MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

9/26/68

GONADAL DYSGENESIS

CASES

[redacted] Gonadal Dysgenesis With Partial Virilization.

This 22 year old woman was admitted to the Gynecology Service in [redacted] of 1968. She was thought to be normal until the age of 10-11 when her extremities seemed to stop growing and she was noted to be shorter than her peers. She has had only three episodes of scanty bleeding - at ages 13, 16, and 21, although she has monthly cramping abdominal pain. During the past 5-6 years she has gained approximately 50 pounds in weight, developed increased hair growth over the chest, back, and arms, and developed acne over the face and shoulders. She had episodes during her early teens suggestive of petit mal epilepsy, and she either quit or was dismissed from school at the age of 16. The remainder of the history was noncontributory; her mother is 5' 8" in height, her father 5' 9". There is a history of diabetes in the mother's family.

Physical examination revealed a young, short, obese, hairy woman with a BP of 150/100, a height of 4' 11", and a weight of 188 pounds. There was acne over the face and shoulders, pubic and axillary hair, a rather spotty increase in hair over the chest, chin, and back, a small buffalo hump, and rudimentary breasts with widely spaced nipples. The cervix was not seen, and no cervix, uterus, or adnexa was palpable. The metacarpals were short. CBC and urinalysis were normal. The FBS varied from 164 to 181, and there was intermittent glycosuria. The buccal smear revealed a chromatin negative (male) pattern, and the karyotype was XO. The laboratory results are as follows:

24 hour urinary 17 ketosteroids - normal PBI = 7.5
urinary gonadotropins - elevated
muscle biopsy - normal capillary basement membrane
blood androstenedione - 0.4 mg% (3 X normal)
urinary 17 OH corticoids 32.2 and 31.5 mg/24 hours with normal dexamethasone suppression (3.6 after day 1 and 1.6 mg after day 2)

Plasma growth hormone
control - 0.2 mμg/ml
30 min. after insulin - 0.2 mμg/ml
60 min. after insulin - 1.0 mμg/ml

[redacted] Gonadal Dysgenesis With Multiple Congenital Abnormalities and Growth Failure.

This 16 year old girl was referred to the Eye Service of [redacted] on [redacted] 1968 with a diagnosis of congenital glaucoma. At the age of 8 she was seen by a pediatrician in [redacted] because of hematuria, and at that time she was found to have a "split kidney" on one side and hypertension, for which she has received Aldomet and Naqua. All subsequent urinalyses have been normal. She has never menstruated and

has been short (4' 5") all her life, at least one foot shorter than her siblings. At the time of admission she had a BP of 110/70, large eyes, no breast development, infantile external genitalia with no visible cervix and a small uterus, no murmurs, and a wide carrying angle of the arms. The CBC, BUN, and urinalysis were normal. The analysis of the buccal mucosa revealed a chromatin negative (male) pattern, and the karyotype revealed an XO pattern. IVP revealed duplication of the kidney on the right with a slight malrotation. The PBI was 5.4. The diagnosis by the eye service was that she had almost "burned-out" congenital glaucoma with marked enlargement of the right eye, exotropia, and disciform keratitis. On 8/16/68 she was begun on Dianabol 2.5 mg per day.

[redacted] Pseudo-Turner's Syndrome.

This 17 year old girl was first seen in the [redacted] in [redacted] of 1967 because of nonspecific abdominal pain, for which a diagnosis was never made but which went away spontaneously over a several month period. She had undergone menarche at age 15 and has regular periods with a normal flow at 28-30 day intervals. PE revealed normal vital signs, wide set eyes, marked webbing of the neck, a strikingly low hairline on the back of the neck, a high arched palate, severe pectus excavatum, and a wide carrying angle of the arms. The height was 5' 1", and the weight was 102 pounds. The breast development was within normal limits, and pelvic examination revealed a healthy appearing vaginal mucosa, a normal cervix and uterus, and no palpable adnexal masses. The PBI was 6.6. Chest X-ray, cervical spine series, and upper GI series were all within normal limits. Karyotype revealed 46 chromosomes in all cells studied, and the morphology of the X chromosome was thought to be normal. Four successive buccal mucosa preparations were all interpreted as demonstrating a negative (male) pattern.

REFERENCES

THE EVOLUTION OF THE MODERN VIEWS OF GONADAL DYSGENESIS

1. Hauser, G. A. Gonadal dysgenesis. Ch. in Intersexuality, C. Overzier, ed. New York Academic Press, 1963.

2. Turner, H. H. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinol. 23:566, 1938.

3. Albright, F., P. H. Smith, and R. Fraser. A syndrome characterized by primary ovarian insufficiency and decreased stature. Am. J. Med. Sciences 204:625, 1942.

While, as Hauser points out in his historical review, congenital ovarian deficiency has been repeatedly described in the clinical literature since the 18th century and although several excellent accounts of the syndrome were published in the German literature in the 1930's, there is no doubt that the important descriptions of the syndrome for science were those by Turner in 1938 and Albright and his co-workers in 1942. The syndrome which Turner described consisted of ovarian "infantilism", short stature, and multiple congenital anomalies - webbing of the neck, cubitus valgus, low posterior hair margin, and delayed closure of the epiphyses. Albright, Smith, and Fraser in assembling a somewhat larger series of patients with ovarian-lack confirmed the clinical characteristics described by Turner and made the important additional observations that urinary FSH excretion was high and consequently that the disease could not be secondary to pituitary deficiency, and that estrogen therapy leads to a normal amount of axillary and pubic hair and normal breast development.

4. Wilkins, L. and W. Fleischmann. Ovarian agenesis. J. Clin. Endocrinol. 4:357, 1944.

These authors studied the abnormal ovaries in some detail and concluded that the disease is due to failure of primordial cells to develop in the genital ridge. They also suggested that the growth defect is fundamental and not just due to a lack of ovarian hormones.

5. Polani, P. E., W. F. Hunter, and B. Lennox. Chromosomal sex in Turner's syndrome with coarctation of the aorta. Lancet 2:120, 1954.

6. Wilkins, L., M. M. Grumbach, and J. J. Van Wyk. Chromosomal sex in ovarian agenesis. J. Clin. Endocrin. 14:1270, 1954.

7. Polani, P. E., M. H. Lessof, and P. M. F. Bishop. Color blindness in ovarian agenesis. Lancet 2:118, 1956.

The first insight into the pathogenesis of this syndrome came with the recognition that the nuclear chromatin pattern in the vast majority of these patients is male and that the incidence of color blindness, an X-linked recessive defect, in these patients is the same as for men.

8. Jost, A. Problems of fetal endocrinology: The gonad and hypophyseal hormones. Rec. Prog. Hormone Res. 8:379, 1953.

9. Grumbach, N. M., J. J. Van Wyk, and L. Wilkins. Chromosomal sex in gonadal dysgenesis: relation to male pseudohermaphrodism and theories of human sex differentiation. J. Clin. Endocrinol. 15:1161, 1955.

The indirect evidence that most individuals with Turner's syndrome were genetic men, together with the demonstration by Jost that destruction of the gonads in embryos of either sex results in the development of a female infant, led most students of the problem to conclude that Turner's syndrome is due to the destruction of the gonad (either in a chromosomal man or woman) before differentiation of the gonad has been completed. The presence or absence of a Y chromosome could not be established, however, and several investigators thought it likely that the patients had an XO constitution.

10. Ford, C. E., K. W. Jones, P. E. Polani, J. C. de Almeida, and J. H. Briggs. A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). Lancet 1: 711, 1959.

That the number of chromosomes in many patients with this syndrome was 45 and that the missing chromosome was the second sex chromosome was established in this now classic paper by Ford and his colleagues in 1959. They concluded that this anomaly arose as the result of a chromosomal non-disjunction. It was also surmised from the color blindness data at hand that the non-disjunction likely occurred in the father rather than the mother. It became apparent almost immediately, however, that only about half of patients have an XO karyotype; the remainder have a diversity of chromosomal disorders, and within the succeeding years at least 15 different karyotypes have been described in this condition. Moreover, it is now apparent that the clinical spectrum is considerably more diverse than was originally believed.

THE SPECTRUM OF THE SYNDROME

Gonadal Dysgenesis (Turner's Syndrome)

11. De la Chapelle, A. Cytogenetical and clinical observations in female gonadal dysgenesis. Acta Endocrinol. Supp. 65, 1962.

12. Linsten, J. The Nature and Origin of X Chromosome Aberrations in Turner's Syndrome. Stockholm: Almquist and Wiksell, 1963.

13. Engel, E. and A. P. Forbes. Cytogenetic and clinical findings in 48 patients with congenitally defective or absent ovaries. Med. 44:135, 1965.

14. Jones, H., M. Ferguson-Smith, and R. Heller. The pathology and cytogenetics of gonadal agenesis. Am. J. Obstetrics and Gynecology 87:578, 1963.

15. Ferguson-Smith, M. A. Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. J. Med. Genetics 2:142, 1965.

16. Greenblatt, R. B., J. R. Byrd, P. G. McDonough, V. B. Mahesh. The spectrum of gonadal dysgenesis. Am. J. Obstet. Gynecol. 98:151, 1967.

In these five papers are summarized the clinical, endocrinological, and genetic findings in some 400 patients with gonadal dysgenesis. Approximately half of such patients are chromatin negative; the remainder have a wide spectrum of chromatin patterns. Essentially three types of chromosomal abnormalities occur: 1.) The second sex chromosome may be missing, 2.) The second sex chromosome (X or Y) may be morphologically abnormal, 3.) Either 1 or 2 may exist in only some cells of an individual - that is mosaicism may be present.

Psudo-Turner's Syndrome

17. Oikawa, K. and R. M. Blizzard. Chromosomal studies of patients with congenital anomalies simulating those of gonadal aplasia. N.E. J. M. 264:1009, 1961.

18. Baker, D. H., W. E. Bendor, A. Morishima, and F. Conte. Turner's syndrome and pseudo-Turner's syndrome. Am. J. Roentgenol. 50:40, 1947.

The clinical abnormalities associated with Turner's syndrome may also occur in phenotypic women with normal chromatin patterns, normal ovarian function, and normal chromosomes. These patients have a high incidence of congenital heart disease.

Turner's Syndrome in the Male

19. Hung, W., W. D. Marman, H. J. Wiggen, and C. Jacobson. Turner's syndrome in a 6-year old Negro boy. J. Urol. 92:317, 1964.

20. Heller, R. H. The Turner phenotype in the male. J. Pediat. 66:48, 1965.

21. Schoer, E. J. Diminished testicular function in 'male Turner's syndrome'. J. Clin. Endocrinol. 25:101, 1965.

The clinical syndrome can also occur in men. These patients may be either XY or Y mosaics; they have a wide diversity of gonadal development varying from normal to totally absent testes, and mental deficiency, cardiac abnormalities, and ocular defects are said to be more common in male than in female cases.

Pure Gonadal Dysgenesis

22. Harnden, D. G. and J. S. S. Stewart. The chromosomes in a case of pure gonadal dysgenesis. Brit. Med. J. 2:1285, 1959.

23. Brogger, A. and A. Strand. Contribution to the study of the so-called pure gonadal dysgenesis. Acta Endocrinol. 48:490, 1965.

24. Sohval, A. R. The syndrome of pure gonadal dysgenesis. Am. J. Med. 38:615, 1965.

25. Federman, D. D. Abnormal Sexual Development. Philadelphia, W. B. Saunders Co., 1967.

At one end of the spectrum is a small group of patients who have just the gonadal abnormality but are of normal height and show none of the stigmata of Turner's. This condition, "pure gonadal dysgenesis" is associated with normal or eunuchoidal height, female appearance, poor breast and vaginal development, primary amenorrhea, and pure Müllerian internal genitalia. This group of patients is striking for the high frequency of malignant gonadal tumors.

26. Bohner, F. A fertile female with XO sex chromosome constitution. Lancet 2:100, 1960.

27. Monardo, A. Gonadal dysgenesis in a woman after seventeen years of regular menses. Am. J. Obstetrics and Gynecology 91:106, 1965.

It has even been suggested that a less severe variant of the syndrome may manifest itself only as a premature menopause. This intriguing suggestion has been based on these two patients (both of whom are XO). One patient had a baby which was also XO; the other had a premature menopause associated with no other clinical abnormalities.

Mixed Gonadal Dysgenesis

28. Greenblatt, R. B. Clinical aspects of sexual abnormalities in man. Rec. Prog. Hormone Research 14:335, 1958.

29. Mellman, W. J., H. D. Klevit, W. C. Yacovoc, P. S. Moorhead, and E. Saksela. XO/XY chromosome mosaicism. J. Clin. Endocrinol. 23:1090, 1963.

30. Turner, H. H., R. B. Greenblatt, and H. Dominguez. Syndrome of gonadal dysgenesis and abdominal testis with an XO/XY chromosome mosaicism. J. Clin. Endocrinol. 23:709, 1963.

31. Atkins, L. and E. Engel. Absence of the Y chromosome (XO chromosome constitution) in a human intersex with an extraabdominal testis. Lancet 2:20, 1962.

32. Sohval, A. R. Hermaphroditism with atypical or mixed gonadal dysgenesis. Am. J. Med. 36:281, 1964.

Finally, there is a group of patients who overlap between Turner's syndrome and pseudohermaphroditism. They may have: 1.) an immature testis on one side and a streak on the other, 2.) unilateral gonadal agenesis, or 3.) a streak gonad on one side and a gonadal tumor on the other. The spectrum includes normal males, males with hypospadias, complete ambiguity of the external genitalia, females with clitoromegaly, normal females, and the Turner phenotype. Most reflect a degree of testicular competence in that the external genital primordia are masculinized. All have Müllerian-derived internal genitalia, and a few have Wolffian vestiges as well.

CHROMOSOMAL NONDISJUNCTION IN MAN

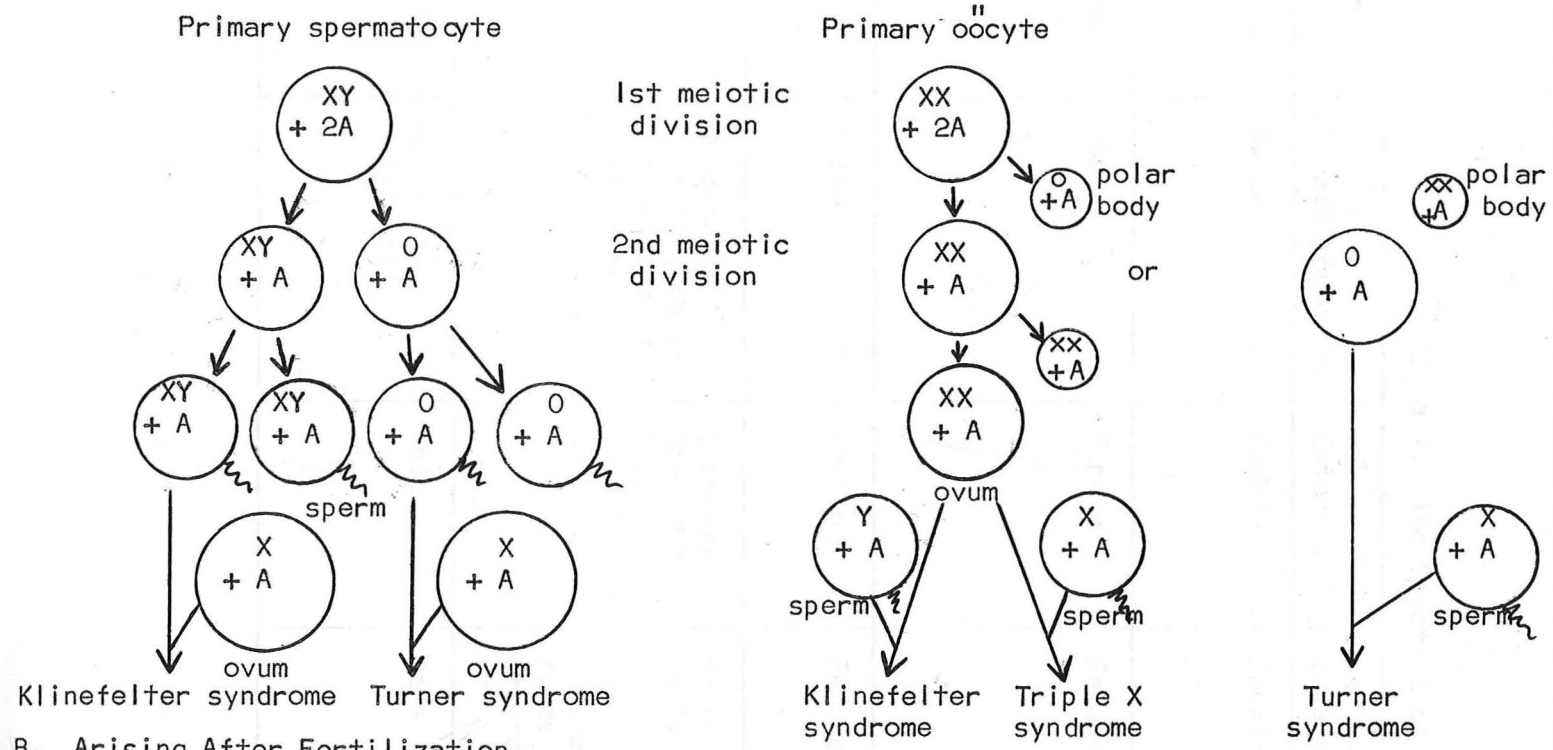
33. Ferguson-Smith, M. A. Chromosomes and human disease. Prog. in Med. Genetics 1:292, 1961.

34. McKusick, V. A. On The X Chromosome of Man. Washington, Am. Inst. of Biolog. Sci., 1964.

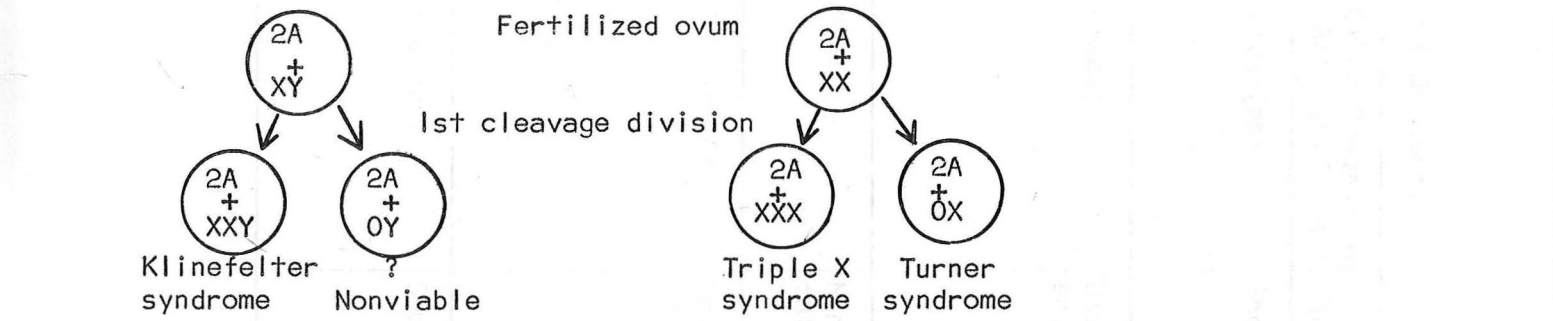
35. Fraccaro, M. and J. Linsten. The nature, origin, and genetic implications of structural abnormalities of the sex chromosomes in man. Sym. of Int. Soc. for Cell Biol. 3:97, 1964.
(Also Ref. 25)

ABNORMALITIES OF CHROMOSOME NUMBER

A. Arising Prior to Fertilization



B. Arising After Fertilization



ABNORMALITIES OF CHROMOSOME STRUCTURE

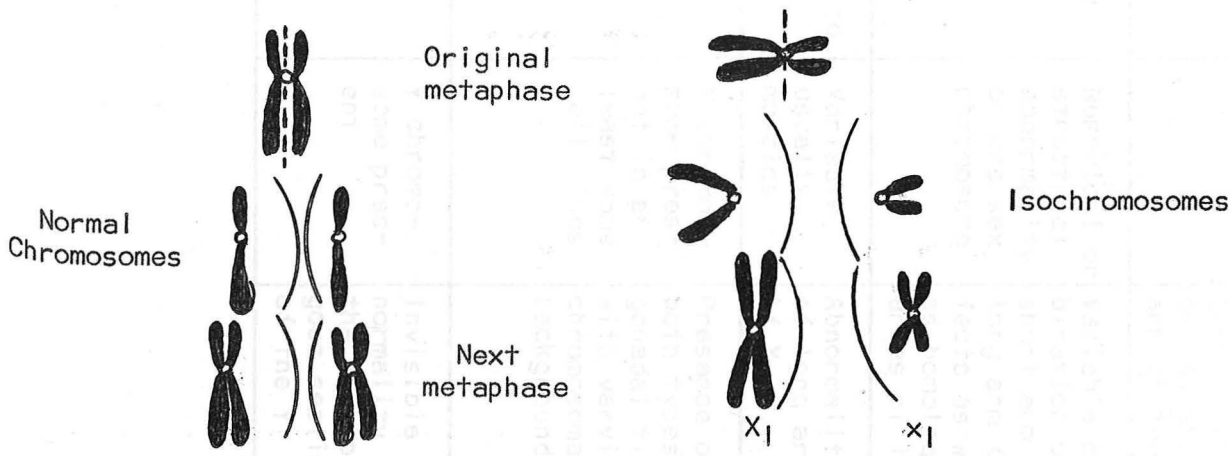


Table I. The Spectrum of Gonadal Dysgenesis

Type	Gonadal Function	Phenotype		Other Congenital Abnormalities	Height	Chromosomal Karyotype	Likely Defect
		External	Internal				
Pseudo-Turner's Syndrome	Normal	Female	Female	Invariably	Short	Normal XX	Invisible abnormality of the short arm of the X
Gonadal Dysgenesis (Turner's Syndrome)	Absent	Female	Female	Frequent	Usually short	Numerical or structural abnormality of one sex chromosome	Variable combination of short arm and long arm X defects as well as homologous areas of the Y
Pure Gonadal Dysgenesis	Absent	Female	Female	None	Normal to tall	Variable, usually mosaics	Abnormality of long arm of X
Mixed Gonadal Dysgenesis	No ovarian function, varying degrees of testicular function	Complete spectrum from normal male to normal female	Principally female; Wolffian derivatives may be present	In half of patients	Normal to short	Y chromosome present in at least some cell lines	Presence of both types of gonadal tissue with varying chromosomal background
Turner's Syndrome in the Male	Normal to deficient	Male	Male	Frequent	Short	Y chromosome present	Invisible abnormality of the homologous section of the Y

Table II. Relative Frequences of Certain Characteristics Found in 287 Patients With Gonadal Dysgenesis, Compared According to Karyotype, and Expressed as Percentage of Informative Cases Affected (Ref. 15)

	XO	XO/XX	XO/XX/XXX XO/XXX	XO/$XX_{|}$	$XX_{|}$	XO/$X\bar{\bar{x}}$	$X\underline{x}$	XO/$X\underline{x}$	XX	$Xx_{|}$	XS	XO/XS	XO/XY	XY(I)	XY(II)
Short stature	100	80	50	100	100	80	40	33	47	0	100	100	74	12	100
Shield chest	80	75	60	78	100	66	0	0	20	0	100	50	42	8	55
Webbed neck	54	16	25	9	18	20	0	25	13	0	0	14	21	0	91
Lymphoedema	39	12	0	5	0	0	0	0	22	0	0	25	0	0	40
Short metacarpal IV	58	44	50	47	100	0	0	25	40	50	100	33	0	0	25
Hypoplastic nails	77	55	50	87	0	25	0	25	25	0	100	75	0	0	50
Pigmented naevi	52	37	100	61	100	60	50	25	29	50	100	33	33	0	50
Congenital heart disease	21	7	0	5	0	0	0	0	10	0	0	0	0	0	75
Menstruation	8	21	17	5	9	0	20	33	47	0	0	0	0	0	-
Streak gonads	92	90	100	100	100	-	100	100	100	-	0	83	44	38	0
Testicular differentiation	0	0	0	0	0	-	0	0	0	-	100	17	55	58	100
Phallic hypertrophy	3	5	12	4	0	0	20	25	7	0	100	29	73	50	100
Other masculinization	0	3	0	0	0	0	0	0	0	0	100	0	45	62	100
Severe mental defect	8	6	12	0	10	0	0	25	0	0	0	29	5	0	18
No. of patients	117	38	8	23	12	5	5	4	15	2	2	7	22	16	11

Turner's syndrome ⟷ Pure Gonadal Dysgenesis ⟷ Mixed Gonadal Dysgenesis ⟷ Male Turner's

Key to Symbols:
XY(I)=phenotypic females with male pseudohermaphrodites with gonadal dysgenesis
XY(II)=phenotypic males with the 'male Turner syndrome'
$X_{|}$=presumptive isochromosome of the long arm of the X chromosome
$x_{|}$=presumptive isochromosome of the short arm of the X chromosome
$\underline{x}$=deletion of the long arm of the X chromosome
$\bar{\bar{x}}$=deletion of the short arm of the X chromosome
S=small abnormal sex chromosome

Abnormalities of chromosome number result from anaphase lag and can occur prior to or after fertilization. Abnormalities of chromosome structure result either from mis-division of the centromere (isochromosome formation), by breakage at the level of the centromere, followed by anaphase lag (deletion of either the short or long arm), or by breakage of the chromosome and abnormal repair (ring formation).

MAKING SENSE OF TURNER'S SYNDROME

36. Ferguson-Smith, M. A., D. S. Alexander, P. Bowen, R. M. Goodman, B. N. Kaufman, H. W. Jones, and R. H. Heller. Clinical and cytogenetical studies in female gonadal dysgenesis and their bearing on the cause of Turner's syndrome. Cytogenetics 3:355, 1964.

37. Leading Article. Making sense of Turner's syndrome. Lancet 2:529, 1965.

38. Egger, R. R. Making sense of Turner's syndrome. Lancet 2:1075, 1965.
Also see Ref. 11 through 16 and 35 and Tables I and II.

On the basis of correlations between the chromosomal and clinical pictures the working hypothesis has been proposed that the main variations in the clinical spectrum, apart from mosaicism, can be explained as follows:

1.) Deletion of the short arm of the X leads to a picture indistinguishable from classical Turner's syndrome.

2.) Loss of the long arm of the X leads to a streak gonad and amenorrhea but little or none of the short stature or other stigmata of Turner's syndrome.

3.) Loss of the portion of the Y chromosome which is theoretically analogous to a portion of the short arm of the X can lead to the clinical stigmata of Turner's syndrome with varying degrees of masculinization.

4.) Mosaicism and the variable severity of these structural defects result in merging of the various types into a continuous spectrum. Although this interpretation of the events is not without its critics (Ref. 38), at present it makes more sense than any other formulation of the relation between the chromosomal composition and the clinical picture.

Unfortunately, the classification of the individual patient may be difficult indeed, since a study of the karyotype of any individual patient is limited to the tissues examined, and one can never be certain that mosaicism does not exist in other tissues.

THE CLINICAL INTERPRETATION OF THE CHROMATIN PATTERN OF THE BUCCAL SMEAR AND PNN's

39. Moore, K. L., ed. The Sex Chromatin. Philadelphia, W. B. Saunders Co., 1966.

40. Klinger, H. P., J. Linsten, M. Fraccaro, I. Barroi, and Z. J. Dalinan. DNA content and area of sex chromatin in subjects with structural and numerical aberrations of the X chromosome. Cytogenetics 4:96, 1965.

It is quite clear that one X chromosome forms the Barr body in all peripheral cell lines of normal women, that the frequency of the barr body correlates well with the frequency of any mosaicism, and that the size of the Barr body correlates well with any structural defect which may be present. It is very likely that this heterochromic X is not totally inactive in genetic transcription as was previously thought.

41. Dakumov, S. E. and S. A. Spasov. Sex chromatin and sex hormones. Am. J. Obstet. and Gynecol. 97:714, 1967.

The mechanism of formation of the Barr body is still obscure. These investigators claim that its formation in part is under hormonal control; this mechanism is not likely to be fundamental to the problem since a normal Barr body is present in Klinefelter's syndrome.

FREQUENCY OF TURNER'S SYNDROME

42. Jacobs, P. A., D. G. Harnden, K. E. Buckton, W. M. Court-Brown, M. J. King, J. A. McBride, T. N. MacGregor, and N. Maclean. Cytogenetic studies in primary amenorrhea. Lancet 1:1183, 1961.

Approximately 28-43% of all patients with primary amenorrhea can be explained by chromosomal karyotyping.

43. Polani, P. E. Turner's syndrome and allied conditions. Brit. Med. Bull. 17:200, 1961.

While the exact incidence of gonadal dysgenesis is uncertain, most authors are agreed that approximately one out of 5000 adult women is affected, making it much less frequent than Klinefelter's syndrome.

44. Carr, D. H. Chromosome studies in spontaneous abortions. Chrom. Newsletter 12:7, 1964.

However, the absolute incidence is very likely a great deal higher. If as this author claims 3% of all spontaneous abortions are of the XO genotype, then it is likely that Turner's and Klinefelter's have the same frequency, but only a small fraction of Turner's patients survive gestation or to adulthood due to the high incidence of other congenital abnormalities which cause a major elimination of affected individuals.

45. Court-Brown, W. M., K. Buckton, P. A. Jacobs, I. M. Tough, E. V. Kuenssberg, and J. D. E. Knox. Chromosome Studies on Adults. Eugenics Laboratory Memoirs XLII, 1966.

Any interpretation of frequency based on karyotype alone must be carefully guarded. In this study of 1020 adults, in both men and women there is an increasing incidence of XO aneuploidy with age if one studies peripheral cells, reaching 1-2% in elderly men and 7% in elderly women.

EPIDEMIOLOGY AND ETIOLOGY OF GONADAL DYSGENESIS

46. Robinson, A. and T. T. Puck. Sex chromatin in newborns: presumptive evidence for external factors in human nondisjunction. Science 148:83, 1965.

47. Nichols, W. W. The role of viruses in the etiology of chromosomal abnormalities. Am. J. Human Genetics 18:81, 1966.

48. Day, R. W. The epidemiology of chromosome aberrations. Am. J. Human Genetics 18: 70, 1966.

While there is no relation between either paternal or maternal age and the incidence of gonadal dysgenesis (in contrast both to Down's and Klinefelter's syndromes) the distributions of the births are non-random in regard to time, space, and selected host characteristics, suggesting to many authors a viral etiology.

49. Mikkelsen, M., A. Froland, and J. Ellebjerg. XO/XX mosaicism in a pair of presumably monozygotic twins with different phenotypes. Cytogenetics 2:86, 1963.

50. Nance, W. and I. Uchida. Turner's syndrome, twinning, and an unusual variant of glucose-6-phosphate dehydrogenase. Am. J. Human Genetics 16:380, 1964.

There is apparently a significant increase in the frequency of gonadal dysgenesis in twins than would be expected on a random basis. Twinning possibly predisposes to chromosome loss during early meiotic cleavage.

51. Sparkes, R. S. and A. G. Motulsky. Hashimoto's disease in Turner's syndrome with isochromosome X. Lancet 1:947, 1963.

52. Williams, E. D., E. Engel, and A. P. Forbes. Thyroiditis and gonadal dysgenesis. N. E. J. M. 270:805, 1964.

53. Williams, E. D., E. Engel, P. D. Tait, and A. P. Forbes. Gonadal dysgenesis and ulcerative colitis. J. Med. Genetics 3:51, 1966.

54. Ferguson-Smith, M. A., J. R. Anderson, A. Froland, and K. G. Gray. Frequency of autoantibodies in patients with chromatin-positive Klinefelter's syndrome and their parents. Lancet 2:566, 1966.

55. Vallatton, M. B. and A. P. Forbes. Autoimmunity in gonadal dysgenesis and Klinefelter's syndrome. Lancet 1:648, 1967.

Three different groups of investigators have observed that there is a high incidence of "autoimmune" disorders in patients with gonadal dysgenesis and their parents - a relationship which is not true in Klinefelter's syndrome. This has suggested to some that autoimmunity might predispose to this type of nondisjunction.

56. Fialkow, P. J. Autoimmunity and chromosomal aberrations. Am. J. Human Genetics 18: 93, 1966.

Lymphocyte extracts from patients with "autoimmune" disorders but not from normal people cause remarkable hyperploidy when added to their own fibroblasts - the only experimental evidence, weak though it is, for an autoimmune basis for the chromosomal nondisjunction.

THE ASSOCIATED CONGENITAL DEFECTS

57. Haddad, H. M. and L. Wilkins. Congenital anomalies associated with gonadal aplasia. Pediatrics 23:885, 1959.
Also Ref. 1, and 11-16 and Table III.

The variety of congenital abnormalities which occurs in gonadal dysgenesis - and particularly the XO syndrome - is now so extensive that it includes almost every known malformation. Unfortunately, there is no recent compendium of the incidence of the extrasexual defects, and these figures are almost certainly too high because the previous means of ascertainment was almost entirely the XO stigmata, and all associated anomalies are less frequent in the other varieties of the disease.

Table III. Non-sexual Abnormalities in 55 Cases of Gonadal Aplasia (Haddad and Wilkins)

Short Stature	55	Keloid formation	10
Shield-like Chest	46	Aortic coarctation	8
Overweight	40	other cardiovascular abnormalities	5
Cubitus Valgus	34	Mental Retardation	8
Abnormal Facies	32	Intestinal telangiectasis	3
high palate	28	Deafness	3
micrognathia	21	Eyes	11
epicanthal folds	18	Strabismus	5
low set ears	14	Exophthalmus	1
Webbed Neck	27	Coloboma	1
Abnormalities of Nails	27	Cataract	1
Osteoporosis	24	Retinitis pigmentosa	1
Pigmented Moles	20	Neck	38
Idiopathic hypertension	14	Webbed	28
Lymphedema	13	Short broad neck	8
Cutis laxa	10	Spina bifida	2

58. Lemli, L. and D. W. Smith. The XO syndrome: a study of the differentiated phenotype in 25 patients. J. of Pediatrics 63:577, 1963.

Several abnormalities - shortness of stature, broad chest, congenital lymphedema, a low posterior hair line, prominent ears, narrow arched palate, abnormal fingernails, and a small mandible - occur with such frequency in the XO syndrome (each above 80%) that it allows for recognition at all ages. Less severely affected individuals are not diagnosed until after the amenorrhea becomes apparent.

59. Forbes, A. P. and E. Engel. The high incidence of diabetes mellitus in 41 patients with gonadal dysgenesis and their close relatives. Metab. 12:428, 1963.

The function of the endocrine organs other than the ovary deserves some comment. In addition to a high frequency of Hashimoto's Thyroiditis, there is also a remarkable incidence of diabetes, approaching 50% of all patients who live past the age of 40. Other endocrine organs - pituitary and adrenal - are normal and have normal reserve.

60. Levin, B. Gonadal dysgenesis. Clinical and roentgenologic manifestations. Am. J. Roentgenol. 87:1116, 1962.

61. Kosowicz, J. The carpal sign in gonadal dysgenesis. J. Clin. Endocrinol. 22:949, 1962.

62. Levin, J. and H. S. Kupperman. Skeletal abnormalities in gonadal dysgenesis. Arch. Int. Med. 113:730, 1964.

While many of the X-ray findings are nonspecific two - abnormally short metacarpals and deformity of the median femoral and tibial condyles - are almost pathognomonic.

63. Henkin, R. I. Abnormalities of taste and olfaction in patients with chromatin negative gonadal dysgenesis. J. Clin. Endocrinol. 27:1436, 1967.

Individuals with Turner's syndrome have a heightened sense of smell in comparison with normal women.

THE NATURE OF THE GROWTH ARREST

64. Acheson, R. M. and G. A. Zampa. Skeletal maturation in ovarian dysgenesis and Turner's syndrome. Lancet 1:917, 1961.

Wilkins' deduction many years ago that the short stature is a fundamental part of the syndrome was very likely correct. As the age increases the lag of skeletal maturation also increases.

65. Fraccaro, M., C. A. Gemzell, and J. Linsten. Plasma level of growth hormone and chromosome complement in four patients with gonadal dysgenesis. Acta Endocrinol. 34: 496, 1960.

66. Filipsson, R., J. Linsten, and S. Almquist. Time of eruption of the permanent teeth, cephalometric and tooth measurement and sulfation factor activity in 45 patients with Turner's syndrome with different types of X chromosome aberrations. Acta Endocrinol. 48:91, 1965.

As measured by a bioassay technique, the serum level of growth hormone is normal or high.

67. Forbes, A. P., J. G. Jacobsen, E. L. Carroll, and M. M. Picket. Studies of growth arrest in gonadal dysgenesis: response to exogenous human growth hormone. Metab. 11: 56, 1962.

68. Almquist, S., K. Hall, S. Linstedt, J. Linsten, R. Luft, and H. E. Sjoberg. Effects of short term administration of physiological doses of human growth hormone in three patients with Turner's syndrome. Acta Endocrinol. 46:451, 1964.

Exogenous growth hormone has normal effects on the retention of nitrogen, phosphorous, magnesium, sodium, potassium, and chloride. It has apparently never been tried for long periods in order to determine whether growth would be promoted.

69. Willemse, C. H. A patient suffering from Turner's syndrome and acromegaly. Acta Endocrinol. 39:204, 1962.

Despite the presence of acromegaly this young woman did not show continued longitudinal growth, and the epiphyses did not close.

All of these findings are in favor of the hypothesis that growth hormone is not deficient but are compatible with the possibility of insensitivity of the bones to growth hormone.

THE TREATMENT OF THE SHORT STATURE

70. Lisser, H., L. E. Curtis, R. F. Escamilla, and M. B. Goldberg. The syndrome of congenitally aplastic ovaries with sexual infantilism, high urinary gonadotropins, short stature, and other congenital abnormalities. J. Clin. Endocrinol. 7:665, 1947.

71. Sosnowski, J. R. Factors to be considered in the treatment of ovarian agenesis. Am. J. Obstet. Gynecol. 78:792, 1959.

72. Schumacher, O. P. Do patients with Turner's syndrome grow with estrogen therapy? Clin. Res. 12:357, 1964.

73. Vogt, J. H. The treatment of retarded growth in Turner's syndrome. J. Norske Laegeforen 86:1401, 1966.

74. Whitelow, M. J., S. F. Thomas, W. Graham, J. N. Foster, and C. Brock. Growth response in gonadal dysgenesis to the anabolic steroid norethandrolone. Am. J. Obstet. Gynecol. 84:501, 1962.

Very few careful studies have been done on the effects of hormone replacement on the growth, and no study is designed with the proper controls. Most authors feel that estrogen which is so important for adequate development of the secondary sex characteristics does not influence the ultimate height. Three authors (69, 71, 72) feel that testosterone or other anabolic steroids in small dosage does cause a growth spurt of about 10 cm if given prior to estrogen therapy. It should be emphasized that all that can be concluded for certain is that these treatments probably do not hinder growth.

THE TUMOR PROBLEM

75. Dominguez, C. J. and R. B. Greenblatt. Dysgerminoma of the ovary in a patient with Turner's syndrome. Am. J. Obstet. Gynecol. 83:674, 1962.

76. Brin, A. D. and J. S. Scott. Mixed gonadal dysgenesis with XX/XY mosaicism. Lancet 1:1035, 1965.

77. Teter, J. and R. Tonlowski. Tumors of the gonads in cases of gonadal dysgenesis and male pseudohermaphroditism. Am. J. Obstet. Gynecol. 79:321, 1960.

78. Warner, J. C., B. Enkman, S. Cheatum, and G. Holman. Hilus cell adenoma in a dysgenetic gonad with XX/XO mosaicism. Lancet 2:141, 1964.

79. Fine, G., R. C. Mellinger, and J. N. Canton. Gonadoblastoma occurring in a patient with familial gonadal dysgenesis. Am. J. Clin. Path. 38:615, 1962.

80. Taylor, H., R. H. Banter, and C. B. Jacobson. Neoplasma of dysgenetic gonads. Am. J. Obstetrics Gynecol. 96:816, 1966.

81. Goldberg, M. B. and A. L. Scully. Gonadal malignancy in gonadal dysgenesis: papillary pseudomucinous cyst adenocarcinoma in a patient with Turner's syndrome. J. Clin. Endocrinol. 27:341, 1967.

While ovarian carcinoma is probably rare in XO individuals (the few case reports may have actually represented undetected mosaics), tumors in XY individuals and in XY mosaics are considerably more common - either dysgerminoma or gonadoblastoma. In view of the blurring of the various phenotypes, a useful guide, if present, is evidence of virilization, which all authors are agreed is a frequent sign of gonadal tumor in gonadal dysgenesis. Whether this alone is a sufficient criteria for exploration or whether all ascertained XY individuals or all patients with definite evidence of gonadal function should be explored is uncertain at present.