MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

28 March 1968

TESTICULAR FEMINIZATION

CASES

Testicular Feminization. ([redacted])

Two sisters, ages 15 and 17, were referred to Dr. Paul MacDonald because of primary amenorrhea. Physical examination revealed that each was tall (5' 8" and 5' 10") and had very well developed breasts and feminine contour. Each had virtually no body hair, and pelvic examination revealed almost complete absence of the vagina. There were no other siblings; the family history is of note only in that the mother is said to have no body hair. A variety of endocrinological studies were performed both before and after operation (summarized below). Abdominal testes were removed at the time of surgery; pathology report was interpreted as revealing Leydig cell hyperplasia. Following castration menopausal symptoms were prominent until they were controlled with estrogen therapy.

Patient		Blood Concentration of Testosterone µg/100 ml	Testosterone Production Rate mg/day	Estradiol Production Rate µg/day	Conversion of Testosterone to Estradiol % (µg)
[redacted]	Pre-Op	1.73	15.2	64	0.13 (20)
	Post-Op	0.033	-	-	-
[redacted]	Pre-Op	1.90	17.0	122	0.24 (41)
	Post-Op	0.037	-	-	-

Reifenstein's Syndrome (S. S., Ref. 43)

This 10 year old boy was born on [redacted] 1953. As had previously occurred in two older brothers, he was noted to have a third degree hypospadias and a bifid scrotum. He was first seen at [redacted] in 1963 for the purpose of beginning surgical repair for the hypospadias. The testes were not completely descended. On cystoscopy an enlarged prostatic utricle was noted, and a urethrogram revealed a 1 X 2 cm posterior extension of the prostatic utricle. The upper urinary tract was normal by intravenous pyelogram.

At surgery exploration of the pelvis was negative. A right orchiopexy was performed, at which time testicular biopsy revealed normal prepubertal seminiferous tubules, lined with spermatogonium and Sertoli cells. No Leydig cells could be identified. The family history revealed several additional affected members, and it was of interest that the affected uncle had had a mastectomy in 1950 because of enlarging breasts. Sex chromatin was negative in each of the six affected men, and the karyotype was XY in the four patients examined.

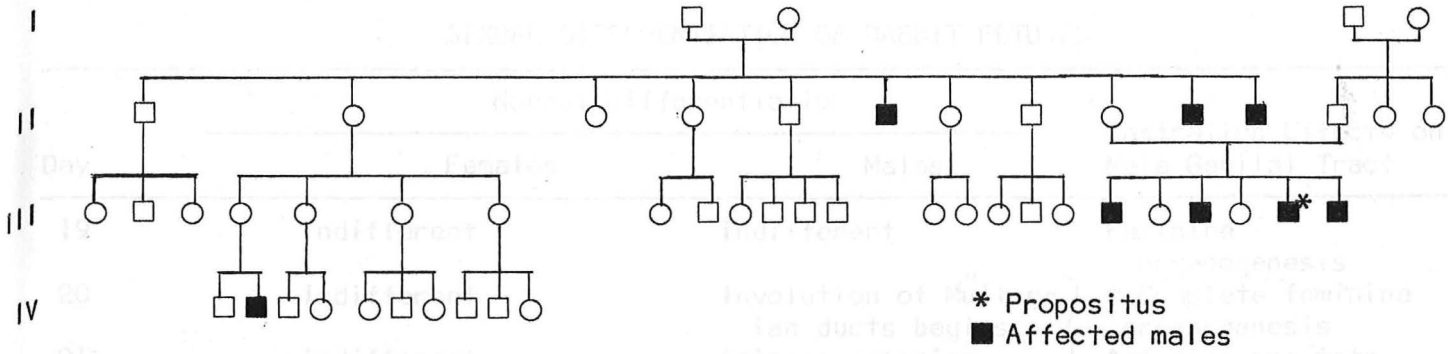

TABLE I

CLINICAL FEATURES OF TESTICULAR FEMINIZATION

(Morris)	1. Female habitus, breast development, and other secondary sex characteristics
	2. Scanty or absent axillary or pubic hair in most cases
	3. Female external genitalia with a tendency to underdevelopment of the labia and a blind-ending vagina
	4. Absence of internal genitalia except for rudimentary anlage and for gonads which may be located intra-abdominally or along the course of the inguinal canal
	5. Gonads histologically consistent with undescended testes
(Stern and Puck)	6. The affected men have male sex chromatin and an XY karyotype.
(Nowakowski and Lenz)	7. High incidence of mothers with scanty or no sexual hair
(Southren and others)	8. Testosterone production rates and blood levels are equivalent to normal men.
(Wilkins)	9. Resistance to the androgenic and anabolic effects of testosterone.

TABLE II

MAIN SUCCESSIVE EVENTS OF SEXUAL DETERMINATION AND DIFFERENTIATION

Genetic sex
↓
Gonadal sex
↓
Body sex or somatic sex

Internal structures	External genitalia	Secondary sex characters

TABLE III

SEXUAL DIFFERENTIATION OF RABBIT FETUSES

Day	Normal Differentiation		Castration Effects on Male Genital Tract
	Females	Males	
19	Indifferent	Indifferent	Feminine organogenesis
20	Indifferent	Involution of Müllerian ducts begins	± Complete feminine organogenesis
21	Indifferent	Anlagen anterior prostate	Anterior prostate present
22	Indifferent	Definite masculine trends	Uterine sections present; hypospadias
23	Fusion of posterior part of Müllerian ducts	Anlagen posterior and lateral prostate	Deferent duct absent; otherwise masculine
24	Involution of Wolffian ducts begins	Differences in genital tubercle	Masculine organogenesis
25 to 26	Definite feminine features	Definite masculine features	

TABLE IV

MORPHOGENETIC EFFECTS OF ANDROGENS AND ANTIANDROGENS ON THE GENITALIA, THE MAMMARY GLANDS AND ON THE HYPOTHALAMIC-PITUITARY SYSTEM

Organ System	Androgens		Antiandrogens	
	Stimulation (definite)	Inhibition (definite)	Stimulation (definite)	Inhibition (definite)
Genitalia	Perineum Accessory genital glands (prostate, seminal vesicle) Penis Corpora cavernosa	Vagina	Vagina	Perineum Accessory genital glands (prostate, seminal vesicle) Penis Corpora cavernosa
Mammary gland	Thickening of mesenchyme near the glandular buds (17th to 19th day)	Nipple and glandular tissue	Nipple and glandular tissue	Thickening of mesenchyme near the glandular buds (17th to 19th day)
Hypothalamic-pituitary system	?	Centers for cyclic regulation	Centers for cyclic regulation	?

TABLE V

COMPARISON OF "TESTICULAR FEMINIZATION" WITH "FEMINIZED" RATS

"Testicular feminization"	"Feminized" rats
Chromosomal sex ♂	Chromosomal sex ♂
Exterior genitalia ♀	Exterior genitalia ♀
Bodily build ♀	Bodily build ♀
Sexual behavior ♀	Sexual behavior ♀
Vagina with blind end	Vagina with blind end
Normal clitoris	Normal clitoris
Absence of uterus	Absence of uterus
Gonads ♂	Gonads ♂
Frequently inguinal hernias with testes	Scrotal development inhibited, therefore testes often not completely descended
Histologic picture of testes found in cryptorchism	Histologic picture of testes found in cryptorchism
Mammary gland development ♀	Mammary gland development ♀
Primary amenorrhea	-
?	Cyclic gonadotropin secretion after ovarian implantation
Less estrogen excretion than in women	?
Normal 17-ketosteroid excretion	?

REFERENCES

GENERAL REVIEWS

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

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

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

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

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

Each of these recent reviews presents a generally sound exposition of this syndrome.

ELUCIDATION OF THE CLINICAL SYNDROME

6. Quervain, F. De. Ein fall von pseudohermaphroditismus masculinus. Schweiz. Med. Wschr. 53:563, 1923.

7. Perkins, C. C. Hereditary genitatism. Am. J. Surg. 21:104, 1933.

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

While the description of this condition in the medical literature goes back at least 150 years, including a very detailed description of the syndrome by de Quervain in the 1920's and family studies published in Germany by Diffenbach in 1910 and in this country in the early 1930's, virtually all reviewers give Morris credit for defining the syndrome in modern terms. In this paper, in which the name "testicular feminization" is first used, he reviewed the 79 published cases which fulfilled all the criteria for inclusion in this category and added two new cases to the literature. The frequency of malignancy in the testes was emphasized, and on the basis of the literature at hand, he concluded that the testes produce both estrogens and androgens and consequently that the disease was not due to testicular inadequacy.

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

This generally ignored paper probably deserves credit as the pioneering work in the field. In addition to reviewing the literature and defining the same clinical characteristics which Morris later used, these authors concluded on the basis of pedigree and clinical analyses that the affected individuals are genetic men, that the defect could be the result either of a sex limited, autosomal defect or a X-linked recessive abnormality, and that the defect might be the result of failure of "male induction" in a type of embryo in which the fundamental developmental trend is toward the female phenotype. Altogether, this view is remarkably close to the current concepts of the problem.

10. Marshall, H. K. and H. I. Harder. Testicular feminizing syndrome in male pseudohermaphrodite. Report of two cases in identical twins. Obstetrics and Gynecology 12:284, 1958.

While subsequent papers have added little to the clinical picture, this paper does emphasize the feature which distinguishes this disease from every other type of intersex, namely the remarkable femininity of the affected individuals.

11. Nowakowski, H. and W. Lenz. Genetic aspects in male hypogonadism. Rec. Prog. Hormone Research 17:53, 1961.

This paper emphasizes that almost all genetic carriers of the disease have no, or almost no, secondary hair.

INCIDENCE OF THE DISEASE

12. Jagiello, G. and J. D. Atwell. Prevalence of testicular feminization. Lancet 1:329, 1962.

While Hauser (Ref. 2) has estimated the frequency in Switzerland at 1 in 20,000, a much more probable figure is arrived at in this study in Great Britain of one case per 62,400 men. In view of the fact that affected individuals do not reproduce (as the result of which the deletion rate of the mutant gene is high) the rate of new mutations is probably of the order of 0.4 to 0.5 X 10^{-5}.

GENETICS

13. Schneider, R. W., R. A. Ommer, and S. O. Hoenn. The hereditary occurrence of testes and absence of sexual hair in amenorrheic women: a type of pseudohermaphroditism. J. Clin. Endocrinol. 12:423, 1952.

14. Burgermeister, J. J. Contribution a l'etude d'un type familial d'intersexualite. J. Genet. Hum. 2:51, 1953

15. McKusick, V. On the X chromosome of man. Quart. Rev. Biol. 37:69, 1962.

16. Stewart, J. S. S. Testicular feminisation and colour-blindness. Lancet 2:592, 1959.

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

The recent extensive pedigree studies have not yielded any new insight as to whether the defect is X-linked or a sex limited, autosomal trait. Under circumstances in which the affected men do not reproduce the only way this dilemma can be resolved is by linkage studies with other X-linked traits. Two such families, one with hemophilia A and the other with color blindness and testicular feminization, have been reported (16 and 17); so many crossovers occurred that both authors concluded that the defect either was not X-linked or that it was so far away from the sites for color blindness and hemophilia A as to preclude mapping. In fact, this type of negative study has no implication whatsoever since several known X-linked traits (i.e. hemophilia B) are so far away from the common marker sites that they cannot be shown to be located on the X chromosome by this type of study.

18. Gayral, L., M. Barrand, J. Carrie, and L. Candebat. Pseudohermaphrodisme A type de "testicule feminisant", II cas. Toulouse Med. 61:637, 1960.

19. McKusick, V. A. Mendelian Inheritance in Man. Baltimore: The Johns Hopkins Press. 1966, p. 278.

The best evidence that the defect is X-linked comes from this remarkable case report by Gayral, et al. of a woman who was the sister, mother, and grandmother of affected individuals. She had asymmetric breast development, body hair, and vulva and had always had menstrual irregularities; McKusick has suggested that these patchy findings can best be explained by an X-linked recessive, which according to the Lyon hypothesis would be expected in the heterozygote to produce a patchy mosaicism, in which some cell lines would contain active normal and some active mutant X chromosomes.

20. Taillard, W. and A. Prader. Etude genetique due syndrome de feminisation testiculaire totale et partielle. J. Genet. hum. (Geneve) 6:13, 1957.

21. Lenz, W. Quelques remarques au sujet du travail de W. Taillard et A. Prader: "Etude genetique du syndrome de feminization testiculaire totale et partielle." J. Genet. Humaine 8:199, 1959.

While the ratio of genetic men to women in the affected sibships is one to one, the preponderance of affected to normal men (4:1) has remained puzzling since the time of Pettersson and Bonnier. Lenz has interpreted this apparent enrichment of affected to normal men as due to a statistical artefact of selection because the family with no affected member or only one affected member tends to be ignored when this type of data is collected. This explanation may not be sufficient, however, since Grumbach and Barr (23) attempted to correct their data for this type of bias and still found a 2:1 enrichment of affected to normal men.

STUDIES OF CHROMOSOMAL AND GENETIC SEX

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

23. Grumbach, M. M. and M. L. Barr. Cytologic tests of chromosomal sex in relation to sexual anomalies in man. Recent Prog. Hormone Research 14:255, 1958.

24. Jacobs, P. A., A. G. Baikie, W. M. Court Brown, H. Forrest, J. R. Roy, J. S. S. Stewart, and B. Lennox. Chromosomal sex in the syndrome of testicular feminization. Lancet 2:591, 1959.

25. 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.

26. Chu, E. H. Y., M. M. Grumbach, and A. Morishima. Karyotypic analysis of a male pseudohermaphrodite with the syndrome of testicular feminization. J. Clin. Endocrinol. Metab. 20:1608, 1960.

These patients are not only men as determined by analyses of the nuclear chromatin, but, in addition, the weight of evidence is that the chromosomal karyotype, both in number and in morphology, is that of normal man.

ENDOCRINOLOGICAL STUDIES IN TESTICULAR FEMINIZATION

27. 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.

28. 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. and Met. 25:518, 1965.

29. Kase, N. and J. McL. Morris. Steroid synthesis in the cryptorchid testes of three cases of the testicular feminization syndrome. Am. J. Obstetrics and Gynecology 91: 102, 1965.

30. Deshparde, N., D. Y. Wong, R. D. Bulbrook, and M. McMillan. Hormone studies in cases of testicular feminization. Steroids 6:437, 1965.

(Also Ref. 3, 4, 5)

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

1. The testosterone secretory rate, blood level, and metabolism is that of a normal man and falls following castration.

2. Estrogen production is probably that of a normal man; it is secreted by the testis, and menopausal symptoms follow castration.

3. The testes respond in a normal fashion to human chorionic gonadotropin.

4. 17-ketosteroids come from predominantly extratesticular tissue, doubtlessly from the adrenal gland, as in normal individuals.

5. While it has variously been reported as high, low, and normal, in view of the methodological variability gonadotropin excretion is probably that of a normal man.

Therefore, it may be concluded that normal testosterone production is an obligatory feature of the testicular feminization syndrome; unusual cases (like the third case of Kase and Morris (29) in which testosterone production is low probably represent another syndrome in which the fetal testes have been damaged and are consequently inadequate for normal virilization.

EVIDENCE FOR END ORGAN UNRESPONSIVENESS TO TESTOSTERONE

31. Albright, F., C. H. Burnett, P. H. Smith, and W. Parson. Pseudohypoparathyroidism, an example of the Seabright-Bantam syndrome. Endocrinology 30:922, 1942.

Albright applied the term "Seabright-Bantam" syndrome to classify those conditions (Vitamin D resistant rickets and pseudohypoparathyroidism) in which it was thought that the primary disturbance was a failure of response by the end organ to the hormone in question. This expression derives its origin from the fact that the male Seabright-Bantam has female feathering despite the fact that the production of male hormone is normal (as evidenced by the fertility and virility of this mutant).

32. Morgan. T. H. Castration in a hen-feathered cockerel. Demonstration of the appearance after castration of cock-feathering in a hen-feathered cockerel. Proc. Soc. Exp. Biol. Med. 13:31, 1915.

33. Morgan, T. H. Demonstration of the effects of castration on Seabright cockerels. Proc. Soc. Exp. Biol. Med. 15:3, 1917.

34. Danforth, C. H. Relation of the follicular hormone to feather form and pattern in the fowl. Yale J. Biol. Med. 17:13, 1944.

This eponym is clearly a misnomer, since following castration of the male Seabright-Bantam, the feathering pattern reverts to the male type. Since the "neuter" feathering pattern in the chicken is the male kind (the type which is also present in the castrate) it has been concluded that the ovary of the normal chicken and the testis of the male Seabright-Bantam produces a substance which inhibits the unconditioned or male type of plumage. From Danforth's studies, it is quite clear that this is an estrogen which causes the formation of lateral barbules on the feathers and consequently allows the feathers to stand upright.

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

36. 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.

37. 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. Metab. 25:661, 1965.

38. 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. Metab. 26:493, 1966.

39. 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.

40. 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).

RELATION OF THE SYNDROME OF TESTICULAR FEMINIZATION TO OTHER FORMS OF MALE PSEUDOHERMAPHRODITISM

41. Lubs, H. A., O. Vilar, and D. M. Bergenstal. Familial male pseudohermaphrodism with labial testes and partial feminization: endocrine studies and genetic aspects. J. Clin. Endocrinol. Metab. 19:1110, 1959.

42. Gilbert-Dreyfus, S., C. A. Sebaoun, and J. Belaisch. Etude d'un cas familial d'androgynoidisme avec hypospadias grave, gynecomastie et hyperoestrogenie. Annales d'Endocrinologie 18:93, 1957.

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

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

Not only can fetal damage to the testes or abnormalities of testosterone production result in phenocopies of the testicular feminization syndrome (29), but in addition four distinct diseases have been described in which the inheritance is identical to that observed in testicular feminization (X-linked recessive or sex-limited, autosomal dominant), but the abnormality is less severe than in testicular feminization. This has led Federman (5) to propose that these diseases might represent different mutations within a given biochemical pathway.

TESTICULAR FEMINIZATION IN ANIMALS OTHER THAN MAN

45. Schultz, M. G. Male pseudohermaphroditism diagnosed with aid of sex chromatin technique. J. Am. Vet. Med. Assoc. 140:241, 1962.

46. Nes, N. Testikulaer feminiseninz has storfe. Nord. Vet. Med. 18:19, 1966.

This anomaly has been clearly documented both in the dog and in the cow and appears to be identical to the disease in man.

47. Stanley, A. J. and L. G. Gumbreck. Male pseudohermaphroditism with feminizing testis in the male rat. Proc. Endocrinol. Society, 1965, p. 40.

Although the disease has been reported in the rat, it is likely that this condition is due to the overproduction of estrogen in the testes of the affected males.

PATHOPHYSIOLOGY OF THE DISEASE

A. The Normal Embryological Development of the Gonads and Accessory Sex Organs in Man

48. Gillman, J. The development of the gonads in man. Contr. Embryol. Carneg. Instn. 32: 81, 1948.

49. McKay, D. G., A. T. Hertig, E. C. Adams, and S. Donzingen. Histochemical observations on the germ cells of human embryos. Anatomical Record 117:201, 1953.

50. Witschi, E. Development of Vertebrates. Philadelphia: W. B. Saunders Co., 1956.

51. Arey, L. B. Developmental Anatomy. 7th Ed. Philadelphia: W. B. Saunders Co., 1965.

(Also see Ref. 5)

The germ cells originate from the endoderm of the yolk sac, from which they migrate to the gut mesentery and thence toward the mesonephric folds. This movement appears to be aided by active pseudopod formation and is terminated with the arrival of the germ cells in the gonadal folds. If the germ cells are XX they localize in the cortex of the germinal fold and give rise to an ovary; if XY they migrate to the medullary portion which proliferates to form a testis. Testicular development takes place earlier (fourth to twelfth weeks) than does that of the ovary (after the twelfth week).

The second stage, differentiation of the duct system or internal genitalia begins before gonadal identity is obvious. In the female, the Müllerian ducts develop and the Wolffian ducts regress, and in the male the opposite sequence occurs; in each case one duct system persists and one regresses.

The external genitalia arises in a different fashion, both the male and female pattern arising from a common analog, whose results are distinguished quantitatively.

B. The Control of Accessory Sex Differentiation by the Fetal Gonads

52. Moore, C. R. Embryonic Sex Hormones and Sexual Differentiation. Springfield: Charles C. Thomas, 1947.

53. Moore, C. The role of the fetal endocrine glands in development. J. Clin. Endocrinol. 10:942, 1950.

It was originally suggested in 1903 that hormone secretions from the embryonic interstitial cells of the testis are responsible for the control of the development and differentiation of the organs of the reproductive system. This thesis was considered proven by most investigators following the studies in Germany and America in 1916-1917 of the freemartin. In heterogametic twinning in cattle in which the fetal circulations intermingle, the internal genitalia of the female twin are invariably masculinized, giving rise to the freemartin. These findings were interpreted as due to the production by the fetal male of a hormone which caused masculinization of the female twin.

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

55. Jost, A. Embryonic sexual differentiation. Ch. in Hermaphroditism, Genital Anomalies, and Related Endocrine Disorders, ed. by H. W. Jones and W. W. Scott. Baltimore, Williams and Wilkins, 1958, p. 15.

56. Jost, A. The role of foetal hormones in prenatal development. Harvey Lectures 55:201, 1961.

57. Witschi, E., W. O. Nelson, and S. J. Segal. Genetic, developmental, and hormonal aspects of gonadal dysgenesis and sex inversion in man. J. Clin. Endocrinol. Metab. 17:737, 1957.

The studies of Jost, summarized in these reviews, have established definitively that the neuter phenotype in the mammal is the female; in the presence of a testis the development of the internal organs is that of the male whereas in the castrate or in the presence of an ovary the phenotype is female. What was not settled by these studies was whether the substance elaborated by the fetus is in fact testosterone or some other hormone. Actually, however, Jost was able to reproduce all the effects of the testis except Müllerian regression by testosterone implants in the fetal castrate.

C. Evidence that the Fetal Hormone is Testosterone; Production of Testicular Feminization in Experimental Animals

58. Hamada, H., F. Neumann, and K. Junkmann. Intrauterine antimaskuline beeinflussung von rattenfeten durch ein stonk gestagen wirksomes steroid. Acta Endocrinol. 44:380, 1963.

59. Neumann, F. and M. Kramer. Antagonism of androgenic and anti-androgenic agents in their action on the rat fetus. Endocrinol. 75:428, 1964.

60. Junkmann, K. and F. Neumann. Zum wirkurgsmechanismus von an feten antimaskulin wirksomen gestagenen. Acta Endocrinol. Supp. 90:139, 1964.

61. Neumann, F. and R. von Berswordt-Wallrobe. Effects of a new anti-androgen on the testicular structure of adult testosterone propionate treated hypophysectomized rats. Acta Endocrinol. Supp. 100:42, 1965.

62. Neumann, F. and W. Elger. Eine neve methode zur prufung antiandrogen wirksomen substanzen on weiblichen ratten. Acta Endocrinol. 52:54, 1966.

63. Neumann, F. and W. Elger. Physiological and psychical intersexuality of male rats by early treatment with an anti-androgenic agent. Acta Endocrinol. Suppl. 100:174, 1965.

64. Neumann, F. and W. Elger. Proof of the activity of androgenic agents on the differentiation of the external genitalia, the mammary gland, and the hypothalamic-pituitary system in rats. Androgens in Normal and Pathological Conditions. Ghent, 1965, p. 168.

65. Neumann, F., W. Elger, and M. Kramer. Development of a vagina in male rats by inhibiting androgen receptors with an anti-androgen during the critical phase of organogenesis. Endocrinol. 78:628, 1966.

66. Neumann, F., W. Elger, and R. von Berswordt-Wallrobe. Aufheburg der testosteron-propionatinduzienten unterdruckburg des vaginalzyklus und der ovulation durch ein antiandrogen wirksome steroid an ratten. Acta Endocrinol. 52:63, 1966.

67. Neumann, F., W. Elger, and M. Kramer. Development of a vagina in male rats by inhibiting androgen receptors with an anti-androgen during the critical phase of organogenesis. Endocrinol. 78:628, 1966.

This remarkable series of papers by Neumann's group in Berlin has established that inhibition of testosterone action at the proper time in fetal development reproduces almost exactly the testicular feminization syndrome. It has been concluded that all the development of the male phenotype, except Müllerian regression, is the result of testosterone action.

PROBLEM OF BREAST ENLARGEMENT

68. Raynaud, A. Morphogenesis of the mammary gland. Ch. in Milk: The Mammary Gland and its Secretion. Vol. I, New York: Academic Press, 1961, p. 3.

The problem of breast development in testicular feminization deserves special comment. Probably under no other circumstance does breast development in the male reach the florid degree seen in testicular feminization. This is almost certainly due to the fact that testosterone in the fetus causes a partial regression of the mammary bud so that estrogen in later life cannot produce a truly feminine development. In the absence of a fetal testosterone effect, however, later estrogen (and/or other hormones) results in a female phenotype.

POSSIBLE MECHANISMS BY WHICH TESTOSTERONE RESISTANCE MIGHT OCCUR

69. Wilson, J. D. Localization of the biochemical site of action of testosterone on protein synthesis in the seminal vesicle of the rat. J. Clin. Invest. 41:153, 1962.

70. Williams-Ashman, H. G. and S. Liao. Incorporation of amino acids into protein by cell-free extracts of the prostate gland: effect of testicular hormones and polyribonucleotides. In Biology of Prostate and Related Tissues (National Cancer Institute Monograph No. 12). Washington, D. C. 1963, p. 281.

71. Wilson, J. D. and P. M. Loeb. Estrogen and androgen control of cell biosynthesis in target organs. Ch. in Developmental and Metabolic Control Mechanisms and Neoplasia. (19th Annual Sympos. on Fundamental Cancer Res., M. D. Anderson Hosp., Houston, Tex.) Williams & Wilkins, Baltimore, 1965.

72. Bruchovsky, N. and J. D. Wilson. The conversion of testosterone to 5α-androstan-17β-ol-3-one. J. Biol. Chem. In Press.

As the result of studies in this and other laboratories over the past few years at least four discrete steps in testosterone action can be identified within target tissues: transport of the hormone to the nuclei of the cells, reduction of the hormone to its active form, dihydrotestosterone, binding of the hormone to its specific site(s) on the chromosomes, and accelerated RNA synthesis by the chromosomes in response to this challenge. Any or all of these mechanisms could be at fault in testicular feminization.