MEDICAL GRAND ROUNDS

Parkland Memorial Hospital October 12, 1961

THE SEXUALLY ABNORMAL MALE

Case Reports

Case 1. Chromatin-positive Klinefelter's syndrome:

This 23 year old male was seen for infertility. He had small testes since birth but assumed a normal male gender in a sexually satisfactory marriage. Erection and ejaculation occur with ease, but no pregnancies have resulted after 3-1/2 years without contraceptive precautions. He shaves daily, but the beard is scanty.

On physical examination, the testis were atrophic and only 1.5 cm. in length. No semen were found in the ejaculate. Gonadotropin assay was 176 mμ/24 hour. The patient's I.Q. was 95. The buccal smear was positive and the testicular biopsy revealed marked fibrosis of small tubules and large masses of interstitial cells.

Case 2. Chromatin-positive Klinefelter's syndrome:

This 18 year old was found to have small testes during a pre-induction physical examination. His development was only slightly slower and less masculine than an older brother who is a jet test pilot.

The patient was 6'2" tall and had small firm testes. The buccal smear was positive, gonadotropin assay = 80 mμ, I.Q. = 106. No sperm were in the ejaculate, but a few areas of complete spermatogenesis were seen in the testicular biopsy.

Case 3. Delayed puberty:

This 17 year old has become concerned over his lack of sexual development with no change noted since the appearance of some axillary and pubic hair at 14.

His testes were normal in size and consistency. No ejaculate could be produced. The gonadotropin assay was 10 mμ/24 hours. Testicular biopsy was essentially normal.

Case 4. Isolated gonadotropin deficiency:

This 19 year old has noted almost no secondary sexual development, although no such delay had been experienced by others in his family.

The testes were about 1 cm in length, no ejaculate could be produced and testicular biopsy revealed marked immaturity of all components. Gonadotropin assay was less than 5 mμ/24 hr. on 3 different specimens. Thyroid and adrenal function was normal.

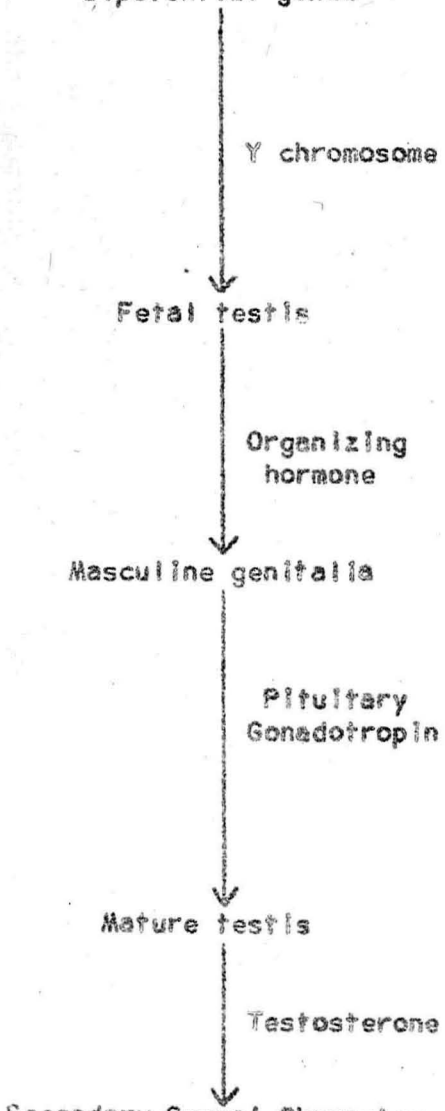
Case 5. Panhypopituitarism:

This 20 year old was found to have small testes. Though he complained of some fatigue, he had begun basic training without difficulty. He had received "hormone shots" at age 17 because of slow sexual development.

The testes were 2 cm in length and no Leydig cells could be seen in the biopsy specimen. Tubular size was less than normal and no spermatogenesis was evident. Gonadotropin excretion was below 5 mμ/24 hour and tests of thyroid and adrenal function revealed low values with brisk rises after stimulation. The sella was not enlarged.

SCHEME OF NORMAL SEXUAL DEVELOPMENT IN THE MALE

ABNORMALITY DUE TO DISTURBANCE AT EACH STAGE OF DEVELOPMENT (Partially Conjectural)



Type Abnormality	Clinical Syndrome
Presence of both XX and XY	True hermaphrodism
Complete absence of Y	Ovarian agenesis (Turner's) — XO or XX/XO
Major deletion of Y	Female pseudohermaphrodism (except congenital adrenal hyperplasia and iatrogenic)
Partial deletion of Y	Male pseudohermaphrodism
Excess X's (including mosaics)	Klinefelter's syndrome
Failure of germ cells to migrate into testis	Germinal cell aplasia
Deficiency of fetal testicular hormone	Male pseudohermaphrodism (testicular feminization)
Hypothalamic failure to stimulate pituitary release of gonadotropin	
Temporary	Delayed puberty
Persistent	Froehlich's syndrome Laurence-Moon-Biedl syndrome
Deficiency of pituitary gonadotropin	Panhypopituitarism Isolated gonadotropin deficiency Malnutrition
Abnormal androgen production	Testicular feminization Feminizing tumors Male climacteric "Fertile eunuch"
Acquired testicular disease usually affecting only spermatogenesis	Orchitis — mumps, leprous, tuberculous Radiation injury Cryptorchidism Trauma Unknown: "False" Klinefelter syndrome

1. Polani, P.E. Sex chromosomes and sex anomalies. Brit. Med. Bull. 16:80, 1960.
An excellent review of the author's opinion on the male-determining property of the mammalian Y chromosome. Discusses also studies involving the mechanisms by which abnormal numbers of sex chromosomes appear, and demonstrates an increase in certain anomalies after irradiation.

2. Grumbach, M.M. Some considerations of the pathogenesis and classification of anomalies of sex in man. Clinical Endocrinology, ed. by Astwood, E.B. Grune & Stratton, New York, 1960.
A good review, although somewhat incomplete, since it was written last year.

3. Turner, C.D. General Endocrinology, 3rd Edition, W.B. Saunders, Philadelphia, 19[illegible]
Excellent review of all but the very recent information on sexual differentiation and development.

4. Jost, A. Problems of foetal endocrinology. Recent Prog. Hormone Res. 8:379, 19[illegible]
Differentiation of the gonads begins at about the 6th week. If tested develop, a unilaterally active "organizentic" secretion causes the internal genitali to become male in type. If ovaries develop, or if the male fetus is castrated, development is along feminine lines. Therefore, the fetus has an inherent tendency to feminize, and this tendency must be counteracted by unilaterally active testicular hormones.

(These experimental findings are accepted as the basis for the development of a feminine phenotype in patients without functioning gonads, i.e. gonadal agenesis or Turner's syndrome)

Chromosomes and their abnormalities

5. Lennox, B. Chromosomes for beginners. Lancet 1:1045, May 13, 1961.
Highly recommended as the most lucid, concise presentation of the subject.

6. Griboff, S.I. and Lawrence, R. The chromosomal etiology of congenital gonadal defects. Am. J. Med. 30:544, April 1961.
A good, though highly inferential, discussion. The authors' manner of presenting previously postulated ideas as their own has led to a counterattack by the British (Stewart, J.S.S. Lancet 1:825, April 9, 1960). The British claim to almost every significant recent advance in the field is well founded.

Many of the theoretical concepts put forth by Griboff and Lawrence may prove correct. Until now, the chromosomal studies have been extremely gross and only until newer technics for resolving the genetic makeup of the chromosomes are available will much further progress be made.

7. Sohval, A. R. Recent progress in human chromosome analysis and its relation to the sex chromatin. Am. J. Med. 31:397, Sept. 1961
An overly comprehensive review with an excellent glossary. A bit of editing would have helped make the paper more palatable for general consumption.

8. Hirschhorn, K. and Cooper, H. L. Chromosomal aberrations in human disease, Am. J. Med. 31:442, Sept. 1961.

The induction of chromosomal aberrations in the human by irradiation has been suggested.

9. Tough, et al. X-ray-induced chromosome damage in man. Lancet 2:849, 1961
Definite abnormalities after therapeutic irradiation (250 rads to the spine) and suggestive changes after RAI therapy of thyrotoxicosis.

10. Boyd, E., et al. Damage to chromosomes by therapeutic doses of radioiodine. Lancet 1:977, 1961
Transient abnormalities after ablative doses (100 mc) of RAI.

The Role of the Y Chromosome

The following reports have substantiated the role of the Y in male-differentiation of the embryonic gonad. Regardless of what else may be present (including 4 X chromosomes) the individual is phenotypically male if most of the Y (including the centromere) is present.

11. Ferguson-Smith, M.A. et al. Lancet 2:184, July 23, 1961
Two patient's with Klinefelter's syndrome and severe mental retardation with an XXXY sex chromosome constitution.

12. Muller, O.J. et al. Lancet 2:78, July 8, 1961
An XXXXY patient - male and mentally retarded.

13. Muldal, S. and Oakey, C. H. Lancet 2:601, Sept. 9, 1961
A small deletion of the long arm of the Y found in 3 males with hypospadias.

If, however, the Y is absent (XO) or only a small fragment is present (X"y"), the individual is a female. In all probability, the larger the Y fragment, the more masculinization. The genes responsible for differentiation of the primordial gonal into a testis must be near the centromere of the Y.

If no Y is present (XO), the individual is female, but since 2 Xs are needed for normal ovarian development, the gonads are undeveloped and Turner's syndrome eventuates.

14. Ford, et al. Lancet 1:711, 1959.
The first demonstration of the XO composition of chromatin-negative Turner's syndrome.

15. Vaharu, T., et al. Lancet 1:1351, June 17, 1961
A little girl with Turner's syndrome and an enlarged clitoris, presumably related to the presence of a small fragment of the Y

16. Conen, P. B., et al. Lancet 2:294, Aug. 5, 1961
Another instance of a partially masculinized female with Turner's syndrome and an XO/X"y" mosaic pattern.

Genes other than those responsible for male differentiation of the primordial gonad may also be present on the Y.

17. Tanner, et al. Lancet 2:141, Aug. 22, 1959
Inferential evidence that genes on the Y are responsible for the retardation in physical development in normal young male compared to the female.

18. Gates, R.R. the human chromosome newsletter, Number 3, p. 17.
The gene for hairy ears is almost certainly on the Y.

The Nature of the Sex Chromatin Body

19. Barr, M. L. and Bertram, B. G. A morphological distinction between neurones of the male and female, etc. Nature 163:606, 1949.
The demonstration of a chromatin body, present in the female, absent in the male. Thereafter, this body was found in 40 to 80% of all somatic cells of the female, and in less than 5% of male cells. (Recent work, using better staining technics, reveals that these bodies are never found in male cells. Maclean, et al, Lancet 2: 406, Aug. 19, 1961).

20. Barr, M.L. Sex chromatin and phenotype in man. Science 130: 679, Sept. 18, 1959
Beautiful summary of previously accepted mechanisms of intersex and the author's original belief that the sex chromatin body is formed by heterochromatic regions of two X chromosomes.

21. Ohno, S. and Makino, S. The single-X nature of sex chromatin in man. Lancet 1:78. Jan. 14, 1961.
Proof that the body represented a single X-chromosome.

22. Stewart, J.S.S. and Sanderson, A.R. Sex-chromatin body in normal human testis. Lancet 1:77, Jan. 14, 1961
The finding of chromatin bodies in 10% of testicular germ-cell nuclei during early prophase supports the view that the body is derived from heterochromatic portion of a single X.

23. Stewart, J. S.S. Genetic mechanisms in human intersexes. Lancet 1:825, Apr. 9, 1960.
Suggests that the heterochromatin of one X is needed for and engaged in metabolic business of the cell and therefore not stainable. The heterochromatin of other X is superfluous, functionally inert and therefore stainable.

24. Editorial. More chromosome anomalies. Lancet 2:191, July 23, 1960.
Proposes that all Xs are naturally heterochromatic, but a single set of autosomes is sufficient to supress heterochromaticity in one X (A shrewd guess, since next reference not published until year later?)

25. Book, J.A. and Santesson, B. Nuclear sex in triploid XXY human cells. Lancet 2:318, Aug.5, 1961
On basis of finding in patient with extra set of autosomes (66), XXY sex chromosomes and no sex chromatin bodies, suggest that formation of body depends on balance between sex chromosomes and autosomes. This reasoning supposes the presence of sex-determining factors in the autosomes.

26. Grumbach, et al. On the sex chromatin etc. Acta Endocrinol. 35 (Supp.51): 633, 1960
Widely quoted as evidence against previously quoted references, but a mistake. Two patients with "XO" Turner's found to have chromatin bodies, but later, one (and probably by now the other) was shown to be a XX/XO mosaic.

Hypogonadism in the Male-Clinical Considerations

General:

27. Kaplan, N.M. and Norfleet, R.G. Hypogonadism in young men. Ann.Int.Med. 54:461, Mar., 1961.
Not bad for a beginning. Based upon the findings in "normal" young men, with a surprisingly high incidence of chromatin-positive (true) Klinefelter's syndrome. Note the normal intelligence of this group.

28. Wilkins, L. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. ed. 2. C. C. Thomas, Springfield, 1957.
The best textbook presentation of hypogonadism, based upon a tremendous patient experience. This book and the last 3 years of Lancet will make an authority of anyone.

29. Ryan, R.J. Male hypogonadism. Disease-a-Month, March, 1961.
A prosaic presentation hardly worth the trouble.

True hermaphroditism (both ovarian and testicular tissue)

13. Hirschhorn, K., et al. A case of true hermaphroditism with mosaicism of type XY/XO. New England J. Med. 265:1046, 1961.

31. Ferguson-Smith, M.A., et al. The chromosome complement in true hermaphrodism. Lancet 2:126, July 16, 1960.

Since these two cases (and others) have been found to have only XX, suggest possibility of translocation of Y.

Male Pseudohermaphrodism (testes and an XY complement)

Reference No. 13.

32. Kaplan, N.M. Male pseudohermaphrodism. New England J. M.

The first (and only?) case following estrogen administration to the mother during pregnancy. This may have been fortuitous.

33. Chu, E.H.Y. et al. Karyotypic Analysis of a Male Pseudohermaphrodite with the Syndrome of Feminizing testes. J.Clin.Endocrinol. 20:1608, Dec.1960

Two hypotheses of genetic transmission: sex-linked recessive or sex-limited autosomal dominant.

Male "Turner's Syndrome"

34. Chu, E.H.Y., et al. Chromosome complement in a case of the "male Turner syndrome". Lancet 1:786, Apr. 15, 1961

The chromosomal count has been 46 with XY in all reported cases of this rare syndrome of phenotypic males with variers stigmata of Turner's syndrome. The defective testes suggest a partial deletion of the Y - see Griboff and Lawrence, Reference No. 6.

Klinefelter's Syndrome

35. Nelson, W.O. Sex differences in human nuclei with particular reference to Klinefelter's syndrome, etc. Acta Endocrinol. 23:227, 1956.

On the basis of Jost's experimental findings and the sex chromatin examination, the theory of cortico-medullary imbalance was proposed as the basis for the various intersexes. Klinefelter's was presumed to result from failure of the cortical (ovarian) component and development of the medullary (testicular) component in genetic females.

(Such a theory could explain the facts as known until 1959.)

36. Jacobs, P.A. and Strong, J.A. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature 183:302, Jan. 31, 1959.

Using recent improvements in direct chromosomal counting, the bone marrow cells of a chromatin-positive Klinefelter's were found to have an XXY complement. This finding led to the presently held concept that the Y chromosome is male-determining. Presumably, the presence of an extra X (genic imbalance) leads to a deficiency of germ cells within the testes and this in turn is responsible for the other manifestations of the syndrome.

Other chromosomal abnormalities, including mosaicism, all with at least 2 Xs and 1Y, have been found with chromatin-positive Klinefelter's. See references 7, 8, 11, and 12 and Muldal and Ockey, Lancet 2:492, Aug.27, 1960 (An XXYY)

A number [illegible] has been proposed [illegible] characterized by [illegible] have it.

Skeletal pathology

[illegible] Endocrinol., 73:47 July 1972.
The relevance of this cause for sterility in normal dysgenic men is unknown.

Seminal pathology

Subsequent [illegible]

[illegible] Society meeting, [illegible].
An attempt to analyze [illegible] abnormal sperm.

Endocrinopathies

[illegible] Isotopes [illegible] of gonadotropin secretion [illegible] of thyroid testing.

[illegible] thyroid hypocitolinemia [illegible] against the assumption that adrenal deficiency will not be present even with severe hypothyroidism.

Sterility caused by antibodies

[illegible] Comparison with this syndrome in the male, [illegible] agrees with Gleason that this is "far more common [illegible] males". An extremely doubtful conclusion, probably based on a selected patient population.

Malnutrition

[illegible] Metroff, V. M. The starvation state and [illegible] hypothalamus. J.A.M.A. 183:1145, Aug. 2, 1963.
A good resume of the "functional" [illegible] may occur with prolonged malnutrition. References [illegible] with starvation.

Male Climacteric

[illegible] Editorial. Is there a male climacteric? J.A.M.A. [illegible] Yes, it is rare.

Sterile Eunuch

[illegible] McCullough, F. P. et al. A syndrome of eunuchoidism with spermatogenesis, etc. J. Clin. Endocrinol. 13:499, May, 1953.
Little further has appeared about this peculiar syndrome, possibly related to a selective ICSH deficiency.

Hypogonadism

45. Ward, B. and Hewett, W.M. The [illegible] Ann. 9, 1900
[illegible] 19,2 had cryptorchidism [illegible] 4.0% at 11, but only 1.2% at 4-7.

46. Brunet, J. et al. Management of the undescended testicle. Brit. M. [illegible] June 14, 1958.
A rather optimistic view about gonadotropin therapy, in part due to the inclusion of many cases that would right themselves spontaneously.

47. Bergstrom, R. G. and [illegible] Treatment of bilateral cryptorchidism [illegible]
Out of the 74 boys successfully treated with HCG, after the age of [illegible] this probably represents the expected result when the spontaneous cures are excluded.

48. Charny, C.W. The spermatogenic potential of the undescended testis before and after treatment. J. Urol. 83:647, May 1960.
A damning report on all therapy, but most of all, orchidopexy.

"False" Klinefelter Syndrome

49. Nelson, W. O. The "Klinefelter syndrome". Fertil. & Steril. 8:497, 1957.
Questions the need for separation of these patients with chromatin-negative testicular fibrosis into a distinct syndrome. Subsequent events have supported Nelson's view.

Gynecomastia

50. Jung, F.T. and Shatton, A.L. The mammary gland in the normal adolescent male. Proc.Soc.Exp. Biol. and Med. 33:455, Dec. 1935.
Mammary enlargement seen most prominently in 14 year olds, but most frequently (100%) in 16-17 year olds.

51. Hall, P. F. Gynecomastia, in Clinical Endocrinology. ed. by E.B. Astwood. Grune & Stratton, New York, 1960.
A complete but frequently confusing and occasionally incorrect discussion.

52. Zubiran, S. and Gomez-Mont, F. Endocrine disturbances in chronic human malnutrition. Vitamins & Hormones 11:97, 1953.
Gynecomastia seen in 20% of 256 patients with malnutrition on admission, but in almost every case during recovery.

53. Treves, N. Gynecomastia. Cancer 11:1083, Nov. 1958
Look at the pictures, but don't bother with the text.

Gynecomastia

Conditions associated with gynecomastia

A. Physiologic
   1. Neonatal
   2. Pubertal
   3. Due to drug- or other stimulation
   4. Involution of senescence (elderly)
   5. Drug intake
      a. estrogens
      b. methyltestosterone (rare and in special cases only)
      c. chorionic gonadotropin
      d. digitalis (rare)
      e. reserpine (rare)
      f. radioiodine therapy of thyrotoxicosis (rare)
      g. DDD
   6. Hereditary

B. Pathologic
   1. Hypogonadism of testicular origin
      a. Klinefelter's syndrome
      b. Associated with myotonia dystrophica
      c. Associated with X-L.A. disease (traumatic paraplegia, hemiplegia etc.)
      d. orchitis (rare)
   2. Estrogen-producing tumors
      a. testicular
         1) embryonal carcinoma
         2) choriocarcinoma
         3) seminoma
      b. adrenal carcinoma
      c. pituitary tumors; rarely reported in males (chromophobe adenoma), usually with acromegaly
   3. Liver disease, in particular Laennec's cirrhosis (rare with pancreatitis)
   4. Hyperthyroidism; reported in about 20 patients
   5. Bronchogenic carcinoma, usually along with osteoarthropathy
   6. Severe malnutrition, possibly related to liver dysfunction or testicular involution

GLOSSARY

Acrocentric: an irregular member of chromosomes 13, 14, 15, 21, 22 (centromere near the end; obfuscation)

Autosome: a non-sex chromosome

Centromere: the constriction where the two arms of the chromosome (chromatids) are joined.

Chromatid: one arm of a chromosome

Chromatin: the dark-staining material within the cell nucleus and chromosomes. A clump of this is seen along the nuclear membrane in cells with 2 X chromosomes (normal female). If the cells have "sex chromatin" body, they are chromatin-positive; if not, chromatin-negative.

Chromosome: aggregates of nuclear chromatin formed before cell division and carrying the genes.

Gene: the structural units of heredity, arranged at points (loci) along the chromosome.

Heterochromatin: chromatin within a chromosome that stains differently. Responsible for the staining of the X chromosome that is seen as the sex chromatin body.

Idiogram: a diagram of the karyotype

Karyotype: a non-diagramed idiogram.

Meiosis: the type of cell division by which the germ cells starting with 46 chromosomes produce sperm and ova with 23.

Mitosis: ordinary cell division, producing exact duplicates of the original.

Mosaic: (same as chimera); cells with different chromosome make-up within the same individual

Non-disjunction: failure of the parts of the chromosome to split during cell division.

Phenotype: the external appearance of the individual; i.e. male or female.

Translocation: transfer of a broken piece of a chromosome to another chromosome.