis in which abnormalities are apparent only after puberty (Fig. 44-2; 9,49,50).

Following puberty the mean serum testosterone levels are slightly below normal, but the values for many subjects fall into the low normal adult male range. In one study, the serum testosterone levels in 48 men with the classic or variant forms of Klinefelter's syndrome ranged from 0.5 to 8.8 ng testosterone/ml (normal, 3-12 ng/ml; Table 44-3). Because sex hormone-binding globulin levels are often elevated in Klinefelter's syndrome, there may be an even greater decrease in the free testosterone levels when compared with normal men than in the equivalent levels of total serum testosterone (51-54). The production rate of testosterone is significantly lower in Klinefelter's syndrome subjects, i.e.,  $3.27 \pm 1.35$  mg/24 hour vs normal men,  $7.04 \pm 2.47$  mg/24 hours (55).

When human chorionic gonadotrophin is administered to patients with Klinefelter's syndrome, their Leydig cells show a subnormal response in serum testosterone increase but an exaggerated rise in 17-hydroxyprogesterone levels compared with that of normal men (56). This finding is considered to be evidence of a "block" in steroidogenesis. This alteration in Leydig cell response may be a reflection of the abnormal histologic appearance of the mitochondria in the portion of

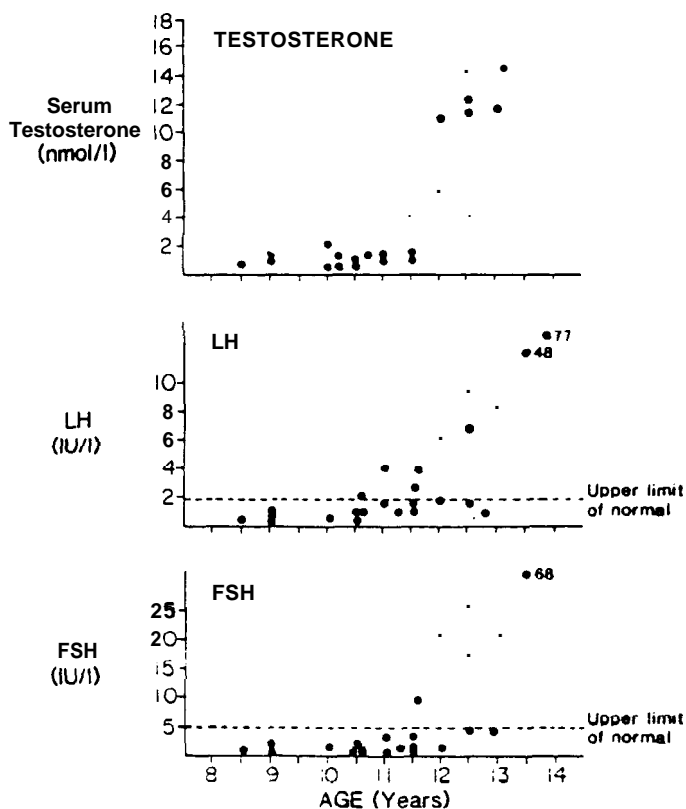


Fig. 44-2. Changes in serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in a cross-sectional sample of patients with Klinefelter's syndrome. Serum LH and FSH levels are not elevated until onset of pubertal process. Some patients exhibit normal serum testosterone levels, i.e., >10 nmol/liter. Modified from Ratcliffe et al. (19).

extra X chromosome. Then the daughter cell may complete the process of normal germ cell maturation, because it now contains a normal chromosomal complement (Fig. 44-3). This hypothesis then favors the idea that the extra X-chromosomal material itself, rather than the abnormal hormonal environment, creates the testicular damage and loss of germ cells.

In spite of the fact that serum testosterone levels may often be in or close to the normal range in patients with Klinefelter's syndrome, examination of the hypothalamic-pituitary axis in these men shows consistent elevations of LH and FSH values as well as exaggerated LH and FSH responses to luteinizing hormone-releasing hormone (LHRH) administration (59). This is evidence that the "feedback" signals from the testes are not normal (Table 44-3). These patients also display an abnormal response to testosterone administration. When testosterone is administered acutely, there is a relative lack of suppression of serum LH levels, whereas serum FSH levels decreased in a manner similar to those of normal adult males (Fig. 44-4) (60). This response is not only characteristic of Klinefelter's syndrome but also is seen in other forms of male primary hypogonadism and in postmenopausal women (61). Therefore, despite the finding that serum testosterone levels may be within the normal adult male range in many patients with Klinefelter's syndrome, the hypothalamic-pituitary system is characteristic of that seen in men with other forms of primary hypogonadism who show consistently elevated serum LH and FSH levels and decreased serum testosterone levels. Other anterior pituitary hormones; such as adrenocorticotrophin (ACTH), thyroid-stimulating (TSH) and growth hormones (GH), are considered to be normal. Some earlier reports suggested that the TSH release following thyrotrophin-releasing

the cell where the desmolase enzyme is active in steroidogenesis.

Serum estradiol levels have also been reported to be elevated in patients with Klinefelter's syndrome. Wang and Baker (55) suggested that this might be due to an increase in peripheral conversion. They noted testosterone:estradiol conversion ratios of  $0.46, \pm 0.16$  in Klinefelter's syndrome subjects versus  $0.19 \pm 0.03$  in normal men. No significant differences in estradiol production rates were noted. Whether these alterations exert any clinical effect is not clear.

The mechanism of damage to the seminiferous tubules and resulting infertility is not known. One possibility is that the extra X-chromosomal material alters the basement membrane and therefore the seminiferous tubules are unable to support spermatogenesis (57). Another idea is that the mechanism is related to the loss of an adequate androgen hormone environment. Ohno (58) has suggested the following hypothesis to resolve this question. He cites data from studies in both XX sex-reversed mice and XXY mice in which he notes that in young adult males the first meiotic metaphase plates show only XO sex chromosomes in XX males and only XY in the case of XXY males, and neither of the cells survive. This suggests that the presence of more than one X chromosome, e.g., XX or XXY, in the germ cells of these testes inhibits survival. However, as the number of mitoses increases, there may be accidental mitotic nondisjunction in the type A spermatogonia that eliminates an

Having two X chromosomes is incompatible with male germinal cell maturation.

XXY males (man and mice)  
XX males (man), XX, Sxr/+ males (mice)

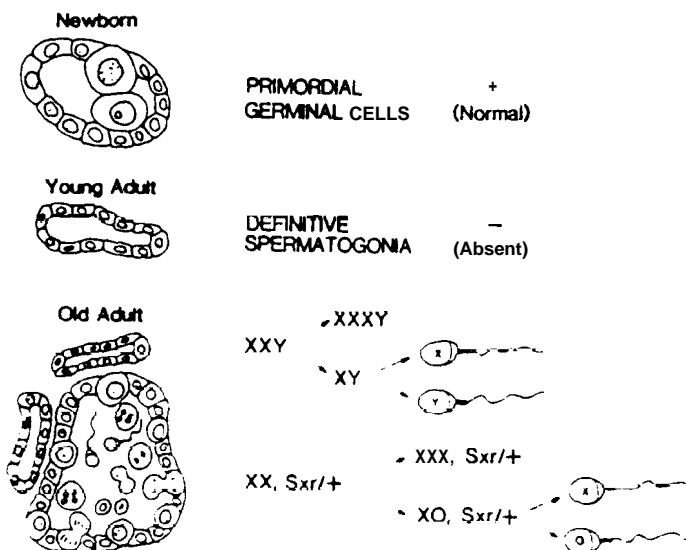


Fig. 44-3. Schematic representation of developmental fate of germ cells from XXY and XX sex-reversed mice. See text for details. From Ohno (58).

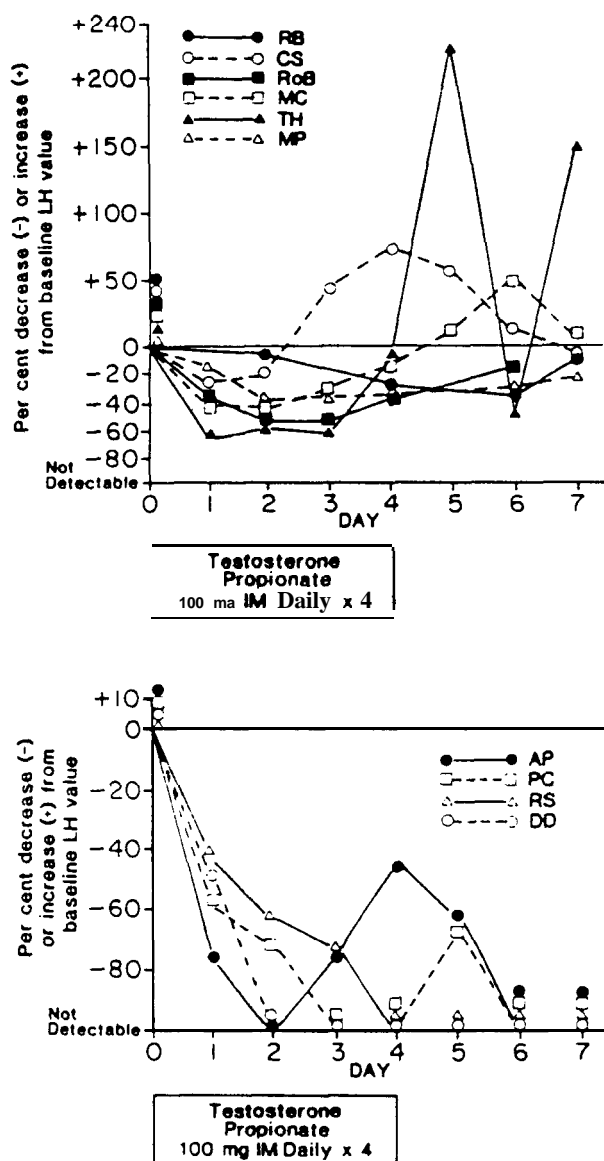


Fig. 44-4. Testosterone administration to normal men (*bottom*) and to patients with Klinefelter's syndrome (*top*). Note the relative resistance to testosterone suppression of gonadotrophins in patients with Klinefelter's syndrome compared with normal men.

factor (TRF) administration was decreased, but more recent data do not support this finding (62-64).

In contrast to the clear evidence of hypogonadism in Klinefelter's syndrome as manifested on physical examination by small testes and gynecomastia, patients often appear more virilized than the hypogonadotropic eunuch or the prepubertal castrate (Fig. 44-3). This is seen in the male hair pattern, decreased subcutaneous fat, and increased penile size as compared with those characteristics of the aforementioned hypogonadal individuals. The increased virilization appears to be a manifestation of the increased testosterone levels seen in some subjects with Klinefelter's syndrome. As has been mentioned previously, the most characteristic physical feature is the presence of small, firm testes, usually <9 ml in volume or <2 cm in length and 1.5 cm in width. In normal adult males the minimum value should be 15 ml

total volume, 3.5 cm length, and 2 cm width (7-10,65). Consonant with the variable serum testosterone levels, typical eunuchoid skeletal measurements are not found in Klinefelter's syndrome. In the true eunuch, because there is no pubertal increase in androgens to cause epiphyseal fusion, the long bones of the arms and lower extremities continue to grow, resulting in an arm span 6 cm greater than the subject's height. For this reason the lower extremity (pubis to floor) measurement is 4 cm greater than the upper extremity (pubis to vertex) measurement. On the other hand, because the subject with Klinefelter's syndrome experiences puberty (albeit variable in magnitude) at the normal age, the long bone epiphyses fuse at the appropriate time. Thus the upper extremities are of a normal length and the arm span is approximately equal to the height. However, for some as yet undefined reason, prior to puberty the lower extremity growth is exaggerated in comparison to the upper extremity such that the lower extremity to upper extremity ratio is > 1 and the mean height of Klinefelter's subjects is 184 cm (11,12).

Gynecomastia is also a common feature, seen in 90% of our subjects with Klinefelter's syndrome, but it is variable in degree. For example, in some subjects gynecomastia is found only after careful physical examination (Fig. 44-6). It has been suggested that the gynecomastia is related to the increased secretion of estrogen that has been shown in some subjects. If so, ductal hyperplasia should be present, which would be characteristic of high estrogen levels in men. However, in Klinefelter's syndrome the gynecomastia is characterized by hyperplasia of the interductal tissue, which is not characteristic of an estrogen-stimulated breast (66,67). Again, the mechanism for these changes is not known; however, it is interesting to speculate that this may be part of the general abnormality found in the connective tissue of these subjects.

Body hair distribution and muscle mass may also be quite variable. Despite the normal-appearing muscle mass (Fig. 44-5), muscle strength and endurance are invariably diminished. This is presumably secondary to the hypogonadism and subsequent hypoandrogenism or delayed androgen effect. Of interest is the fact that even in those subjects with relatively normal total serum testosterone levels one can elicit signs and symptoms of decreased muscle strength. Not uncommonly, patients with Klinefelter's syndrome may be first recognized in a population of military recruits because of their inability to keep up with their peers when performing vigorous physical training for the first time in their lives. Normal adult male heard growth does not occur, and the ability to maintain heard growth decreases with age.

Finally, the question of sexual activity or sexual orientation is of concern because of the clinical associations often made between hypogonadism and sexual dysfunction. Patients with Klinefelter's syndrome do not appear to demonstrate a greater tendency toward homosexual orientation than do normal males (68,69). However, heterosexual activity, including masturbation and sexual intercourse, at the time of presentation is usually less than that found in age-matched normal heterosexual men (70). The patients in this category are primarily concerned with their infertility and small gonads. It is of interest that many of these men when questioned will specifically deny achieving orgasm during sexual activity. It is clear that one needs to be careful with respect to self-reported definitions of sexuality.

### Associated Physical and Developmental Abnormalities

Numerous diseases have been associated with Klinefelter's syndrome. Care must be taken to distinguish between those diseases genetically associated with Klinefelter's syndrome and those that are the sequelae of these patients' hormonal deficiencies. For example, decreased learning ability in Klinefelter's subjects following puberty could be considered to correlate with the state of androgen deficiency and consequent inability to concentrate. On the other hand, learning disabilities are also common in these patients prior to puberty when there is no apparent difference in androgen levels between boys with Klinefelter's syndrome and normal boys with an XY sex chromosomal pattern. These observations suggest that the extra X-chromosomal material is directly responsible for the decreased mental abilities as well as the androgen insufficiency. This is further supported by the fact that hypogonadotrophic males do not necessarily display academic problems prior to puberty.

Another important issue is that once individuals have been identified as having Klinefelter's syndrome, they will be subjected to more intense medical scrutiny, making the identification of other associated disorders more likely. These

considerations should be kept in mind when reading the following sections.

### Psychiatric Problems

The most striking evidence of an association between psychiatric difficulties and Klinefelter's syndrome comes from studies of men who are institutionalized criminal offenders (14-19). The prevalence of Klinefelter's syndrome in this group of men ranges from 3.3 to 19.8 per 1,000 individuals compared with 1.97 per 1,000 individuals in the normal adult male population. Types of psychiatric disorders in Klinefelter's subjects vary from mild anxiety neuroses to schizophrenia and severe sociopathic personalities. In studies from Denmark, the incidence of criminal offense was 9.3% in men



Fig. 44-5. A: Twenty-one-year old man with Klinefelter's syndrome. B: Adult male with functional prepubertal castrate syndrome. Note normal masculine appearance of the patient with Klinefelter's syndrome. Many

patients show almost normal features. In contrast, patients with total absence of functioning testes appear uniformly hypogonadal.

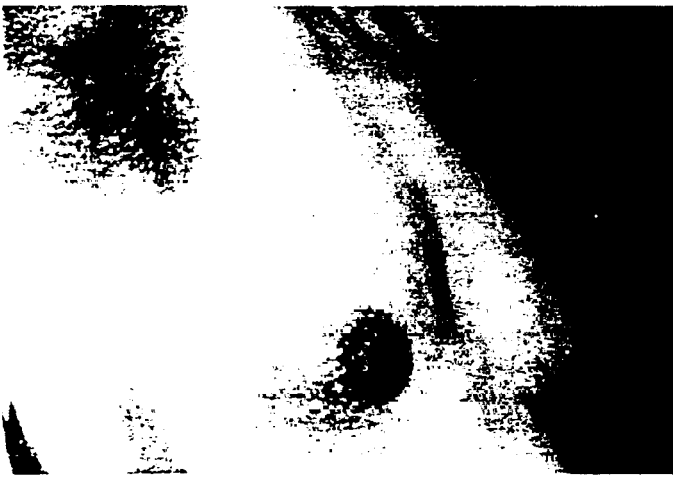
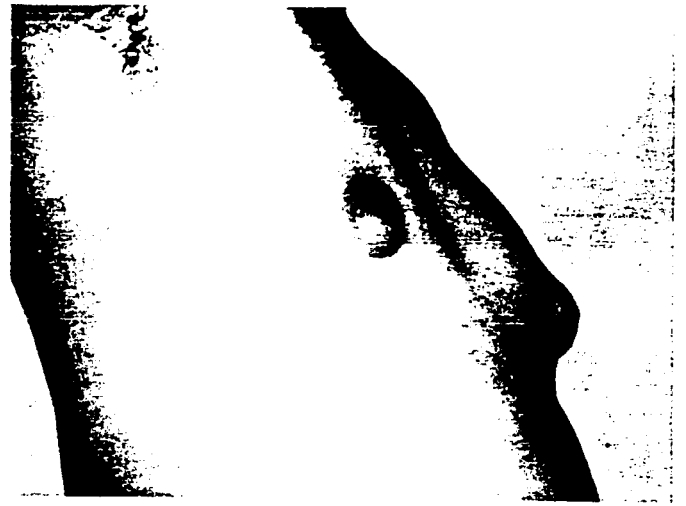


Fig. 44-Y. A-D: Examples of varied degrees of gynecomastia in patients with Klinefelter's syndrome

with an XY chromosome pattern, 41.7% in **XYY** men, and 18.8% in **XXY** men. Of considerable interest was the finding that the criminal offenses of the **XXY** and **XYY** men were inversely related to their I.Q. (18,20). In another study in a group of 70 **XXY** men who were primarily outpatients in an endocrinology clinic, Becker (68) found that 75% of these men experienced some obvious psychiatric problems. In particular, these patients were more likely to exhibit personality traits of timidity; introspective behavior; and lack of self-restraint, social drive, and aggressiveness (69,70). Because these men are often aware of their small testes and are concerned about their gynecomastia and their inability to perform physically, as well as their worry about detection by their peers, they become secretive and avoid potentially embarrassing contacts. All of these factors reinforce their feelings of inadequacy and tend to generate withdrawal behavior and depression. The extra X-chromosomal material may be responsible for their decreased mentation, but their somatic abnormality must also play a role in their overall behavior. For these reasons and because psychiatric counseling support may help, prepubertal screening examinations are important in identifying a population that may be at risk of having Klinefelter's syndrome and in conducting clinical trials to determine the importance of early diagnosis.

### **Mental Retardation**

The incidence of mental retardation among patients with Klinefelter's syndrome has been considered to be high. However, there may be some bias in these numbers. Certainly several studies among institutionalized mentally retarded subjects do demonstrate that **XXY** males are present at a rate of -4 per 1,000. However, among noninstitutionalized populations of males with learning disabilities, the rate may be as high as 9 per 1,000 (36,37). In a study by Ratcliffe and coworkers of **XXY** adolescents not specifically selected for learning disabilities (Table 45-2), a significant decrease in verbal I.Q. but no differences in the performance on full-scale I.Q. were observed (17,21). Because the control population in this study was from a higher socioeconomic class than the **XXY** men, these differences may not persist if the populations compared were better matched. The pathophysiologic relationships between the mental retardation and the presence of the extra X chromosome is not fully understood. However, as will be described further in this chapter, patients with variants (**XXXY** and **XXXXY** sex chromosomal patterns) of Klinefelter's syndrome are more severely mentally retarded. This indicates that the presence of extra X-chromosomal material does indeed exert an effect on higher cerebral cortical function.

### **Malignancies**

The incidence of breast cancer in men with Klinefelter's syndrome is estimated from Danish studies to be -0.9% (71-73). Although still relatively low compared with the 10%-20% seen in the general female population, it is 20 times greater than that observed in the normal male population (74,75). This association would at first seem obvious because of the high incidence of gynecomastia in Klinefelter's syndrome. However, gynecomastia may not be a risk factor for breast cancer in the normal XY male population possibly because the gynecomastia in these men is not present for the same

duration as in **XXY** men. Other factors such as immune deficiency, chromosomal aberrations, and the abnormalities in the serum **estrogen** and testosterone levels may also play a significant role in the higher incidence of breast cancer.

Leydig cell tumors have also been reported in Klinefelter's syndrome. It has been suggested that this is due to chronic stimulation from elevated gonadotrophins (76-78). However, when estimates are made of the actual incidence of testicular tumors, including germ cell and Leydig cell tumors, in Klinefelter's syndrome, the rate is much lower than that expected for the general population (79).

Leukemia, lymphoma, and myelodysplastic syndromes have all been reported to be associated with Klinefelter's syndrome (80,81), but studies showing estimates of frequencies higher than the general population are limited. One study estimated that the prevalence of Klinefelter's syndrome in patients with acute nonlymphocytic leukemia is 40 per 1,000 (82). Another study did not report this high of an incidence (83). If an increased frequency of leukemia in these patients is established, one possible etiologic factor could be an abnormal chromosome linkage such as the Philadelphia chromosome (9 to 22 autosomal translocation; see Chapter 35), especially because 11/22 translocation has been found to be associated with Klinefelter's syndrome (80,84). The decreased immune competence may also be an etiologic factor.

### **Autoimmunity**

Autoimmune diseases, particularly systemic lupus erythematosus and thyroid abnormalities, have been suggested to occur more frequently in patients with Klinefelter's syndrome (85,86). But in recent articles Alarcon-Segovia and Sauza (87) and Burman et al. (87) concluded that when the patient data are carefully evaluated this association is not very striking.

The appearance of such unusual autoimmune diseases as Takayasu's arteritis and ankylosing spondylitis in patients with Klinefelter's syndrome strengthens the idea that there may be an increased association with immunologically mediated disease (88,89). The reasons for the possible increase in immunologic problems of patients with Klinefelter's syndrome may be multiple. First, there are lower numbers of total lymphocytes as well as OKT8' (suppressor) lymphocytes in such patients. This results in an increased OKT4/OKT8 ratio. These lymphocytic abnormalities are similar to those found in eugonadal men and women who exhibit autoimmune diseases (90).

The facts that these abnormalities may be partially corrected with testosterone treatment and that androgen receptors have been found in the thymus suggest another mechanism for altered immune surveillance (90,91). However, because autoimmune problems are not more common in other male hypogonadal syndromes, decreased levels of circulating androgens cannot fully explain these observations. Once again, the adverse impact of extra X chromosomes on various body systems in a phenotypic male is noted.

### **Taurodontism**

Taurodontism is an abnormality of the teeth in which they are enlarged by an extension of the dental pulp with a decrease in the size of the root portion (Fig. 44-7) (92).

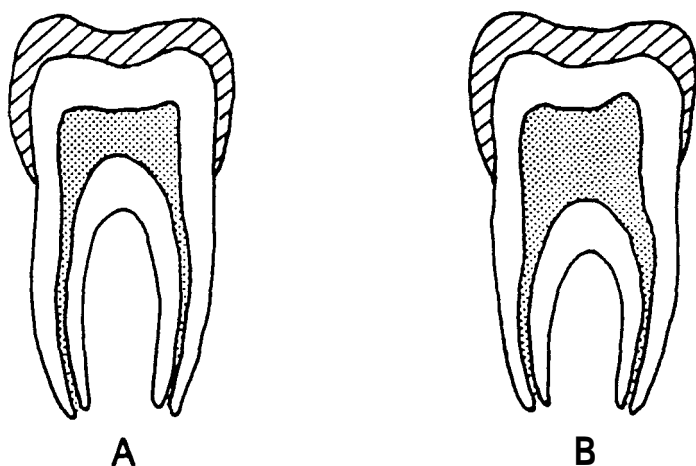


Fig. 44-7. Normal tooth (A) compared to taurodontism (B). Note increased pulp width in B.

Although this defect does not result in a severe functional abnormality, early tooth decay does occur. Taurodontism is relatively uncommon in the general population, i.e., 0.5%-2.5% in the normal XY male population and 1%-3% in normal females. It is present in >40% of patients with Klinefelter's syndrome and therefore may be used as a marker in screening studies to detect an increased X-chromosomal pattern in males. Likewise, the presence of taurodontism can be used as an indicator when routine dental x-rays are done for appropriate consultation in early diagnosis of Klinefelter's syndrome. This finding and the presence of testes <1.5 ml volume after the age of 6 years are 2 clinical clues to the presence of Klinefelter's syndrome prior to puberty.

#### Venostasis Disease

Hypostatic venous ulcers in the lower legs and thrombophlebitis have been reported to be increased in patients with an XXY chromosomal pattern. Whereas 10% of XY males have varicose veins of the lower extremities, 40% or more of patients with Klinefelter's syndrome have varicosities. This is presumably due to defective venous valves and raises the issue again that these patients may possess a basic defect in their basement membranes. Associated with the varicosities is a 10-20-fold increase in hypostatic leg ulceration. In addition, there is an associated increase in thromboembolic events (93-96). This increase may be due entirely to the venostasis; however, a hypercoagulable state may also account for this because of the increased levels of beta-thromboglobulins in these individuals (9'7).

#### Osteoporosis

The incidence of osteoporosis and subsequent fractures is increased in Klinefelter's syndrome patients secondary to the lowered androgen levels and does not appear to be different than that in other forms of hypogonadism (98,99). It is of interest that the patients who also have osteoporosis are reported to have low serum calcitonin levels that increase to the normal range with testosterone replacement. How this affects the osteoporosis is not known (100). The potential for osteoporosis is another cogent reason for testosterone replacement in these individuals.

#### Respiratory Diseases

An increased association with asthma, chronic bronchitis, and cystic fibrosis has been suggested in patients with Klinefelter's syndrome (101,102). However, the number of reported cases has been small, and at this point in time whether there is an actual increased frequency of these disorders is not entirely clear. If true, it may be due to the previously described changes in the immune system, to pulmonary structural defects that have not been elucidated, or to both.

#### Thyroid Disease

Various investigators have reported an increased incidence of autoimmune primary thyroid disease, either euthyroiditis or hyperthyroiditis. Decreased TSH response to TRH in patients with Klinefelter's syndrome has also been noted regardless of metabolic status (103). Recent studies by several investigators have failed to confirm the presence of the abnormal TSH response (62-64). Again, as in some of the other disease associations, whether there is an actual increase in thyroid disease is still in question. Larger population studies are needed with such tests as antithyroid antibody titers to establish a definite relationship.

#### Cardiac Abnormalities

In several studies an increase in mitral valve prolapse has been demonstrated in Klinefelter's syndrome patients (1.04). Like the increase in varicosities, this may be another piece of evidence that abnormal basement membrane or connective tissue abnormalities exist in patients with XXY-chromosomal patterns. For example, 55% of Klinefelter's subjects in one study have been demonstrated to have mitral valve prolapse by echocardiography, and 10% of these were considered to have mitral regurgitation. In contrast, there is a 6% incidence of mitral valve prolapse in the normal XY male population. A prolapsed mitral valve is a significant finding, because it may require prophylactic antibiotic administration before dental procedures, surgery, and so forth.

#### Abnormal Glucose Metabolism

An increased incidence of abnormal glucose tolerance tests has also been described in patients with Klinefelter's syndrome (105). Nielsen (106) has shown this abnormality to occur in -19% of these patients (106). However, clinically evident diabetes mellitus is only seen in -8% of patients with Klinefelter's syndrome, which is close to the prevalence in the general population. Recent studies have demonstrated an increase in insulin binding by red blood cell membranes, which suggests the presence of a receptor or postreceptor defect in insulin action in these patients (107).

#### Precocious Puberty

Precocious puberty from both human chorionic gonadotrophin-secreting dysgerminomas and increased testosterone secretion from Leydig cell adenomas has been reported in patients with Klinefelter's syndrome (77,108,109). This is an interesting association, but the exact prevalence compared with the normal population has not yet been determined.

### Rare Disease Associations

More rare syndrome associations with Klinefelter's syndrome have been suggested, but because the frequency of Klinefelter's syndrome is high (~ 1 in 500 males) and because Klinefelter's syndrome is not a lethal mutation, a large population will be exposed to a number of diseases both acquired and inherited. Therefore, although Klinefelter's syndrome has been reported to occur with a number of less common diseases such as alcaptonuria and holoprosencephaly, it is difficult to conclude that the incidence of these disease associations is greater than in the normal male population (110-114).

### Family and Twin Studies

In general, Klinefelter's syndrome is a spontaneous chromosomal abnormality thought to occur during gametogenesis in one of the parents. However, several cases of monozygotic twins have been reported, which suggests unique modes of transmission (115,116). One interesting report describes 2 twin brothers who exhibited a mosaic form of Klinefelter's syndrome, i.e., 46,XX/47,XXY (5). Their mother also displayed a chromosomal mosaic pattern, i.e., 46,XX/47,XXX. Thus she appears to have transmitted 2 X chromosomes to each of her sons. Whether this XXX/XX mosaic pattern was also present in previous generations in the same pedigree could not be ascertained. Because her sex chromosomal abnormality did not clinically impair her fertility status, transmission through female family members could occur. The 2 sons were infertile; therefore, passage through several generations would be difficult. Furthermore, because XXX/XX females are common in the general population and are usually fertile and because only 5 additional cases of XXY children with XXX mothers have been reported in the English literature, this method of transmission appears to be rare (117-120).

Another possible pathogenic mechanism is suggested by the above family, as well as by the occurrence of monozygotic twins with Klinefelter's syndrome. There is the possibility that there are some families or individuals who develop some factor that promotes chromosomal nondisjunction. At present there is no concrete evidence for such a factor.

Although the hallmark physical finding of Klinefelter's syndrome is small, firm testes, which is directly associated with the loss of seminiferous tubule function and impaired fertility, persistence of spermatogenesis postpubertally has occasionally been demonstrated in testicular biopsy specimens (27,121,122-124). Furthermore, in some instances sperm have been noted in the ejaculate, and fertility has been reported by several authors. In most instances paternity was established by either blood grouping or HLA typing (121-124). It should be emphasized that each of the men with established fertility has been an example of mosaicism with the presence of an XY stem cell line in addition to the abnormal stem cell line(s). None of the offspring reported of these individuals with Klinefelter's syndrome has subsequently been demonstrated to have an XXY karyotype. However, the sperm and germ cells of these fertile patients have not been subjected to chromosomal analyses. Therefore, whether diploid XX or XY sperm would be capable of fertilization is not known.

## BIOLOGIC BASIS OF GENETIC SUSCEPTIBILITY

### Genetic Pathophysiology

Harry Klinefelter, Jr., along with Edward Reifstein, Jr., while research fellows with Fuller Albright in 1942, described the clinical syndrome and suggested that it was a disorder involving the sex chromosomes (1). Fourteen years later, when the human chromosomal complement was finally established, some of their original patients were studied and found to exhibit an XXY karyotype (4). Thus the accuracy of the original investigators' predictions became apparent.

The classic XXY karyotype pattern usually arises from nondisjunction of a maternal or paternal sex chromosome during the first meiotic division of either oocytes or sperm (Fig. 44-8). Recent data from Jacobs et al. (125), who used X-linked RFLPs in 32 XXY patients, demonstrated 53% of nondisjunction attributable to paternal meiosis I errors, 34% to maternal meiosis I errors, 9% to maternal meiosis II errors, and 3% to postzygotic mitotic errors. Other mechanisms are less common and include so-called anaphase lag, which results in an isolated X chromosome eventually being included in one of the daughter nuclei.

An extremely rare cause of Klinefelter's syndrome is seen in those unusual familial forms in which the mother is mosaic and has an XXX/XX sex chromosome pattern (5). In this example, the meiotic distribution of her sex chromosomal XX/X pattern should lead to a 50% incidence of Klinefelter's syndrome in her children. Of all the factors that have been identified to be involved in creating the supernumerary X-chromosomal pattern, maternal age seems to show the strongest correlation. Caruthers et al. (126) initially iden-

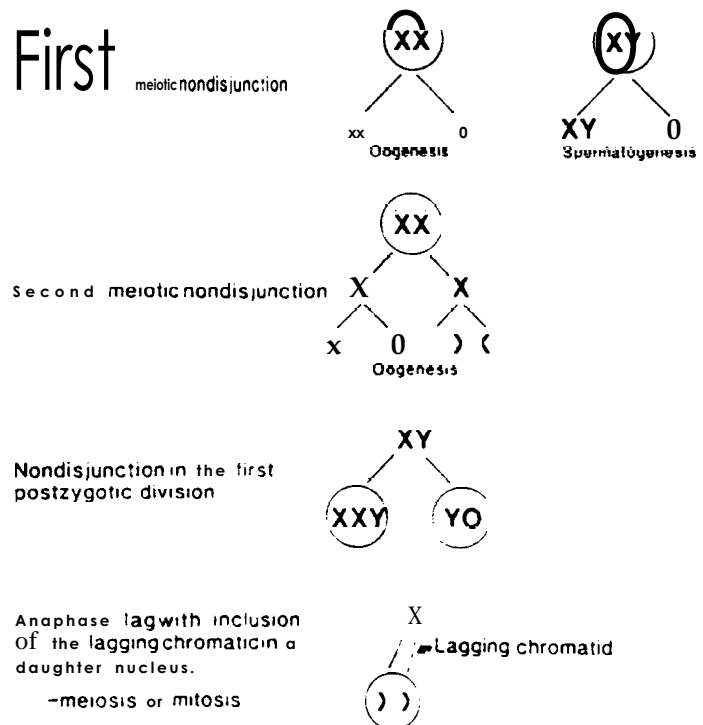


Fig. 44-8. Four errors in chromosome segregation that lead to patterns observed in patients with Klinefelter's syndrome

TABLE 44-4. EFFECT OF MATERNAL AGE ON INCIDENCE OF KLINEFELTER'S SYNDROME

Maternal Age (years)	Incidence of Klinefelter's Syndrome (%)
20-24	0.9
25-29	1.8
30-34	5.1

From Ferguson-Smith (127).

Maternal age as being a risk factor. Subsequently, Ferguson-Smith (127), using data from a prenatal genetic screening study of 6,023 patients who underwent amniocentesis, confirmed the maternal age effect (Table 44-4). On the other hand, establishing paternal age as a factor has not been straightforward. In the study of Caruthers et al. (126) no relation with paternal age was found. On the other hand, more recent study by Ferguson-Smith and Yates (128) showed a positive effect of paternal age in Klinefelter's syndrome.

Trumbach and Conte (129) have suggested that maternal age is important because of the long diplotene stage of the human ova. Because ova are in the first, meiotic prophase from birth to ovulation, the length of the chiasma between X and Y and the 21 chromosomes is decreased by the long diplotene stage. This may predispose to the occurrence of nondisjunction. Another possible influence in the development of nondisjunction is a familial factor allowing increased liability toward nondisjunction occurring in meiosis or mitosis. In a study by Zang (121) of pregnancies in couples who had a child with Down's syndrome, 0.5% exhibited various sex chromosomal anomalies. This percentage is small, but because there is a known increase in occurrence of a second child with Down's syndrome in mothers whose first child was afflicted with this syndrome even when the mother is less than 30 years old, there is the possibility of some unidentified factor that contributes to the nondisjunction. This existence of a "nondisjunction" factor is also suggested by the 2 siblings with Klinefelter's syndrome born to a mother with an XXX/XX mosaic sex chromosomal pattern mentioned previously (5).

Another issue that must be considered in the overall pathophysiology of Klinefelter's syndrome is Lyon's hypothesis (130), which holds that there is a random genetic inactivation of supernumerary X chromosomes when more than one X chromosome is present. This is based on the observation that only one X chromosome remains active in a cell after the first 2 weeks of fetal life. This hypothesis was originally proposed to explain why normal females with 2 X chromosomes and therefore 2 genes for each product did not have more of these gene products than did males with only a single dose of the gene. Lyon's hypothesis poses a problem, however, in ascribing the abnormalities of Klinefelter's syndrome to the extra dose(s) of X-gene material. If true, then the extra X-chromosomal material should be inactivated and thus XXY individuals should have no more active X-chromosomal material than normal XY males.

Modifications of this hypothesis have been proposed to answer this question. First, because the sex chromatin body in the body, is not present until the second or third week of

embryonic life, the X chromosomes may be active during this early period of development. Therefore, the abnormalities present in patients with Klinefelter's syndrome could be initiated during this time frame. Second, the inactivation of extra X chromosome(s) is not random and/or is not complete, such as in "ring" or "isochromosome" abnormalities. These cells with increased X material then could give rise to the abnormal phenotype (131). Further evidence that Lyon's original hypothesis does not completely apply to patients with Klinefelter's syndrome is the occurrence of patients with the "poly-X" syndromes in which the abnormalities are more severe as the number of X chromosomes are increased.

Mosaic forms of Klinefelter's syndrome have been reported to occur in 10%-20% of the entire population with the diagnosis of Klinefelter's syndrome (27,132-134). This percentage may be higher, because the mosaic pattern of the stem cell line may not occur in all tissues routinely studied such as peripheral lymphocytes or the buccal mucosa. These cell lines would be detected only by extensive examination of all available tissues, e.g., buccal smear, blood leukocyte culture, and testicular biopsy with culture of the testicular specimen. Mosaicism usually occurs when nondisjunction or

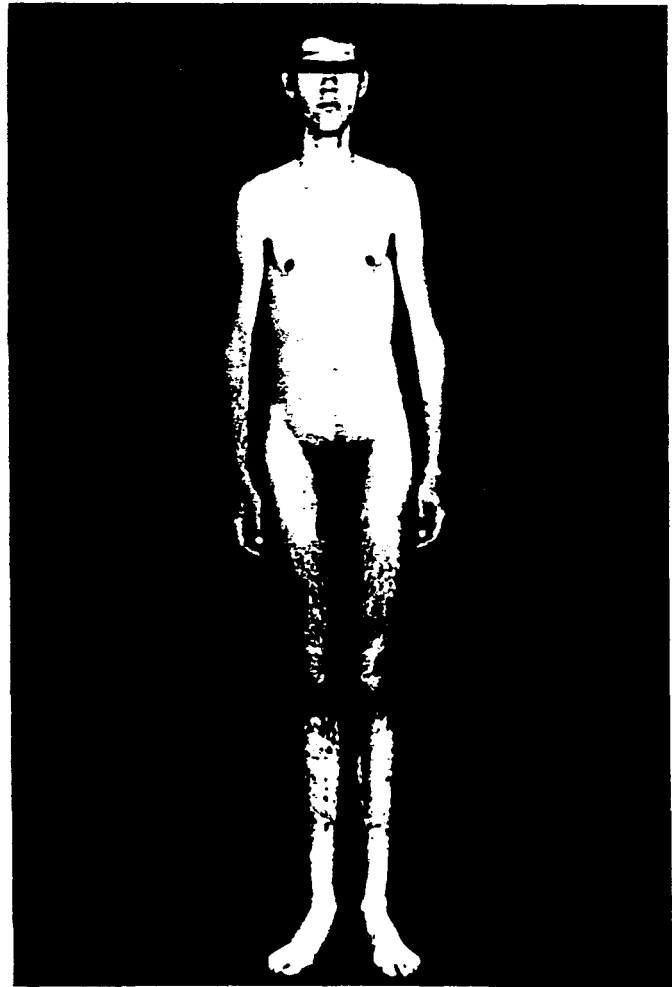


Fig. 44-9. Patient with mosaic form of Klinefelter's syndrome (XY/XXY). Note small testes with normal penile size, male hair distribution, and increased length of lower body segment.

anaphase lag occurs in a 47,XXY zygote. In general the mosaic subjects are less affected than the classic XXY counterparts (Fig. 34-9). Various degrees and forms of mosaicism have been described (Table 44-1), and Sarkar and Marimuthu (130) have shown in a study of 85 patients with Klinefelter's syndrome in which 70 were examples of mosaicism that the severity of the syndrome increases with the relative increase in the abnormal stem cell line population. The influence of mosaicism is especially relevant in patients with Klinefelter's syndrome who are fertile. Most of these patients possess a normal XY stem cell line present in addition to the abnormal stem cell lines. Detecting mosaic forms of Klinefelter's syndrome or any mosaic genetic disease can be a formidable problem. Because mosaicism results in 2 or more cell lines with different chromosomal constitutions, selecting the appropriate tissue to check for abnormal chromosome constitution may be difficult. For example, the skin and peripheral lymphocytes may not contain the abnormal stem cell line, whereas the testes may. Therefore, the true incidence of XXY mosaicism may be markedly underestimated. This could raise such questions as whether chromosomal analyses should be performed on testicular biopsy material from all infertile men. The answer is obviously *no* as a general rule, but the physician should have a high degree of suspicion when there is evidence of abnormal Leydig cell function, behavioral abnormalities, or other features commonly present in patients with Klinefelter's syndrome.

#### Additional Variant Subtypes of Klinefelter's Syndrome

Other variant forms of Klinefelter's syndrome have been described that usually arise from consecutive nondisjunctions in either oogenesis or spermiogenesis. A summary of these variants is given in Table 44-1. Several of the syndromes have characteristic clinical features.

The XXXXY syndrome is characterized by marked mental retardation, prepubertal testicular damage, cryptorchidism, and skeletal abnormalities, especially proximal radial ulnar synostosis or overgrowth of the radial ulnar heads (135). Interestingly, the seminiferous tubules in the testes of patients with the XXXXY disorder are usually hyalinized prior to puberty. This is unlike the testes of patients with the XXY form of the syndrome. Also these XXXXY boys have testes much smaller than those of their age-matched peers. The scrotum may also be bifid and the penis hypoplastic, consistent with a more severely retarded genital development. Other systemic manifestations include epicanthal folds, hypertelorism, cubitus valgus, and incurving of the fifth digit. Many of these patients also exhibit microcephaly.

Patients with the XXXXY pattern can be classified by phenotype and symptomatic characteristics somewhere between the classic XXY individuals and the more severe XXXXY disorder (136). However, severe mental retardation is more characteristic of the latter. Radioulnar synostosis may also be present in patients with an XXXXY sex chromosomal pattern. In these patients the gonads before puberty are similar to XX and XXY males, but cryptorchidism is more common than the low occurrence in the classic patients with XXY sex chromosomal pattern.

#### The XYY Disorder

Patients with the XYY chromosomal pattern are interesting in that they represent phenotypically a cross between the XXY and XYY syndromes. Their mean height is -9 cm greater than patients with the classic form of Klinefelter's syndrome and is similar to that of XYY males (137). They exhibit a high frequency of delinquency and aggressive social behavior. They are more severely mentally retarded than either XXY or XYY subjects. Their testicular development is very similar to that of the classic Klinefelter's syndrome, and they are also infertile. They may have varicose veins and stasis dermatitis with hypostatic ulcers as seen in men with Klinefelter's syndrome but not in men with more than 2 Y chromosomes. These individuals may comprise -3% of the chromatin-"positive" males. This incidence may be underestimated, because a routine buccal smear would only show one condensed chromatin body such as is seen in XXY genotypic men. These individuals have been shown to develop from successive first and second paternal nondisjunction.

#### XX Males

The XX karyotype may appear in the female with gonadal dysgenesis, in a true hermaphrodite, or in a patient with the classic features of Klinefelter's syndrome. The estimated incidence in the male phenotypic population varies from 1 in 9,000 to 1 in 20,000 men (138). This syndrome is of significance in that it resembles Klinefelter's syndrome. Because these men have testes and because the male differentiating factors have been considered to be present on the Y chromosome, the question has been: Where is the "Y" chromosome? Therefore, the syndrome has elicited a renewed interest in finding the location of the genetic material, which is sometimes called the testes-determining factor (TDF) that determines the development of the testes (139).

The XX syndrome is different from the classic Klinefelter's syndrome in etiology, the former resulting from paternal gamete meiotic translocation of Y to X (i.e., exchange of chromosomal material) and the latter usually emanating from nondisjunction during maternal germ cell meiosis. The relationship of the XX syndrome to the classic XXY syndrome is significant, first, in that it demonstrates that the underlying pathology is due to an extra X chromosome. Second, although animal models of Klinefelter's syndrome are known, they cannot be bred. The described XX SR (sex reversal) in the mouse has been shown to be transmitted through normal males, thus providing an animal model in which to study the pathogenic features of the extra X-chromosomal material in a male, but not necessarily the pattern of transmission.

Phenotypically, patients with an XX-chromosomal pattern exhibit low-normal to normal serum testosterone levels and elevated serum LH and FSH levels (140). These patients also present with gynecomastia and small testes following puberty. Usually they are azoospermic, although in the early postpubertal periods spermatogenesis may be present. Abnormal skeletal proportions and taurodontism are not present. Cattanach et al. (141) have developed a strain of XX male mice that has been used as an animal model for this disorder.

Two predominant possibilities exist to explain this entity:

One possibility is that these patients were originally examples of the classic XXY syndrome but lost their Y chromosome early in embryogenesis (142). This would allow the H-Y antigen production site to be turned on by a regulatory site on the Y chromosome before it was lost in some fashion, such as in anaphase lag.

The second possibility would require a Y to X translocation. However, for this to be the case the H-Y antigen should be expressed in all subjects, and this was not found to be true. It may be that the current tests available for detecting the H-Y antigen are not sensitive or specific enough to detect the antigen in all cases. Recently Andersson et al. (139), using a Y-specific DNA probe, pDP 105, showed that the Y chromosome material may be located on the X chromosome in XX males. The Y material present on the X chromosome probably contains the TDF, which may also control the general regulating production of the H-Y antigen. de la Chapelle and coworkers (139) used the pDP 105 oligonucleotide probe, which hybridized to the metaphase chromosomes from 3 XX males and 2 normal XY males (139). In the 3 XX males the label was clustered on the distal portion of X<sub>p</sub>22. None of the normal XX mitoses showed a label on the terminal arms of both X chromosomes. These findings support the hypothesis that in the XX syndrome the testes are present because of transfer of DNA from the Y to the X chromosome during meiosis in the male. Because recombination occurs between the distal short arms of the human X and Y chromosomes, it would not be unusual to see this syndrome occur with regular frequency.

A limited number of other sex chromosome aberrations such as 47,XXX and 47,Xi(Xq)Y, presenting with clinical features similar to Klinefelter's syndrome, have been reported (143). Because there are not enough examples of these patients to characterize them as distinct variants of Klinefelter's syndrome, their existence is only noted in Table 44-1.

## CLINICAL APPLICATIONS

### Diagnosis

The original description of this syndrome by Klinefelter et al. (1) was based on clinical features and limited laboratory data. Subsequently, when these patients were examined for their chromatin pattern by buccal smear or when the chromosomes were determined through tissue culture, the etiology of the syndrome became more specific. However, the diagnosis of Klinefelter's syndrome may be made with reasonable accuracy, for several reasons. In the postpubertal male with hypergonadotrophic hypogonadism who exhibits small, firm testes, certain characteristic skeletal proportions and gynecomastia. First, patients with Klinefelter's syndrome undergo puberty close to the same time as their unaffected peers, whereas hypogonadotrophic eunuchoidal patients and functional prepubertal castrate patients remain prepubertal. Second, the latter 2 groups of patients develop true eunuchoidal body proportions, have no beard, and maintain their prepubertal subcutaneous fat pattern. Third, the testes are usually small but softer than those of patients with Klinefelter's syndrome, who characteristically show small, firm "acorn" testes because of the marked seminifer-

ous tubular fibrosis. Acquired forms of hypogonadism such as mumps orchitis or hyperprolactinemia can be differentiated clinically from Klinefelter's syndrome on the basis of normal skeletal proportions, lack of taurodontism, normal height, and testes that are larger and softer than those of patients with an XXY chromosome pattern. However, other forms of hypogonadism that occur after puberty can be difficult to distinguish from Klinefelter's syndrome, especially from those patients with mosaic forms of Klinefelter's syndrome, unless more definitive testing is carried out.

Prior to puberty, the only consistent finding that would suggest the diagnosis of Klinefelter's syndrome is decreased testicular volume. Testicular volume has been shown to be consistently lower than that in normal boys of comparable age; when testicular volume in boys older than 5 years is <1.5 ml, the diagnosis should be strongly considered (46,56). Hypogonadotrophic hypogonadal patients are not usually confused, because their testes are of normal prepubertal size. The reason for this is that they may have normal, immature germ cell numbers.

Regardless of the results of any clinical diagnosis, actual demonstration of the chromosomal constitution is necessary for a completely accurate diagnosis. The most common, rapid, and inexpensive of these procedures is the buccal smear (Fig. 44-10). Although this does not actually demon-



Fig. 44-10. Buccal smears from normal male (A) and patient with Klinefelter's syndrome (B). ( $\times 400$ ). The appearance of a Barr body denotes presence of supernumerary X chromosomes.

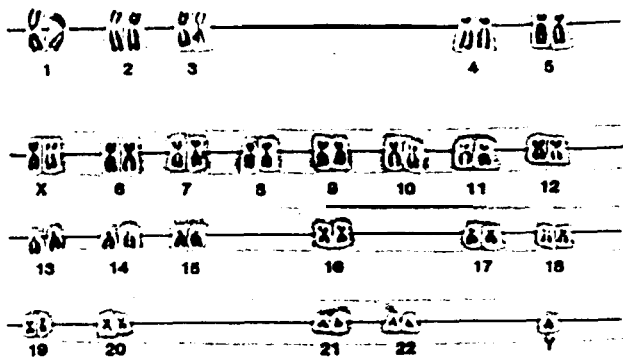


Fig. 44-11. Karyotype from lymphocyte culture of a patient with Klinefelter's syndrome, XXY sex chromosomal pattern.

strate the chromosomal configuration, it does demonstrate that an extra X chromosome exists by the presence of a Barr body or condensed chromatin material. However, because of folds in some buccal cells and other artifacts of fixation, an inexperienced person may falsely conclude that the smear shows a chromatin-positive pattern. In that instance, the only definitive technique is chromosomal analysis by tissue culture (Fig. 44-11). The advantages of using chromosomal analysis are its accuracy and the ability to study multiple tissues. Accuracy is important in confirming Klinefelter's syndrome in screening programs (27,33). Furthermore, the ability to perform an examination on different tissues may be the only way to identify the mosaic forms of the syndrome in which different stem cell lines exist in different tissues. The existence of sex chromosomal **mosaicism** may be suspected when an intermediate number of buccal cells contain Barr bodies. For example, the presence of 5%–10% chromatin-positive cells may indicate a **karyotype** of XY/XXY, whereas > 10% chromatin-positive cells is characteristic of the classic XXY syndrome. Specific chromosomal analysis is also necessary to identify such variants as XX males, XXYY males, and XYY males. "Poly-X" disorders may be suggested on buccal smear by the inactivated extra X chromosomes appearing as additional "Barr bodies." It is a rule that the number of Barr bodies is one less than the number of X chromosomes.

### Counseling and Family Management

Counseling and family management have been very difficult issues to deal with in Klinefelter's syndrome. In fact, no systematic prepubertal counseling studies have been reported other than a series of case reports. Because amniocenteses are being performed with increased frequency when maternal age is >35 years and because maternal age is a risk factor for Klinefelter's syndrome, increasing numbers of prenatal diagnoses will be made. Whether prepubertal supportive psychiatric therapy will prevent or alleviate the behavioral disorders that may occur in these patients is not known. However, because the antisocial behavior in these individuals is inversely related to their I.Q., early recognition of intelligence deficits with appropriate supportive therapy may significantly improve the outlook for these individuals (13).

If the diagnosis is made prior to puberty, the family and instructors will be alerted to the possibility of learning disabilities so that appropriate treatment may lessen the bur-

den to the patient and family beyond the physical abnormalities associated with Klinefelter's syndrome. Similarly, appropriate educational and occupational goals can be set when needed to avoid subsequent frustration associated with repeated failure as a consequence of the extra X-chromosomal material. Again, no guidelines have been described to deal with Klinefelter's syndrome because of the wide range of intellectual capabilities in these individuals. Even with the present lack of information, it is clear that no single predetermined therapy would be appropriate for all individuals. Finally, the increased incidence of prenatal diagnosis raises the issue of termination of pregnancy. The physician needs to present the available data with great care and understanding, particularly because adequate prospective studies are not available.

The issue of infertility needs to be addressed with the parents at the time of diagnosis. How and when the problem of infertility is discussed with patients depend on their age and understanding of the significance of the problem. However, we believe that patients with Klinefelter's syndrome should **not** be told that fertility is absolutely impossible: First, prior to puberty one cannot determine whether the patient may be the unusual case of Klinefelter's syndrome who could be fertile. Second, the patient's spouse may become pregnant at some time and unnecessary problems are created that have no reasonable solution. In our experience, both patients with Klinefelter's syndrome and their wives are quite elated and satisfied with the pregnancy.

### Screening and Prevention

If therapeutic intervention is to be undertaken early, appropriate screening programs are necessary. Also, because the incidence of the disease is ~1 in 500 male births, the cost of initial screening should be kept minimal. When maternal age is a potential risk factor, amniocentesis should be performed to detect not only Klinefelter's syndrome but also a number of other chromosomal abnormalities. In this instance complete chromosomal analysis is justified.

Another situation in which screening prior to puberty may be useful is in boys with learning disabilities. A school nurse can perform a genital examination and then further confirmation obtained by buccal smear and/or chromosomal analysis in those subjects with testes volume <1.5 ml or a history of taurodontism determined from dental records. Indeed, all medical personnel who perform physical examinations on prepubertal boys should be aware of the significance of smaller than normal testes.

A third group that should be considered for screening consists of preadolescent or adolescent males who have a history of criminal behavior. Testicular size could be the screening end point, and postpubertally one can use the additional criterion of boys >184 cm in height. The need to screen specific groups such as infertile men has been considered previously. It is clear that great care and attention to all of these issues should be considered when screening is performed prepubertally or in individuals who are in trouble with legal authorities.

The only means known at the present time to prevent Klinefelter's syndrome, as opposed to preventing or minimizing its complication, is through termination of pregnancy following diagnosis by amniocentesis. Given the variable outcome of the XXY karyotype, it is difficult to counsel the

ent in a dogmatic way. The physician should provide the available information and assist the couple in arriving at a decision that is compatible with their attitudes.

It is not feasible to screen the population to identify fertile males with such sex chromosomal abnormalities as an XXY pattern who would be at increased risk for an XXY offspring, because of the rarity of such disorders. However, it may be reasonable to obtain karyotypes on mothers of infants with Klinefelter's syndrome.

### Treatment

#### Androgen Therapy

The purpose of androgen replacement therapy in men with Klinefelter's syndrome is severalfold. First, it is important to prevent such long-term clinical consequences of androgen deficiency as osteoporosis. Second, there is a need to improve decreased physical strength, endurance, and libido that accompany androgen insufficiency. Through these accomplishments, the patient with Klinefelter's syndrome usually develops an improved self-image, becomes more aggressive, and is more capable of coping with life in general. Thus, improvement in psychosocial adjustment also becomes a result of androgen replacement (Fig. 44-12).

Almost all individuals with Klinefelter's syndrome have evidence of androgen deficiency regardless of serum testosterone levels as evidenced by their elevated serum LH levels (Table 44-3), muscle weakness, timidity, and decreased bone growth. Furthermore, with advancing age there is a

decrease in testosterone secretion in Klinefelter's syndrome, which may be an exaggerated example of the decline in testosterone in the normal male with age. The only exclusion criteria for testosterone replacement therapy would be the presence of another medical problem, such as carcinoma of the prostate, that could be harmed by androgen administration and in those instances in which severe mental retardation might be aggravated by the stress of normal libido associated with androgen therapy. However, even in the latter case the increased stamina provided by testosterone therapy may be helpful (144). Recent long-term follow-up studies have shown that 80% of men benefited from testosterone treatment as assessed by better mood, more energy and drive, endurance, strength, better concentrating ability, and better relations with others. Although these benefits occur even when treatment is begun as an adult, ideally treatment should begin at puberty (24).

One precautionary note is that both the patients and their spouses need to be adequately counseled with respect to the forthcoming change in sexual feeling and increased sexual activity brought on by androgen therapy (145). Both partners may have established a comfortable sexual pattern and even with counseling the sharp increase in libido can present a problem. Thus, when initiating such therapy, the physician should carefully monitor the effects of treatment by seeing the patients and their spouses more frequently than one would ordinarily do.

The goal of replacement therapy is to mimic the pattern of testosterone level seen in normal males. Myers et al. (146) have shown that there is a diurnal variation of both total and

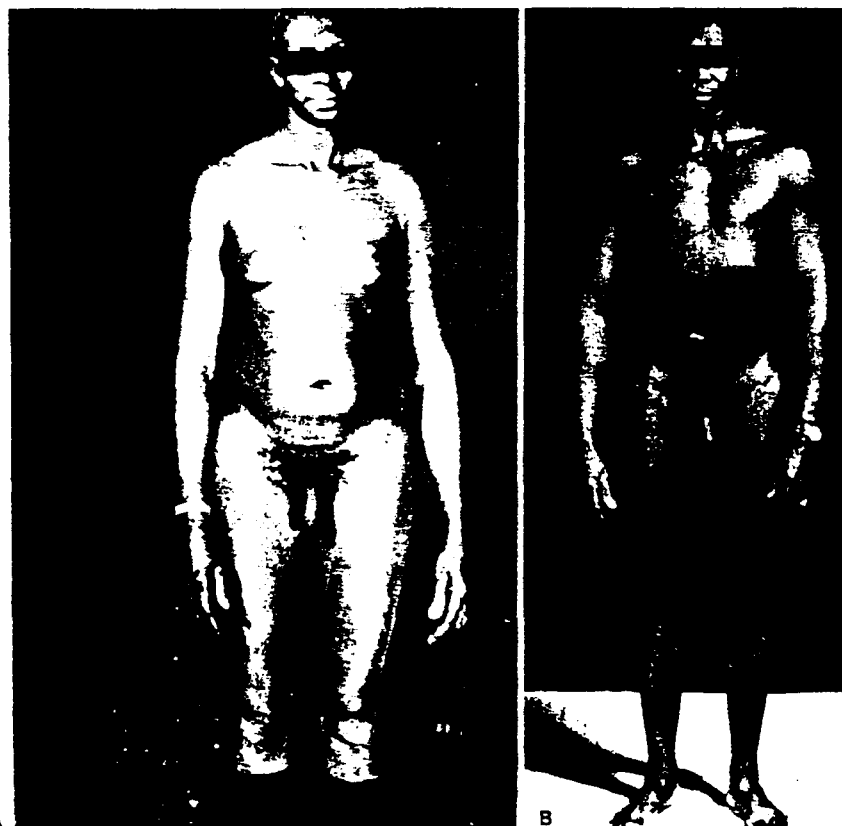


Fig. 44-12. Patient with Klinefelter's syndrome before treatment (A) and 1 year after testosterone treatment and subcutaneous mastectomy (B).

and testosterone in normal men. Their data demonstrate that a large portion of the steroid is tightly bound to sex hormone-binding globulin (SHBG). With testosterone replacement therapy in Klinefelter's syndrome, Plymate et al. (53) have shown that not only do serum testosterone levels rise but SHBG levels fall. This means that 2 changes must be taken into account in measuring the effects of androgen replacement. For instance, a man receiving 200 mg of testosterone enanthate intramuscularly every 2 weeks may have a total testosterone measurement based on the pharmacokinetics of the preparation of 2 ng/dl at 12-14 days postinjection. This level would ordinarily be considered too low, but, because his SHBG may still be suppressed by the androgen administration, his free testosterone level may still be normal. Thus careful attention to the patient's response to therapy is necessary to schedule the injection interval properly. Several options are available for androgen replacement.

The time to begin androgen replacement is when the diagnosis is made, provided that the patient is at the usual time for onset of puberty or later. This is a crucial time to achieve normal physical strength and endurance so as not to make the patient with Klinefelter's syndrome feel different from his normal peers. For the first year following the onset of puberty, 50 mg of testosterone enanthate every 2-3 weeks is sufficient followed by an increase in dose over the next 2 years to the full adult dose. At the present time none of the replacement doses will mimic precisely the normal diurnal testosterone levels. Replacement treatment can be followed by serial plasma testosterone levels; however, adequate knowledge of the pharmacokinetics of the preparation must be known to interpret these steroid levels.

Risks of androgen administration other than the precautions already mentioned are usually related to changes in serum lipid levels. Administration of a metabolizable steroid preparation such as testosterone enanthate has not been shown by itself consistently and adversely to affect LDL or HDL cholesterol levels (146a,147).

### Correction of Gynecomastia

A final consideration of treatment is the management of clinically significant gynecomastia. When handled properly, reduction of gynecomastia greatly decreases the patient's anxiety regarding his body image and decreases ridicule by peers in such settings as the adolescent locker room. Some authors have suggested removal to prevent breast carcinoma; however, the incidence of breast carcinoma in Klinefelter's syndrome is significantly lower than that in the normal female, and thus this is not a justifiable cause in itself. The main reason for removal by plastic surgery is the psychologic trauma sustained by the adolescent patient.

Because there is no adequate medical means to remove or to decrease the gynecomastia, the physician should encourage plastic surgery for removal of the glandular tissue. The time when the surgery should be performed can be determined by mutual consent between the physician and the patient. If the patient is overweight, attention should be paid to weight reduction for optimal results. A passive approach to the problem of gynecomastia is not appropriate because of the obvious adverse impact on the patient's attitudes and self-image. Even in young adults over 20 years of age, surgical correction is associated with tremendous improvement in their psyche.

It is quite clear that there is a need for prospective studies in these patients at an early age. Many individuals are astounded that such little effort has been paid to a condition that affects at least 0.2% of the male population. The challenge is there.

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