KLINEFELTER SYNDROME

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Grand Rounds

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Patient 1 Klinefelter syndrome with varicose veins, obesity, and diabetes.

F.D. was diagnosed as having Klinefelter syndrome at age 45 at DVAH in 1963 based on the clinical features of small testes, female escutcheon, gynecomastia, absence of facial hair and tall stature. He had cholecystectomy at this hospitalization. He was first seen at PMH medicine clinic in 1967 at the age of 49 where he was found to have diabetes mellitus. He gave a history of having had problems with leg ulcers for twenty years secondary to his severe varicose veins and chronic venous stasis. In 1970 he was hospitalized for a pulmonary embolism associated with thrombophlebitis. He had a mother with diabetes. He was noted to be quite obese (240 pounds) and to have marked gynecomastia and "atrophic testes" and slightly "small" penis. He was followed frequently in the diabetic foot care clinic for his right ankle ulcers and eventually had a right BKA in 1974. In April 1977 he was hospitalized for an upper GI bleed secondary to a pre-pyloric gastric ulcer and had a vagotomy and gastroenterostomy. He returned in September 1977 after having lost almost 30 pounds over five months following his operation. On 9/26/77 he presented as a cardiopulmonary arrest to PMH ER and could not be resuscitated.

Patient 2 Klinefelter syndrome with mental retardation and behavior disorder.

H.K. is a 17 year old young man who was seen by a private physician after being assaulted. The physician obtained a history that the young man is a slow learner and had run away from home several times declaring amnesia. But he was able to recount homosexual encounters and transvestite behavior during these "spells of amnesia". He has an I.Q. of about 60 and dropped out of school in the eleventh grade. The physician noted the presence of small testes and obtained the history of shaving only twice a month. On referral to SMS he was noted to be 73 in. tall, to have a small button of bilateral subareolar breast tissue, a female escutcheon, and testes with volumes of 5 and 8 ml. The external genitalia were normal with a normal sized penis and no hypospadias. A karyotype of peripheral lymphocytes was 47,XXY. Plasma testosterone was normal at 4.1 ng/ml. His androgen-estrogen dynamics were studied by Dr. Aiman in the GCRC. His testosterone production rate was low normal at 3.7 mg/day. Estradiol production rate was elevated at 107 µg/day (nl < 50), 86 µg of which was from direct secretion by the testis (nl < 15 µg).

Patient 3 Klinefelter syndrome with mosaicism limited to the testes.

R.P., a CPA, was seen at age 27 in 1969 at Scott and White Clinic for gynecomastia. He had normal height and normal body proportions, normal phallus, and "questionably" small testes. Urinary estrogens were 58 µg/24 hr (nl 4-25). Buccal smear showed one Barr body. Ejaculate volume was 3.5 ml with sperm count of 1.3 mil/ml. Karyotype of peripheral leukocytes examining 36 cells was 46,XY. Testis biopsy did not have evidence of hyalinization, but two-thirds of the tubules contained only Sertoli cells. Karyotype of the testis by Dr. Paulson in Seattle was 46,XY/47,XXY mosaicism. Prior to this evaluation and up to the present time he has also had recurrent fevers that occur approximately every 28 days. No etiology of the recurrent fever has been found. In the last few years he has had impotence and depression requiring outpatient psychiatric treatment. He has also had a bilateral mastectomy.

I. HISTORICAL CONSIDERATIONS AND NOMENCLATURE

In 1942 Klinefelter, Reifenstein and Albright described for the first time as a specific syndrome nine males with small testes, azoospermia, normal external genitalia, gynecomastia, inadequate pubertal virilization, and increased urinary gonadotropin (1). The spectrum of the phenotype was further defined by Heller and Nelson in 1945 to suggest that there could be quite variable degrees of apparent androgen deficiency (2). Several investigators in 1956 then documented that the majority of individuals (but not all) with Klinefelter syndrome had a positive sex chromatin (female pattern) in the nuclei of epithelial cells in smears from the oral mucosa (3-5). Finally in 1959 Jacobs and Strong demonstrated that the karyotype of an affected X-chromatin positive individual was 47,XXY (6).

As originally described by Klinefelter, the phenotype could include X-chromatin positive or X-chromatin negative individuals. Most authors have come to apply the term Klinefelter syndrome only to X-chromatin positive individuals or more specifically to individuals who demonstrate at least one Y chromosome and two or more X chromosomes in at least a portion of their body cells. A number of individuals with 48,XXYY, 49,XXXXY, and 48,XXXY karyotypes have been reported. Since the frequency and severity of other abnormalities not typically associated with Klinefelter syndrome increase with additional X chromosomes (7), these forms of the disorder will not be considered in this review.

1 Klinefelter, H.F., Jr., Reifenstein, E.C.,Jr., and Albright, F. Syndrome characterized by gynecomastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle-stimulating hormone. J Clin Endocrinol 2: 615-627, 1942.

2 Heller, C.G., and Nelson, W.O. Hyalinization of the seminiferous tubules associated with normal or failing Leydig-cell function. Discussion of relationship to eunuchoidism, gynecomastia, elevated gonadotropins, depressed 17-ketosteroids and estrogens. J Clin Endocrinol. 5: 1-12, 1945.

3 Plunkett, E.R., and Barr, M.L. Testicular dysgenesis affecting the seminiferous tubules principally, with chromatin-positive nuclei. Lancet 2: 853-856, 1956.

4 Jackson, W.P.U., Shapiro, B.G., Uys, C.J., and Hoffenberg, R. Primary male hypogonadism with female nuclear sex. Lancet 2: 857-859, 1956.

5 Raboch, J. Thirty-one men with female sex chromatin. J Clin Endocrinol Metab 17: 1429-1439, 1957.

6 Jacobs, P.A. and Strong, J.A. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature 183: 302-303, 1959.

7 Day, R.W., Levinson, J., Larson, W., and Wright, S.W. An XXXXY male. J Pediatr 63: 589-598, 1963.

II. INCIDENCE AND PREVALENCE OF THE CHROMOSOMAL COMPLEMENTS ASSOCIATED WITH KLINEFELTER SYNDROME

A. Newborn Males

Using the nuclear sex chromatin as a screening test, a number of series of consecutively born males have indicated an incidence of about 1-3 per 1000 with X-chromatin. The results of 8 of these series of newborn males totaling almost 42,000 individuals are summarized in Table I giving the proportion of the two most common Klinefelter karyotypes, 47,XXY and 46,XY/47,XXY mosaicism as found in peripheral leukocytes after screening for X-chromatin on buccal smear.

Table I. Number and Frequency of the Two Most Common Klinefelter Karyotypes in Newborn Males (Ref. 8-14)

Series	Total Males	XXY	XY/XXY	%
Edinburgh (UK) 1964	10,725	15	5	0.19
Edinburgh (UK) 1974	7,849	9	2	0.14
Arhus (Denmark) 1973	2,615	4	-	0.15
Ontario (Canada) 1969	1,066	1	-	0.09
Winnipeg (Canada) 1975	7,176	6	-	0.08
Boston (USA) 1974	9,048	6	-	0.07
New Haven (USA) 1970	2,176	4	-	0.18
Moscow (USSR) 1974	1,303	1	1	0.15
	41,958	46	8	0.13

Thus the incidence of Klinefelter syndrome in newborn males is at least a little greater than 1 in 1000.

8 Maclean, N, Harnden, D.G., Court Brown, W.M., Bond, J., and Mantle, D.J. Sex-chromosome abnormalities in newborn babies. Lancet 1: 286-290, 1964.

9 Jacobs, P.A., Melville, M. Ratcliffe, S. A cytogenetic survey of 11,680 newborn infants. Ann Hum Genet, Lond 37: 359-376, 1974.

10 Friedrich, U., and Nielsen, J. Chromosome studies in 5,049 consecutive newborn children. Clin Genet 4: 333-343, 1973.

11 Sergovich, F., Valentine, M.B., Chen, A.T.L., Kinch, R.A.H., and Smout, M.S. Chromosome aberrations in 2159 consecutive newborn babies. New Engl J Med 280: 851-855, 1969.

12 Hamerton, J.L., Canning, N., Ray, M., and Smith, S. A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. Clin Genet 8: 223-243, 1975.

13 Lubs, H.A., and Ruddle, F.H. Chromosomal abnormalities in the human population: estimation of rates based on New Haven newborn study. Science 169: 495-497, 1970.

14 Bochkov, N.P., Kuleshov, N.P., Chebotarev, A.N., Alekhin, V.I., and Midian, S.A. Population cytogenetic investigation of newborns in Moscow. Humangenetik 22: 139-152, 1974.

B. Non-institutionalized Adult Males

Fewer prospective studies of adult males have been performed and only small groups have been surveyed. However, two studies of about 1000 subjects each suggest that the prevalence in the adult male population is about 1 in 500 (15,16). This points to the fact that Klinefelter syndrome (unlike Turner syndrome) is not associated with major malformations that preclude some individuals from reaching adulthood.

The major unanswered question regarding the prevalence of Klinefelter syndrome is whether the mosaic XY/XXY form is more common than currently recognized. Since these individuals are in general less severely affected than those with the classic XXY form (see below), they might be overlooked. There are several ways in which they might be missed: 1) If a sex chromatin buccal smear screening test is used, the mosaicism might be missed because of the lack of sensitivity of this test. 2) If a formal karyotype of blood lymphocytes is obtained, an inadequate number of cells may be examined to assure the likelihood of detection of a minor cell line with a low frequency (17,18). To exclude a mosaicism of 10% or greater with 95% confidence 29 cells must be examined. Our cytogenetics lab routinely examines 20 cells which will exclude mosaicism greater than 15% with 95% confidence. 3) The proper tissue may not be studied for chromosome analysis. Although most studies in which mosaicism is carefully sought on cultured lymphocytes have found that about 10% of Klinefelter patients to be mosaics (19), prospective studies in which both blood and testis karyotypes were performed on potential Klinefelter patients have shown that 70% of patients eventually demonstrated to be mosaics had the abnormal cell line only in the testis (20). 4) Finally, the diagnosis might not be suspected because of the mild degree of phenotypic abnormality present in some individuals with mosaicism.

15 Kaplan, N.M., and Norfleet, R.G. Hypogonadism in young men (with emphasis on Klinefelter's syndrome). Ann Intern Med 54: 461-481, 1961.

16 Paulsen, C.A., de Souza, A., Yoshizumi, T., and Lewis, B.M. Results of a buccal smear survey in noninstitutionalized adult males. J Clin Endocrinol 24: 1182-1187, 1964.

17 Ford, C.E. Mosaics and chimaeras. Brit Med Bull 25: 104-109, 1969.

18 Hook, E.B. Exclusion of chromosomal mosaicism: Tables of 90%, 95%, and 99% confidence limits and comments on use. Amer J Human Genet 29: 94-97, 1977.

19 Nielsen, J. Chromosome mosaicism in a population sample. Humangenetik 29: 155-159, 1975.

20 Leonard, J.M. Personal communication.

III. CLINICAL FEATURES OF THE CLASSIC AND MOSAIC KLINEFELTER SYNDROME

A number of excellent reviews have documented the general clinical features of Klinefelter syndrome (21-25) and two have documented the differences between the classic and mosaic forms (26,27). The patients with the mosaic form are less severely affected in many of the prominent clinical features.

Table II. Characteristics of Patients with Classic versus Mosaic Klinefelter Syndrome (Ref. 27)

Pathologic Feature	47,XXY	46,XY/47,XXY
Abnormal testicular histology	100%	94% *
Decreased length of testis	99	73 *
Azoospermia	93	50 *
Decreased testosterone	79	33
Decreased facial hair	77	64
Increased gonadotropins	75	33 *
Decreased sexual function	68	56
Decreased pubic hair (female pattern)	61	62
Gynecomastia	55	33 *
Decreased axillary hair	49	46
Decreased length of penis	41	21

*Significantly different at p <.05 or better

Table based on 519 XXY patients and 51 XY/XXY patients.

21 Becker, K.L., Hoffman, D.L., Albert, A., Underdahl, L.O., and Mason, H.L. Klinefelter's syndrome. Arch Intern Med 118: 314-321, 1966.

22 Ferguson-Smith, M.A. Sex chromatin, Klinefelter's syndrome and mental deficiency. In The Sex Chromatin, K. L. Moore (ed.) Philadelphia, W. B. Saunders Co., 1966, pp 277-315.

23 Zuppinger, K., Engel, E., Forbes, A.P., Mantooth, L., and Claffey, J. Klinefelter's syndrome, a clinical and cytogenetic study in twenty-four cases. Acta Endocrinol Suppl. 113: 5-36, 1967.

24 Froland, A. Klinefelter's syndrome. Danish Medical Bulletin Vol. 16, Suppl VI. pp 1-108, 1969.

25 Becker, K.L. Clinical and therapeutic experiences with Klinefelter's syndrome. Fertil Steril 23: 568-578, 1972.

26 Paulsen, C.A., Gordon, D.L., Carpenter, R.W. Klinefelter's syndrome and its variants: A hormonal and chromosomal study. In Recent Progress in Hormone Research, Vol. 24, IV. Clinical Endocrinology, pp 321-353, 1968.

27 Gordon, D.L, Krmpotic, E., Thomas, W., Gandy, H.M., and Paulsen, C.A. Pathologic testicular findings in Klinefelter's syndrome. Arch Intern Med 130: 726-729, 1972.

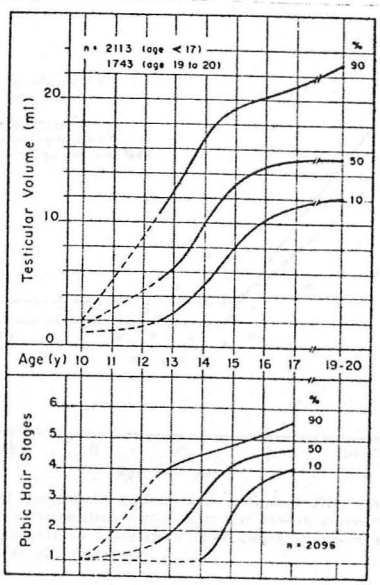
A. Gonadal Pathology

The most consistent clinical feature of Klinefelter syndrome and the one that most frequently leads to a suspicion of the diagnosis is the abnormal testes. In fact, except for a few features of the syndrome (see below) almost every abnormality can be traced to a primary testicular lesion with secondary hormonal changes.

The examination of the testes is one of the aspects of the general physical exam that is often performed inadequately (even on our medical wards). We are frequently told that the testes are "small" or "atrophic" without any quantitative assessment of size. The size of the testis can be assessed by measurement of its length or, more accurately, its volume with the aid of an orchidometer (28). The length of the testis is greater than 4.0 cm (about 12 ml) in over 90% of young adults. This value also applies to men over 50 (29). In this group no normal individual had a length less than 3.5 cm. In contrast almost all patients with Klinefelter syndrome have a testis length less than 2.5 cm (about 4 ml).

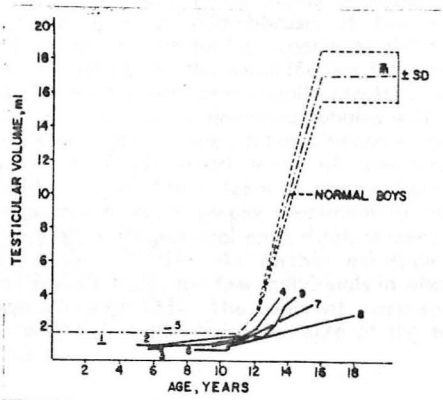
In Fig. 1 is shown the range of testicular volumes for normal boys in a cross sectional study according to age. Two groups of investigators have reported that prepubertal boys with Klinefelter syndrome have testicular volumes somewhat lower than normal that become unequivocally abnormal during puberty (Fig. 2 and 3) (30,31).

Figure 1



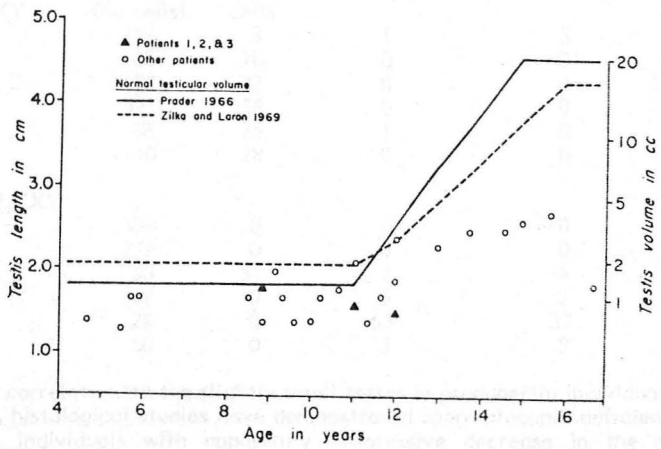
Testicular volumes in relation to chronological age (upper part) and Tanner's pubic hair stages (lower part). 10th, 50th and 90th percentile from the cross-sectional study.

Figure 2



Growth of testes in 9 children with Klinefelter's syndrome diagnosed before puberty.

Figure 3



Testis size of the present patients and additional XXY patients from the literature[9, 10, 12-14, 17] with representative normal testicular growth curves.[36] Note the tendency of testis size to be in the small to low-normal range during childhood with subsequent lack of normal enlargement through adolescence.

The typical histologic pattern of the testis of a patient with Klinefelter syndrome consists of hyalinization and fibrosis of the seminiferous tubules, absence of elastic fibers around the tunica propria of the tubules and apparent Leydig cell hyperplasia. Damage to the seminiferous tubules in the patient with the classical form of Klinefelter syndrome usually results in complete loss of the germinal epithelium. The moderately damaged tubules will usually contain only Sertoli cells. The more severely involved tubules become completely hyalinized, fibrotic, and shrunken. However small areas of spermatogenesis have been reported in a few tubules in the classic form of the syndrome (32). Less severe testicular damage is usually found in biopsy specimens of the patients with the mosaic form of the disorder with germinal epithelium present in about 26% of the tubules in one study (Table 3) (27). As further evidence of the less severe testicular lesion in the mosaic form, the few individuals in whom fertility has been documented have been XY/XXY (33). The apparent increase in Leydig cells has been shown to be an artifact of the decreased size of the tubules in a study of Leydig cell volume (34).

Table III. Correlation of Karyotype with the Degree of Testicular Abnormality (Ref. 27)

Patients	Most Mature Cell Type in Tubules (Number of Tubules)				
47,XXY	Hyalinized (no cells)	Sertoli cells	Spermatogonia	Spermatocytes	Spermatids
1	196	3	1	3	0
2	63	10	0	0	0
3	132	22	0	0	0
4	320	58	0	0	0
5	68	25	1	0	0
6	110	28	0	0	1
46,XY/47,XXY					
7	380	0	0	0	0
8	276	0	0	0	0
9	60	51	2	4	22
10	67	0	5	2	54
11	26	0	63	37	21
12	50	0	3	9	96

To correlate with the slightly small testes in prepubertal individuals with the disorder, histological studies have demonstrated spermatogonia deficiency even in neonatal individuals with apparently progressive decrease in the number of spermatogonia in the first year of life (35,36).

28 Zachmann, M., Prader, A., Kind, H.P., Häfliger, H. and Budliger, H. Testicular volume during adolescence Cross-sectional and longitudinal studies. Helv paediat Acta 29: 61-72, 1974.

29 Lubs, H.A.,Jr. Testicular size in Klinefelter's syndrome in men over fifty Report of a case with XXY/XY mosaicism. N Engl J Med 267: 326-331, 1962.

30 Laron, Z., and Hochman, I.H. Small testes in prepubertal boys with Klinefelter's syndrome. J Clin Endocrinol Metab 32: 671-672, 1971.

31 Caldwell, P.D., and Smith D.W. The XXY Klinefelter's syndrome in childhood: detection and treatment. J Pediatr 80: 250-258, 1972.

32 Steinberger, E., Smith, K.D., and Perloff, W.H. Spermatogenesis in Klinefelter's syndrome. J Clin Encocrinol Metab 25: 1325-1330, 1965.

33 Warberg, E. A fertile patient with Klinefelter's syndrome. Acta Endocrinol 43: 12-26, 1963.

34 Ahmad, K.N., Dykes, J.R.W., Ferguson-Smith, M.A., Lennox, B., and Mack, W.S. Leydig cell volume in chromatin-positive Klinefelter's syndrome. J Clin Endocrinol 33: 517-520, 1971.

35 Edlow, J.B., Shapiro, L.R., Hsu, L.Y., and Hirschhorn. Neonatal Klinefelter's syndrome. Amer J Dis Child 118: 788-791, 1969.

36 Mikamo, K., Aguercif, M., Hazeghi, P., and Martin-Du Pan, R. Chromatin-positive Klinefelter's syndrome. Fertil Steril 19, 731-739, 1968.

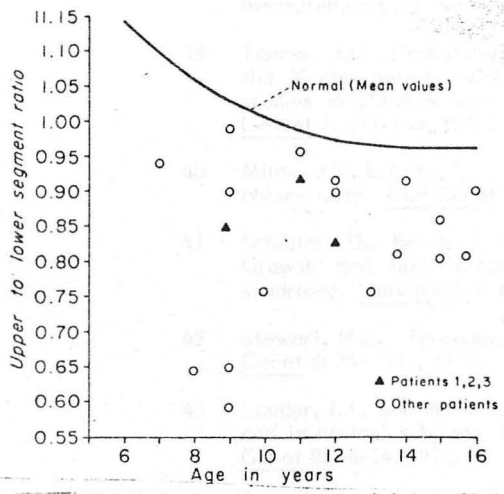
B. Other Physical Findings

In Klinefelter syndrome the external genitalia are usually well differentiated. Hypospadias probably occurs no more often than in normal males. In about 80% of individuals the penis is normal in length. However, a 1-3 cm increase in length may follow administration of androgens (25). The prostate is smaller than usual presumably reflecting decreased androgen levels. Cryptorchidism is rare.

Decreased androgen production results in lack of normal male secondary sexual development with the extent of the impairment probably roughly proportional to testosterone levels and with mosaic individuals usually less severely affected. Decreased facial hair and lack of temporal balding are prominent features. Muscle development is often poor with fat distribution more reminiscent of females than of males. The figure of 55% for the occurrence of gynecomastia given in Table II. is probably a minimal estimate. Large series in which it is checked for carefully suggest an incidence approaching 85% (26). This is another area of the physical exam of the male that is often improperly performed. The patient should not be examined with the flat of the hand while he is in the supine position but with the fingertips while he is sitting. The examiner should make an effort to feel a border of glandular tissue palpating from the periphery toward the nipple. The gynecomastia in this condition, as in others in which appropriate studies have been done, is related to an androgen-estrogen imbalance (see below).

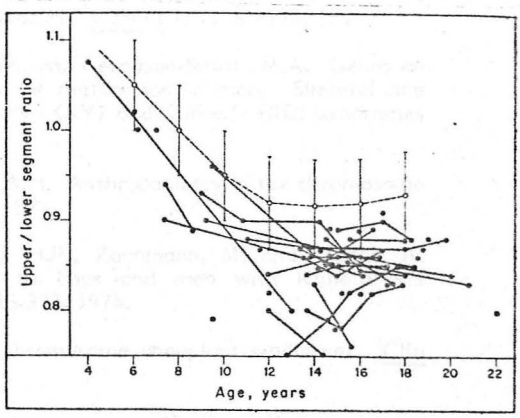
One of the striking features of many Klinefelter patients is their abnormal growth. Klinefelter patients are taller than normal males and often have abnormal body proportions. One study of the occurrence of the disorder in men 184 cm or taller indicated a 4-fold increase in the prevalence compared with the general population (37). The legs are relatively long compared to the trunk and arms, a disproportion manifested by an increased pubis-to-sole length (or decreased upper to lower segment ratio) (38-40). In one large anthropometric study the subischial height in Klinefelter patients averaged almost 2.5 cm greater than a control group matched for height and weight (40). Because of this increased lower segment the span does not usually exceed the height by as great a margin as in other eunuchoid patients. The most interesting aspect of this increased growth of the lower segment is that it begins prior to puberty and thus seems unlikely to be related to delayed epiphyseal closure secondary to androgen deficiency (Fig. 4 and 5) (21). The etiology of these abnormal proportions is unknown.

Figure 4



Diminished upper-to-lower segment ratio in boys with the XXY syndrome in the present patients and others from the literature.[2, 9-12] Normal standards from Wilkins, L.: The diagnosis and treatment of endocrine disorders in childhood and adolescence, Springfield, Ill., 1965, Charles C Thomas, Publisher.

Figure 5



Upper/lower segment ratios in patients with Klinefelter's syndrome in comparison with normal mean values and standard deviations [10].

Minor somatic anomalies probably occur more often in Klinefelter syndrome than in normal. Skeletal defects of the thorax or spine were reported in 25% of patients in one series (25), but others have not reported so frequent an occurrence with 5% being the usual figure. Dental abnormalities may be present, especially taurodontism (pulp chamber enlargement and external root elongation in molar teeth) (42). Cortical thickness of bone in these patients is more similar to that of

normal women than normal men (43). Radiographic features of the skull in Klinefelter syndrome are apparently distinct from other forms of male hypogonadism (44). An elevation in neurosensory hearing threshold in the middle frequency ranges was reported in 5 of 26 47,XXY individuals (45). This type of hearing pattern is frequently seen in Turner syndrome. But unlike the Turner syndrome, pathologically high stapedius-reflex thresholds were recorded in 9 of these patients. Both of these findings are similar to the type of disorder found in presumptive carriers of autosomal recessive genes for deafness. The frequency of congenital heart defects may be slightly increased (46), but there is no single anomaly consistently described. Specific dermatoglyphic abnormalities of decreased mean digital ridge count to about 120 and distal displacement of the axial triradius have been described (47,48).

37 Philip, J., Lundsteen, C., Owen, D., and Hirschhorn, K. The frequency of chromosome aberrations in tall men with special reference to 47,XYY and 47,XXY. Am J Hum Genet 28: 404-411, 1976.

38 Stewart, J.S.S. Medullary gonadal dysgenesis (Chromatin-positive Klinefelter's syndrome). A genetically determined condition with eunuchoid measurements but early epiphyseal closure. Lancet 1: 1176-1178, 1959.

39 Tanner, J.M., Prader, A., Habich, H., and Ferguson-Smith, M.A. Genes on the Y chromosme influencing rate of maturation in man. Skeletal age studies in children with Klinefelter's (XXY) and Turner's (XO) syndromes Lancet 2: 141-144, 1959.

40 Milne, J.S., Lauder, I.J., and Price, W.H. Anthropometry in sex chromosome abnormality. Clin Genet 5: 96-106, 1974.

41 Schibler, D., Brook, C.G.D., Kind, H.P., Zachmann, M. and Prader, A. Growth and body proportions in 54 boys and men with Klinefelter's syndrome. Helv paediat Acta 29: 325-333, 1974.

42 Stewart, R.E. Taurodontism in X-chromosome aneuploid syndromes. Clin Genet 6: 341-344, 1974.

43 Lauder, I.J., and Milne, J.S. Bone mass in men with Klinefelter's syndrome and in normal subjects, estimated by the cortical thickness of bone. Clin Genet 8: 48-54, 1975.

44 Kosowicz, J. and Rzymski, K. Radiological features of the skull in Klinefelter's syndrome and male hypogonadism. Clin Radiol. 26: 371-378, 1975.

45 Anderson, H., Lindsten, J., and Wedenberg, E. Hearing defects in males with sex chromosome anomalies. Acta Otolaryngol 72: 55-58, 1971.

46 Rosenthal, A. Cardiovascular malformations in Klinefelter's syndrome: report of three cases. J Pediatr 80: 471-473, 1972.

47 Borgaonkar, D.S., and Mules, E. Comments on patients with sex chromosome aneuploidy: dermatoglyphs, parental ages, Xg^a blood group. J Med Genet 7: 345-350, 1970.

48 Komatz, Y. and Yoshida, O. Position of axial triradius in 51 cases of 47,XXY Klinefelter's syndrome. Jap J Human Genet 21: 123-128, 1976.

C. Hormonal Studies

Most of the clinical features of Klinefelter syndrome can be accounted for by the well recognized hormonal alterations. The mean plasma testosterone level is about half that of normal males (26), but the range is so wide that levels overlap the normals. The plasma gonadotropins are elevated with FSH usually more increased than LH. In Table IV. is summarized a very complete study of the hormonal changes in 19 Klinefelter patients including androgen-estrogen dynamics (49). The plasma production rate, the total and free levels of testosterone, and the metabolic clearance rate of testosterone and estradiol were low in these patients. Plasma estradiol, LH and FSH were elevated, and there was increased peripheral conversion of testosterone to estradiol. The production rate of estradiol was normal.

Table IV. Hormonal Studies in Klinefelter Syndrome (Ref. 49)

Mean with range or ± SD

	Klinefelter syndrome	Healthy men	P
Serum LH (mIU/ml)	7.8 (4.2-12.7)	1.8 (0.6.-2.8)	< .001
Serum FSH (mIU/ml)	29.4 (12-61)	2.7 (0.5-5.2)	< .001
Plasma Testosterone (ng/ml)	3.16 (0.81-8.49)	6.8 (3.46-10.75)	< .001
Plasma Estradiol (pg/ml)	34 (3-65)	16 (UD-34)	< .001
MCR T ($l/h/m^2$)	423 ± 135	582 ± 126	< .01
MCR E_2 ($l/h/m^2$)	601 ± 121	934 ± 273	< .005
Production rate T (mg/24 h)	3.27 ± 1.35	7.04 ± 2.47	< .001
Production rate E_2 (µg/24 h)	41.2 ± 19.0	34.3 ± 21.6	NS
Conversion Ratio TE_2 (%)	0.46 ± 0.16	0.19 ± .03	< .01
Transfer Constant TE_2 (%)	0.60 ± .21	0.28 ± .06	< .05

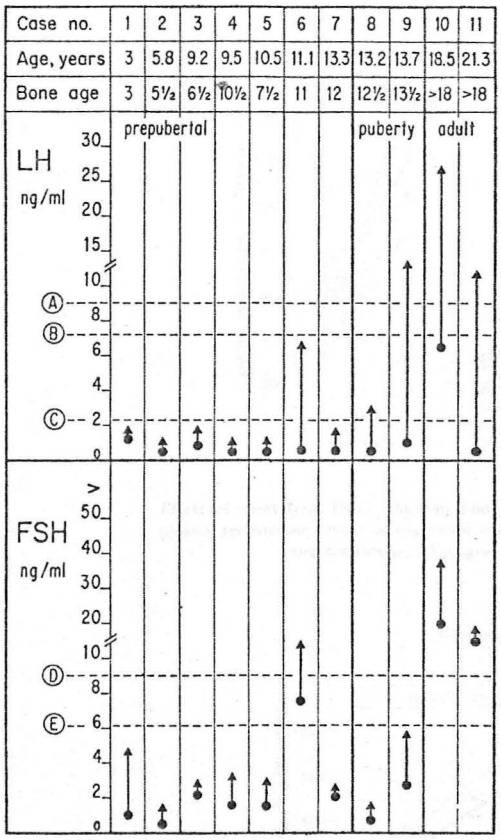
Thus the hormonal setting in Klinefelter syndrome of altered androgen/estrogen ratios that favors gynecomastia is basically a decreased testosterone production in the setting of a normal estradiol production. Plasma estradiol is somewhat elevated, however, due to the decreased clearance rate.

Although prepubertal Klinefelter patients might be suspected of having the disorder because of altered lower segment or small testes, they are usually not found to have any hormonal abnormalities. Stimulation with GnRH (LH-RH) is a sensitive means of testing for alterations in the hypothalamic-pituitary-gonadal axis (50). Unlike patients with Turner syndrome who exhibit hyperresponsiveness

to LH-RH prepubertally, Klinefelter patients do not show an abnormal responsiveness until puberty (Fig 6 and 7) (51-52).

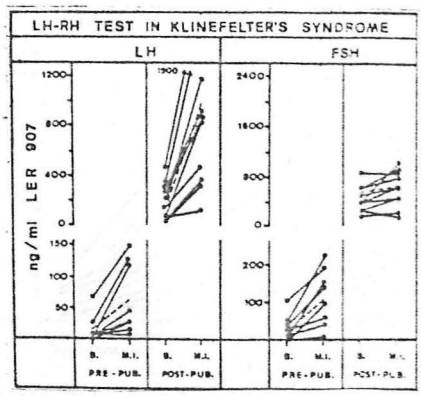
Response of LH and FSH to prolonged infusions of LH-RH has been shown to be a more discriminating test for an abnormal axis in some individuals (53).

Figure 6



Effect of LH-RH (25 µg/m² i.v.) on plasma LH and FSH in 11 patients with chromatin-positive Klinefelter's syndrome.
● = basal values, ▲ = peak values. The horizontal lines indicate the upper limits of the normal range ($\bar{x} \pm 1$ SD) for LH in adults (A), during puberty (B), and before puberty (C), and for FSH in adults and during puberty (D), and before puberty (E).

Figure 7

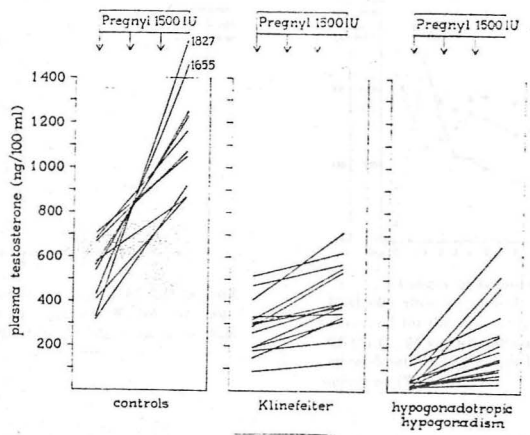


Basal levels (B) and maximal increments (MI) of LH and FSH after LHRH in prepubertal Klinefelter's syndrome. Broken lines represent the mean.

One of the major hormonal alterations in Klinefelter syndrome that has been recognized for some time is the decreased Leydig cell reserve (26). Thus, although baseline testosterone levels may be within the statistically normal range,

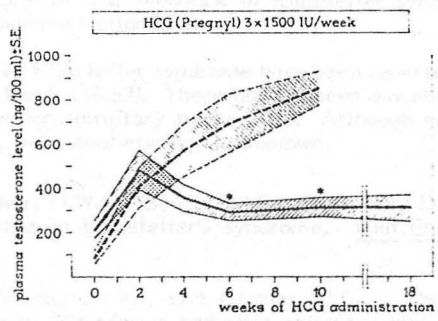
response to hCG is impaired. Recently the effect of both short and long term hCG administration in Klinefelter patients has been evaluated and compared with normal men and patients with hypogonadotropic hypogonadism (Fig 8 and 9) (54). Short term hCG administration resulted in significant increase in testosterone in both Klinefelter and hypogonadotropic hypogonadal patients, but the magnitude was less than in controls. During long term treatment with hCG, the testosterone levels initially increased in both patient groups, but levels tended to decrease in Klinefelter patients on continued treatment.

Figure 8



Effect of short term HCG administration (Pregnyl®, 1500 IU/day for 3 days) on plasma testosterone levels in eugonadal males, patients with Klinefelter's syndrome and patients with hypogonadotrophic hypogonadism.

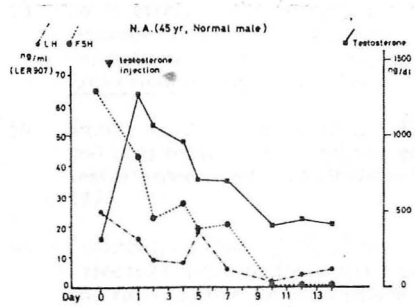
Figure 9



Effect of chronic HCG administration (Pregnyl®, 3 x 1500 IU/week) on plasma testosterone levels in Klinefelter patients (solid line) and patients with hypogonadotrophic hypogonadism (broken line). The asterisks indicate significant differences of testosterone means between the two patient groups ($P_w < 0.05$).

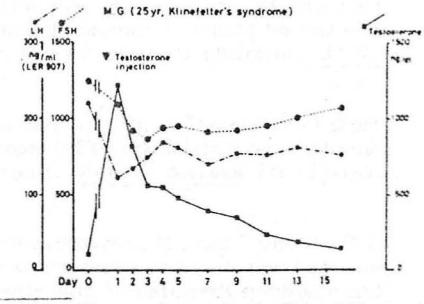
Another feature of the altered hormonal state in Klinefelter syndrome is the lack of normal feedback inhibition of gonadal steroids on pituitary gonadotropin secretion. While a normal man has a rapid fall in both LH and FSH after a single injection of a long-acting testosterone preparation (Fig. 10), a typical patient with Klinefelter syndrome has only a minor transient decrease in both hormones (Fig 11)(55).

Figure 10



Changes of serum levels of T(■), LH (●) and FSH (⊙) after a single T injection (▼, im, 100 mg), observed for the following 14 days in a normal man (N.A., 45 yr).

Figure 11



Changes of serum levels of T(■), LH (●) and FSH (⊙) after a single T injection (▼, im, 100 mg), observed for the following 16 days in a patient with KS (M.G., 25 yr) before treatment. Basal levels (Day 0) were determined 10 days before the date of actual T injection (▼).

Another way to assess the normality of feedback inhibition by gonadal steroids on gonadotropins is the inhibition in the stimulation normally induced by administration of GnRH. Recently the time required for the inhibition of this response in normal men and Klinefelter patients has been compared. On the same high dose of exogenous testosterone (200 mg weekly) that resulted in similar high blood testosterone levels (over 1100ng/dl), normal men had complete inhibition of gonadotropin responsiveness in 4 weeks while the Klinefelter patients still had normal or supranormal responses at 8 weeks (56). This higher setting of hypothalamic-pituitary-gonadal feedback in Klinefelter syndrome has also been shown for estrogen administration (57).

Several cases of Klinefelter syndrome have been reported in which there are low FSH and/or LH levels (58,59). There has not been any obvious explanation for this unusual combination (pituitary tumor, etc). Although pituitary "exhaustion" has been postulated, the actual etiology is unknown.

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D. Associated Acquired Disorders

Certain acquired disorders appear to be more prevalent in Klinefelter patients than in the general population. While clinical hypothyroidism is uncommon in Klinefelter syndrome, a number of investigators have reported abnormalities in the hypothalamic-pituitary-thyroid axis in these patients. One of the initial reports of thyroid abnormalities was that of a low ^{131}I uptake in several individuals who were not clinically hypothyroid and who responded to exogenous TSH (60). Since the availability of the TRH test to assess pituitary responsiveness to the hypothalamic releasing hormone, several types of hypothalamic-pituitary abnormalities have been reported. One group noted an increased prolactin response to TRH in the presence of a normal basal level (61).

After testosterone therapy the degree of abnormality decreased but was still abnormal. TSH response in these individuals was normal. In a larger study of clinically euthyroid Klinefelter patients a decreased TSH response to TRH was consistently noted (62). The defect seemed to be less severe in patients on testosterone treatment. These authors interpreted the change as being secondary to the chronic hypergonadotropic state leading to functional hypoplasia of the pituitary TSH producing apparatus. This idea is given some support by similar findings in Turner syndrome and congenital anorchia patients (their unpublished observations) (62). Finally, there have been isolated case reports of clinical hypothyroidism with TSH deficiency, one associated with normal TRH response (hypothalamic hypothyroidism) (63) and one with lack of TRH-induced TSH secretion (64).

In several series there appears to be an increased incidence of diabetes mellitus (23,25). However, this may be due to the simultaneously reported increased family history of diabetes or to marked obesity that has been noted in 25-50% of the individuals in these same series. One report of an association of hypercholesterolemia and hypertriglycemidemia in 11 of 24 Klinefelter patients (23) has not been observed by others. A higher incidence of peptic ulcer has been noted in 2 series (22, 23). Pulmonary disease, usually fitting into the category of what we call chronic obstructive pulmonary disease, seems to be more common in Klinefelter patients, but this has not been examined in any one controlled series (65). One associated acquired disorder that most authors have noted is the presence of varicose veins. Some reports suggest that one-fourth to one-third of Klinefelter patients may have this problem (23,25). Since varicose veins are more common in women and Klinefelter patients have feminization due to decreased testosterone with normal (or increased) estrogen, this acquired disorder might be secondary to the hormonal abnormalities.

There are a number of isolated case reports of the association of Klinefelter syndrome and a variety of autoimmune and/or neoplastic disorders. There is probably no documented increase in association with any of these except breast cancer (66-70). In pooling series of cases of male breast cancer, 9 of 242 patients were sex chromatin positive (3.7%). This suggests that the incidence of breast cancer among patients with the Klinefelter syndrome is about one-fifth the incidence of breast cancer in women and about 20 times the incidence of breast cancer in normal men. The histological features of the breast cancer found is not different from that found in men without Klinefelter syndrome. The decreased androgen to estrogen ratio and the gynecomastia seem to be likely predisposing factors.

In summary, Klinefelter syndrome patients often have subtle abnormalities of thyroid function and probably have a greater frequency of obesity, pulmonary disease, and varicose veins. Although breast cancer is uncommon, the risk in these patients appears to be greater than in normal men.

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E. Mental Deficiency and Behavioral Disorders

When the ability to assess nuclear sex by the buccal smear became available, not only newborns but other groups were screened for the prevalence of chromatin positive males. Institutionalized mentally defective patients were screened in several countries (71-73). Based on a combination of series totaling almost 12,000 individuals, it is clear that the incidence of chromatin positive males is about 4 to 5 fold increased compared with the general population (about 0.85% vs. 0.20%) (22). However unlike the general population, only about two-thirds of these individuals were XXY or XY/XXY (the most common Klinefelter karyotypes).

More of the individuals with mental retardation have more than two X chromosomes and/or more than one Y chromosome. This is in keeping with the greater number of somatic abnormalities with increasing number of X chromosomes. Interestingly, there were very few mosaic XY/XXY patients in these groups, again suggesting that the presence of a normal XY cell line correlates with a less severe disorder. The prevalence of 47,XXY is higher among individuals with an I.Q. between 50-85 than among those with a lower I.Q. Still, most 47,XXY individuals have normal or nearly normal intelligence (74).

Klinefelter patients are often passive, poorly motivated and unable to complete their goals (75). Others have suggested that the feeling of inadequacy and inferiority may be a secondary result of the gynecomastia and testicular atrophy (76). Since most of the studies of personality traits of Klinefelter patients have utilized populations which included a large proportion of institutionalized individuals, it should not be assumed that all Klinefelter patients have personality defects. One type of psychiatric disorder, schizophrenia, has been claimed to occur with greater frequency among Klinefelter patients (77,78). Although there have been claims that Klinefelter patients may display inappropriately aggressive behavior when confronted with stressful situations, studies in which there was careful control of ascertainment could not demonstrate a significantly increased frequency of criminality in XXY individuals compared to XY men (79). Finally prospective studies in which early childhood development was evaluated in XXYindividuals identified at birth and followed through 6 to 9 years of age suggested that there were no inherent psychologic abnormalities and that prior reports of symptomatology may be the result of factors other than the chromosomal constitution (80).

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IV. CELLULAR ORIGIN OF ABNORMAL CHROMOSOME COMPLEMENTS AND PATHOGENESIS

A. Origin of XXY and XY/XXY

Although the XXY chromosomal constitution could theoretically arise either from meiotic nondisjunction or mitotic nondisjunction, most cases are thought to arise from a nondisjunction during meiosis (Fig 12). This uneven separation of the chromosomes results in either sperm with both an X and Y chromosome or ova with two X chromosomes. The evidence that meiotic nondisjunction can be maternal or paternal in origin has come from a study of X-linked genes utilizing primarily red-green color blindness and the Xg blood group (81,82). The existence of XY sperm has also been directly demonstrated (83). A listing of some of the matings that are informative for the Xg antigen is given in Table V. When evaluated this way the chromosome constitution in a given Klinefelter patient can sometimes be classified as being either $X^{m}X^{p}Y$ to indicate paternal nondisjunction or $X^{m}X^{m}Y$ to indicate maternal nondisjunction (22). In fact the abnormality can often be localized to the first or second meiotic division.

Figure 12

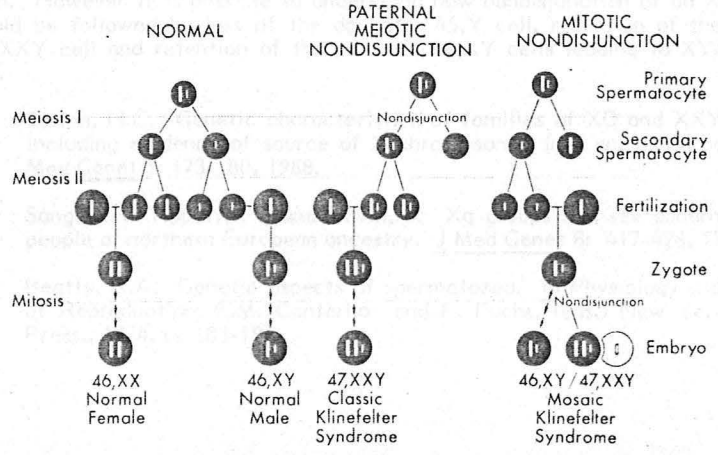

Table V. A List of Some Matings Informative for the X-Linked Antigen Xg (from Ref. 74)

Phenotypes			
Father	Mother	47,XXY	Probable origin of additional X
Xg(a+)	Xg(a+)	Xg(a-)	Maternal meiosis I (Mother heterozygous)
Xg(a+)	Xg(a-)	Xg(a-)	Maternal meiosis I or II
Xg(a+)	Xg(a-)	Xg(a+)	Paternal meiosis I

Using studies of this blood group and assuming no mitotic nondisjunction it has been estimated that approximately 40% of XXY individuals are $X^{m}X^{p}Y$ presumably resulting from an error at paternal meiosis I. 42% are $X^{m_1}X^{m_2}Y$, presumably resulting from an error at maternal meiosis I; and 18% were either $X^{m_1}X^{m_1}Y$ or $X^{m_2}X^{m_2}Y$, suggesting an error at maternal meiosis II (X^{m_1} and X^{m_2} refer to the two maternal X chromosomes which segregate at meiosis I). However, the frequency of both monozygotic and dizygotic twins has been reported to be increased in XXY individuals (22). This suggests that a single disruptive event was responsible for the twinning and nondisjunction and that postzygotic errors may be a more common etiology of XXY than is generally recognized.

In contrast to the classic XXY form of Klinefelter syndrome, the XY/XXY mosaics in general are thought to arise from mitotic nondisjunction or be a zygotic or postzygotic error (Fig 12). Studies of Xg blood groups suggest that the majority of Klinefelter mosaics are caused by mitotic nondisjunction in an XXY zygote (82). This might thus account for the apparently lower frequency of the mosaics in comparison to the classic Klinefelter since mosaics would of necessity result only from a mitotic nondisjunction superimposed on a meiotic nondisjunction. However it is possible to understand how nondisjunction of an XY embryo could be followed by loss of the daughter 45,Y cell, retention of the daughter 47,XXY cell and retention of the parental 46,XY cells leading to XY/XXY (Fig 12).

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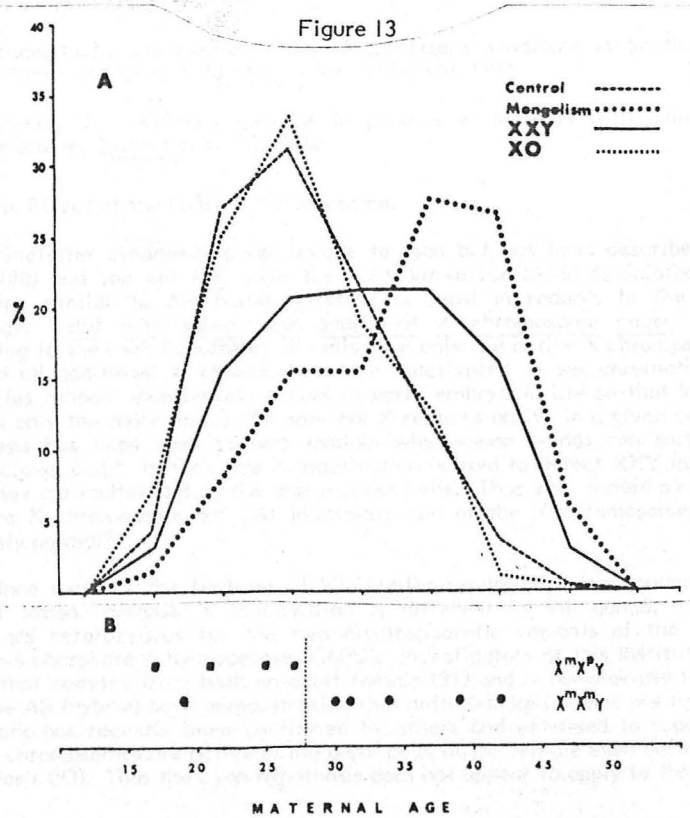
B. Factors that May Predispose to Nondisjunction

One group of investigators has reported a seasonal variation in the incidence of XXY conceptions to suggest an association with viral illnesses (84). Others have not been able to document this association and have in fact suggested that XXY individuals were more likely to be conceived in summer months (85). Studies in this country suggest that all races are affected (84), but a decreased frequency has been claimed for Indian and black South Africans (86). Some individuals have used the high incidence of diabetes mellitus in relatives of Klinefelter patients (see above) to suggest that diabetes might predispose to nondisjunction (87).

The one predisposing factor that has received the greatest attention is the maternal age effect. Fig 13A shows the distribution of maternal age in a control population and individuals with Down syndrome (mongolism), XXY, and XO Turner syndrome. The maternal age distribution among XO is almost identical to that of the control population (mean about 28 years) and contrasts markedly with the distribution in Down syndrome (mean 35 years). The XXY curve is almost characteristic of a normal distribution and suggests contributions from maternal age-dependent and maternal age-independent groups (22). With only a few informative studies by Xg typing, it appears that all of the individuals in whom the maternal age is increased are X^mX^mY (Fig 13 B).

Figure 13



A, The percentage distribution of maternal ages in XXY Klinefelter's syndrome (175 cases), compared with the distributions in XO Turner's syndrome (105 cases[34]), in mongolism (883 cases[33]) and in a control population.[83] *B*, The distribution of maternal ages in 4 X^mX^pY and 6 X^mX^mY patients.

As maternal age advances the risk of having both Down syndrome and Klinefelter syndrome together is increased. In 13 reported cases the mean maternal age was 42 years (22). The effect of high maternal age in nondisjunction is probably best explained by an aging effect on the ovum. In women the ova remain "resting" in the late prophase of the first meiotic division for anywhere from 12 to 50 years. Since spermatogenesis starts at puberty and spermatozoa are produced continuously throughout adult life, aging involves the resting spermatogonia only before they enter meiosis. It thus seems likely that aging damages the meiotic spindle mechanism and not the chromosomes, and it is confined to oogenesis because the critical period of the meiotic prophase is prolonged in the mother but not in the father.

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C. The Effect of the Extra X Chromosome.

Klinefelter syndrome is not unique to man but has been described in the mouse (88) and the cat (89) with the XXY karyotype being associated with a phenotype similar to the human disorder at least in regards to the gonadal pathology. But why should one additional X chromosome cause disease? According to the Lyon hypothesis all cells have only one active X chromosome and any and all additional X chromosomes are inactivated as sex chromatin bodies (90). This random inactivation occurs in early embryonic life so that in normal females only the maternal or the paternal X remains active in a given cell. This hypothesis has been used to help explain why human beings can survive this "genetic overload." In fact this X inactivation is used to detect XXY individuals by the sex chromatin test of the oral mucosa cells. Thus why should a male with an extra X chromosome not just inactivate one of the X chromosomes and be relatively normal?

Since most of the features of Klinefelter syndrome are secondary to the gonadal lesion, perhaps X inactivation is different in the gonad. Utilizing individuals heterozygous for the two electrophoretic variants of the X-linked glucose-6-phosphate dehydrogenase (G6PD), investigators at this institution have shown that oocytes from both an adult female (91) and a 16-week-old fetus (92) have the AB (hybrid) band demonstrating that both X-linked alleles are functional. This work has recently been confirmed by others and extended to suggest that both X chromosomes are active in the germ cells of the female even before entering meiosis (93). Thus the Lyon hypothesis does not appear to apply to the ovary.

But what about additional X chromosomes in the testis? There are no reports of the activity or inactivity of additional X chromosomes in the testis. However, several studies of the normal testis suggest that the single X chromosome is not active in the same way that it is in non-testicular tissue (94,95). Early condensation of the X chromosome in mouse spermatocytes is correlated with late replication (96) and apparent inactivation with cessation of uridine incorporation (97). In support of the idea that the X chromosome must be somehow less active in the testis is the fact that X-autosome translocations are often infertile (95,98). Perhaps the best evidence for this altered X activity in the testis is the study of the two forms of phosphoglycerate kinase (99). In a number of mammals including man all the somatic cells utilize the X-linked form of the enzyme while only in the testis and male germ cells has the alternate autosomally inherited isozyme been found. Finally, to suggest that the X chromosome might be unnecessary for normal testis function, one rodent species has completely eliminated the X chromosome from male germ cells at the stage of differentiation to definitive spermatogonia (100). Thus one might postulate that an additional X chromosome in the testis might be more than can be inactivated and thereby lead to the Klinefelter testicular lesion.

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100 Ohno, S., Jainchill, J., and Stenius, C. The creeping vole (Microtus oregoni) as a gonosomic mosaic. I. The OY/XY constitution of the male. Cytogenetics 2: 232-239 1963.

V. THERAPY

Individuals with Klinefelter syndrome who have a low serum testosterone and inadequate virilization can often have a dramatic improvement in virilization by the administration of exogenous testosterone (25). Facial and body hair increase and there is loss of the feminine countours of the body with increased muscular development. A long acting parenteral testosterone ester preparation (either testosterone cypionate or testosterone enanthate) should be given in a dose of 200 mg IM, initially at weekly intervals and subsequently at 2 to 3 week intervals to maintain a level in the normal range.

There is no suitable therapy for the azoospermia. When gynecomastia is severe and symptomatic, the only completely successful treatment is mastectomy. Although some individuals who are markedly testosterone deficient may have improvement in gynecomastia on androgen therapy (101), others may experience no change or even a worsening. The explanation offered for the worsening of gynecomastia in some patients on testosterone therapy is that with an increased transfer constant for peripheral conversion to estradiol (see above) the extra testosterone merely serves as substrate for formation of additional estrogen that "outweighs" the effect of the androgen.

101 Myhre, S.A., Ruvalcaba, R.H.A., Johnson, H.R., Thuline, H.C., and Kelley, V.C. The effects of testosterone treatment in Klinefelter's syndrome. J Pediat 76: 267-276, 1970.

VI. XX MALES (THE SEX REVERSAL SYNDROME) — A KLINEFELTER VARIANT?

A. Historical and Incidence

In 1964 there were two case reports of males with the 46,XX chromosomal constitution in all tissues examined (including the testes) and no evidence of mosaicism (102, 103). Since then over 50 phenotypic men with this chromosomal complement have been described. Cytogenetic studies of newborn males would suggest that this disorder is relatively uncommon with an incidence of about 1 per 10,000-15,000 births (9), less than one twentieth as common as the two most common Klinefelter karyotypes combined. Some series of Klinefelter patients have reported individuals with this karyotype accounting for 5% of the cases (104).

102 de la Chapelle, A. Hortling, H., Niemi, M. and Wennström, J. XX sex chromosomes in a human male. First Case. Acta Medica Scandinavica Suppl. 412: 25-38, 1964.

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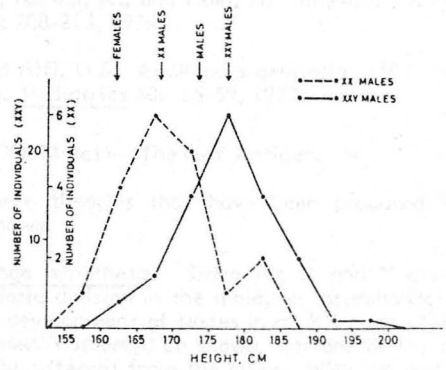
B. Clinical Features

The reason these individuals have been considered as a Klinefelter variant becomes obvious on reviewing the usual clinical features (105-107). By definition the general clinical appearance of these individuals is male. The testes are small and firm (usually less than 2 cm in length), and there is azoospermia with hyalinization of the tubules and absence of spermatogenesis seen on biopsy. Gynecomastia is frequent and facial, pubic and body hair is decreased, often with a feminine pattern. The serum testosterone is usually low with elevated gonadotropins and evidence of decreased Leydig cell reserve on hCG testing. Androgen-estrogen dynamics have not been studied. Thus XX males seem similar to XXY males in many respects.

However there are several clinical features in which these patients differ from the usual Klinefelter patient. The height of XX males is not increased (Fig 14) (105). The mean height of 19 XX males was 168.2 cm or almost 10 cm less than a typical population of XXY individuals ($p < .001$) and some 5 cm less than a population of XY men. These individuals do not have the increased lower body segment typical of Klinefelter syndrome.

Figure 14



Distribution of heights in 19 males with 46,XX and 73 males with 47,XXY (table 3). Arrows indicate mean values.

Unlike patients with Klinefelter syndrome, the incidence of XX males is not increased among the mentally retarded. Screening of 21,252 mentally retarded institutionalized men did not disclose a single XX male (105). If there were the same four to fivefold enrichment compared with the general population as seen in Klinefelter syndrome, 8 to 10 XX males would have been anticipated in this population. However, psychologic disturbances with "psychoasthenic" personality traits have been reported.

A third way in which XX males appear to differ significantly from the usual Klinefelter patient is in the development of the external genitalia. The majority of individuals have external genital development similar to Klinefelter patients, i.e. a normal scrotum and a penis that is usually normal in size with no greater incidence of hypospadias than the normal population (105). However, recent reports indicate that 10 of the 16 XX males diagnosed before age 15 have had penile abnormalities, most commonly hypospadias (often perineoscrotal) and/or chordee (108-110). In fact some of these individuals presented initially as problems in gender assignment. Thus XX males may have a greater frequency of developmental defects of the external genitalia. However, the number of individuals described is still relatively small.

105 de la Chapelle, A. Analytic review: Nature and origin of males with XX sex chromosomes. Amer J Hum Genet 24: 21-105, 1972.

106 Lyons, N.F. Karyotype 46,XX in a black male. S Afr Med J 48: 1847-1848, 1974.

107 Cullen, M., Greally, M., and Greally, J. The XX male syndrome — a case report. Clin Genet 10: 73-76, 1976.

108 de la Chapelle, A., Similä, S., Lanning, M., Kontturi, M., and Johansson, C-J. Two further males with female karyotypes. Humangenetik 11: 286294, 1971.

109 Miyashita, A., Isurugi, K., and Aoki, H. Infantile XX male: a case report. Clin Genet 10: 208-213, 1976.

110 Roe, T.F., and Alfi, O.S. Ambiguous genitalia in XX male children: report of two infants. Pediatrics 60: 55-59, 1977.

C. The Origin of XX Males — The H-Y Antigen.

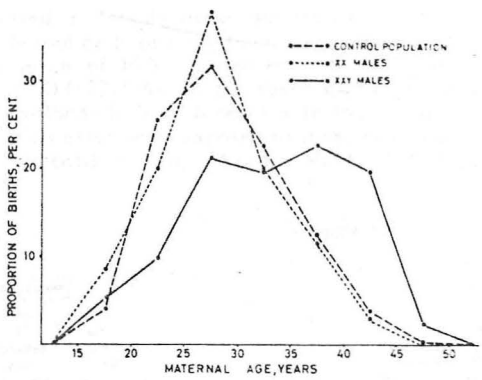
There are three theories that have been proposed to account for the occurrence of XX males:

X-Y interchange hypothesis. Since the X and Y chromosomes associate during the first meiotic division in the male, an interchange seems an attractive explanation for the development of testes in an XX male. Support for this hypothesis would be gained if it could be shown that one of the two X chromosomes were morphologically different from the other. With the development of banding

procedures and quinacrine fluorescence, attempts have been made to assess the presence of extra material on the X chromosome (105). Most studies have failed to document any difference in the two X chromosomes (111,112). However, two recent reports suggest instances in which an X-Y interchange seems a likely explanation for the origin of the XX male (113,114). In the first, extra material is present on one of the X chromosomes. In the second the X chromosomes were characteristic enough to attribute one from each parent based on comparison with the parents' X chromosomes, and the Xg (a+) allele had not been passed from the father to his son as expected. This suggests an interchange so that the X from the father contained the testis determining gene but had translocated simultaneously its Xg(a+) allele. It should be noted that the failure to find the brilliant fluorescence characteristic of the distal long arm of the Y chromosome does not disprove the interchange theory since this region of the Y chromosome does not contain testicular determinants. It thus seems likely that a portion of the XX males could arise from an X-Y interchange.

Mosaicism theory. According to this theory a Y chromosome may occur in small numbers of cells, in circumscribed areas, or may have occurred but has been eliminated. Evaluation for interphase Y chromatin in eight XX males examining over 14,000 cells did not lead to evidence of a Y. However, mosaicism confined to the testis still could be possible. Initially brightly fluorescent chromatin limited to Sertoli cells was taken as evidence for the presence of a Y chromosome. However, this now appears to be an artifact related to the peculiar fluorescence pattern of interphase Sertoli cell nuclei unrelated to a Y chromosome. In 4 XX males in whom as many as 500 cells or more per individual were examined cytogenetically, XXY mosaicism was demonstrated at less than a 1% level in one of the multiple tissues sampled in each individual (blood, skin, and/or testis) (105). Certainly this represents an extremely small proportion of cells with a Y chromosome and is of questionable significance. If all XX males have XX/XXY mosaicism, this would be inconsistent with the absence of a maternal age effect in XX males, which is different than Klinefelter syndrome (Fig 15) (105). Two interesting case reports suggest this mosaic possibility with loss of a Y chromosome. Two monozygotic twins who are XX males point to the idea that twinning and maternal nondisjunction, both frequent in XXY individuals, may be associated with some XX males (115). The other case report concerns a 15 year old XX male who at the age of 3 had a 46 XY karyotype on bone marrow culture but no Y-containing cells demonstrable in peripheral blood, bone marrow, skin, or testis at age 15 (116). This suggests a Y-containing cell line might be lost with time. The mosaicism theory would also account for some of the Xg blood group findings (82,117,118). In four family studies of Xg blood group in which the pattern is informative, it appears that unless an interchange has taken place both X chromosomes must have come from the mother. This suggests an XXY origin with loss of the Y line and is consistent with the Xg phenotype frequencies in 34 individuals which fits an XXY distribution better than the female distribution and much better than the male. However, caution must be exercised in interpretation of these frequencies since a relatively small number of individuals have been tested.

Figure 15



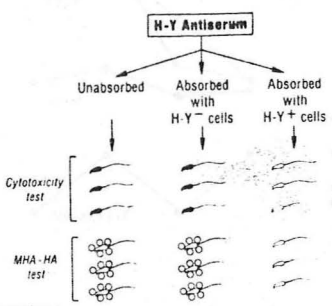
Distribution of maternal ages in a control population [77], in 35 XX males, and in 133 XXY males (table 8).

Mutant gene theory. The finding of the familial occurrence of this disorder in two instances with paternal transmission is suggestive of a gene effect (119, 120). An inherited X-Y translocation would seem unlikely in a family in which the gene has been passed from common ancestors through several generations with male to male transmission. A Y-autosome translocation is a possibility, but one would still predict a greater incidence of XX males in the pedigrees. This hypothesis involves mutations in postulated sex-determining autosomal genes or sex-determining mechanisms other than the chromosomal one. The idea of a mutant autosomal gene leading to XX males has precedence because such genes do occur in other species. Perhaps the best studied of these is the Sxr gene in mice (121). In this disorder an autosomal dominant gene causes XX males with a phenotype similar to the human disorder, i.e., small testes devoid of germ cells. Given the few individuals affected in the two families reported and the lack of consanguinity, we would have to postulate an autosomal dominant inheritance with variable expressivity for human XX males. In one of these families (119), the presence of an apparently abnormal sex ratio with increased numbers of males was supportive of two male determining factors, one on the Y chromosome and one due to the mutant gene. Since familial aggregates have been rare among XX males, the mutant gene theory has been felt to be an uncommon etiology for the disorder. However, if an autosomal dominant gene results in sterility, most affected individuals would result from new mutations since the fitness (reproductive) of the affected individuals is very low.

In summary all three theories offer explanatory potential for the origin of some XX males. The emergence of the H-Y antigen as a useful tool in evaluating Y chromosome testicular determinants has offered further insight into the phenomenon of XX males. The Y-linked histocompatibility (H-Y) antigen has been recognized as one of the minor histocompatibility antigens for some time. It was detected due to the unexpected phenomenon of male skin graft rejection by females of the same inbred mouse strain. The demonstration that humoral H-Y

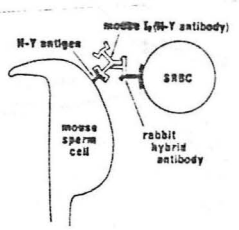
antibody can be raised in female mice and its cytotoxicity titrated on either spermatozoa or epidermal cells of male mice paved the way for the evaluation of the presence or absence of H-Y antigen on cells of other animal species by absorption tests (Fig 16) (122-124). In the absence of H-Y antigen on the cells to be tested, the H-Y antibody is free to react with the mouse sperm and kill them, or allow formation of rosettes when exposed to sheep red blood cells coated with a rabbit synthetic hybrid antibody (Fig 17) in the MHA.HA or mixed hemabsorption-hybrid antibody test.

Figure 16



H-Y typing by absorption. Cells were suspended in selected pools of diluted H-Y antiserum. H-Y⁺ cells absorb H-Y antibodies, thereby decreasing the ability of the antiserum to react with sperm. Positive absorption was manifested as a fall (i) in the number of sperm killed (stained with trypan-blue dye) in the cytotoxicity test and (ii) in the frequency of rosettes formed in the MHA-HA test (*44*).

Figure 17

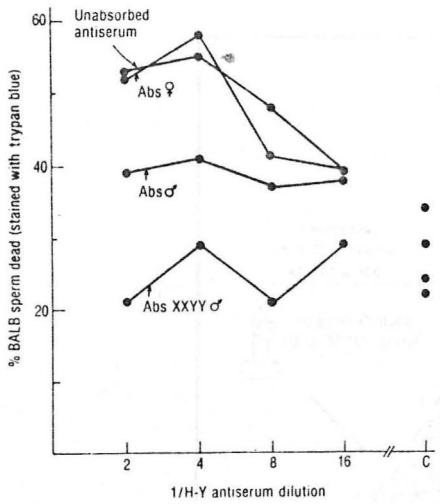


Binding of SRBC to sperm membrane in the MHA.HA test.

The presence of the H-Y antigen on the tested cell is then noted by a fall in the titer of the antibody that will react with the mouse sperm after absorption. The important discovery of Wachtel and his associates was the remarkable evolutionary conservation of the H-Y antigen in that male cells of all other mammalian species tested, including man, specifically absorbed H-Y antibody while female cells of these species possessed no cross-reacting plasma membrane components (125). In a number of disorders in man the presence of H-Y antigen seems to correlate with the presence of the Y chromosome and the development of the testis (126-128). It is unclear at present whether the Y chromosome carries the structural gene that codes for H-Y antigen or instead carries a regulatory gene that activates the structural gene for H-Y antigen on some other chromosome. In either case the Y chromosome activates testicular development by inducing the synthesis of H-Y antigen. Males with more than one Y chromosome express an increased amount of H-Y antigen as if they had a "double dose" from the two Y chromosomes (Fig 18) (126). That this antigenic expression is independent of androgen action is suggested by the presence of the antigen in patients who have testicular feminization with total failure of virilization due to androgen receptor deficiency (127). The occurrence of the antigen on eight-cell mouse embryos suggest that actual male differentiation is not required prior to its expression

(129). Limited mapping studies suggest the proximity of H-Y antigen and the testis-determining region on the short arm of the Y-chromosome (130). Studies in Sxr sex reversed mice and XX human males have shown the presence of apparently normal levels of H -Y antigen in both cases (Fig 19) (131-133).

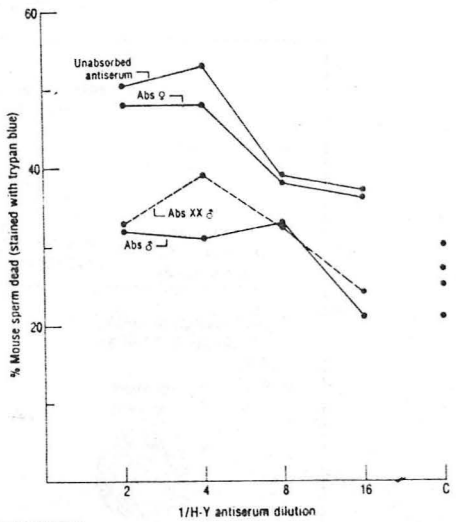
Figure 18



Cytotoxicity Tests on Mouse Sperm with Mouse H-Y Antiserum Absorbed with White Blood Cells from Females (XX) and Males (XY and XXYY).

Abs denotes absorption with cells of the indicated sex. Each point represents an average value from three separate tests. C denotes control (including complement, but not antiserum). Serum aliquots were read as coded samples.

Figure 19



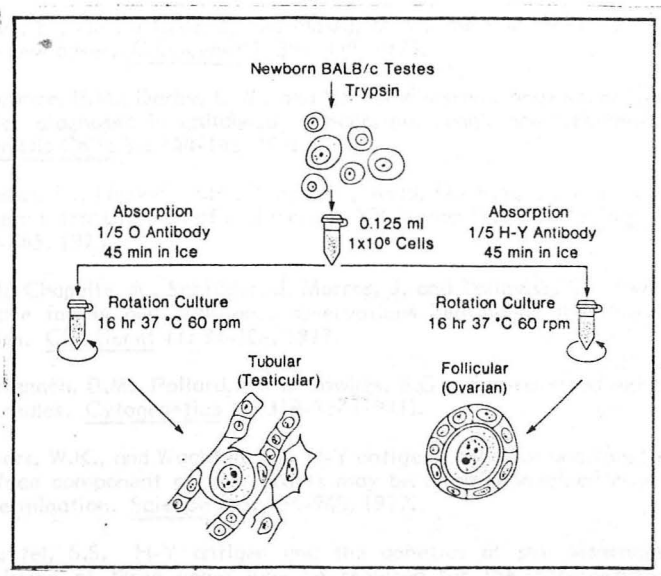
Cytotoxicity Tests on Mouse Sperm with Mouse H-Y Antiserum Absorbed with Leukocytes from Females (XX), Normal Males (XY) and XX Males (Cases 1-4).

Abs denotes absorption with cells of the indicated sex. Each point represents an average value from four separate tests. C denotes control (including complement but not antiserum). Control values are a background above which sperm-cell death is attributable to cytotoxic H-Y antibody and complement. Sperm-cell suspensions were read as coded samples.

The finding of H-Y antigen in four XX males suggests that at least the portion of the Y chromosome that determines testis formation is present in these individuals. Unfortunately, this is not necessarily incompatible with any of the three theories given for the origin of XX males except perhaps the mosaicism theory. It seems unlikely that the less than 1% mosaicism that has been detected in some XX males could account for "normal" levels of the H-Y antigen when it appears to have a demonstrable dosage effect in XYY males. None of the XX males from the two familial occurrences have been tested for H-Y antigen. Perhaps the antigen will be lacking in these individuals adding insight into the nature of the mutant autosomal gene.

If the H-Y antigen is the cell surface component that induces the organogenesis of the testis as proposed (134,135), then one would like some way to test this. Perhaps the most interesting data regarding this is the preliminary report of data to be published suggesting that mouse testis cells dissociated with trypsin and "stripped" of H-Y antigen by exposure to antibody reaggregate to something that resembles an ovarian follicle (Fig 20) (136).

Figure 20



Moscona type of reaggregation experiment in vitro performed on dissociated XY gonadal cells from newborn mouse testis. These cells, lysostripped of H-Y antigen, reorganized in vitro to yield ovarian follicle-like aggregates (right), whereas same cells retaining H-Y antigen readily reorganized seminiferous tubule-like aggregates.

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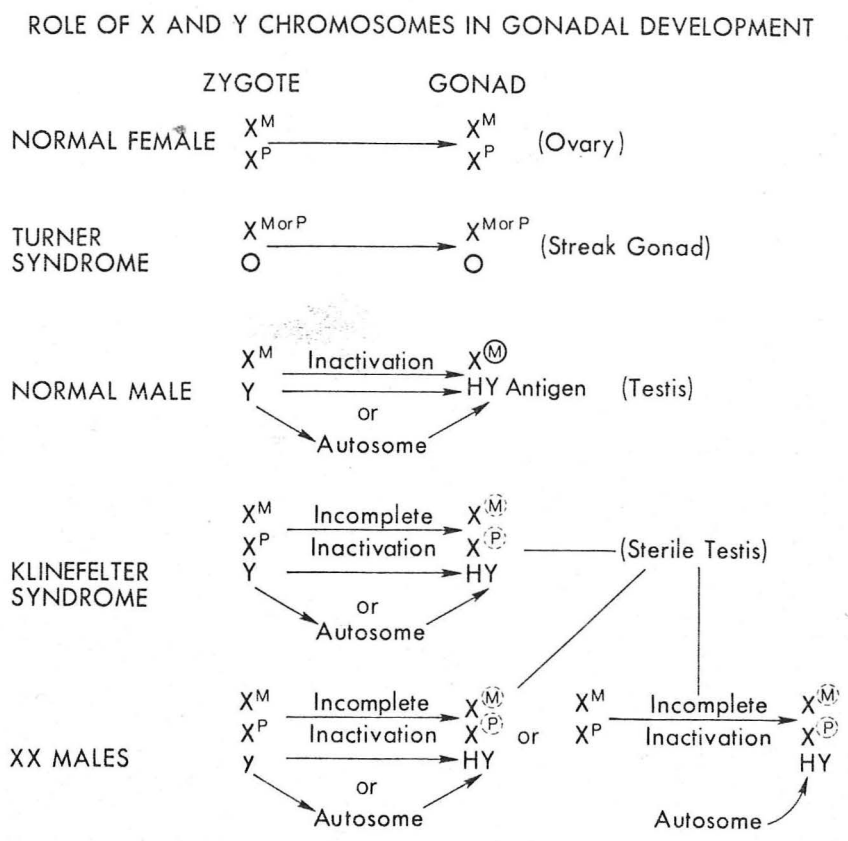
The overall schema for the role of the X and Y chromosomes and the H–Y antigen in the development of the gonad in the normal embryo and three disorders of sexual differentiation is summarized in Fig 21. In the normal female both X chromosomes are active to lead to normal ovarian development. In Turner syndrome the absence of one X chromosome leads to inadequate X material in the gonad and a resultant streak gonad. In the normal male the presence of the Y chromosome and the production of H–Y antigen (perhaps via an autosome) along with some X inactivation leads to a normal testis. The additional X material in Klinefelter syndrome is more than can be adequately inactivated and a sterile testis results. In XX males either a portion of the Y chromosome (y) is present and activates testicular development in the usual manner or there is a mutation in the autosomal locus so that it becomes constitutive and no longer requires activation from the H–Y activating gene. But again, a sterile testis results from the inability to inactivate both X chromosomes.

Figure 21


ROLE OF X AND Y CHROMOSOMES IN GONADAL DEVELOPMENT
ZYGOTE
GONAD
NORMAL FEMALE
X^M X^P
X^M X^P
(Ovary)
TURNER SYNDROME
$X^{M or P}$ O
$X^{M or P}$ O
(Streak Gonad)
NORMAL MALE
X^M Y
Inactivation
X^M
HY Antigen
or
Autosome
(Testis)
KLINEFELTER SYNDROME
X^M X^P Y
Incomplete Inactivation
X^M X^P HY
or
Autosome
(Sterile Testis)
XX MALES
X^M X^P y
Incomplete Inactivation
X^M X^P HY
or
Autosome
or
X^M X^P
Incomplete Inactivation
X^M X^P HY
Autosome