Eponyms

# Klinefelter's syndrome

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**SUB_MT_GREENCase presentation**

A 27-year-old white man presented complaining that despite frequent sexual intercourse with his wife during the preceding 9 months, his wife had not become pregnant. He had had a normal birth and childhood, but a delayed onset of puberty, and had only begun shaving at age 19 years. His testes did not enlarge during puberty and became somewhat firm. At age 18 years he noted the onset of bilateral breast enlargement and at age 20 years had a breast reduction procedure. On physical examination the man was noted to be thin and depressed. He was 185 cm in height and weighed 59 kg (body-mass index 17), with minimal muscular development (figure 1). Examination showed small, firm testes, the right measured 6 $cm^3$ (figure 2) and the left measured 5 $cm^3$ (normal size 15–30 $cm^3$). We noted no excess breast tissue; however, scars from previous breast surgery could be seen. He was a high-school graduate, was employed as a crewman on a fishing boat, and had no other medical problems. His laboratory data showed normal blood counts and normal concentrations of serum metabolites. The serum testosterone concentration was 3·8 μg/L (normal 2·1–10·0 μg/L). Follicle-stimulating hormone (FSH) was substantially increased at 35·9 IU/L (normal 1·5–11·0 IU/L), and luteinising hormone (LH) was 21·0 IU/L (normal 0·4–9·0 IU/L). Serum oestradiol was increased to 58·0 ng/L (normal 10·0–50·0 ng/L). His chest radiograph and electrocardiogram were normal. His sperm count was zero (azoospermia) and chromosome analysis showed that he had karyotype 47XXY, confirming the diagnosis of Klinefelter's syndrome. Because he had substantially increased concentrations of LH, suggesting hypotestosteronaemia, he was given testosterone therapy (200 mg testosterone enanthate intramuscularly every 2 weeks). He noted improvements in fatigue and libido. We recommended referral to an infertility clinic for artificial insemination with donor sperm.

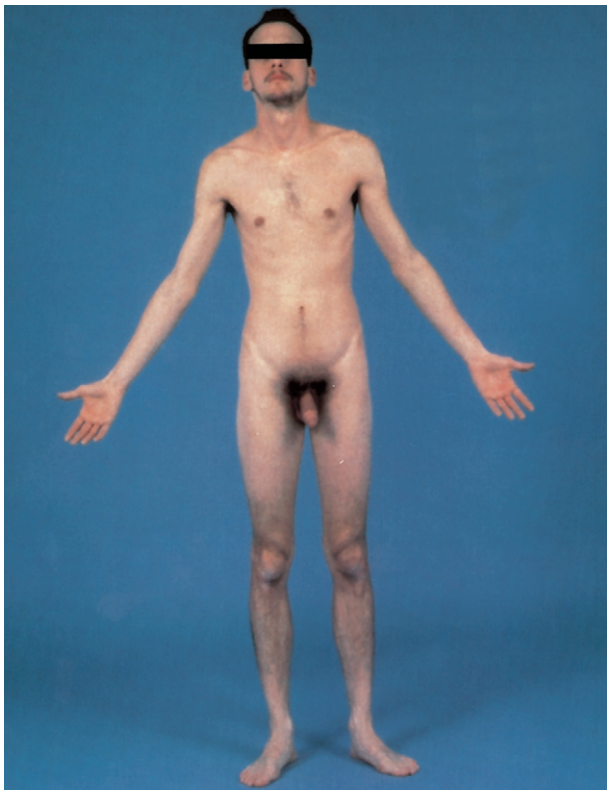

Figure 1: **Patient with Klinefelter's syndrome after several months of testosterone therapy**
Note eunuchoidal body proportions, lack of muscular development, and scant body hair after several months of testosterone therapy. Gynaecomastia has been surgically corrected.

## Klinefelter's syndrome

Klinefelter's syndrome is the most common cause of testicular failure that results in impairments in both spermatogenesis and—to a lesser extent—testosterone production. This syndrome is the most common sex-chromosome disorder affecting 1 in 500 men across all ethnic groups, but the diagnosis is often delayed because of substantial variation in clinical presentation. Those affected possess an additional or "supernumerary" X chromosome that results in a 47XXY genotype. Those affected have severely impaired spermatogenesis (usually azoospermia) and varying degrees of hypotestosteronaemia, manifested by eunuchoidal body habitus with sparse body and facial hair, gynaecomastia, diminished libido (but usually heterosexual orientation), and very small testes. In childhood, the common presenting features include delayed speech development, learning difficulties at school, unusually rapid growth in mid-childhood, and truncal obesity. The risk of breast cancer is 20 times higher in patients with Klinefelter's syndrome. Patient's with this syndrome account for 4% of breast-cancer cases in men.[1]

Laboratory analysis shows low or low-normal serum testosterone concentrations and raised serum gonadotropin concentrations. FSH concentrations are greater than those of LH. The clinical diagnosis confirmed by means of chromosomal analysis (karyotyping), which mostly shows a 47XXY genotype, although infrequently additional X chromosomes may be present or an individual may be mosaic (47XXY/46XY). Treatment consists of testosterone therapy for improved libido, bone density, and quality of life. Gynaecomastia is

*Lancet* 2000; **356:** 333–35

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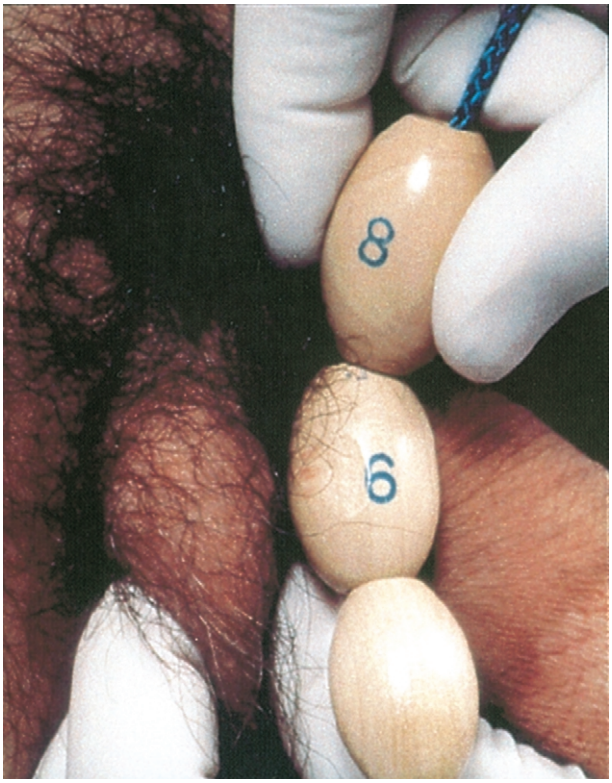


Figure 2: **Testicle of patient with Klinefelter's syndrome**

treated with cosmetic surgery after androgen replacement has begun. Recent advances in the treatment of male infertility, including intracytoplasmic injection of sperm aspirated from the testes of men with Klinefelter's syndrome have been reported,[2] but for most patients artificial insemination with donor sperm is the only option for fertility.

## Harry F Klinefelter Jr

Harry F Klinefelter Jr was born in Baltimore, Maryland, USA on March 20, 1912, and attended the University of Virginia before entering Johns Hopkins Medical School.[3] After graduating in 1937, he trained in internal medicine at Johns Hopkins for 3 years. In 1940 he spent a year working as a "travelling fellow" with one of the founders of modern endocrinology, Fuller Albright, at the Massachusetts General Hospital in Boston. At that time, Fuller Albright was at the height of his formidable intellectual powers and had wide-ranging interest in the endocrinology of sexual development, calcium homeostasis, and the applications of steroid hormone therapy.

Fuller Albright had been collecting the names of a series of patients who he felt had an uncharacterised syndrome typified by gynaecomastia, very small testes, and varying degrees of hypogonadism. With characteristic generosity, Albright assigned Harry Klinefelter the task of further describing this syndrome for publication. Harry Klinefelter therefore began a study of the medical and laboratory abnormalities of these patients.

Harry Klinefelter, Fuller Albright, and their colleague Edward Reifenstein Jr, published their results in the *Journal of Clinical Endocrinology* in 1942.[4] They described a cohort of nine men "characterised by gynecomastia, aspermatogenesis without a-Leydigism, and increased excretion of follicle-stimulating hormone." In this paper, the investigators noted the presence of Leydig cells in these patients which produced testosterone, and a substantial increase in FSH production, comparable to that seen in castrated men. The investigators suggested that the substantially increased concentrations of FSH were caused by the lack of a testicular hormone other than testosterone. This postulated hormone, called inhibin by previous researchers, was in fact lacking in these patients, but it took more than 50 years to confirm their hypothesis.[5]

As to the cause of the syndrome, they were less certain. They ruled out testicular inflammation, infection, or obstruction of the vas deferens, and noted that the lesion seen in testicular biopsy samples involved the seminiferous tubules without affecting the histology of the Leydig cells, testicular interstitium, or epididymis. They recommended testosterone therapy (available since the late 1930s) for those with signs or symptoms of hypotestosteronism, but noted that this therapy did not improve the gynaecomastia or fertility.

Following his tenure with Fuller Albright, Harry Klinefelter served in the US army for 3 years during the Second World War, advancing from the rank of First Lieutenant to Major before gaining an honorable discharge. He then returned to his native Baltimore to join the medical faculty at Johns Hopkins. He became interested in rheumatology and began a career in both private practice and on the clinical faculty, eventually becoming an Associate Professor of Medicine in 1966. Harry Klinefelter remained active in patient care in Baltimore until retiring in 1988 at age 76 years. He died in 1990.

## Pathophysiology

After the initial description of the syndrome by Harry Klinefelter, Edward Reifenstein, and Fuller Albright, it was another 15 years before I A Jacobs and J A Strong confirmed the association between the extra X-chromosome and Klinefelter's syndrome, establishing it as a genetic disease.[6] Most cases occur through sporadic chromosomal non-disjunction during parental gametogenesis in either the sperm (53%) or the egg (44%). The remaining 3% of cases are caused by postzygotic mitotic errors.[1] The extra X chromosome forms a dense chromatin mass, or Barr body, within the nuclei of somatic cells, but exactly how the presence of this extra chromosome leads to testicular failure is unknown. Testicular biopsy samples from infants with Klinefelter's syndrome sometimes show only a reduced number of germ cells. After puberty, fibrosis of the seminiferous tubules begins, eventually leading to small, firm testes and azoospermia. The lack of functional sertoli cells in the seminiferous tubules is accompanied by low concentrations of inhibin B in serum, the hormone whose existence Harry Klinefelter and his colleagues had hypothesised in their original paper.

- Klinefelter's syndrome is a common genetic disorder resulting in testicular failure, variable degrees of androgen deficiency, and infertility.
- Treatment with testosterone can rectify the androgen deficiency but does not improve fertility.
- Although developments in assisted-reproductive technology could make fertility for some patients, artificial insemination with the donor

## New developments

There have been recent advances in the options for the treatment of infertility in patients with Klinefelter syndrome. Until recently, the use of donated sperm or adoption were the only options available for those patients who were infertile; however reports of successful, karyotypically normal pregnancies after intracytoplasmic injection of sperm, obtained from testicular biopsy samples from patients with Klinefelter's syndrome have been published.[2] Although some patients with Klinefelter's syndrome do not have any sperm,[7] this technique could offer a chance at fertility for those who do. However, analysis of these intratesticular germ cells has shown some spermatozoa with extra X chromosomes, which is cause for concern.[8] This finding implies that Klinefelter's syndrome may be transmissible by assisted reproductive techniques, and that sperm from testicular biopsy samples might require further selection to prevent transmission of the syndrome.

We thank W Parsons and M Klinefelter for their personal recollections of the life of Harry Klinefelter. Physicians and patients interested in obtaining further information about Klinefelter syndrome, including support-group resources can contact the British Klinefelters Support Group (www.ksa-uk.co.uk) or the Klinefelter Syndrome and Associates, PO Box 119, Roseville, CA 95678-0119 (e-mail: ksxxy@ix.netcom.com).

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