MEDICAL GRAND ROUNDS

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COMMON DEVELOPMENTAL DEFECTS OF THE MALE GENITAL SYSTEM - HYPOSPADIAS AND CRYPTORCHIDISM

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IV. Summary

Two recent grand rounds have been devoted to reviews of the advances in our understanding of normal male sexual differentiation and the pseudohermaphroditism syndromes that result from single gene mutations involving individual steps in the differentiative process. Added together, the single gene causes of abnormal sexual development are rare; testicular feminization, the commonest of these mutations, occurs in approximately one in 100,000 or more male births. In contrast, hypospadias and cryptorchidism, which also result from failure in androgen-mediated events in male phenotypic development, are among the most common of all birth defects, involving in some populations one per cent or more of all men. Although it is widely believed that these disorders are polyfactoral in origin rather than due to a single cause, there have been very few attempts to analyze systematically the various syndromes that cause the defects. What I propose to do in this presentation is to review the development of the normal male external genitalia and to examine the epidemiology, genetics, and pathogenesis of these defects.

I Male Sexual Differentiation

1. Patten, B. M. Human Embryology. New York: McGraw-Hill Book Co. 1953.

2. Hamilton, W. J., J. D. Boyd, and H. W. Mossman. Human Embryology. Baltimore: Williams and Wilkins, 1962, p. 267-314.

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

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

5. Wilson, J. D., and P. K. Siiteri. Developmental pattern of testosterone synthesis in the fetal gonad of the rabbit. Endocrinology 92:1182, 1973.

6. Siiteri, P. K., and J. D. Wilson. Testosterone formation and metabolism during male sexual differentiation in the human embryo. J. Clin. Endocrinol. 38:113, 1974.

7. Gillman, J. The development of the gonads in man, with a consideration of the role of fetal endocrines and the histogenesis of ovarian tumors. Carnegie Contributions to Embryology 210, 1948.

The formation of phenotypic sex is dependent upon gonadal sex, which in turn is determined by the genetic sex established. In the development of phenotypic sex, indifferent internal and external genital anlage are converted either to a male or female form.

The process that eventually in male phenotypic sex development is regulated by the action of three fetal hormones. Two of the three hormones - mullerian regression factor and testosterone - are secretory products of the fetal testis. 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. It may also play a role in the initial phases of testicular descent. The factors that regulate testosterone secretion by the fetal testis are not yet clear, but the evidence at hand is compatible with the possibility that the function is turned on initially by

the placenta and that regulation by the fetal pituitary (LH) commences somewhat later. The role (if any) of chorionic gonadotrophin in this process is unknown.

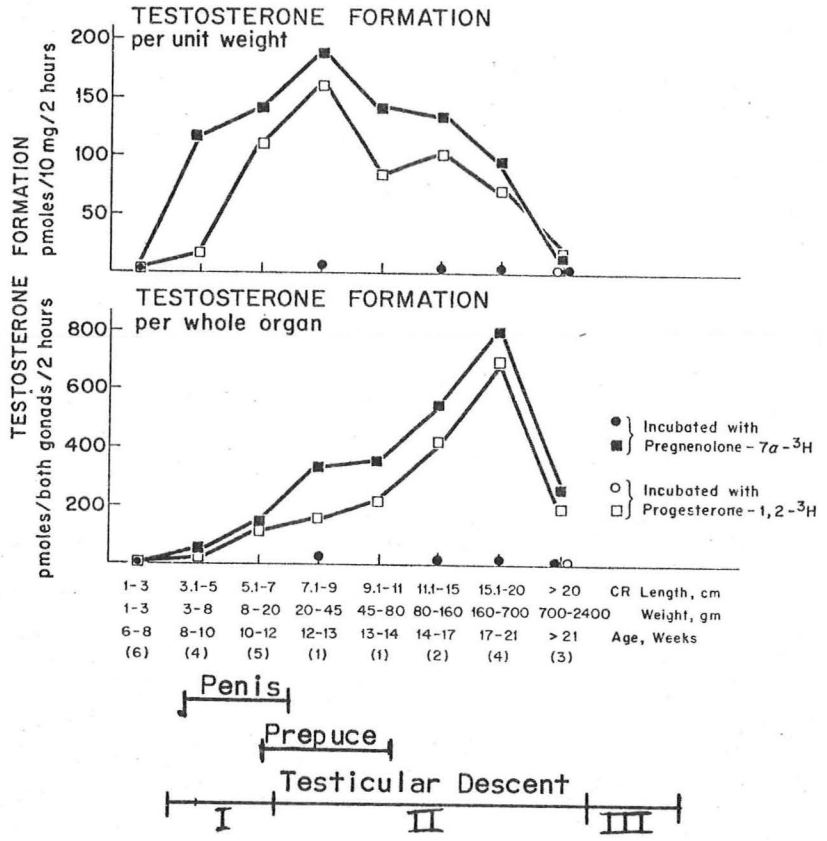

Figure 1. Correlation Between Testosterone Formation and Development of the External Genitalia in the Human Male Embryo. (Ref. 2 and 5)

Testosterone formation is measurable by the 3.1 cm stage of development, increases until approximately 20 cm stage of development, and falls during the weeks prior to delivery. The penis and male urethra are completed by 7 cm, and the prepuce is formed subsequently. The transabdominal phase of testicular descent (I) is finished by the end of the 12th week so that the testis lies at the external inguinal ring (II). The processus vaginalis and scrotum are then formed, and inguinal descent occurs after the 7th month (III).

II Hypospadias

A. Development of the Penis and Male Urethra

8. Spaulding, M. H. The development of the external genitalia in the human embryo. Carnegie Contributions to Embryology 61, 1921.

9. Wilson, K. M. Correlation of external genitalia and sex-glands in the human embryo. Carnegie Contributions to Embryology 91, 1926.

10. Glenister, T. W. The origin and fate of the urethral plate in man. J. Anat. 88:413-427, 1954.

11. Johnson, F. P. The later development of the urethra in the male. J. Urol. 4:447-500, 1920.

12. Jirasek, J. E. Development of the Genital System and Male Pseudohermaphroditism. Baltimore: The Johns Hopkins Press, 1971.

13. Jirasek, J. E., J. Roback, and J. Uher. The relationship between the development of gonads and external genitals in human fetuses. Am. J. Obstet. Gynecol. 101:830-833, 1968.

14. Jirasek, J. E. The relationship between the structure of the testis and differentiation of the external genitalia and phenotype in man. Ciba Found. Colloq. Endocrinol. 16:3-27, 1967.

At the end of the indifferent stage of embryonic development, the external genitalia of both sexes consist of a genital tubercle (penis). On each side are the genital swellings, and between the genital swellings lie the urethral folds.

In the male, growth of the genital tubercle is especially pronounced as it elongates to become the penis. On the caudal surface of the penis the genital folds elevate and elongate as the urethral groove, and by the end of the 12th week, the folds close over the groove to form the penile portion of the male urethra. The line of closure of the urethral groove remains marked by a scarlike vestige known as the penile raphe. As the penis grows it migrates anteriorly to become distant from the anus.

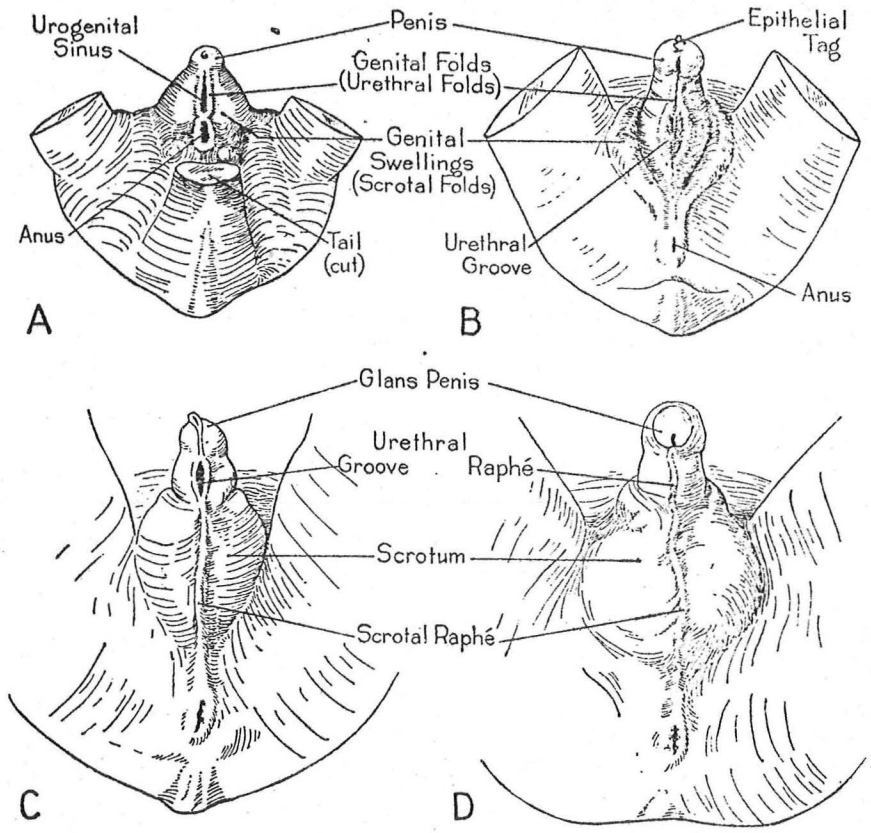

Figure 2. Stages in Development of the External Genitals in the Male (Ref.

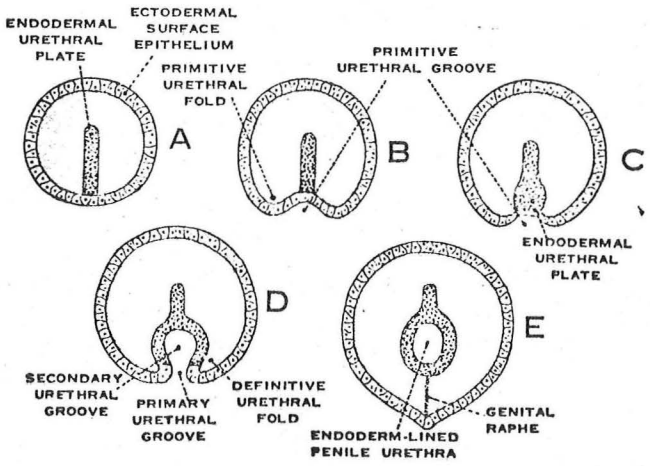

Figure 3. Schematic Transverse Section Through the Developing Phallus to Show the Definitive Development of the Penile Urethra (Ref.

There is now abundant evidence (summarized in Ref. 3 and 4) that the formation, lengthening, and migration of the penis and the formation and closure of the urethral folds are mediated by androgens secreted by the fetal testis during embryogenesis. Testosterone secreted by the testis is converted in the urogenital tubercle to dihydrotestosterone, the third hormone of fetal virilization and which is believed to be the active intracellular hormone that mediates the androgen effect in this tissue.

15. Deibert, G. A. The separation of the prepuce in the human penis. Anat. Record 57:387-399, 1933.

16. Hunter, R. H. Notes on the development of the prepuce. J. Anat. 70: 68-75, 1935.

At approximately 55 mm of development, when the urethra is almost completed, the prepuce starts to differentiate as a fold of skin that grows out to cover the glans penis completely by approximately the 11-12 cm stage. The formation of the prepuce is the only aspect of penile development that is independent of androgen; prepuce development is equal in both sexes except that because of lack of closure of the urethral groove in the female it can develop only around the upper half of the clitoris as a hood. Furthermore, the prepuce is normal in size in many cases of severe hypospadias, although in this instance it may also be in the form of a semicircle.

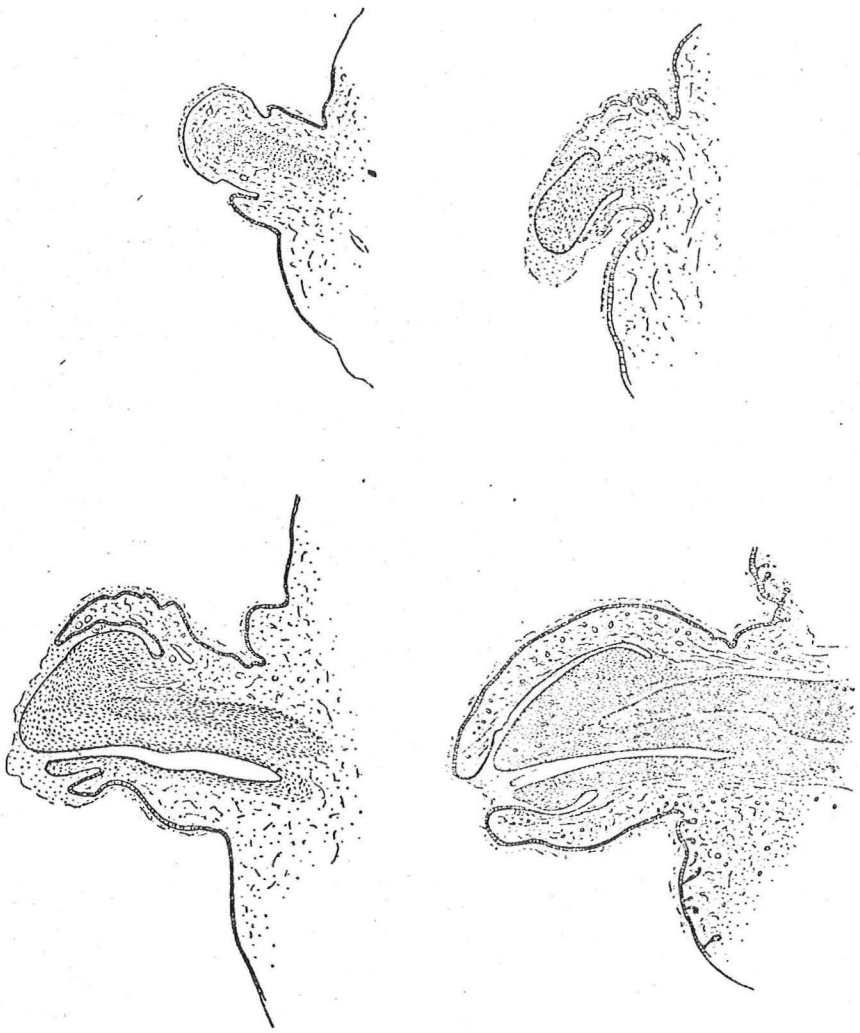

Figure 4. Progressive Stages in the Development and Separation of the Prepuce (Ref. 16)

The time sequence for the development of the penis is shown in Figure 1, but K. M. Wilson (Ref. 9) has emphasized that development of the male external genitalia is often retarded and that among putatively normal embryos there is considerable variation in the timing of its development.

B. Classification

17. Jones, H. W. Jr., and W. W. Scott. Hermaphroditism, Genital Anomalies, and Related Disorders. Baltimore, The Williams and Wilkins Co., 1971.

Hypospadias is a congenital anomaly in which the urethra terminates in an abnormal position along the mid-line of the ventral surface of the penis anywhere between the site of the normal external urethral meatus and the perineum. This malformation is often associated with some degree of chordee manifested by ventral contraction and bowing of the penis. With severe forms the entire penis appears underdeveloped, and in all types the prepuce is hooded, with redundancy of the preputial skin dorsally and laterally and deficiency ventrally. Almost no two authors use the same classification. For the purpose of this discussion, we will resort to a simplified classification: glandular, penile, and perineoscrotal.

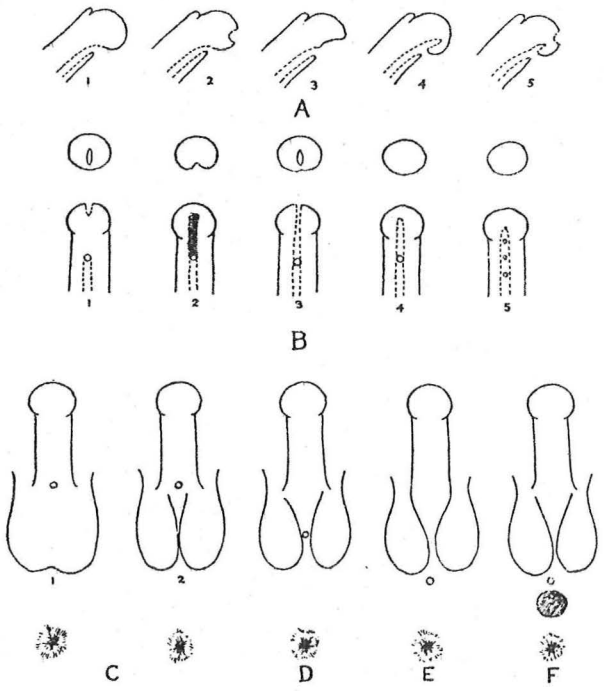

Figure 5. Varieties of Hypospadias (Ref. 17)

A. Glandular (coronal, subcoronal, first degree)
B. Penile (second degree)
C-F. Perineoscrotal (perineal, scrotal, pseudovaginal, penoscrotal, third degree)

C. Incidence and Epidemiology

18. Book, J. A. The incidence of congenital diseases and defects in a South Swedish population. Acta Genetica and Statistica Medica 2: 289-311, 1951.

19. Harris, L. F. and A. G. Steinberg. Abnormalities observed during the first 6 days of life in 8716 live-born infants. Pediatrics 14:314-326, 1954.

20. Sorensen, H. R. Hypospadias. Copenhagen: Munksgaard, 1953.

21. Wallace, H. M., L. Baumgartner, and H. Rich. Congenital malformations and birth injuries in New York City. Pediatrics 12:525-535, 1953.

22. Shapiro, R. N., W. Eddy, J. Fitzgibbon, and G. O'Brien. The incidence of congenital anomalies discovered in the Neonatal Period. Am. J. Surg. 96:396-400, 1958.

23. Kennedy, P. A. Hypospadias: A twenty year review of 489 cases. J. Urol. 85:814-817, 1961.

24. McIntosh, R., K. K. Merritt, M. R. Richards, M. H. Samuels, and M.T. Bellows. The incidence of congenital malformations: A study of 5964 pregnancies. Pediatrics 14:505-522, 1964.

25. Hay, S. Incidence of selected congenital malformations in Iowa. Am. J. Epidemiology 94:572-584, 1971.

26. Sweet, R. A., H. G. Schrott, R. Kurland, and O. S. Culp. Study of the incidence of hypospadias in Rochester, Minn., 1940-70, and a case-control comparison of possible etiologic factors. Mayo Clin. Proc. 49: 52-58, 1974.

The incidence of hypospadias varies rather strikingly in different localities:

Table I. Frequency of Hypospadias in Different Studies.

Locale	Rate per 1000 Live Male Births
Sweden	0.8
New York	5.4
England	2.6
Denmark	3.3
Iowa	4.1
Minnesota	7.9

Approximately two-thirds of all cases are of the glandular variety, and one-sixth are of the penile and perineoscrotal varieties each (20 and 23). Approximately one-third of all cases are associated with other congenital anomalies (23).

Table 2. System Involvement of 216 Anomalies in Patients with Hypospadias

Other Genitourinary	65%
Neuromuscular	14%
Gastrointestinal	7%
Cardiac	7%
Respiratory	2%
Ear, Nose, and Throat	2%
Eye	2%
Miscellaneous	2%

Table 3. Types of Genitourinary Anomalies Associated with Hypospadias in 140 Cases

	Cases
Cryptorchidism	50
Bifid Scrotum	31
Pseudohermaphroditism	14
Bladder Neck Obstruction	10
Hydrocele	8
Microphallus	5
True Hermaphroditism	3
Other	19

27. Chung, C. S. and N. C. Myrionthopoulos. Racial and prenatal factors in major congenital malformations. Am. J. Human Genetics 20:44-60, 1968.

In all studies hypospadias is approximately twice as common in whites as in blacks, whereas the opposite is true for many birth defects.

28. C. J. Roberts and S. Lloyd. Observations on the epidemiology of simple hypospadias. Brit. Med. J. 1:768-770, 1973.

It is probably more common in identical twins than in single births or in non-identical twins.

29. Slater, B. C. S., G. I. Watson, and J. C. McDonald. Seasonal variation in congenital abnormalities. Brit. J. Prev. Soc. Med. (1964) 18, 1-7.

30. Wehrung, D. A. and S. Hay. A study of seasonal incidence of congenital malformations in the United States. Brit. J. Prev. Soc. Med. 24:24-32, 1970.

31. Theonder, G. Seasonal Distribution of births of boys with anomalies of the urethra. Scand. J. Urol. Nephrol. 4:1-5, 1970.

32. Hay, S. and H. Barbaro. Independent effects of maternal age and birth order on the incidence of selected congenital malformations. Teratology 6:271-280, 1972.

33. Roberts, C. J., C. R. Lowe, and S. Lloyd. Cyclic variations in date of last menstrual period of mothers of infants with congenital malformations in South Wales, 1964-66. Brit. J. Prev. Soc. Med. 26:212-218, 1972.

The remainder of the incidence figures are not so clear-cut, particularly in regard to whether there is a seasonal variation in the birth rates of boys with hypospadias and whether there is an effect of maternal age and birth order. Data have been published on both sides of these issues. It is of some interest that the highest incidence of hypospadias ever recorded (18.5 per 1000 live male births in Rochester, Minn. in 1944) corresponded with the highest rates for spina bifida, hydrocephalus, and anencephaly during the period 1935-71 and followed a severe epidemic of rubeola in the community in the preceding year (26).

D. Pathogenesis

Since the original studies of Jost documenting the androgenic control of penile development, it has been widely assumed that hypospadias must result from some defect in androgen biosynthesis or androgen action during embryogenesis. In keeping with this concept a number of distinct etiologies for hypospadias have been elucidated during the recent past.

1.) Hereditary Defects in Testosterone Biosynthesis

20,22-Desmolase

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

3β-Hydroxysteroid Dehydrogenase

35. Bongiovanni, A. M. Disorders of adrenocortical steroid biogenesis. 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

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

17,20-Desmolase

37. Zachman, M., J. A. Vollmin, W. Hamilton, and A. Prader. Steroid 17,20-desmolase deficiency. Clin. Endocrinol. 1:369-385, 1972.

17-Ketosteroid Reductase

38. Goebelsmann, U., R. Horton, J. H. Mestman, J. J. Ance, Y. Nogata, R. M. Nokamura, I. H. Thorneycroft, and D. R. Mishell, Jr. Male pseudohermaphroditism due to 17β-hydroxysteroid dehydrogenase deficiency. J. Clin. Endocrinol. 36:867, 1973.

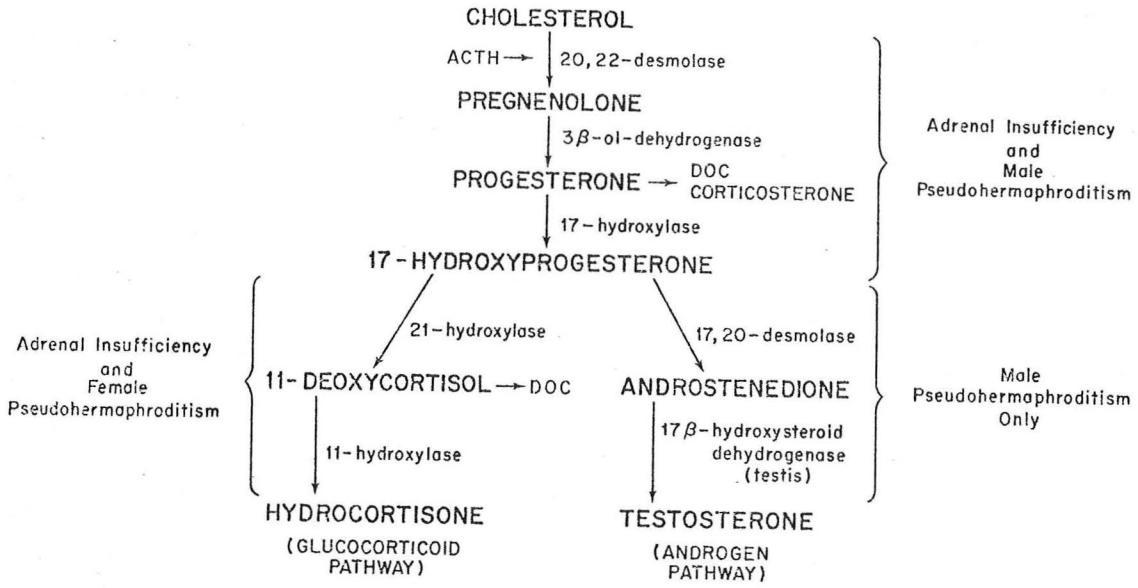

Figure 6. Defects in Androgen Action

These syndromes share a number of traits in common. Each is transmitted as a recessive trait, autosomal or X-linked, and in affected males the phenotype is variable in that affected males range from mild hypospadias to complete male pseudohermaphroditism. This variability is presumed to be due to variation in the completeness of the enzymatic defects in different patients.

2.) Hereditary Defects in Androgen Action

Familial Incomplete Male Pseudohermaphroditism, Type I

39. Ford, E. Congenital abnormalities of the genitalia in related Bathurst Island natives. Med. J. Australia 1:450-451, 1941.

40. Walker, A. C. and W. A. Horsfall. Familial male pseudohermaphroditism. Med. J. Australia 1:156-160, 1970.

41. Wilson, J. D., M. J. Harrod, J. L. Goldstein, D. L. Hemsell, and P. C. MacDonald. Familial incomplete male pseudohermaphroditism, Type I. NEJM 290:1097-1103, 1974.

(Also Ref. 12)

This apparent X-linked trait is apparently due to a partial resistance to androgen action, as the result of which affected males exhibit manifestations that vary from faulty scrotal fusion and/or hypospadias to pseudovaginal hypospadias so severe that some affected men may be identified as females at birth. The nature of the biochemical defect that gives rise to the androgen resistance in this disorder is not known; it is presumed to be less severe than the defect in testicular feminization in which resistance to androgen action is complete.

Familial Incomplete Male Pseudohermaphroditism, Type 2

42. DeVaal, O. M. Genetic intersexuality in three brothers, connected with consanguineous marriages in three previous generations. Acta Paediatrica 44:35-39, 1955.

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

44. 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.

45. Imperato-McGinley J., L. Guerrero, T. Gautier, R. E. Peterson. An unusual inherited form of male pseudohermaphroditism. A model of 5α-reductase deficiency in man. J. Clin. Invest. 53:35a, 1974.

46. Walsh, P. C., J. D. Madden, M. J. Harrod, J. L. Goldstein, P. C. MacDonald, and J. D. Wilson. Familial incomplete male pseudohermaphroditism, Type 2. Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal-hypospadias. NEJM, In Press.

(Also Ref. 20)

A second form of familial incomplete male pseudohermaphroditism is inherited as an autosomal recessive trait. Affected males have severe perineal hypospadias, a cleft scrotum, testes in the labioscrotal folds, and a vagina (50%). The internal genitalia and testosterone secretion rates are those of normal men. On the basis of work done in two laboratories, it seems clear that this disorder is due to a deficiency of the 5α-reductase enzymes, as the result of which affected individuals cannot convert testosterone to dihydrotestosterone, the active androgen in the external genitalia.

3.) Hereditary Defects in Gonadal Differentiation

Familial True Hermaphroditism

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

(Also Ref. 17)

Phenotypic sex in these XX individuals (who have ovarian and testicular elements in the gonads) is basically masculine, but gynecomastia and hypospadias are commonly present. Hypospadias can also occur in the sporadic form of true hermaphroditism (in 67 or 82 patients in ref. 17).

4.) Sporadic Defects in Gonadal Differentiation

Mixed Gonadal Dysgenesis

48. Davidoff, F. and D. D. Federman. Mixed gonadal dysgenesis. Pediatrics 52: 725-742, 1973.

49. Hartling, H., A. de la Chapelle, L. Teppo, and O. Kiwioja. Mixed gonadal dysgenesis. A case with male phenotype and 45X/46XY mosaicism. Acta Endocrinol. 65:229-243, 1970.

Virtually all patients with mixed gonadal dysgenesis have some ambiguity of the external genitalia, particularly hypospadias. These individuals are chromatin-negative and appear to represent mosaicism of XO and XY cells, probably resulting from dismutation early in embryogenesis.

50. Chen, Y. C. and P. V. Woolley, Jr. Genetic studies on hypospadias in males. J. Med. Genetics 8:153-159, 1971.

The statement has also been made in several reviews that XXY (Klinefelter's) and XYY individuals also have a higher incidence of hypospadias, but the evidence for this is poor. At best, in the latter conditions hypospadias is the exception rather than the rule.

5.) Hereditary Defects of Uncertain Type

51. Smith, D. W., L. Lemli, and J. M. Opitz. A newly recognized syndrome of multiple congenital anomalies. J. Pediatrics 64:210-217, 1964.

52. Blair, H. R. and J. K. Martin. A syndrome characterized by mental retardation, short stature, craniofacial dysplasia, and genital anomalies occurring in siblings. J. Pediatrics 69:457-459, 1966.

53. Pinsky, L. and A. M. DiGeorge. A familial syndrome of facial and skeletal anomalies associated with genital abnormality in the male and normal genitals in the female. Pediatrics 66:1049-1054, 1965.

54. Dallaine, L. and F. C. Fraser. The syndrome of retardation with urogenital and skeletal anomalies in siblings. J. Pediatrics 69:459-460, 1966.

This disorder is inherited as a recessive defect, and in affected males hypospadias occurs in addition to multiple other congenital anomalies.

55. Opitz, J. M., J. L. Frias, J. E. Gutenberger, and J. R. Pellett. The G syndrome of multiple congenital anomalies. Birth Defects Original Article Series 5, 2, p. 95-101, 1974.

This disorder is either an X-linked or X-limited trait in which hypospadias and bifid scrotum occur in addition to other congenital anomalies.

6.) Sporadic Chromosomal Abnormalities

56. Leno, J. C., G. J. Borgman, R. L. New, T. Kojii, and L. I. Gardener. A new syndrome associated with partial deletion of short arms of chromosome No. 4. JAMA 202:434-437, 1967.

57. Aarskog, D. A familial 3/18 reciprocal translocation resulting in chromosome duplication deficiency. Acta Paediat. Scand. 58:397-406, 1969.

Hypospadias can also be a part of multiple birth defect syndromes due to abnormalities of chromosomes other than X and Y.

7.) Environmental Factors

58. Goldman, A. S. and A. M. Bongiovanni. Induced genital anomalies. Ann. N. Y. Acad. Sci. 142:755-767, 1967.

59. Aarskog, D. Clinical and cytogenetic studies in hypospadias. Acta Paediatr. Scand. Supp. 203, 1970.

(Also Ref. 35)

There are two known ways in which drugs can cause hypospadias. In female embryos, the ingestion of a virilizing drug by the mother or the synthesis of excess androgens by the fetus or mother can result in virilization of the external genitalia and marked clitoromegaly with varying degrees of hypospadias. In male embryos, drugs can either interfere with testosterone synthesis or testosterone action. Goldman has studied several experimental drugs that inhibit testosterone synthesis (58), but the only instance in which drug ingestion by the mother has been reported to result in hypospadias in male infants is that of Aarskog (59) who described hypospadias in five infants whose mothers took progestin containing birth control pills early in the pregnancy. It was felt that the time sequence data constituted strong support for a cause and effect relationship.

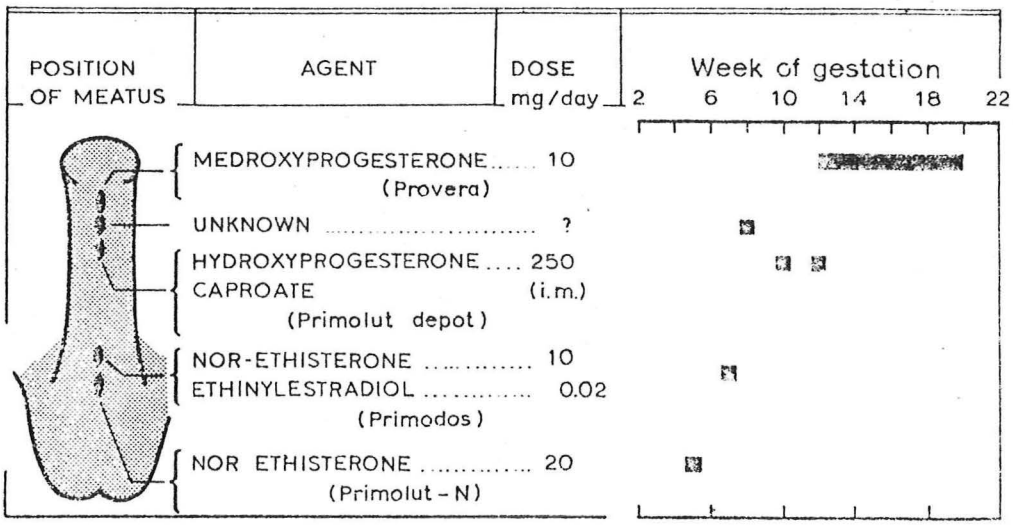

Figure 7. Hypospadias Associated with Maternal Treatment with Progestins (Ref. 59)

Other investigators have not been able to show an increased incidence of hypospadias in the mothers taking birth control pills or other progestins as compared to the mothers of normal males, but it is conceivable that this is entirely a matter of timing (26).

The question is whether the known causes can explain the pathogenesis of ordinary hypospadias. In large patient surveys Aarskog (59) concluded that 6 of 80 patients, and Chen and Wooley (50) reported that 3 of 50 patients had chromosomal abnormalities. The frequency with which the known monogenic abnormalities may be the cause is not entirely clear, but in a survey of 107 families of index patients in Rochester, Minnesota Sweet and his colleagues (26) found that in 9 families one or more first degree relatives (father or sibling) was involved. If Aarskog is correct that progestins administration to the mother may be a significant cause, then the breakdown would be approximately:

7% Chromosomal Abnormalities
8% Single Gene Defects
10% Progestin Ingestion

It is true that if the analysis of these data is limited to the more severe forms of the disorder (penile and perineoscrotal hypospadias), the percentage of known etiologies becomes somewhat higher, but no matter how the data are viewed, the cause of at least three-fourths of cases cannot be explained by the known causes.

Sweet and co-workers (26) have analyzed the 103 pedigrees of hypospadias that were published by Sorenson (20) and have concluded that the disease is inherited as a polygenic trait; this analysis cannot be correct since the 103 families contain several pedigrees that are clearly due to single gene defects, e.g. one family in which hypospadias was passed through six generations, the first pedigree of familial incomplete male pseudohermaphroditism, type 2, etc. Furthermore, the selection is clearly biased in favor of familial cases so that even if the analysis were true, it would still not be clear as to how important polygenic mechanisms are statistically. In view of the fact that there are several known autosomal recessive causes of hypospadias (four of the enzyme defects in testosterone biosynthesis, familial incomplete male pseudohermaphroditism, type 2, and the Smith-Lemli-Opitz syndrome), and since all these disorders exhibit variable expressivity, it is tempting to speculate that some of the familial cases might be due to heterozygous manifestation of these genes.

It is clear that what is needed is a survey of a large group of unselected patients designed to determine the frequency of all known causes - genetic, hormonal, chromosomal.

E. Treatment

60. Horton, C. E., Editor. Plastic and Reconstructive Surgery of the Genital Area. Boston: Little Brown and Co., 973. 679 pp.

(Also Ref. 17)

The treatment is covered extensively in the surgical sections of these two books.

III Cryptorchidism

A. Normal Testicular Movement and Descent

61. Wyndham, N. R. A morphologic study of testicular descent. J. Anat. 77:179-188, 1943.

62. Backhouse, K. M. and H. Butler. The gubernaculum testis of the pig. (Sus. Scropha) J. Anat. (London) 94:107-120, 1960.

63. Backhouse, K. M. The gubernaculum testis Hunteri: Testicular descent and maldescent. Ann. Roy. Coll. Surgeons of England 35:15-33, 1964.

64. Gier, H. T. and G. B. Marion. Development of mammalian testes and genital ducts. Biol. Reprod. 1, Supp. 1, p. 1-22, 1969.

65. Gier, H. T. and G. B. Marion. Development of the mammalian testis. Ch. in The Testis, v. 1, New York: Academic Press, p. 2-45.

The descent of the testis is less well understood than is the differentiation of the penis, both in regard to the nature of the forces that result in "movement" and in regard to the hormonal factors that regulate the process. For the purposes of this discussion, the process can be divided into three separate and distinct phases. The first process involves nephric displacement and transabdominal movement. The second involves formation of the processus vaginalis and the development of the inguinal canal and scrotum. The third and final stage is the actual movement of the testis down the inguinal canal into its permanent site in the scrotum. This entire process requires about 6-7 months' time during embryogenesis, beginning at about the sixth week and not being completed in some instances until after birth. It is almost certainly the lack of recognition of the different stages involved in this complicated process that has resulted in clinical confusion as to the various etiologies involved and physiological uncertainty as to the factors that regulate it. The anatomical events, at least, are well described.

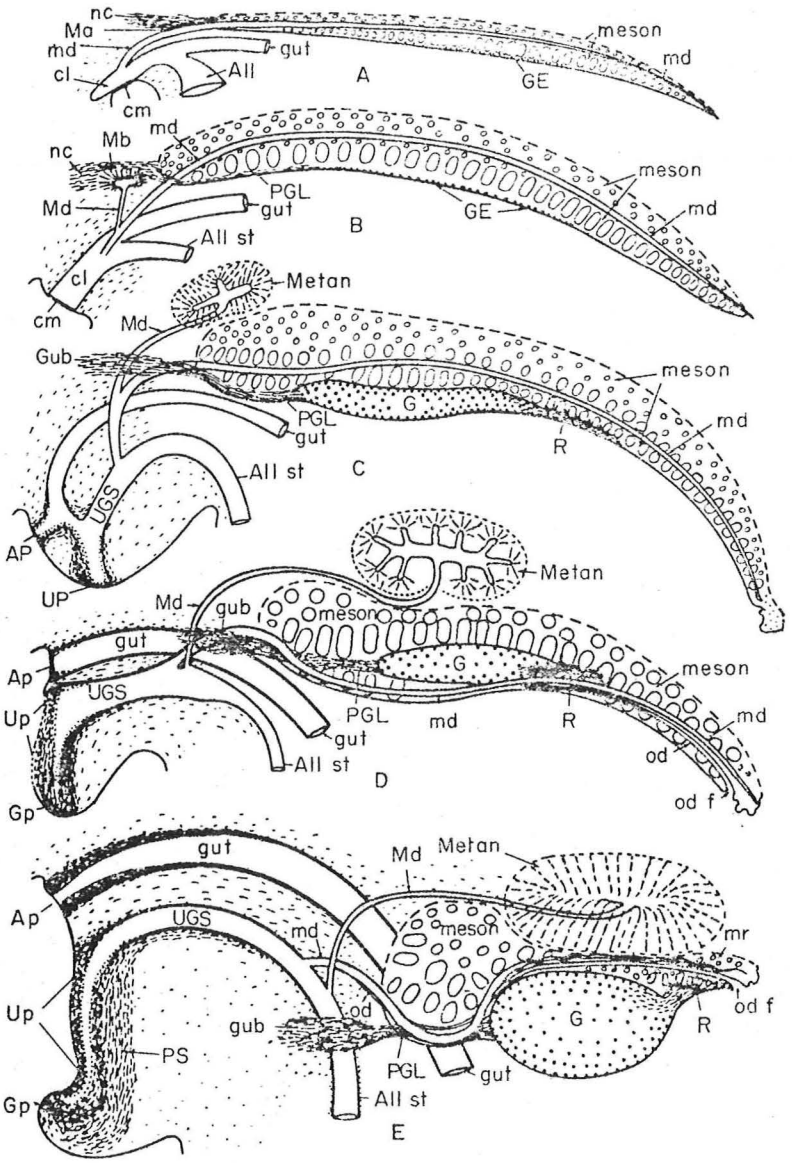

Figure 8. The First Stage of Testicular Descent: Nephric Displacement (Ref. 65)

Initially, the gonad is anterior to the kidney, but as the kidney develops it tends to move anteriorly and displace the mesonephros and gonad posteriorly. This stage of movement is complete by 55 days development in the human embryo.

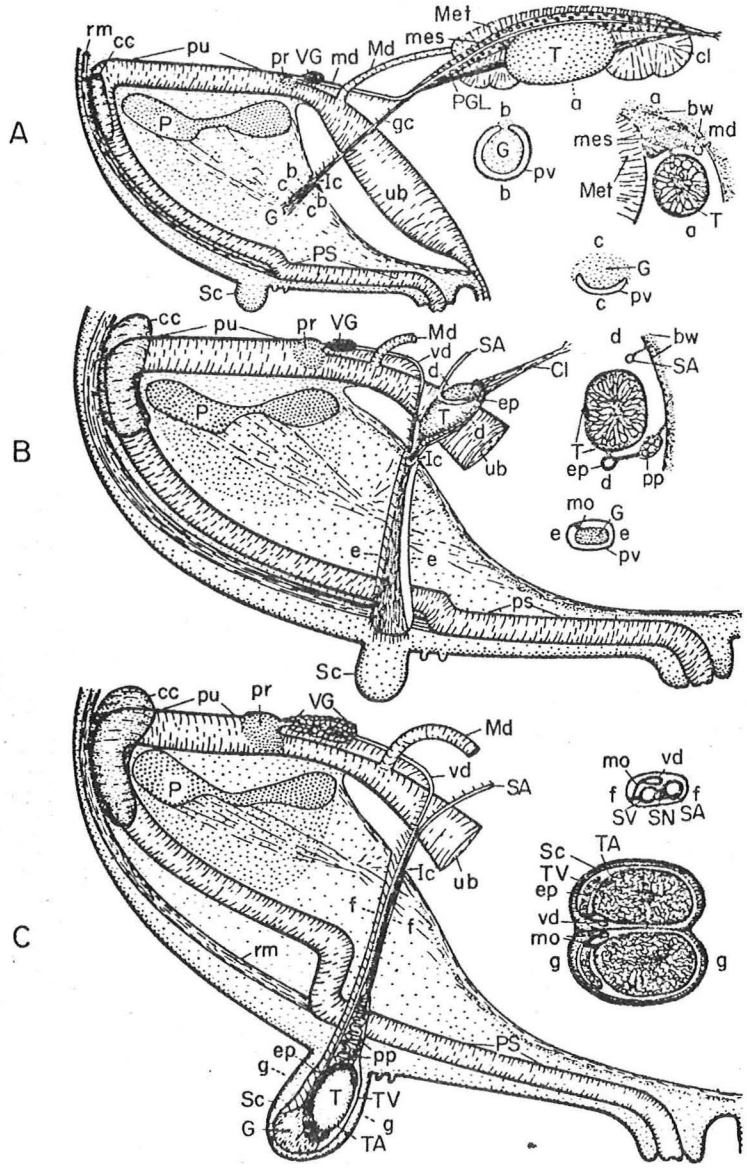

Figure 9. The First and Second Stages of Testicular Descent: Transabdominal Movement (A and B) and Formation of the Processus Vaginalis and Inguinal Canal (B and C) (65)

As the mesonephros degenerates the posterior gonadal ligament shortens from 6 mm in the 62 day human embryo to 2 mm in the 112 day human, and the gonad comes to rest against the anterior abdominal wall as a result, and due to the development of the gubernaculum. The gubernaculum - a thin cord between the tip of the mesonephric cord (posterior gonadal ligament) and the abdominal wall - begins to grow ventrally and to be surrounded by a crescentic evagination, the processus vaginalis.

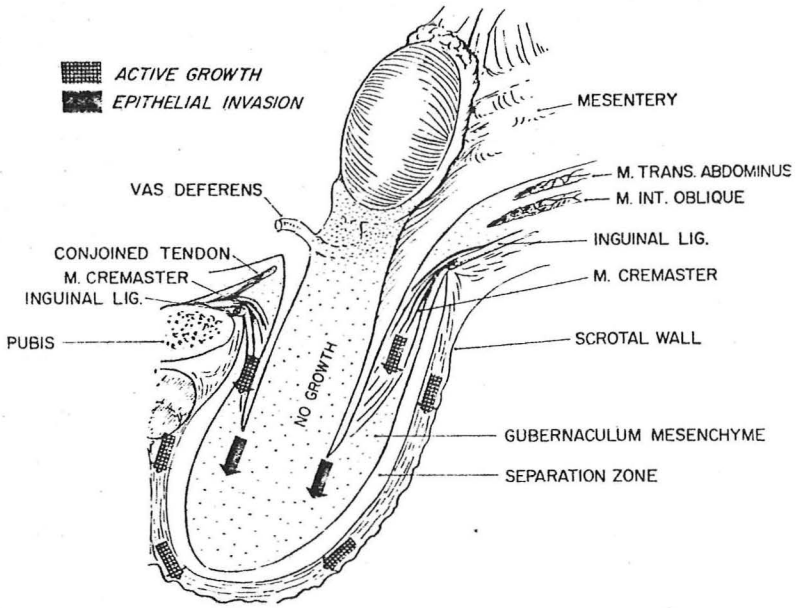

Figure 19. Stage Three of Testicular Descent: Diagram of the Human Gubernacular Apparatus Shortly Before Testicular Descent (63)

Figure 11. Sectional Diagram of the Gubernacular Apparatus of an Ungulate Shortly After the Testis Has Traversed the Inguinal Canal (63)

The processus vaginalis forms as a hernia in the weak triangle that consists of peritoneum backed only by the jelly of the gubernacular periphery while the margins of the triangle are strengthened by the iliac vein and artery, the external pudic artery and rectus abdominis muscle, and the transverse abdominis and external oblique muscles. Herniation results from internal abdominal pressure that is intensified by rapid organ development after closure of the umbilical cord. Continued pressure results in enlargement of the processus vaginalis around and into the bulb of the gubernaculum. Expansion of the processus vaginalis other than in length is resisted by the surrounding muscle. As the processus progressively elongates and encompasses more of the gubernacular bulb, the free end of the bulb is directed toward the scrotum. In the hernias at 112 days the tip of the gubernaculum reaches the scrotal swellings and by 150 days presses into the scrotum.

The third stage is the true "descent" or movement of testis from peritoneal cavity into the lumen of the processus vaginalis. As the testis approaches the inguinal ring the epididymis are pulled into the canal and serve as a wedge for opening of the canal. In the ensuing period, before passage, the gubernacular epididymis and posterior gonadal ligament increase in thickness until the diameter of the mass in the inguinal canal approaches that of the testis. Increased abdominal pressure, transferred into the processus vaginalis by fluid, results in continuous tension being exerted on the testis. Pressure from expanding visceral organs undoubtedly assists in moving the testis through the ring. The testis passes the inguinal ring at 7 months to shortly after birth. The ring subsequently contracts, and the external-internal oblique muscles aid in sealing it off from the gubernaculum, which subsequently becomes shorter as the testis settles farther down.

The scrotum begins as scrotal swellings on either side of the urethral plate before sex is determined. In the male they migrate ventrally and anteriorly and fuse prior to descent of the testes.

66. McLelland, E. Decline and fall of undescended testis. Lancet 1:99-1001, 1936.

In summary, this complicated process involves, at a minimum: disappearance of the cephalic end of the mesonephros, return of the gut from the cord to the abdomen causing an increase in intraabdominal pressure, contraction of the distal end of the mesonephros, development of the processus vaginalis, and passage of the testis through the inguinal canal. In simplistic terms, the force that seems to be involved is intraabdominal pressure which appears to cause physiological herniation of the processus vaginalis, but the factors that regulate the developmental and degenerative aspects of the problem are poorly understood.

67. Engle, E. T. Experimentally induced descent of the testis in the Macacus monkey by hormones from the anterior pituitary and pregnancy urine. Endocrinol. 16:513-520, 1933.

68. Wells, L. J. Descent of testis: Anatomic and hormonal considerations. Surgery 14:436, 1943.

69. Martins, T. Mechanism of the descent of the testicle under the action of sex hormones. Ch. in Essays in Biology, Minion E. Simpson, Ed., Berkeley: Univ. of California Press, p. 389-394, 1943.

The human is unusual among large animals in that testicular movement into the scrotum usually takes place prior to birth whereas in most species this is accomplished after birth. Engle made the interesting observation in the early 1930's that when pregnancy urine was administered to the newborn male rhesus monkey, almost immediate testicular descent took place (67). Wells subsequently demonstrated that testosterone administration to newborn males of several species has the same affect (68), and Martins extended this study by demonstrating that if the testis is removed from the tunica albuginea of a newborn monkey and replaced by a paraffin ball and if the tunica albuginea is then reconstructed, testosterone administration causes descent of the paraffin testis into the scrotum (69).

This type of study has resulted in the widespread belief that descent of the testis is mediated by androgen secreted by the fetal testis. At best, however, these studies pertain only to the final phase of the process. Whatever its involvement in testicular descent, androgen is probably not the sole hormone responsible for the following reasons:

1.) Androgen administration to the female rat embryo - sufficient to cause complete virilization of the wolffian duct system, the urogenital sinus, and the urogenital tubercle - does not result in descent of the ovary. (It is conceivable of course that this failure could be because the local concentration required for this process is too high to be duplicated by systemically administered hormone.)

2.) Some 46XY males with the complete form of testicular feminization who evidence total resistance to all known androgen actions have testes that descend all the way into the labia majora.

Thus, no matter how important androgen action may be in the process, the presence of other testicular hormones or the lack of some ovarian hormone must also be required.

B. Classification

70. Scorer, C. G. The descent of the testis. Arch. Dis. Child. 39:605-609, 1964.

71. Scorer, C. G. and G. H. Farrington. Congenital Deformities of the Testis and Epididymis. New York: Appleton-Century-Crofts, 1971, 199 pp.

For the purposes of this discussion, the following classification has been adapted from Scorer and Daniels:

1.) Canalicular Testis (Retractile) cannot be felt when it lies beneath the external oblique aponeurosis, but at other times it is felt in the groin.

2.) Obstructed Testis emerges from the external inguinal ring but stays permanently in the groin. This is thought to result from a fascial obstruction across the neck of the scrotum. In this type the spermatic cord is normal and the histology of the testis is usually normal, making surgical treatment easy and successful.

3.) Intraabdominal Testis is one in which descent has usually failed altogether; occasionally it does move down into the entrance of the canal, but it gets no further.

4.) The High Scrotal Testis reaches the scrotal cavity at or shortly after birth but never reaches the low normal position of the opposite testis.

C. Incidence

(Ref. 70, 71)

Approximately 2.7% of full term boys and 21-30% of premature male infants have failure of descent of one or both testes. Most of these are really retractile testes or cases of testes that descend during early infancy. Of 100 cryptorchid patients followed from birth to puberty, descent never occurred after 6 weeks of life in full term infants or 3 months of life in premature infants. Thus there is no real basis for the concept of late descent during boyhood or puberty, but during puberty retractile testes become easier to differentiate from true cryptorchidism. Bilateral undescended testes occur only about 10% as frequently as the unilateral variety.

Table 4. The Final Position of Arrest in 221 Undescended Testes Observed from Birth

	Unilateral	Bilateral
High scrotal	49%	25%
Canalicular	19%	28%
Intraabdominal or anorchia	9%	7%
Obstructed	23%	40%

Many normal testes are retractile during infancy and boyhood, and this condition is not always easy at the time of birth to separate from true cryptorchidism. Consequently, few epidemiological studies appear to have been done. However, in one large scale survey of 22,000 boys in East Anglia, the incidence in late teenagers was approximately 0.6 and 0.1% for true unilateral and bilateral cryptorchidism respectively, and the figures are identical in studies of live adult males and autopsy series (0.7%). It is the contention of Scorer and Daniels that this incidence is the same in late infancy and childhood and that variations from this range in reported series are largely due to confusion as to the definition of what constitutes an undescended testis.

D. Pathology of the Undescended Testis

72. Sniffen, R. C. Histology of the normal and abnormal testis at puberty. Ann. N. Y. Acad. Sci. 55:609, 1952.

73. Sohval, A. R. Histopathology of cryptorchidism. Am. J. Med. 16:346-362,

74. Morcini, R. A., E. Rosenberg, M. Caller, J. C. Laviene, O. Villar, C. Bergada, and J. A. Andrada. Cryptorchid and scrotal human testes. I. Cytological, cytochemical, and quantitative studies. J. Clin. Endocrinol. Metab. 25:927, 1965.

(Also Ref. 71)

75. Mock, W. S., L. S. Scott, M. A. Ferguson-Smith, and B. Lennox. Ectopic testis and true undescended testis: A histological comparison. J. Path. Bact. 82:439, 1961.

76. Andersen, H., M. Andreassen, and F. Quaade. Testicular biopsies in cryptorchidism. Acta Endocr. 18:567-569, 1955.

It is well documented that testicular descent is necessary because spermatogenesis cannot occur at the temperature of the abdominal cavity. (However, it is not clear at least to me how or when this temperature sensitivity of spermatogenesis was acquired during evolution; it is certainly not true in lower animals.) At any rate the cryptorchid testis degenerates both in regard to spermatogenesis and later in respect to Leydig cell function, and it has been moot for many years as to which comes first, maldescent or degeneration.

In a now classical pathological study of 47 cryptorchid testes age matched with 62 normal testes Sohval concluded that there was little difference in most between the retained and scrotal testis until the end of the prepubertal period. Distinct differences appear during puberty as retardation of spermatogenesis and a tendency toward fibrosis of the tubular basement membrane; the Sertoli and Leydig cells at this stage are normal. By early adulthood degeneration of the seminal epithelium and tubules takes place and there is fibrosis of the tubules that eventually involves the intertubular elements including Leydig cells.

Nevertheless, in all series there is a variable incidence (4 to 50%) of testes that appear to have had germinal aplasia from the first, and these congenital defects may play a significant role in the etiology of certain cases of cryptorchidism.

77. Eik-Nes. Secretion of testosterone by the ectopic and the cryptorchid testes in the same dog. Can. J. Physiol. Pharmacol. 44:629-633, 1966.

Following surgical induction of cryptorchidism in the dog average secretion of testosterone falls from 26 µg/hour/testis to 10 µg/hour/testis.

78. Macnab, G. H. Maldescent of the testicles. J. Roy. Coll. Surg. 1:126-140, 1955.

Of all the complications of maldescent of the testis, malignancy is the most serious. This article was selected from an enormous literature on the subject because it contains an extensive review. Approximately one in 64 undescended testes becomes malignant, and the incidence is about 4 times as common in abdominal as in inguinal testes. In normal men, the risk is about one in 1600 of developing malignancy. However, in large case series only about 10% of all cases of testicular malignancy are associated with maldescent. The risk appears to be less if the abnormality is surgically corrected before puberty, but cases are on record in which tumors have developed after orchiopexy.

D. Pathogenesis

There are two general theories as to the etiology of cryptorchidism:

1.) Inadequate Intraabdominal Pressure

79. Adams, O. R. An improved method of diagnosis and castration of cryptorchid horses. Proc. Am. Ass. Equine Pract. 295_299, 1965.

80. Bergin, W. C., J. R. Coffman, H. T. Grier, and G. B. Marion. A developmental concept of equine cryptorchidism. Biol. Reprod. 3: 82-92, 1970.

Cryptorchidism is a common problem in the horse, and as the result of extensive studies in embryos and newborn foals, it has been concluded that a major cause of this disorder is late closure of the umbilical hernia and late return of the gut to the abdominal canal, as the result of which insufficient intraabdominal pressure develops to cause development of an adequate processus vaginalis. Other possible factors in equine cryptorchidism include inadequate growth of the post-testicular mass and failure to expand the inguinal ring and displacement of the testis into the pelvic cavity.

81. Burke, E. C., M. H. Shin, and P. P. Kelalis. Prune belly syndrome. Clinical findings and survival. Am. J. Dis. Child. 117:668-671, 1969.

82. Roberts, P. Congenital absence of the abdominal muscles with associated abnormalities of the genito-urinary tract. Arch. Dis. Child. 31: 236-239, 1965.

83. Texter, J. H. and G. P. Murphy. The right-sided syndrome. Congenital absence of the right testis, kidney, and rectus. Johns Hopkins Med. J. 224-228, 1969.

84. Williams, D. I. and G. V. Burkholder. The prune belly syndrome. J. Urol. 98:244-251, 1967.

110 of 114 males with this syndrome in which the abdominal muscles are absent had bilateral cryptorchidism. (There is also distention of the bladder, hydroureter, and hydronephrosis.) The inguinal canal is absent, and in most there is an inadequate gubernaculum. This relationship strongly suggests that the development of adequate intraabdominal pressure may be of as much importance to the development of a processus vaginalis in man as in the horse. Unfortunately, there seems to be no solid evidence as to whether late return of the viscera to the abdominal cavity plays a significant role in the ordinary case of human cryptorchidism. It is not clear whether cryptorchidism is a common feature in other syndromes associated with lax abdominal musculature. It is striking that it is exceedingly common in the Smith-Lemli-Opitz syndrome (51-54) in which the abdominal musculature is also lax.

2. Hormonal Causes

a. Deficient Androgenization

Since the early work of Engle and Wells demonstrated that androgen and/or chorionic gonadotrophin could hasten completion of the third phase of testicular descent, namely inguinal passage, it has been widely assumed by most students of the subject that deficient androgenization is a common, if not the common, cause of cryptorchidism. According to current concepts there are three ways in which this can arise.

1.) Hypogonadotrophic Hypogonadism

85. Bardin, C. W., G. T. Ross, A. B. Rifkind, C. M. Cargille, and M. B. Lipsett. Studies of the pituitary-Leydig cell axis in young men with hypogonadotrophic hypogonadism and anosmia. Comparison with normal men, prepubertal boys, and hypopituitary patients. J. Clin. Invest. 48: 2046-2056, 1969.

86. Steiner, M. M. and J. D. Boggs. Absence of pituitary gland, hypothyroidism, hypoadrenalism and hypogonadism in a 17-year old dwarf. J. Clin. Endocrinol. 25:1591-1598, 1965.

87. Kirchhoff, H. W., W. Lehmann, and U. Schaefer. Clinical, hereditary-biologic and constitutional studies of primordial dwarfs. Z. Kinderheilk 75:243-266, 1954.

Cryptorchidism is common in those forms of dwarfism associated with hypogonadotrophin (but not in sexual ateliotic dwarfism). It is rather interesting that in most cases in which the description is complete, the testes lie in the inguinal canal. If this relation is indeed representative, then it implies that the first two phases of testicular descent take place normally. It is also of considerable interest that hypospadias appears to be rare in these disorders. This is in keeping with the concept that the gonadotrophic phase of testicular control occurs late in fetal life and that male phenotypic differentiation in general is independent of the anterior pituitary (but not necessarily of chorionic gonadotrophin)

2.) Hereditary Defects in Testosterone Biosynthesis

All the known enzyme defects that result in deficient androgen biosynthesis - 20,22 desmolase, 3β-hydroxysteroid, 16-dehydrogenase, 17-hydroxylase, 17,20-desmolase, and 17-ketosteroid reductase (34-38) - also have cryptorchidism as a common feature. The diseases are rare, the syndromes that result from them are variable in their expressivity presumably as the result of variations in the severity of the enzyme deficiencies, and the cryptorchidism has not been described adequately in the vast majority of cases. However, it is my impression that as is true in hypogonadotrophic states, the testes usually lie low in the abdomen or somewhere along the inguinal canals.

3.) Hereditary Defects in Androgen Action

The known hereditary defects in androgen action, complete and partial testicular feminization and familial incomplete male pseudohermaphroditism, types 1 and 2 also have a high (but not universal) incidence of cryptorchidism (Ref. 39-46). As is true for the defects in testosterone synthesis, cryptorchidism, when it occurs, seems to involve primarily the terminal phases of testicular descent, and the incidence may be no more than 50% over-all.

4.) Defective Mullerian Duct Regression

88. Nilson, O. Hernia uteri inguinalis. Acta Chir. Scand. 83:231, 1939.

89. Guell-Gonzalez, J. R., A. Paramio-Ruibal, and B. Delgado-Norales. Male pseudohermaphroditism with internal bisexual genitals. Revue Roumaine d'Endocrinologie 7:343-347, 1970.

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

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

92. Brook, C. G. D., H. Wagner, M. Zachmann, A. Prader, S. Armendares, S. Frenk, P. Alemon, S. S. Najjan, M. S. Slim, N. Genton, and C. Bozic. Familial occurrence of persistent mullerian structures in otherwise normal males. Brit. Med. J. 1:771-773, 1973.

This disorder, an autosomal recessive defect in which phenotypic males also have a uterus and fallopian tubes, is presumed to be the result either of deficient formation or resistance to the action of mullerian regression factor. It is very striking that in virtually all cases the cryptorchid testes are described at surgery as occupying the position of normal ovaries whereas the uterus descends into the inguinal canal. This implies a total failure of all phases of testicular migration. It is tempting to speculate that mullerian regression factor might be involved in the initiation of the first phase of testicular descent, namely in degeneration of the anterior mesodermal ligament. However, it is also the case that in mixed gonadal dysgenesis (48-49) testes can descend into the scrotum accompanied by uterus and/or fallopian tube, and it is also true that no careful endocrinological studies of androgen and estrogen metabolism have been performed on patients with the persistent mullerian duct syndrome. It is possible that a systematic analysis of the pathogenesis of this defect could provide major insight into the initiation of testicular descent.

3. Birth Defects of Uncertain Pathogenesis

93. Hanley, W. B., V. A. McKusick, and F. T. Barrance. Osteochondritis dissecans with associated malformation in two brothers. J. Bone Joint Surg. 49A:925-937, 1967.

94. Corbos, B. C. and V. J. O'Conor. The familial occurrence of undescended testes. Report of six brothers with testicular anomalies. Surg. Gynec. Obstet. 34:237-240, 1922.

95. Perrett, L. J. and D. A. O'Rourke. Med. J. Aust. 1:1289-1290, 1969.

Although the hereditary occurrence of cryptorchidism is less well documented than in the case of hypospadias, it is a general impression that familial occurrence is common, both in association with other birth defects as in Ref. 93 and as an isolated finding in families (94, 95).

As was the case for hypospadias, it is not clear at present whether the known etiologies of cryptorchidism constitute a significant cause of common cryptorchidism or whether the critical environmental, hormonal, or genetic factors involved remain to be identified.

96. Walsh, P. C., N. Curry, R. C. Mills, and P. K. Siiteri. Plasma androgen response to HCG stimulation in prepubertal boys with hypospadias and cryptorchidism. In Press.

Table 5. Serum Androgen Levels in Prepubertal Boys Before and After HCG

Group	#	Serum Testosterone, ng/ml		
		Before	After	Increment
Unilateral cryptorchidism	24	24	0.71 ± 0.10	2.36 ± 0.28
Bilateral cryptorchidism	8	8	0.29 ± 0.05	1.76 ± 0.50
Hypospadias	11	11	0.60 ± 0.07	3.22 ± 0.45
Monorchism	4	4	0.74 ± 0.36	2.19 ± 0.88

To investigate this problem, Drs. Walsh and Siiteri measured serum testosterone in a large group of prepubertal patients before and after HCG administration. Clearly, in the case of unilateral cryptorchidism and hypospadias the response is normal, implying that subtle defects in testosterone biosynthesis (as might occur in heterozygotes for one of the known enzyme deficiencies) are not likely to be major factors in the pathogenesis of the unilateral defect. The implications of the findings in the bilateral disease are unclear, namely as to whether the defect is primary or secondary. In addition, no implications can be drawn as to whether partial abnormalities in the regulation of LH secretion or in the action of androgens might be involved.

D. Treatment

97. Deming, C. The evaluation of hormonal therapy in cryptorchidism. J. Urol. 68:354, 1952.

Only about 5 per cent of cryptorchid testes descend after treatment with large doses of HCG for 4 weeks, and it is not clear (to me at least) whether these are cases of true cryptorchidism. However, it is possible that HCG may be an important adjunct to surgical therapy in that it may cause lengthening of the cord and aid in a more normal final placement of the gland in the scrotum. The surgical therapy is adequately reviewed in Ref. 71.

V. Summary

The processes that eventuate in differentiation of the male external genitalia and descent of the testes are complex. While it is certain that androgens play an important role in both processes, it is equally clear that additional hormonal factors are probably involved and that the enzymatic mechanism involved in the various phases have never been analyzed. In the past few years, more and more discrete causes for these common developmental defects have been delineated, and it is certain that additional causes will continue to come to light. It will be necessary to explore the pathogenesis of these various syndromes and to study the process in normal embryogenesis at both cellular and molecular levels before either normal or abnormal development of the male genitalia can be completely understood.