the X chromosome (Turner syndrome: 45,X) have severe somatic and gonadal abnormalities. If a single dose of X-linked genes were sufficient, no detrimental effect would be expected in such cases. Furthermore, although one X chromosome is inactivated in all cells during embryogenesis, it is selectively reactivated in oogonia before the first meiotic division. Thus, it seems that both X chromosomes are required for normal oogenesis.

With respect to the Y chromosome, it is well known that this chromosome is both necessary and sufficient for male development. **Regardless of the number of X chromosomes, the presence of a single Y determines the male sex.** The gene that dictates testicular development (*SRY*: sex-determining region Y gene) is located on its distal short arm. For quite some time this was considered to be the only gene of significance on the Y chromosome. Recent studies of the Y chromosome, however, have yielded a rich harvest of gene families in the so-called "male-specific Y," or MSY region encoding at least 75 protein coding genes All of these are believed to be testes-specific and are involved in spermatogenesis. In keeping with this, all Y chromosome deletions are associated with azoospermia. The following features are common to all sex chromosome disorders.

- In general, sex chromosome disorders cause subtle, chronic problems relating to sexual development and fertility.
- Sex chromosome disorders are often difficult to diagnose at birth, and many are first recognized at the time of puberty.
- In general, the greater the number of X chromosomes, in both male and female, the greater the likelihood of mental retardation.

The two most important disorders arising in aberrations of sex chromosomes are described briefly here.

Klinefelter Syndrome

Klinefelter syndrome is best defined as male hypogonadism that occurs when there are two or more X chromosomes and one or more Y chromosomes. It is one of the most frequent forms of genetic disease involving the sex chromosomes as well as one of the most common causes of hypogonadism in the male. The incidence of this condition is approximately 1 in 660 live male births.

Klinefelter syndrome can rarely be diagnosed before puberty, particularly because the testicular abnormality does not develop before early puberty. Most patients have a distinctive body habitus with an increase in length between the soles and the pubic bone, which creates the appearance of an elongated body. Also characteristic are eunuchoid body habitus with abnormally long legs; small atrophic testes often associated with a small penis; and lack of such secondary male characteristics as deep voice, beard, and male distribution of pubic hair. Gynecomastia may be present. The mean IQ is somewhat lower than normal, but mental retardation is uncommon. There is increased incidence of type 2 diabetes and the metabolic syndrome that gives rise to insulin resistance. Curiously, mitral valve prolapse is seen in about 50% of adults with Klinefelter syndrome. There is also an increased incidence of osteoporosis and fractures due to sex hormonal imbalance.

It should be evident that the clinical features of this condition are variable, the only consistent finding being hypogonadism. Plasma gonadotropin concentrations, particularly follicle-stimulating hormone, are consistently elevated, whereas testosterone levels are variably reduced. Mean plasma estradiol levels are elevated by an as yet unknown mechanism. The ratio of estrogens and testosterone determines the degree of feminization in individual cases.

Klinefelter syndrome is an important genetic cause of reduced spermatogenesis and male infertility. In some patients the testicular tubules are totally atrophied and replaced by pink, hyaline, collagenous ghosts. In others, apparently normal tubules are interspersed with atrophic tubules. In some patients all tubules are primitive and appear embryonic, consisting of cords of cells that never developed a lumen or progressed to mature spermatogenesis. Leydig cells appear prominent, as a result of the atrophy and crowding of the tubules and elevation of gonadotropin concentrations.

Patients with Klinefelter syndrome have a higher risk for breast cancer (20 times more common than in normal males), extragonadal germ cell tumors, and autoimmune diseases such as systemic lupus erythematosus.

The classic pattern of Klinefelter syndrome is associated with a 47,XXY karyotype (90% of cases). This complement of chromosomes results from nondisjunction during the meiotic divisions in the germ cells of one of the parents. Maternal and paternal nondisjunction at the first meiotic division are roughly equally involved. There is no phenotypic difference between those who receive the extra X chromosome from their father and those who receive it from their mother. Maternal age is increased in the cases associated with errors in oogenesis. In addition to this classic karyotype, approximately 15% of patients with Klinefelter syndrome have been found to have a variety of mosaic patterns, most of them being 46,XY/47,XXY. Other patterns are 47,XXY/48,XXXY and variations on this theme.

As is the case with normal females, all but one X chromosome undergoes inactivation in patients with Klinefelter syndrome. Why then, do the patients with this disorder have hypogonadism and associated features? The explanation for this lies in genes on the X chromosome that escape lyonization and in the pattern of X inactivation.

- One pathogenic mechanism is related to uneven dosage compensation during X-inactivation. In some cases about 15% of the X-linked genes escape inactivation. Thus, there is an extra dose of these genes compared to normal males in whom only one copy of X is active, and it appears that "overexpression" of one or more of these genes leads to hypogonadism.
- A second mechanism involves the gene encoding the androgen receptor, through which testosterone mediates its effects. The androgen receptor gene maps to the X chromosome and contains highly polymorphic CAG (trinucleotide) repeats. The functional response of the receptor to any particular dose of androgen is dictated, in part, by the number of CAG repeats, as receptors with shorter CAG repeats are more sensitive to androgens than those with long CAG repeats. In persons with Klinefelter syndrome, the X chromosome bearing the androgen receptor allele with the shortest CAG repeat is preferentially inactivated. In XXY males with low testosterone levels, expression of androgen receptors with long CAG repeats exacerbates the hypogonadism and