MEDICAL GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL
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HEREDITARY MALE PSEUDOHERMAPHRODITISM

I. NORMAL SEXUAL DEVELOPMENT

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- B. Gonadal Sex
- C. Phenotypic Sex
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- A. Errors in Genetic Sex
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- C. Errors of Phenotypic Sex
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      - 1. Defective Androgen Synthesis
      - 2. Defective Androgen Action
    - b.) Failure of Mullerian Regression
  - 2.) Familial Female Pseudohermaphroditism
  - 3.) Familial Defects of Wolffian-Mullerian Development

HEREDITARY DISORDERS OF SEXUAL DEVELOPMENT IN MAN CLASSIFIED IN TERMS OF THE SITE OF ACTION OF THE ABNORMAL GENE DURING EMBRYOGENESIS

A. ERRORS OF GENETIC SEX

No monogenic disorders have been identified to date

B. ERRORS OF GONADAL SEX

Familial True Hermaphroditism
Sex Reversal Syndrome
Pure Gonadal Dysgenesis, Familial XX Type
Pure Gonadal Dysgenesis, Familial XY Type

C. ERRORS OF PHENOTYPIC SEX

1.) FAMILIAL MALE PSEUDOHERMAPHRODITISM

a.) Defective Virilization

1. Defective Androgen Synthesis
   - Desmolase Deficiency
   - 3β-Hydroxysteroid Dehydrogenase Deficiency
   - 17-Hydroxylase Deficiency
   - 17-Ketosteroid Reductase Deficiency

2. Defective Androgen Action
   1. Testicular Feminization, Complete and Partial Types
   2. Incomplete Male Pseudohermaphroditism, type I
      - Gilbert-Dreyfus Syndrome
      - Lubs Syndrome
      - Reifenstein Syndrome
      - Rosewater Syndrome
   3. Incomplete Male Pseudohermaphroditism, type II
      - Familial Pseudovaginal Perineoscrotal Hypospadias

b.) Defective Mullerian Duct Regression
- Persistent Mullerian Duct Syndrome

2.) FAMILIAL FEMALE PSEUDOHERMAPHRODITISM

- 21-Hydroxylase Deficiency
- 11-Hydroxylase Deficiency

3.) FAMILIAL DEFECTS OF WOLFFIAN-MULLERIAN DEVELOPMENT

- Rokitansky-Kuster-Hauser Syndrome
- Cystic Fibrosis

The subject under consideration today has stemmed from two converging interests in our laboratory for the past several years - investigation into the mechanisms of androgen action at a cellular level and puzzlement at a clinical level as to the pathogenesis of abnormal sexual development in a variety of states. These disorders of sexual development in man are the result of disturbances in the physiology of sexual differentiation during embryogenesis. Such errors may be genetic or nongenetic in origin, and because of our own clinical experience it is the hereditary types of such abnormalities that will be the principal focus of our discussion. In approaching the subject of the hereditary causes of abnormal human sexual development, it is useful to consider briefly the mechanisms by which sexual differentiation takes place in the normal.

I. NORMAL SEXUAL DEVELOPMENT

1. Patten, B. M., Human Embryology. 2d Ed., 1953, McGraw-Hill, London.

2. Beatty, R. A. Genetic basis for the determination of sex. Phil. Trans. Roy. Soc. Lond. B. 259:3, 1970.

3. Jost, A. A new look at the mechanisms controlling sex differentiation in mammals. Johns Hopkins Med. J. 130:38, 1972.

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

5. Wilson, K. M. Correlation of external genitalia and sex-glands in the human embryo. Contributions to Embryology, No. 91, Vol. 18, 1926.

6. Gillman, J. The development of the gonads in man, with a consideration of the role of fetal endocrines and the histogenesis of ovarian tumors. Contributions to Embryology, No. 210, Vol. 32, 1948.

Normal sexual development in embryos consists of three sequential processes. The first involves the establishment of genetic sex. This is determined by the sex chromosome constitution established at the time of fertilization. In the mammal, the heterogametic sex (XY) is male, and the homogametic sex (XX) is female. In the second step, genetic sex is translated into gonadal sex. By an as yet undetermined series of events the genetic information determines that an indifferent gonad differentiates into a testis in the male or an ovary in the female. The final process, the translation of gonadal sex into phenotypic sex, is the direct consequence of the type of gonad formed. In the development of phenotypic sex, indifferent internal and external genital anlage are converted either to a male or female form.

The internal genitalia arise from the Wolffian and Mullerian ducts that exist side by side in early embryos of both sexes. In the male, the Wolffian ducts give rise to the epididymis, vas deferens, and seminal vesicles. In the female the fallopian tubes, uterus, and upper vagina are derived from the Mullerian ducts. In contrast to the internal genitalia, which develop from different anlage in the two sexes, the external genitalia and urethra develop from common anlage - the urogenital sinus, the genital tubercle, and the genital folds and swelling. The urogenital sinus gives rise in the male to the prostate and prostatic urethra and in the female to the lower two thirds of the vagina and urethra. The genital tubercle is the origin of the glans penis in the male and the clitoris in the female. The urogenital swelling becomes the scrotum or the labia majora, and the genital folds develop into the labia minora or the shaft of the penis.

7. Jost, A. Recherches sur la différenciation sexuelle de l'embryon de lapin. Arch. d'Anat. Microsc. 36:271, 1946-47.

8. Jost, A. Problems of fetal endocrinology: The gonadal and hypophyseal hormones. Rec. Progr. Horm. Res. 8:379, 1953.

9. Jost, A. Embryonic sexual differentiation (morphology, physiology, abnormalities). Ch. 2 in Hermaphroditism, Genital Anomalies & Related Endocrine Disorders, Eds. H. W. Jones, Jr. & W. W. Scott. 1958. Williams & Wilkins, Baltimore, p. 15.

10. Jost, A. The role of fetal hormones in prenatal development. In Harvey Lectures, Series 55. 1961. Academic Press, New York & London, p. 201.

11. Jost, A. Gonadal hormones in the sex differentiation of the mammalian fetus. In Organogenesis, Eds. R. L. DeHaan & H. Ursprung. 1965. Holt, Rinehart & Winston, New York, p. 611.

12. Jost, A. Steroids and sex differentiation of the mammalian foetus. In Proc. 2d Internat. Congr. on Hormonal Steroids, Milan, May 1966. Eds. L. Martini, F. Fraschini & M. Motta. 1967. Internat. Congr. Ser. #132, Excerpta Medica Found., Amsterdam, p. 74.

13. Jost, A. Modalities in the action of androgens on the foetus. In Research on Steroids, Proc. 3d Meeting of the Internat. Study Group for Steroid Hormones, Vol. III. Eds. C. Cassano, M. Finkelstein, A. Klopper, C. Conti. 1968. North-Holland Publ. Co., Amsterdam, p. 207.

14. Jost, A. Hormonal factors in the development of the male genital system. In The Human Testis, Proc. Workshop Conf., Positano, Italy, April 1970. Eds. E. Rosemberg & C. A. Paulsen. 1970. Plenum Press, New York-London, p. 11.

15. Jost, A. Hormonal factors in the sex differentiation of the mammalian foetus. Phil. Trans. Roy. Soc. Lond. B. 259:119, 1970.

16. Jost, A. General outline about reproductive physiology and its developmental background. In Mammalian Reproduction, Colloq. der Gesellschaft fur Biologische Chemie, Mosbach/Baden, April 1970. Springer-Verlag, New York-Heidelberg-Berlin, p. 4.

17. Jost, A., B. Vigier, and J. Prepin. Freemartins in cattle: The first steps of sexual organogenesis. J. Reprod. Fert. 29:349, 1972.

The control over the processes that eventuate in phenotypic sex resides in the action of three fetal hormones. Two of the three hormones - Mullerian regression factor and testosterone - are secretory products of the fetal testis.

18. Josso, N. Interspecific character of the Mullerian inhibiting substance: Action of the human fetal testes, ovary, and adrenal on the fetal rat Mullerian duct in organ culture. J. Clin. Endocrinol. 32:404, 1971.

19. Josso, N. Permeability of membranes to the Mullerian-inhibiting substance synthesized by the human fetal testis in vitro: A clue to its biochemical nature. J. Clin. Endocrinol. 34:265, 1972.

20. Josso, N. Evolution of the Mullerian-Inhibiting activity of the human testis. Biol. Neonate 20:368, 1972.

Mullerian regression factor is as yet a partially characterized secretory product of the embryonic testis, possibly a macromolecule of > 15,000 M.W. The Mullerian regression factor acts in male embryos to suppress the Mullerian ducts and consequently to prevent development of the uterus and fallopian tubes in the male.

21. Wilson, J. D., and I. Lasnitzki. Dihydrotestosterone formation in fetal tissues of the rabbit and rat. Endocrinol. 89:659, 1971.

22. Wilson, J. D. Testosterone uptake by the urogenital tract of the rabbit embryo. Endocrinol. 92:1192, 1973.

23. Siiteri, P. K., and J. D. Wilson. Testosterone formation and metabolism during male sexual differentiation in the human embryo. J. Clin. Endocrinol. In Press.

Testosterone promotes virilization of the urogenital tract in two ways. It acts directly to stimulate the Wolffian ducts to induce development of the epididymis, vas deferens, and seminal vesicle, and it acts as a prohormone for the third fetal hormone - dihydrotestosterone. Dihydrotestosterone, which is not secreted by the fetal testis in appreciable quantities, is formed in the urogenital tract by enzymatic reduction of testosterone. Dihydrotestosterone acts in the urogenital

sinus to induce formation of the prostate and in the genital tubercle, swelling and fold to cause formation of the male external genitalia.

In the absence of the two testicular hormones, as in the normal female or in male embryos castrated prior to the onset of phenotypic differentiation, the development of phenotypic sex proceeds along female lines. Thus, masculinization of the fetus is the positive result of action by testicular hormones while development of the female phenotype appears to be a passive process that does not require the action of a hormone made in the fetal gonad. Under normal circumstances the development of the sexual phenotype conforms ultimately to the chromosomal or genetic sex. That is, genetic sex dictates the gonadal sex, and gonadal sex in turn determines phenotypic sex.

II. CAUSES OF ABNORMAL SEXUAL DEVELOPMENT

A disturbance at any step of this developmental process may be reflected clinically as a disorder of sexual development. There are four known mechanisms by which an abnormality in human sexual development may arise: first, by an environmental insult such as the ingestion of a virilizing drug during pregnancy; second, by a non familial aberration in one of the sex chromosomes as in the Turner and Klinefelter's syndromes; third, by a developmental birth defect of multifactorial etiology as in most cases of hypospadias; and fourth, by an hereditary disorder due to a single gene mutation such as the testicular feminization syndrome.

III. HEREDITARY DISORDERS OF SEXUAL DEVELOPMENT IN MAN

It is this last category of single gene disorders that will be the focus of this review. These disorders are of prime clinical and investigative importance. Identification of the underlying biochemical lesion in each of these hereditary syndromes may ultimately provide the insights necessary to unravel the complexities of how genes act in regulating sexual differentiation and how sex hormones regulate gene expression. It is clear that therapeutic intervention in the disorders depends in a major way upon such insight.

24. Goldstein, J. L., and A. G. Motulsky. Genetics and endocrinology. Ch. 25 in Textbook of Endocrinology, Ed. R. H. Williams. In Press. W. B. Saunders Co., Philadelphia.

25. Goldstein, J. L., and J. D. Wilson. Hereditary disorders of sexual development in man. In Press.

At least 16 simply inherited disorders of sexual development have been described. All previous classifications of these disorders have been based upon phenotypic characteristics of the various syndromes. However, as the result of studies done in this department on the various forms of male pseudohermaphroditism and of a detailed family study of a large kindred of affected individuals, Dr. Goldstein and I (Ref. 25) have proposed a new classification for these defects

based on the presumed site of action of the abnormal gene during embryogenesis. This classification will be reviewed in considerable detail, and the evidences for the various aspects will be summarized. On theoretical grounds, such mutant genes could act at any one of the major steps in normal embryonic sexual development to cause errors in genetic sex, errors in gonadal sex, or errors in phenotypic sex.

A. Errors in Genetic Sex

To date, no monogenic disorders of genetic sex have been described in man. The human intersex syndromes that result from abnormalities in genetic sex appear to be due to sporadic aberrations in meiosis or mitosis of the X and Y chromosomes, as in the Turner syndrome, the Klinefelter syndrome, the double fertilization chimera, and the mixed gonadal dysgenesis syndromes associated with sex chromosome mosaicism.

B. Errors of Gonadal Sex

In contrast, several hereditary errors of gonadal sex are the consequence of single gene mutations, as a result of which the embryonic programming of the indifferent gonad does not correspond to the chromosomal sex. Although many such errors may be sporadic in nature, the familial defects are of special importance because they provide the first evidence in man that autosomal genes may be critical to normal gonadal differentiation.

FAMILIAL TRUE HERMAPHRODITISM

26. Clayton, G. W., J. D. Smith, and H. S. Rosenberg. Familial true hermaphroditism in pre- and post-pubertal genetic females: Hormonal and morphological studies. J. Clin. Endocrinol. Metab. 18:1349, 1958.

27. Milner, W. A., W. B. Gorlick, A. J. Flink, and A. A. Stein. True hermaphrodite siblings. J. Urology 79:1003, 1958.

28. Rosenberg, H. S., G. W. Clayton, and T. C. Hsu. Familial true hermaphroditism. J. Clin. Endocrinol. Metab. 23:203, 1963.

29. Mori, Y., and S. Mizutani. Familial true hermaphroditism in genetic females. Japanese J. Urol. 59:10, 1968.

The familial form of true hermaphroditism is one such example. Affected individuals characteristically have a 46XX karyotype, but the gonadal sex is a misture of male and female elements with both testicular and ovarian tissues being present. Phenotypic sex is basically masculine, but gynecomastia and hypospadias are commonly present. A number of pedigrees have now been described in which multiple sibs have been affected, suggesting that this form of true hermaphroditism may be determined by an autosomal recessive gene. If testicular tissue does, in fact, occur in the absence of a Y chromosome as is presumed in these single gene determined cases of 46XX true hermaphroditism, the

generally accepted view that testicular development depends predominantly on the presence of genes carried on the Y chromosome must be oversimplified.

SEX REVERSAL SYNDROME

30. Hamerton, J. L., J. M. Dickson, C. E. Pollard, S. A. Frieves, and R. V. Short. J. Reprod. Fert., Suppl. 7:25, 1969.

31. Short, R. V. Germ cell sex. In Proc. Int. Symp. The Genetics of the Spermatozoon, Edinburgh, August 1971. Eds. R. A. Beatty & S. Gluecksohn-Waelsch. p. 325.

32. Cattanach, B. M., C. E. Pollard, and S. G. Hawkes. Sex-reversed mice: XX and XO males. Cytogenetics 10:318, 1971.

Another autosomal gene that contributes to testicular differentiation has been identified as a result of the discovery of the sex reversal mutation in the goat (Ref. 30, 31) and in the mouse (Ref. 32). In these syndromes, an autosomal gene, either recessive or dominant, apparently causes the indifferent gonad of genetic females to differentiate into a testis or an ovary.

33. de la Chapelle, A. Nature and origin of males with XX sex chromosomes. Am. J. Human Genetics 24:71, 1972.

Over 40 men with a karyotype 46XX have been documented to date. The phenotype of these individuals is almost identical to that of Klinefelter's syndrome, e.g. gynecomastia (30%), small testes (1-2 cm) with azospermia, and small but anatomically normal external genitalia (90%).

34. Kasdan, R., H. R. Nankin, P. Troen, N. Wald, S. Pan, and T. Yanahara. Paternal transmission of maleness in XX human beings. New Eng. J. Med. 288:539, 1973.

35. Boczkowski, K. Sex determination and gonadal differentiation in man. Clin. Gen. 2:379, 1971.

Although most patients with this disorder have been sporadic cases, one pedigree strongly suggestive of familial occurrence in man has been described (Ref. 34). It is entirely possible that either new autosomal mutations or autosomal recessive inheritance may be responsible for the apparently sporadic nature of the usual case. A most attractive hypothesis to explain the mechanism of action of this mutation in man and animals has been offered in Ref. 35.

PURE GONADAL DYSGENESIS, FAMILIAL XX TYPE

36. Josso, N., J. de Grouchy, J. Frezal, and M. Lomy. Le Syndrome de Turner familial étude de deux families auec caryotypes XO et XX. Bull. Soc. méd. Paris (Ann. Paediat.) 39:775, 1963.

37. Guisti, G., A. Borghi, M. Salti, and V. Bizozzi. "Disgenesia gonadica pura" con conietipo 44A + XX in sorelle figlie di cugini. Acta Genetica Medica (Roma) 15:51, 1966.

38. Simpson, J. L., and A. C. Christakos. Hereditary factors in obstetrics and gynecology. Obstetrical Gynecological Survey 24:480, 1969.

39. Christakos, A. C., J. L. Simpson, J. B. Younger, and C. D. Christian. Gonadal dysgenesis as an autosomal recessive condition. Am. J. Obstet. Gynec. 104:1027, 1969.

40. Simpson, J. L., A. C. Christakos, M. Horwith, and F. S. Silverman. Gonadal dysgenesis in individuals with apparently normal chromosomal complements: Tabulation of cases and compilation of genetic data. Birth Defects: Original Articles Series 7:215, 1971.

It is also clear that an autosomal gene is involved in the syndrome of pure gonadal dysgenesis of the familial 46XX type. In this disorder streak gonads develop despite the presence of a normal female karyotype. At least seven sibships are highly suggestive of autosomal recessive inheritance (three of which are consanguineous), a finding that implies that at least one autosomal gene is required in normal ovarian development.

PURE GONADAL DYSGENESIS, FAMILIAL XY TYPE

41. Cohen, M. M., and M. W. Shaw. Two XY siblings with gonadal dysgenesis and a female phenotype. New Eng. J. Med. 272:1083, 1965.

42. Sternberg, W. H., D. L. Barclay, and H. W. Kloepfer. Familial XY gonadal dysgenesis. New Eng. J. Med. 278:695, 1968.

43. Chemke, J., R. Carmichael, J. M. Stewart, R. H. Green, and A. Robinson. Familial XY gonadal dysgenesis. J. Med. Genetics 7:105, 1970.

44. Espiner, E. A., A. M. O. Veale, V. E. Sands, and P. H. Fitzgerald. Familial syndrome of streak gonads and normal male karyotype in five phenotypic females. New Eng. J. Med. 283:6, 1970.

45. Federman, D. D. Genetic control of sexual differences. Ch. in Progress in Medical Genetics 9:215, 1973.

(Also Ref. 40 for review)

Recent studies of pure gonadal dysgenesis of the Familial XY variety have also provided insight into the genetic control of gonadal differentiation. This type of pure gonadal dysgenesis is characterized by the occurrence of streak gonads in genetic men who appear as phenotypic females without the somatic anomalies characteristic of the 46 XO variety of the Turner syndrome. The unique feature of this syndrome is the presence of a streak gonad despite the presence of a Y chromosome. A number of pedigrees have now been identified to suggest that this disorder is probably determined by a X-linked locus. And since the defect results in a failure of testicular differentiation it may be inferred that a factor necessary for development of the indifferent gonad into a normal testis is specified on the X chromosome.

In summary, several lines of evidence, derived from clinical observations of patients with various hereditary disorders of gonadal sex, indicate that normal differentiation of ovary and testis is controlled by specific autosomal genes as well as by genes on the sex chromosomes. Furthermore, it is clear that development of a normal testis requires genes carried on the X chromosome and autosomes as well as those on the Y chromosome. Thus, it is clear that the development of gonadal sex is determined by other genetic factors in addition to those on the X and Y chromosomes.

C. Errors of Phenotypic Sex

Several hereditary syndromes have been delineated in which gonadal differentiation is normal but phenotypic differentiation is defective. Three broad categories can be distinguished: 1.) Familial Male Pseudohermaphroditism in which genetic males differentiate, completely or in part, as phenotypic females; 2.) Familial Female Pseudohermaphroditism in which genetic females are virilized in utero, and 3.) Familial Defects of Wolffian-Mullerian duct system.

1.) FAMILIAL MALE PSEUDOHERMAPHRODITISM

Inherited male pseudohermaphroditism can result either from defective virilization of the Wolffian duct, urogenital sinus, and external genitalia or from a defect in Mullerian duct regression.

a.) Defective Virilization

Two mechanisms that result in defective virilization of the male embryo have been delineated in man, defective androgen synthesis and defective androgen action.

I. Defective Androgen Synthesis

Five inherited syndromes of androgen deficiency have been identified. Each is the result of the deficiency of a specific enzyme in testosterone formation:

20,21-Desmolase Deficiency (Lipoid adrenal hyperplasia)

46. Prader, A., and Guntner, H. P. Das Syndrom des pseudo-hermaphroditismus masculinus bei korgenitalen neberrierennirden hyperplasie ohne androgeniiberproduktion. Helv. Paediat. Acta 10:397, 1955.

47. Prader, A., and R. E. Siebenmann. Nebernierenin-suffizierz bei kongenitalen lipodhyperplasia den nebennieren. Helvet. Paediatrica Acta 12:569, 1957.

48. Comarcho, A. M., A. Kowarski, C. Migeon, and A. J. Brough. Congenital adrenal hyperplasia due to a deficiency of one of the enzymes involved in the biosynthesis of pregnenolone. J. Clin. Endocrinol. 28:153, 1968.

3β-Hydroxysteroid Dehydrogenase Deficiency

49. Bongiovanni, A. M. Unusual steroid pattern in congenital adrenal hyperplasia: deficiency of 3β-hydroxysteroid dehydrogenase. J. Clin. Endocrinol. 21:860, 1961.

50. Bongiovanni, A. M. The adrenogenital syndrome with deficiency of 3β-hydroxysteroid dehydrogenase. J. Clin. Invest. 41:2086, 1962.

51. Bongiovanni, A. M., W. R. Eberlein, A. S. Goldman, and M. New. Disorders of adrenal steroid biogenesis. Rec. Progr. Hormone Res. 23:375, 1967.

52. Kogut, M. D. Adrenogenital syndrome associated with 3β-hydroxysteroid dehydrogenase deficiency. Am. J. Dis. Child. 110:562, 1968.

53. Jönne, O., J. Perheentupee, and R. Vikho. Plasma and urinary steroids in an eight-year-old boy with 3β-hydroxysteroid dehydrogenase deficiency. J. Clin. Endocrinol. 531:162, 1970.

54. Zachman, M., J. A. Vollmin, G. Murset, H. Ch. Curtius, and A. Prader. Unusual type of adrenal hyperplasia probably due to deficiency of 3β-hydroxysteroid dehydrogenase. J. Clin. Endocrinol. 30:719, 1970.

55. Bongiovanni, A. M. Disorders of adrenocortical steroid biogenesis (The adrenogenital syndrome associated with congenital adrenal hyperplasia). Ch. in The Metabolic Basis of Inherited Disease, 3d ed., Eds. J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson. 1972. McGraw-Hill, New York, p. 857.

17-Hydroxylase Deficiency

56. Biglieri, E. G., M. A. Herron, and N. Brust. 17-Hydroxylation deficiency in man. J. Clin. Invest. 45:1946, 1966.

57. New, M. I., and R. E. Peterson. A new form of congenital adrenal hyperplasia. J. Clin. Endocrinol. 27:300, 1967.

58. Mallin, S. R. Congenital adrenal hyperplasia secondary to 17-hydroxylase deficiency. Ann. Int. Med. 70:69, 1969.

59. Goldsmith, O., D. H. Solomon, and R. Horton. Hypogonadism and mineralocorticoid excess. New Eng. J. Med. 277:673, 1967.

60. Miura, K., K. Yoshinaga, K. Goto, I. Katsushima, M. Maebashi, H. Demura, M. Iino, R. Demura, and T. Torikai. A case of glucocorticoid-responsive hyperaldosteronism. J. Clin. Endocrinol. 28:1807, 1968.

61. Linquette, M., A. Dupont, A. Racadot, J. Lefebvre, J. P. May, and J. P. Cappoen. Déficit en 17-hydroxylase. Ann. d'Endocrinologie 32:574, 1971.

62. Mantero, F., B. Busnardo, A. Riondel, R. Veyrat, and M. Austoni. Hypertension artérielle, alcalose hypokaliémique et pseudohermaphrodisme male par déficit en 17α-hydroxylase. Schweiz. med. Wschr. 101:38, 1971.

63. New, M. I. Male pseudohermaphroditism due to 17α-hydroxylase deficiency. J. Clin. Invest. 49:1930, 1970.

64. Bricaire, H., J. P. Luton, P. Laudat, J. C. Legrand, G. Turpin, P. Corvol, and M. Lemmer. A new male pseudohermaphroditism associated with hypertension due to a block of 17α-hydroxylation. J. Clin. Endocrinol. 35:67, 1972.

65. Alvarez, M. N., M. D. Cloutier, and A. B. Hayles. Male pseudohermaphroditism due to 17α-hydroxylase deficiency in two siblings. Ped. Res. 7:325, 1973.

17,20-Desmolase Deficiency

66. Zachmann, M., W. Hamilton, J. A. Völlmin, and A. Prader. Testicular 17,20-desmolase deficiency causing male pseudohermaphroditism. Acta endocr., Suppl. 155:65, 1971.

17-Ketosteroid Reductase Deficiency

67. Saez, J. M., E. de Peretti, A. M. Morera, M. David, and J. Bertrand. Familial male pseudohermaphroditism with gynecomastia due to a testicular 17-ketosteroid reductase defect. I. Studies in vivo. J. Clin. Endocrinol. 32:604, 1971.

68. Saez, J. M., A. M. Morera, E. de Peretti, and J. Bertrand. Further in vivo studies in male pseudohermaphroditism with gynecomastia due to a testicular 17-ketosteroid reductase defect (compared to a case of testicular feminization). J. Clin. Endocrinol. 34:598, 1972.

69. Goebelsmann, U., R. Horton, J. H. Mestman, J. J. Arce, Y. Nagata, R. M. Nakamura, I. H. Thorneycroft, and D. R. Mishell, Jr. Male pseudohermaphroditism due to testicular 17β-hydroxysteroid dehydrogenase deficiency. J. Clin. Endocrinol. 36:867, 1973.

These disorders share a number of traits in common. Each is transmitted as an autosomal recessive trait, and in each the degree of male pseudohermaphroditism is variable in that the phenotypes of affected XY individuals can span the range from males with mild hypospadias to females resembling the testicular feminization syndrome. This variability is presumed to be due to variation in the completeness of the enzymatic defects in different patients.

Three of these defects (21,22-Desmolase, 3β-Hydroxysteroid dehydrogenase, and 17-Hydroxylase) involve enzymes that are required for the formation of hydrocortisone as well as testosterone, and as a consequence each is associated with a compensatory increase in ACTH secretion and congenital adrenal hyperplasia (with or without a resulting secondary increase in other adrenal steroids, such as mineralocorticoid, depending on the specific enzyme defect). The other two defects involve enzymes that are obligatory intermediates in the synthesis of C-19 steroids only (17-Ketosteroid Reductase and C17-21 Desmolase), and consequently the only clinical findings are the consequence of deficient formation of the sex steroids.

Although affected males generally exhibit complete or partial male pseudohermaphroditism, affected females can undergo normal sexual differentiation in utero, and consequently they are phenotypically normal up until the time of puberty.

Case Report. 17-Hydroxylase Deficiency.

P. N., a black female with normal genitalia at birth in 1954 was noted to be hypertensive at age 2 (140/70), and at age 3 she had a normal regitine test. She was subsequently followed in the OPD with blood pressures from 135/90 to 145/110, and in 1964 she was hospitalized at the CMC for a diagnostic workup. BP in the arms was 136/90-140/100 and in the legs from 170/100-170/110, and she had segmental spasm of the retinal arterioles. Catechol excretion was normal. Renal arteriography demonstrated two arteries on the left with a stenotic superior branch with post stenotic dilation, and generalized fibro-muscular hyperplasia was suspected. A 20 mm rise in diastolic blood pressure was documented after an infusion of 4 μg/kg/min of

angiotensin. Surgical exploration was decided upon, and repair of the left renal artery was accomplished by homograft. After surgery there was no change in her blood pressure.

In 1965 she was first noted to be hypokalemic (2.8-3.9 mEq/L) and to waste large amounts of potassium in the urine. Her growth and development were within normal limits, but by April of 1969 (age 15) she showed no evidence of puberty. At this time the diagnosis of 17α-hydroxylase deficiency was suspected by Dr. John L. Baskin, and the assembly of data was begun to confirm the diagnosis. In the course of this study chromosome analyses of two cell lines, leucocytes and testis revealed a 46 XY karyotype and established the diagnosis as male pseudohermaphroditism. A vaginogram revealed a short vaginal canal that ended blindly with no cervix. (Some of the laboratory studies are summarized below.)

PARAMETER		PRE-TREATMENT	NORMAL RANGE
Secretion Rates			
	Desoxycorticosterone	1935 µg/day	50-350 µg/day
	Corticosterone	18 mg/day	0.9-4.4 mg/day
	Aldosterone	13.5 µg/day	50-168 µg/day
	Cortisol	< 1 mg/day	9-31 mg/day
Excretion Rates			
	FSH	100 units/day	< 6 before puberty 6-50 after puberty
	Pregnanediol	1.2 mg/day	0.5-1.5 mg in proliferative phase
	Pregnanetriol	4.5 mg/day	0.2-4.0 mg/day
	17-Hydroxycorticoids	undetected	3.1 mg/M^2/day
	17-Ketosteroids	3.5 mg/day	2-10 mg/day
	Aldosterone	2 µg/day	3-29 µg/day
	Estradiol, Estrone	< 1 µg/day of each	-
Plasma Values			
	Plasma Renin	70 ng/100 ml	73-490 ng/100 ml
	ACTH	80 pg/100 ml	36-94 pg/ml
	Desoxycorticosterone	6 µg/100 ml	0.034 µg/100 ml
	Corticosterone	24.3 µg/100 ml	0.3-1 µg/100 ml
	Pregnenolone	10.2 ng/ml	1 ng/ml
	Progesterone	1.7 ng/ml	0.3 ng/ml
	Cortisol	0.4 µg/100 ml	5-25 µg/100 ml
	Testosterone	not detected	0.5-1 µg/100 ml

Because of the possibility of eventual tumor development in the retained testes, exploratory laporatomy was performed. Intraabdominal testes were noted (1 X 1.5 cm) with small tubular structures adjacent, but no other internal genitalia were present. The gonads were removed, and no spermatogonia were identified in the tubules; Leydig cell number was normal, and the adjacent tubes had histological features characteristic of a Mullerian remnant.

Therapy was with glucocorticoid replacement (dexamethasone 0.15 mg to 0.75 mg twice daily) and estrogens (premarin 1.25 mg b.i.d.). On this regimen she developed normal secondary sex characteristics including pubic hair, and both the hypertension and hypokalemia ameliorated. However, she has been very lax in maintaining this therapy over a long term.

At the time that the testes were removed, the activity of several enzymatic pathways of steroid biosynthesis was assessed in tissue slices:

ENZYMATIC PATHWAY	TESTIS	
	17-HYDROXYLASE DEFICIENCY	TESTICULAR FEMINIZATION
	pmoles/100 mg/hour	
17-Hydroxylase		
Progesterone → 17-Hydroxyprogesterone	4	387
Pregnenolone → 17-Hydroxypregnenolone	4	472
3β-Hydroxysteroid Dehydrogenase		
Dehydroisoandrosterone → Testosterone plus Androstenedione	899	960
17,20-Lyase		
17-Hydroxyprogesterone → Testosterone + Androstenedione	202	253
17-Ketosteroid Reductase		
Androstenedione → Testosterone	1515	2102

In summary: It was possible to demonstrate directly for the first time a virtual absence of the 17-hydroxylase enzyme in the testis of this patient and to show that three other critical enzymes in the later phases of testosterone synthesis are intact. In every regard, this patient is typical of the 17-Hydroxylase Deficiency Syndrome of the complete type, resulting in hypertension, hypokalemia, and (in XY patients) male pseudohermaphroditism.

2. Defective Androgen Action

In addition to the androgen deficiency states, defective virilization in the embryo can result from inherited abnormalities in androgen action.

1. Testicular Feminization

70. Morris, J. McL. The syndrome of testicular feminization in male pseudohermaphrodites. Am. J. Obstetrics & Gynecology 65:1192, 1953.

71. Morris, J. McL., and V. B. Mahesh. Further observations on the syndrome, "testicular feminization". Am. J. Obstetrics & Gynecology 87:738, 1963.

72. Hauser, G. A. Testicular feminization. Ch. in Intersexuality ed. by C. Overzier. London, Academic Press, 1963, p. 255.

73. Southren, A. L. The syndrome of testicular feminization. Advances in Metabolic Diseases 2:227, 1965.

74. Simmer, H. H., R. J. Pion, and W. J. Dignom. Testicular Feminization. Springfield, Charles C. Thomas, 1965.

75. Polani, P. E. Hormonal and clinical aspects of hermaphroditism and the testicular feminizing syndrome in man. Phil. Trans. Roy. Soc. Lond. B. 259:187, 1970.

(also Ref. 4 and Grand Rounds Protocol 28 March 1968)

While the description of the syndrome goes back at least 150 years, Morris is credited with defining the syndrome in modern terms, namely the female habitus, breast development, and other secondary sex characteristics, the scanty or absent axillary or pubic hair in most cases, the female genitalia with small labia and a blind-ending vagina, the absence of internal genitalia except for gonads that are histologically characteristic of undescended testes.

76. Pettersson, G., and G. Bonnier. Inherited sex-mosaic in man. Hereditas 23:49, 1937.

77. Nilsson, I. M., S. Bergman, J. Recitalu, and J. Waldenström. Hemophilia in a "girl" with male-sex chromatin pattern. Lancet 2:264, 1959.

78. Lyon, M. F., and S. G. Hawkes. X-linked gene for testicular feminization in the mouse. Nature 227:1217, 1970.

In man, the pattern of inheritance is compatible either with a X-linked recessive pattern or an X-limited autosomal trait. Since on the basis of linkage studies it is established that the defect in the mouse is X-linked, it is assumed generally that such is the case with the human disease.

79. Stern, O. N., and W. J. Vandervort. Testicular feminization in a male pseudohermaphrodite. New Eng. J. Med. 254:787, 1956.

80. Puck, T. T., A. Robinson, and J. H. Tjio. Familial primary amenorrhea due to testicular feminization: A human gene affecting sex differentiation. Proc. Soc. Exper. Biol. Med. 103:192, 1960.

These patients not only have testes, but in addition the nuclear chromatin and the chromosomal karyotype are that of a 46 XY male.

81. Southren, A. L. and A. Saito. The syndrome of testicular feminization. A report of three cases with chromatographic analysis of the urinary neutral 17-ketosteroids. Ann. Int. Med. 55:925, 1961.

82. Southren, A. L., H. Ross, D. C. Sharma, G. Gordon, A. B. Weingold, and R. I. Dorfman. Plasma concentration and biosynthesis of testosterone in the syndrome of feminizing testes. J. Clin. Endocrinol. 25:518, 1965.

83. Judd, H. L., C. R. Hamilton, J. J. Barlow, S. S. C. Yen, and B. Kliman. Androgen and gonadotropin dynamics in testicular feminization syndrome. J. Clin. Endocrinol. 34:229, 1972.

84. MacDonald, P. C. Unpublished studies.

The endocrinological studies from a variety of laboratories can be summarized as follows:

a. The testosterone secretory rate and blood level are in the high normal range for men and fall following castration.

b. Plasma LH is high, compatible with a deficient feedback mechanism.

c. Estrogen production is higher than that of a normal man, and a large fraction of the total comes from direct secretion from the testis.

85. Wilkins, L. M. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Springfield: Charles C. Thomas, 1950.

86. Prader, A. Gonaden dysgenesie und testiculare feminisierung. Schweiz. Med. Wschr. 87:278, 1957.

Wilkins was the first to propose that the syndrome of testicular feminization is the result of end organ unresponsiveness to testosterone; he studied a patient in whom methyltestosterone, despite high dosages, caused no growth of sexual hair in spite of the fact that pubic hair follicles were demonstrated by biopsy. This finding was endorsed by Prader, who suggested that the entire disease was the result of resistance to testosterone.

87. French, F. S., B. Baggett, J. J. Van Wyk, L. M. Talbert, W. R. Hubbard, F. R. Johnston, and R. P. Weaver. Testicular feminization: clinical, morphological, and biochemical studies. J. Clin. Endocrinol. 25:661, 1965.

88. French, F. S., J. J. Van Wyk, B. Baggett, W. F. Easterling, L. M. Talbert, F. R. Johnston. Further evidence of a target organ defect in the syndrome of testicular feminization. J. Clin. Endocrinol. 26:493, 1966.

89. Volpe, R., T. G. Knowlton, A. D. Foster, and P. E. Conen. Testicular feminization: A study of two cases, one with a seminoma. Canad. Med. Assoc. J. 98:438, 1968.

Not only is the disappearance rate of testosterone normal, but testosterone administration caused no effect on the urinary excretion of N, P, or citric acid. If an inhibitor to testosterone action is present it cannot be produced by the testis since this non-responsiveness persists after castration.

90. Gwinup, G., R. G. Wieland, P. K. Besch, and G. J. Homivi. Studies on the mechanism of the production of the testicular feminization syndrome. Am. J. Med. 41:448, 1966.

In addition to a lack of clinical response to testosterone (200 mg/week for 3 mos.) in that there was no change in facial, axillary or pubic hair, deepening of the voice, clitoral enlargement, or acne, there was also no change in sebum production as measured by the Strauss technique (0.71 mg and 1.0 mg/6.25 cm^2 skin surface/3 hours before and after treatment).

91. Goldstein, J. L., and J. D. Wilson. Studies on the pathogenesis of the pseudohermaphroditism in the mouse with testicular feminization. J. Clin. Invest. 51:1647, 1972.

It has recently been possible in the mouse to obtain direct evidence that the male pseudohermaphroditism in testicular feminization is the result of resistance to androgen action during androgen-mediated sexual differentiation in embryos.

Thus, it can be concluded that the fundamental defect in this disorder is a defect in normal androgen action, as the result of which these genetic men are resistant to testosterone as embryos and throughout life.

92. Wilson, J. D., and J. D. Walker. The conversion of testosterone to 5α-androstan-17β-ol-3-one (dihydrotestosterone) by skin slices of man. J. Clin. Invest. 48:371, 1969.

93. Northcutt, R. C., D. P. Island, and G. W. Liddle. An explanation for the target organ unresponsiveness to testosterone in the testicular feminization syndrome. J. Clin. Endocrinol. 29:422, 1969.

The nature of the molecular defect in androgen action has been the subject of a great deal of interest in the past several years. Because the formation of dihydrotestosterone was low in perineal skin biopsies as compared to normal men, it was proposed that a defect in dihydrotestosterone formation might be fundamental to the disorder. However, evidence of a variety of types has been accumulated that this defect is the secondary consequence of some other defect.

One type of such evidence is summarized below:

CONVERSION OF TESTOSTERONE-1,2-^{3}H TO DIHYDROTESTOSTERONE-^{3}H BY SKIN SLICES FROM NORMAL SUBJECTS AND FROM PATIENTS WITH MALE PSEUDOHERMAPHRODITISM

	AGES	DIHYDROTESTOSTERONE FORMATION pmoles/100 mg/hour ± SEM				
		Scrotum	Foreskin	Clitoris	Labia majora	Abdominal skin
Controls	6-85	526 ± 60 (14)	211 ± 26 (7)	199 ± 72 (3)	183 ± 25 (9)	49 ± 6 (20)
Testicular Feminization	2,17,19, 23,44,56				101 ± 15 (6)	77 ± 22 (5)
Reifenstein Syndrome	9	422 (1)	87 (1)			
17-Hydroxylase Deficiency	17				17 (1)	6 (1)

Since dihydrotestosterone formation is even lower in 17-Hydroxylase Deficiency than in testicular feminization, it seems safe to conclude that this defect must be the result of some primary abnormality in androgen action.

94. Ohno, S., and M. F. Lyon. X-linked testicular feminization in the mouse as a non-inducible regulatory mutation of the Jacob-Monod type. Clin. Gen. 1: 121, 1970.

95. Ohno, S., R. Dofuku, and U. Tettenborn. More about X-linked testicular feminization of the mouse as a noninducible (i^{s}) mutation of a regulatory locus: 5α-androstan-3α-17β-diol as the true inducer of kidney alcohol dehydrogenase and β-glucuronidase. Clin. Gen. 2:128, 1971.

96. Tettenborn, U., R. Dofuku, and S. Ohno. Noninducible phenotype exhibited by a proportion of female mice heterozygous for the X-linked testicular feminization mutation. Nature New Biol. 234:37, 1971.

97. Ohno, S., U. Tettenborn, and R. Dofuku. Molecular biology of sex differentiation. Hereditas 69:107, 1971.

98. Gehring, U., and G. M. Tomkins. Effect of the androgen-insensitivity mutation on a cytoplasmic receptor for dihydrotestosterone. Nature New Biol. 232:106, 1971.

99. Drews, U., H. Itakura, R. Dofuku, U. Tettenborn, and S. Ohno. Nuclear DHT-receptor in Tfm/Y kidney cell. Nature New Biol. 238:216, 1972.

100. Bullock, L. P., and C. W. Bardin. Androgen receptors in testicular feminization. J. Clin. Endocrinol. 35:935, 1972.

101. Andrews, E. J., and L. P. Bullock. A morphological and histochemical evaluation of sexual dimorphism in androgen-insensitive pseudohermaphroditic mice. Anat. Rec. 174:361, 1972.

102. Wilson, J. D., and J. L. Goldstein. Evidence for increased cytoplasmic androgen binding in the submandibular gland of the mouse with testicular feminization. J. Biol. Chem. 247:7342, 1972.

103. Dunn, J. F., J. L. Goldstein, and J. D. Wilson. Development of increased cytoplasmic binding of androgen in the submandibular gland of the mouse with testicular feminization. J. Biol. Chem. In Press.

104. Schenkein, I., M. Levy, E. D. Bueker, and J. D. Wilson. Immunological and enzymatic evidence for the absence of an esteroproteolytic enzyme (protease "D") in the submandibular gland of the Tfm mouse. Endocrinol. In Press.

Although the problem is still one of great controversy, we would favor the view that the fundamental defect lies at the level of translocation of the cytosol androgen binding protein into the nucleus, as the result of which the binding protein accumulates in the nucleus. Bardin and his co-workers feel that the cytosol binding protein itself is deficient.

105. Winterborn, M. H., N. E. France, and S. Raiti. Incomplete testicular feminization. Arch. Dis. Child. 45:811, 1970.

106. Rosenfield, R. L., A. M. Lawrence, S. Liao, and R. L. Landau. Androgens and androgen responsiveness in the feminizing testis syndrome. Comparison of complete and "incomplete" forms. J. Clin. Endocrinol. 32:625, 1971.

107. Philip, J., and D. Trolle. Familial male hermaphroditism with delayed and partial masculinization. Am. J. Obst. & Gynec. 93:1076, 1965.

(Also Ref. 71)

Closely akin to the complete form of testicular feminization but clinically distinct is the partial form of the disorder. The partial or incomplete variety resembles the majority of the cases in respect to male genotype, female phenotype, and bilateral intraabdominal testes, but it differs in that ambiguous genitalia may be present at birth and in that some degree of virilization occurs at puberty. The degree of masculinization, although similar within a family can be quite variable in different families. Little is known about the pathogenesis of the disorder, but the available evidence suggests that like the complete form it is due to androgen resistance. In fact, it is possible that it should be classified with the disorders to be discussed below.

2. Incomplete Male Pseudohermaphroditism, Type I

108. Gilbert-Dreyfus, S., C. A. Sebarun, and J. Blaisch. Etude d'un cos familial d'androgyroidisme avec hypospadias grave, gynecomastie et hyperestrogenie. Annales D'Endocrinologie 18:93, 1957.

109. Lubs, H. A., O. Vilan, and D. M. Bergerstal. Familial male pseudohermaphroditism with labial testes and partial feminization: endocrine studies and genetic aspects. J. Clin. Endocrinol. 19:1110, 1959.

110. Reifenstein, E. C., Jr. Hereditary familial hypogonadism. Recent Prog. Hormone Res. 3:224, 1948.

111. Bowen, P., C. S. N. Lee, C. J. Migeon, N. M. Kaplan, P. J. Whalley, V. A. McKusick, and E. C. Reifenstein. Hereditary male pseudohermaphroditism with hypogonadism, hypospadias, and gynecomastia (Reifenstein's syndrome). Ann. Int. Med. 62:252, 1965.

112. Borzkowski, K., R. Wowryk, B. Krupa, and E. Mickiewiez. Familial occurrence of male pseudohermaphrodites with ambiguous external genitals. Am. J. Ob. Gyn. 112:92, 1972.

113. Rosewater, S., G. Gwinup, and G. J. Hameric. Familial gynecomastia. Ann. Int. Med. 63:377, 1965.

114. Hashiem, N. Familial male pseudohermaphroditism. Human Heredity 22:225, 1972.

(Also Ref. 4)

Several familial syndromes of incomplete male pseudohermaphroditism have been described in which the phenotype is either male or ambiguous. These disorders - designated here familial incomplete male pseudohermaphroditism, Type I - comprise a variety of abnormalities from minimal virilization to virtually complete masculinization. As a group, they are distinguished by the fact that all affected males are sterile and have a normal male 46 XY karyotype, and by the fact that each is inherited in a manner consistent with an X-linked recessive trait. At the feminine end of the spectrum is the syndrome of Lubs in that four of the five affected individuals in the one family were raised as females. It differs from testicular feminization in the presence of partial Wolffian development, partial labioscrotal fusion, descended testes, and the development of pubic and axillary hair and a masculine type of skeletal muscle at puberty. The Gilbert-Dreyfus syndrome is a step closer to normal male development in that the general habitus is masculine. The major abnormalities in virilization in this disorder involve the occurrence of a small phallus, hypospadias, gynecomastia, and incompletely developed Wolffian derivatives. Further toward the masculine end of the spectrum is the Reifenstein syndrome in which the typical features are severe hypospadias and the development of gynecomastia after puberty. The Rosewater syndrome represents the mildest expression of incomplete male pseudohermaphroditism in that affected males show only gynecomastia and infertility without defective virilization of the internal or external genitalia. It has generally been believed that these syndromes represent distinct mutations, and it has not been clear up to the present whether these disorders represent partial defects in androgen formation or partial abnormalities in androgen action. Since no female internal genitalia have ever been reported in any affected individual it seems clear that the formation and action of Mullerian regression factor during embryogenesis must be normal.

115. Walker, A. C., E. M. Stark, and W. A. Horsfall. Familial male pseudohermaphroditism. The Medical J. of Australia 1:156, 1970.

116. Wilson, J. D., M. J. Harrod, J. L. Goldstein, D. Hemsell, and P. C. MacDonald. Familial incomplete male pseudohermaphroditism, Type I. Evidence for androgen resistance and variable clinical manifestations in a family with the Reifenstein syndrome. In preparation.

The most common and best studied of these incomplete forms of familial male pseudohermaphroditism is the Reifenstein syndrome. Two large pedigrees with this disorder have recently been studied, one in Australia (Ref. 115) and one here at Parkland (Ref. 116), and the findings in these families strongly suggest that the syndromes described by Gilbert-Dreyfus, Lubs, Reifenstein, and Rosewater are in fact variable manifestations of the same mutant gene. In our family (see pedigree chart) most of the eleven affected individuals have a typical Reifenstein syndrome, with hypospadias, faulty scrotal fusion, and gynecomastia. However, one affected individual had a vagina and absent vas deferens characteristic of the Lubs syndrome,

and two have incomplete scrotal fusion and sterility without hypospadias. In the family reported by Walker, Stark, and Horsfall the manifestations extended from microphallus and gynecomastia to severe hypospadias and failure of scrotal fusion so severe that three of twelve affected individuals were identified initially as females. Thus, on the basis of the findings in these two large families involving 23 affected males, it seems reasonable to conclude that the defect that gives rise to this form of male pseudohermaphroditism may be variably expressed in affected individuals and that the various syndromes may represent different manifestations of the same mutation.

Furthermore, as the result of studies done on the Parkland family in the Department of Obstetrics and Gynecology it has been possible to deduce that this disorder, like testicular feminization, is due to an inherited resistance to testosterone action. Indeed, the finding that blood testosterone levels as well as the concentration of luteinizing hormone were higher on an average than in unaffected men in the same family is strong evidence not only that the capacity to form testosterone in this disorder is intact but that the capacity of testosterone to perform one of its central actions, namely the feedback regulation of LH secretion, is impaired. Furthermore, from an endocrine standpoint (elevated blood testosterone, high testosterone secretion rates, elevated blood LH, and marked enhancement of testicular estrogen secretion) the findings in this disorder are identical to those in the testicular feminization syndrome.

Our findings allow several clinical deductions to be drawn. First, the clinical features that appear to be primary to the disorder include some combination of the following: microphallus, bifid scrotum, hypospadias, defective Wolffian duct and urogenital sinus derivatives, and a partial vaginal orifice. Second, gynecomastia appears only after puberty and only in some affected men. Since gynecomastia is almost inevitably due to relative or absolute excess of estrogen, it seems likely that the gynecomastia is the result of enhanced estrogen secretion in the face of partial resistance to androgen action and is not a primary abnormality in itself. Third, all affected males so far described have been sterile. Since testosterone action is required for normal tubule development in the testes and for normal spermatogenesis and since the genitalia are frequently abnormal the sterility is certainly not unexpected. However, since the manifestations of the defect are so variable and since some individuals have been described that produced sperm, sterility is probably not obligatory in the defect. If this hypothesis is correct, then it is predictable that some men with the defect may transmit the gene to the offspring.

FAMILY REPORT. Familial Incomplete Male Pseudohermaphroditism, Type I (Reifenstein syndrome)

On the following three pages are summarized recent studies on a Dallas family in which 11 affected males have incomplete male pseudohermaphroditism. The family has already been reported in part (Ref. 111) and will be published in detail (Ref. 116).

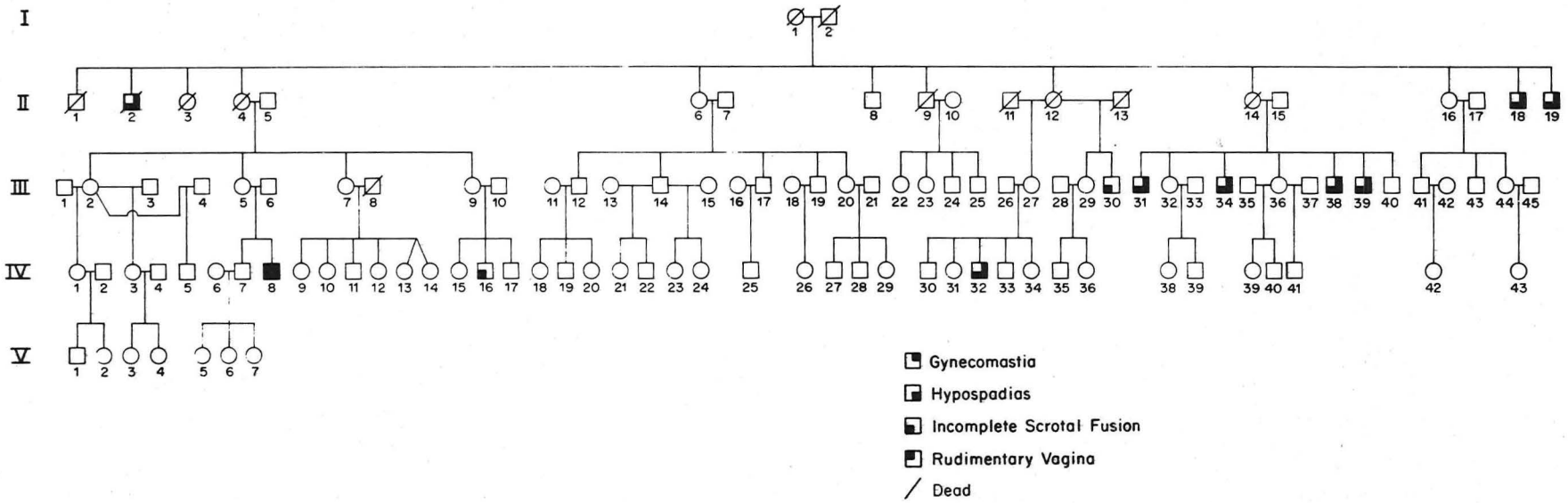

I
II
III
IV
V
Gynecomastia
Hypospadias
Incomplete Scrotal Fusion
Rudimentary Vagina
Dead

TABLE I

Clinical and Laboratory Findings in Affected Members of the Pedigree Shown in Fig. I

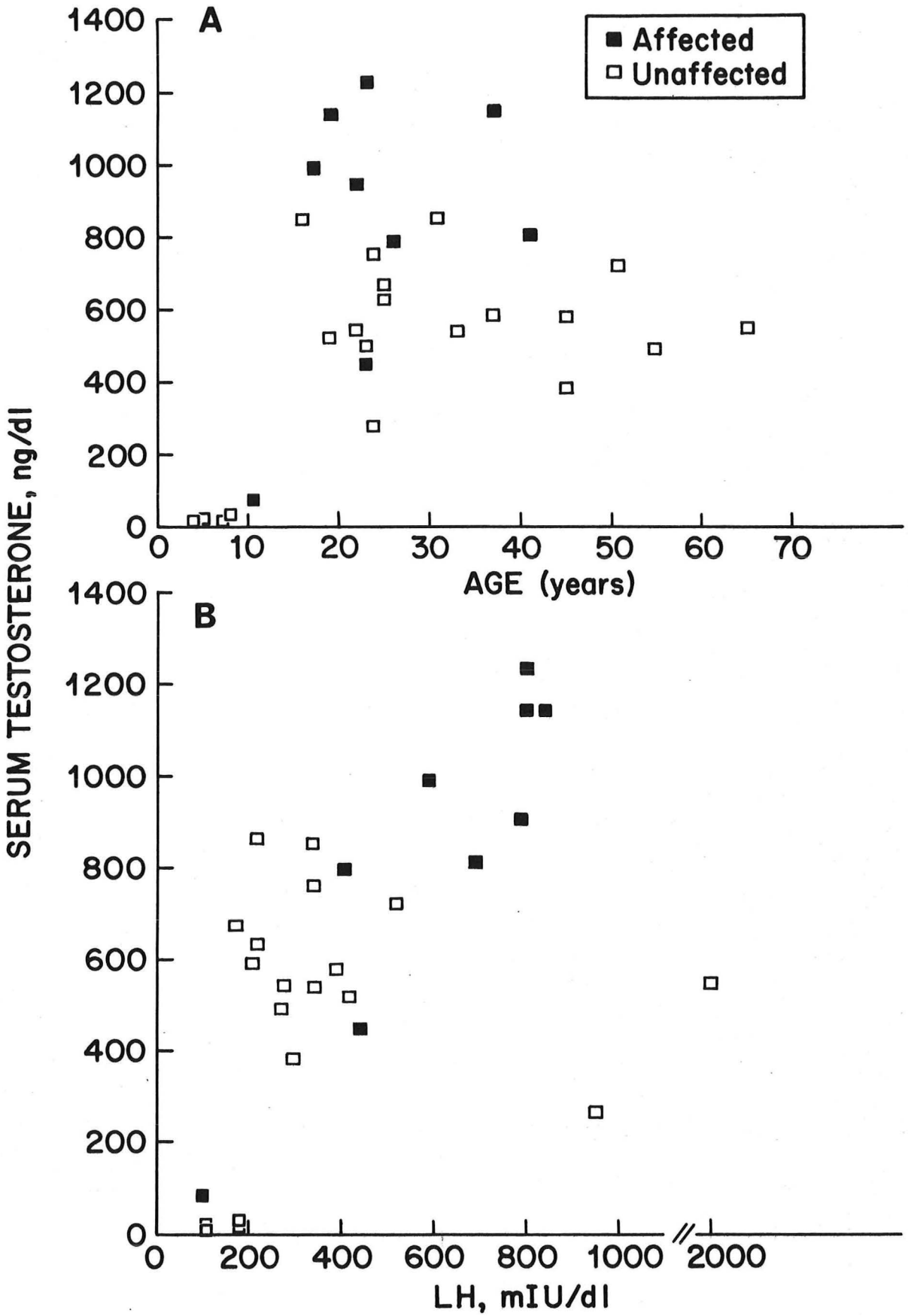
Pedigree Position[a]	Age (Year of Birth)	Phenotypic Characteristics							Serum Hormones			Comment
		External Genitalia	Testes	Wolffian Duct Derivatives	Urogenital Sinus	Gynecomastia	Body Hair	Voice	Testosterone[b]	LH[b]	FSH[b]	
									ng/dl	MIU/dl	MIU/dl	
II-2	22[c]	Hypospadias[d]				Yes[d]						
II-18	39 (1933)	Penoscrotal hypospadias; marked chordee; small penis	Size: 2 X 2 cm; no biopsy		Prostate normal	Yes	Diminished chest and facial hair	High	803	678	330	Normal IVP
II-19	38 (1934)	Penoscrotal hypospadias; marked chordee; small penis	Small; no biopsy		Small prostate	Yes	Diminished chest and facial hair		1145	840	310	
III-30	22 (1951)	No hypospadias; bifid scrotum with prominent scrotal raphe; small penis	Undescended testes; complete aspermia X 2	Epididymis and vas deferens palpable on both sides		No	Diminished chest and facial hair	High	905	786	280	Bilateral orchiopexy for undescended testes
III-31	26 (1946)	Penoscrotal hypospadias; bifid scrotum	Biopsy: spermatogonia but no spermatids; Leydig cells present; thickened basement membranes of tubules	Normal vas deferens and epididymis on right; malformed vas deferens and epididymis on left		Yes; confirmed by biopsy; bilateral mastectomy at age 14	Diminished chest and facial hair	High	789	408	240	Normal IVP
III-34	23 (1949)	Penoscrotal hypospadias; small penis	Biopsy: spermatogonia and Sertoli cells but no spermatids; Leydig cells present; thickening and hyalinization of tubules. Size: 2 X 1 cm		Enlarged prostatic utricle	Yes	Diminished chest and facial hair	High	448	492	220	Left indirect inguinal hernia and hydrocele; normal IVP
III-38	19 (1953)	Penoscrotal hypospadias; marked chordee; bifid scrotum	Biopsy: normal prepubertal testis at age 10; undescended right testis	Hypoplastic vas deferens on right	Enlarged prostatic utricle	Yes	Diminished chest and facial hair	High	1144	810	230	Right orchiopexy for undescended testis; normal IVP
III-39	17 (1955)	Penoscrotal hypospadias; marked chordee; bifid scrotum	Bilateral undescended testes; Biopsy: normal prepubertal testes at age 8			Yes	Diminished chest and facial hair	High	987	588	< 100	Right orchiopexy for undescended testis; normal IVP
IV-8	24 (1948)	Perineoscrotal hypospadias	Biopsy: immature tubules at age 13; bilateral undescended testes	No vas deferens detected on either side	No prostatic tissue; vaginal opening proximal to perineal skin fold	Yes	Diminished chest and facial hair	High	1108	712	721	Hypoplastic kidney on right by retrograde pyelography
IV-16	3 (1968)	No hypospadias; bifid scrotum with prominent scrotal raphe; small penis with chordee	Undescended									
IV-32	11 (1962)	Penoscrotal hypospadias; marked chordee		Epididymis and vas deferens palpable on both sides	Enlarged prostatic utricle with rudimentary vaginal orifice				70	110	300	Normal IVP

[a] Refers to Fig. I

[b] Normal values as determined on 12 unaffected male family members, age 16-50; testosterone, 561 ± SEM 40 ng/dl; LH, 308 ± SEM 97 MIU/dl; FSH, 407 ± SEM 38 MIU/dl.

[c] Age at time of death

[d] Not examined. Information obtained by history only.


A
Affected
Unaffected
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
50
60
70
AGE (years)
B
SERUM TESTOSTERONE, ng/dl
1400
1200
1000
800
600
400
200
0
0
200
400
600
800
1000
2000
LH, mIU/dl

3. Incomplete Male Pseudohermaphroditism, Type II
(Familial Pseudovaginal Perineoscrotal Hypospadias)

117. Simpson, J. L., M. New, R. E. Peterson, and J. German. Pseudovaginal perineoscrotal hypospadias in sibs. Birth Defects Original Articles Series 7:140, 1971.

118. Opitz, J. M., J. L. Simpson, G. E. Sarto, R. L. Summitt, M. New, and J. German. Pseudovaginal perineoscrotal hypospadias. Clin. Genetics 3:1, 1972.

On genetic grounds it is possible to delineate a second form of incomplete male pseudohermaphroditism, designated here as type II and by other workers as familial pseudovaginal perineoscrotal hypospadias. This disorder is characterized by anomalous development of the external genitalia in otherwise normal men. The affected individuals are nearly always raised as females because at birth they have severe perineal hypospadias associated with a cleft scrotum, testes in the labioscrotal folds, and a phallus that is mistaken for an enlarged clitoris. Unlike the other forms of hereditary androgen resistance there is no gynecomastia. The pathogenesis is unclear, but the abnormal gene appears to confer androgen resistance to the external genitalia without affecting the Wolffian ducts. It is unclear from the available data whether the urogenital sinus derivatives are male or female in character. The description of at least eleven families with multiple affected sibs and parental consanguinity in several of these families suggests that this disorder is inherited as an autosomal recessive trait and is thus genetically distinct from the type I variety which is inherited in a manner consistent with a X-linked trait.

Considered together these various syndromes of defective androgen action constitute a broad spectrum of defects in virilization. Several different genes appear to be involved (on both the X chromosome and the autosomes), each of which probably specifies a different function in the action of the male sex hormone(s). The elucidation of the detailed biochemical basis of each of these disorders will provide major insight into the normal processes of sexual differentiation and hormone action.

b.) Defective Mullerian Duct Regression
(Persistent Mullerian Duct Syndrome: Hernia uteri inguinali)

119. Nilson, O. Hernia uteri inguinalis. Acta chir. Scand. 83:231, 1939.

120. Guell-Gonzalez, J. R., A. Paramino-Ruibal, and B. Delgado-Norales. Revue Roumaine d'Endocrinologie 7:343, 1970.

121. Morillo-Cucci, G., and J. German. Males with a uterus and fallopian tubes, a rare disorder of sexual development. Birth Defects: Original Article Series 7:229, 1971.

122. David, L., J. M. Saenz, and R. Francois. Male pseudohermaphroditism in two brothers. Acta Paediatrica Scand. 61:249, 1972.

123. Brook, C. G. D., H. Wagner, M. Zachmann, A. Prader, S. Armendares, S. Frenk, P. Aleman, S. S. Nijjar, M. S. Slim, N. Genton, and C. Bozic. Familial occurrence of persistent Mullerian structures in otherwise normal males. Brit. Med. Journal 1:771, March 31, 1973.

The persistent Mullerian duct syndrome is clearly the result of a defect not of androgen-mediated virilization but of the second process of male sexual differentiation, namely failure of Mullerian duct regression in otherwise normal 46 XY males. The typical case is that of a man with cryptorchidism and inguinal hernias but otherwise normal external genitalia. At the time of hernia repair, a uterus and fallopian tubes are found in the inguinal canal. The gonads are testes without ovarian elements. The Wolffian duct derivatives are of normal male character, although the vas deferens may course through the edge of the uterus. In short, the syndrome appears to be due to an abnormality in either the formation or action of the Mullerian regression factor in otherwise virile men. At least six different sibships have been reported, each having multiple affected males, suggesting that the disorder is probably inherited as an autosomal recessive trait.

2.) FAMILIAL FEMALE PSEUDOHERMAPHRODITISM

124. Borgiovanni, A. M. Disorders of adrenocortical steroid biogenesis. Ch. in Metabolic Basis of Inherited Disease, 3d Ed., McGraw-Hill, N. Y., 1972, p. 857.

Female pseudohermaphroditism, in which genetic and gonadal females exhibit varying degrees of virilization, is the result of the exposure of female embryos to androgens of exogenous or endogenous origin. All affected individuals have a uterus, fallopian tubes, and ovaries, and there are no testes or persistent Wolffian duct derivatives. Virilization of the external genitalia can vary from simple clitoral enlargement to virtually complete masculinization of the phallus, labial folds, and urethra. Familial female pseudohermaphroditism is usually due to one of two autosomal recessive enzyme defects involving steroid synthesis by the fetal adrenal gland - either 21-Hydroxylase or 11-Hydroxylase. In both disorders, the metabolic block is restricted to enzymatic reactions unique to glucocorticoid synthesis; as a result hydrocortisone production is deficient and leads to increased ACTH, which in turn results in massive overproduction of adrenal androgens. In men overproduction of androgen leads only to precocious puberty whereas in women a unique form of pseudohermaphroditism results in which virilization of the external genitalia but not of the internal genitalia results.

125. Schultz, F. M., and J. D. Wilson. Virilization of the Wolffian duct in the rat fetus by various androgens. Endocrinology, 1973. In Press.

Lack of virilization of the internal genitalia is probably the consequence of two phenomena. First, the capacity of the adrenal gland to synthesize steroid hormones probably matures after the time of completion of sexual differentiation of the internal genitalia. Second, the predominant steroid that accumulates in these disorders is the adrenal androgen androstenedione, a less potent androgen for male sexual differentiation than either testosterone or dihydrotestosterone.

3.) FAMILIAL DEFECTS OF WOLFFIAN-MULLERIAN DEVELOPMENT

Hereditary errors in phenotypic sex can also result from developmental defects in the differentiation of the genital anlage:

Mayer-Rokitansky-Kuster-Hauser Syndrome (Congenital Absence of the Uterus

126. Bryan, A. L., J. A. Nigro, and V. S. Counseller. One hundred cases of congenital absence of the vagina. Surg. Gynec. Obstet. 88:79, 1949.

127. Wharton, L. R. Congenital malformations associated with developmental defects of the female reproductive organs. Am. J. Ob. & Gyn. 53:37, 1947.

128. Bloch, P., A. Curchod, and R. Cordey. Confection d'un néo-vagin par dedoublement du ligament large dans un cas de Rokitansky-Küster-Hauser. Soc. Suisse Obstet. Gyn. Ass. Ann. Fribourg 1960. Gynaecologia 151:113, 1961.

129. Hauser, G. A., M. Keller, T. Koller, and R. Wenner. Das Rokitansky-Küster-Syndrom. Gynaecologia 151:111, 1961.

130. Leduc, B., J. Van Campenhout, and R. Simard. Congenital absence of the vagina. Am. J. Ob. & Gyn. 100:512, 1968.

131. Hauser, G. A., and W. E. Schreiner. Das Mayer-Rokitansky-Küster-Syndrom. Schweiz. Mediz. Wochenschr. 91:381, 1961.

132. Onger, D., J. Hemet, and J. Ensel. Bulletin de la Federation des Societies de Gynecologie et d'Obstetrique de Langue Francaise (Paris) 18:229, 1966.

133. Van Campenhout, J., and B. Leduc. Unusual features in the Rokitansky-Kuster-Hauser syndrome. Lancet, Oct. 23, 1971.

134. Jones, H. W., and S. Mermut. Familial occurrence of congenital absence of the vagina. Am. J. Ob. Gynecol. 114:1100, 1972.

The Mayer-Rokitansky-Kuster-Hauser syndrome is characterized by congenital absence of the uterus and vagina in otherwise normal females with functional ovaries. The disorder is surprisingly common and probably constitutes, next to the Turner syndrome, the most frequent cause of primary amenorrhea in young women. Many of the women with the syndrome also have a variety of skeletal and renal defects and a conductive hearing loss. Although most cases have been sporadic, an increasing number of well documented familial cases are now being recorded. The pedigree patterns thus far suggest an autosomal recessive trait. The importance of the familial form of the disorder lies in the implication it has for the physiology of normal Mullerian duct development, namely that there must exist a normal gene whose function is critical to the development of the Mullerian duct.

135. Gruenwald, P. The relation of the growing Mullerian duct to the Wolffian duct and its importance for the genesis of malformations. Anat. Rec. 81:1, 1941.

A striking feature of the disorder is the presence in most patients of fallopian tubes, suggesting that the defect lies in the lower portion of the Mullerian duct only. It is very fascinating that the caudal end of the Wolffian and Mullerian ducts develop independently, but it is clear that completion of development of the distal end of the Mullerian duct depends upon the presence of the Wolffian duct. Thus, the embryological and anatomical evidence suggests that the defect is likely the passive consequence of the absence of the Wolffian duct.

136. Michelson, L. Congenital anomalies of the ductus deferens and epididymis. J. Urol. 61:384, 1949.

137. Sandler, B. Sterility due to congenital absence of the vasa. Lancet, Dec. 9, 1950.

138. Foss, G. L., and A. Miller. Aplasia of the vasa deferentia as a cause of sterility. Lancet, Dec. 9, 1950.

Therefore, it seems reasonable to propose that the fundamental defect is a developmental defect in the Wolffian duct; this would lead to congenital absence of the vas deferens in the male and to congenital absence of the caudal Mullerian duct derivatives in the female.

CYSTIC FIBROSIS

139. Holsclaw, D. S., A. D. Perlmutter, H. Jackin, and H. Schwachman. Genital abnormalities in male patients with cystic fibrosis. J. Urol. 106:568, 1971.

Cystic fibrosis is of interest in regard to sexual differentiation. Males with cystic fibrosis are infertile due to a failure of development of a vas deferens. In addition, the epididymis is often immature, and the seminal vesicles are sometimes absent. The prostate and external genitalia develop normally. In

contrast, females with cystic fibrosis are fertile and exhibit no abnormalities in development of their internal sex structures. Thus, the mutant gene in cystic fibrosis, in addition to its postnatal effects on respiratory and pancreatic function, may have an earlier prenatal action that interferes with normal differentiation of Wolffian duct derivatives in the male.

CONCLUSION

A great deal of clinical and biochemical information concerning the hereditary disorders of sexual development has become available in recent years, and formal genetic analysis of these disorders will soon be feasible. Since some 18 hereditary, single gene-determined disorders of sexual development are currently recognized involving loci on both autosomes and the X chromosome, it can be inferred that at a minimum 18 genes and hence 18 discrete biochemical steps are involved in the translation of genetic sex into phenotypic sex. Undoubtedly, many more as yet unidentified genes must participate in this complex differentiation process. The identification of these genes will depend on the continued delineation of new, simply inherited clinical disorders of sexual differentiation. It is clear, however, that any fundamental understanding of the programming of events in sexual differentiation will require not only the identification of the genes involved but also the elucidation of the molecular mechanisms by which each of these genes is expressed.