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Male pseudohermaphroditism
Donna J. Levy, MD, Lenore S. Levine, MD,* and Maria I. New, MD*

Male pseudohermaphroditism is the condition of incomplete male differentiation of the external genitalia in an individual with a Y chromosome. The gonads of the male pseudohermaphrodite, when present, are either streak gonads or testes.

A wide range of disorders and phenotypic presentations are encompassed by the term male pseudohermaphroditism. The following case describes a male pseudohermaphrodite who presented with ambiguous genitalia. However, as will be discussed in greater detail below, the external genitalia of male pseudohermaphrodites may be unambiguously female or may appear to be almost completely masculinized.

CASE HISTORY
The infant, a 9 lb 3 oz product of a full-term gestation, was born to a 23-year-old gravida 1, para 0 mother via normal spontaneous vaginal delivery. Pregnancy was uncomplicated and there was no history of maternal ingestion of medication. At birth, ambiguity of the external genitalia was noted with a 1-cm phallus, one opening on the perineum, and a small palpable mass in each of the large unfused labia. No uterus was palpable on rectal examination. Serial serum electrolytes remained normal. Genetic evaluation revealed a chromatin-negative buccal smear, with Y fluorescence. Karyotype analysis of peripheral lymphocytes revealed a 46,XY chromosomal complement. Radiologic studies included an excretory urogram revealing normal functioning kidneys with intact pelvocalyceal systems, ureters, and bladder, and a blind-ending vagina, with no evidence of cervical indentation. Base line 24-hour urinary 17-ketosteroid and 17-hydroxycorticosteroid determinations were all normal. Because the small phallic size would have been incompatible with male sexual function, a female sexual assignment was made, and vaginoplasty, gonadectomy, and clitoral recession were planned for the future. At 3 weeks of age, gonadal function was evaluated by stimulation testing with human chorionic gonadotropin (HCG). 1,000 units, administered intramuscularly on three consecutive days. Serum estrogens and androgens were measured pre- and postadministration of HCG. Estrone (E₁) and estradiol (E₂) were not detectable in the serum before and after administration of HCG. However, the ratio of the serum concentration of Δ4-androstenedione to testosterone in both the pre-HCG and post-HCG samples was clearly elevated. The abnormally elevated Δ4-androstenedione/testosterone ratio strongly suggested the presence of 17-hydroxysteroid dehydrogenase deficiency. At 4 weeks of age surgery was performed, and intraperitoneal immature testes with epididymides and vas deferens were excised. A Cortrosyn test, which utilizes a synthetic form of adrenocorticotropic hormone to evaluate adrenal function, was performed several months after the surgery. The results showed normal adrenal function with respect to the glucocorticoid and mineralocorticoid responses. There was no detectable response of adrenal testosterone or Δ4-androstenedione, to Cortrosyn stimulation. However, dehydroepiandrostosterone sulfate levels rose minimally. The response of the adrenal androgens to cortrosyn was judged to be entirely normal for a prepubertal child.

The above case of male pseudohermaphroditism thus appears to have been due to an enzymatic deficiency, of 17-hydroxysteroid dehydrogenase, which results in impaired testosterone biosynthesis. This enzyme deficiency will be discussed in more detail below.

In this article, we will review normal sexual development and then discuss the differential diagnosis and management of male pseudohermaphroditism. For the purpose of the ensuing discussion, we have classified the disorders resulting in male pseudohermaphroditism into three groups, on the basis of pathophysiology: disorders of testosterone biosynthesis, disorders of testosterone metabolism, and disorders of androgen receptors.

NORMAL SEXUAL DEVELOPMENT
The genetic sex of the human embryo is determined at conception. However, in the first few weeks of gestation, the gonads of the male and female are morphologically indistinguishable and are referred to as undifferentiated gonads.1-3 With respect to gonadal and genital development, the human embryo is initially bipotential. In an embryo with a Y chromosome, transformation of the indifferent gonad into a testis occurs in the seventh week of gestation.3 A gene, or set of genes, on the Y chromosome appears to be responsible for the differentiation of the indifferent gonad into a testis. It is theorized that the Y chromosome carries the genetic information necessary for the production of a substance referred to as the testis-organizing plasma membrane protein, or the H-Y antigen. The role of the H-Y antigen is limited to the induction of the male gonad.4,5 In the absence of H-Y antigen, the indifferent gonad becomes an ovary.6,7 The development of the indifferent gonad into an ovary occurs relatively slowly, in comparison with the development of the testis. Hence, the ovary is not positively identifiable as such until almost the tenth week of gestation.1

The hormonal secretions of the fetal testes are responsible for the translation of the male gonadal sex into male phenotypic sex. Like the early undifferentiated gonad, the internal and external genitalia of the human fetus are initially not distinguishable as male and female. Two sets of paramedian internal genital ducts develop in both sexes: Wolf-
Pseudohermaphroditism

Fig 1. Sexual differentiation of internal genitalia (A) and external genitalia (B). (Reproduced with permission from Griffin and Wilson.16)

Thus, in normal males, Wolffian ducts give rise to the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts12,13 (Fig 1, A). However, testosterone does not inhibit Müllerian duct development.14 Rather, Müllerian inhibiting factor, produced by the fetal testis, results in regression of the Müllerian ducts. Müllerian inhibiting factor is local in its effect and its inhibitory influence is restricted to the Müllerian duct in direct contact with the fetal testis.15 Regression of the Müllerian ducts is first noted in the 50- to 60-day embryo.2

Development of the female internal genitalia does not depend on hormonal effect and occurs normally in the absence of Müllerian inhibiting factor.7 The Müllerian ducts give rise to the uterus, the Fallopian tubes, and the upper part of the vagina (Fig 1, A). The Wolffian ducts regress in the absence of high levels of testosterone.6

In normal males, masculinization of the external genitalia and the urethra occurs under the influence of dihydrotestosterone. Dihydrotestosterone results from the intracellular reduction of testosterone, which is first noted at approximately 65 days of life.2 Under the influence of dihydrotestosterone, the genital tubercle gives rise to the glans penis. Fusion of the labioscrotal swellings also occurs, resulting in the formation of the scrotal raphe and scrotum. Fusion of the urethral grooves results in the formation of the penile raphe and the shaft of the penis. The urogenital sinus, under the influence of dihydrotestosterone, gives rise to the prostate and the prostatic urethra (Fig 1, A and B). The process of masculinization of the genitalia is largely completed by the 14th week of gestation. During the remainder of gestation, descent of the testes and further differential growth of the male external genitalia occur.1-3,16

In normal female embryos, the urogenital sinus gives rise to the urethra and the lower part of the vagina. The genital tubercle becomes the clitoris and the urogenital swellings the labia majora. The rims of the urethral grooves become the labia minora (Fig 1, A and B). The process of feminization of the external geni-
talia and the urogenital sinus is completely independent of the fetal ovaries.\(^5\)\(^{-17}\)

**DISORDERS OF TESTOSTERONE BIOSYNTHESIS**

**Gonadal Dysgenesis**

Individuals with this form of male pseudohermaphroditism fail to masculinize completely, presumably as a result of impaired androgen production by the dysgenetic testes. These individuals may have apparently normal 46,XY chromosomal complements, in which case the term XY gonadal dysgenesis is applied. Gonadal dysgenesis can also be found in mosaics, who have a 45,X cell line and at least one additional cell line containing Y chromosomal material.\(^3\)

In XY gonadal dysgenesis somatic anomalies are usually absent and the external genitalia are female. However, in some cases the clitoris is enlarged. Internally, a hypoplastic uterus and Fallopian tubes may be present. The gonads are characterized by streaks that are histologically similar to the gonads of patients with only a 45,X cell line.\(^18\)\(^{19}\) However, unlike the case in 45,X individuals, approximately 20% to 30% of these individuals with 46,XY gonadal dysgenesis will develop a gonadal neoplasm, such as a gonadoblastoma, gynandroblastoma, or dysgerminoma.\(^3\) The gonadoblastomas and gynandroblastomas are benign, but may be associated with dysgerminomas or other malignant tumors.\(^19\)

Because of the high risk of neoplastic transformation, excision of the gonads in all individuals with 46,XY gonadal dysgenesis is recommended.

The etiology of the gonadal dysgenesis in 46,XY individuals is not entirely clear. Studies on the blood leukocytes and cultured skin fibroblasts of such patients have revealed individuals who are HY antigen negative (H-Y\(^-\)) and individuals who are HY antigen positive (H-Y\(^+\)).\(^18\) It has been proposed that absence of HY antigen, leading to failure of testicular differentiation, may be a result of suppression of Y-situated H-Y structural genes by mutated regulatory elements of the X chromosome. An alternative explanation for the absence of demonstrable H-Y antigen in 46,XY individuals is that damage to, or loss of, the H-Y genes of the Y chromosome may have occurred.\(^18\)\(^{20}\) Deletions of the Y chromosome have been documented in cases of male pseudohermaphroditism presenting with phenotypically female genitalia.\(^15\)\(^{21}\) It has recently been proposed that damage or deletions which are not demonstrable by our current techniques of chromosomal analysis, can occur to the testis-determining genes (H-Y genes) on the Y chromosome.\(^13\)\(^{15}\) In those cases of 46,XY gonadal dysgenesis, clearly associated with the presence of H-Y antigen in leukocytes and skin fibroblasts, the lack of testicular differentiation is theorized to be a result of failure of specific binding of H-Y antigen to gonadal receptors.\(^18\)

Gonadal dysgenesis occurring in mosaics most commonly is associated with the 46,X/46XY chromosomal complement. This form of mosaicism is thought to be a result of mitotic non-disjunction or anaphase lag.\(^3\) The external genitalia of these patients with gonadal dysgenesis due to mosaicism demonstrate a wide range of phenotypic expression as described below. The different phenotypes do not correlate well with the tissue distribution of the various cell lines.\(^22\)

Approximately 5% of patients with gonadal dysgenesis and unambiguous female genitalia have a 45,X cell line and a cell line containing a Y chromosome. Most of these patients have manifestations of Ullrich-Turner syndrome (45,X cell line only). The genitalia, in this subgroup, are those of a normal female. The uterus remains unstimulated and breasts fail to develop because of decreased levels of sex steroids. The gonads of these 45,X/46XY individuals are found to be streak gonads, and are usually histologically indistinguishable from the streak gonads of those with Ullrich-Turner syndrome. However, occasionally mesonephric remnants and the presence of dysgenetic germ cells and Leydig cells are noted on examination of the internal genitalia.

Gonadal neoplasms similar to those found in 46,XY gonadal dysgenesis and usually arising during the first two decades of life, occur in 15% to 20% of 45,X/46XY individuals. Because these neoplasms may be associated with malignant tumors, removal of the streak gonad is also recommended in all 45,X/46XY individuals.\(^21\) In view of the risk of neoplasia, in those forms of gonadal dysplasia associated with the presence of a Y chromosome, a chromosomal analysis should be performed in all patients with gonadal dysgenesis. A buccal smear indicating the absence of Barr bodies, or the finding of an increased total digital ridge count, is suggestive of a 45,X cell line, but does not rule out mosaicism with a cell line containing a Y chromosome.

Some individuals with gonadal dysgenesis due to 45,X/46XY mosaicism have ambiguous genitalia. Most of these individuals have a streak gonad and a dysgenetic testes and are said to have mixed gonadal dysgenesis. However, other individuals, with apparently identical chromosomal complements have bilateral dysgenetic testes. Mullerian derivatives are present in all of these cases. The uterus, however, is usually rudimentary and the Fallopian tube may fail to develop on the side on which a testis is present, as a consequence of local diffusion of Mullerian inhibiting factor from the embryonic testis.\(^3\)

45,X/46XY mosaicism is occasionally documented in individuals with predominantly male external genitalia, ranging from various degrees of hypospadias to normal male external genitalia. Testes are present, although absent spermatogenesis has been documented in several cases.\(^3\)\(^{22}\) Mullerian derivatives are also present. However, there have been a few reports of individuals with 45,X/46XY mosaicism and with hypospadias, who had bilateral testes, and no evidence of uterus or Fallopian tubes.\(^2\)\(^{23}\) These individuals represent exceptions to the previously noted generalization that Mullerian derivatives are usually present in 45,X/46XY mosaicism.

Individuals with 45,X/47XY and 45,X/46XY/47XYY chromosomal...
Deficient Testosterone Synthesis Due to Enzyme Defects

Male pseudohermaphroditism may be the result of decreased secretion of testosterone due to enzymatic deficiencies of steroidogenesis. Deficiencies have been described for each of the five enzymes necessary for the biosynthesis of testosterone, namely: cholesterol desmolase, 3β-hydroxysteroid dehydrogenase (3β-HSD), 17α-hydroxylase (17α-OHase), 17,20-desmolase, and 17β-hydroxysteroid dehydrogenase (17β-HSD). The first three enzyme deficiencies are forms of congenital adrenal hyperplasia and result in inadequate cortisol and testosterone production. The inheritance of 17α-hydroxylase and 3β-hydroxylase deficiencies is autosomal recessive. In the other three defects, 17β,20-desmolase, 17β-HSD, and cholesterol desmolase deficiency, the form of inheritance has not been established due to rarity of cases. It is assumed that they also are transmitted by an autosomal recessive gene, although an X-linked form of inheritance has been postulated in 17,20-desmolase deficiency. Heterozygous subjects are phenotypically normal. In all five of these disorders of testosterone synthesis, secretion of Mullerian inhibiting factor by the fetal testis is normal and inhibition of the Mullerian ducts is complete. Thus, the uterus and Fallopian tubes are absent. Each of the enzyme deficiencies shows considerable phenotypic heterogeneity. This is probably a reflection of differing degrees of impairment of enzyme activity.

1. Congenital Lipoid Adrenal Hyperplasia. A male pseudohermaphrodite with severe salt wasting and impairment of synthesis of all three classes of adrenal steroids, mineralocorticoids, glucocorticoids, and sex steroids, was first described by Prader and Gurtner in 1955. Urinary 17-ketosteroid (17KS) and 17-hydroxyprogesterone (17OHCS) excretion was low and did not rise in response to adrenocorticotropin hormone (ACTH). The patient was a genetic male with female external genitalia. At autopsy, male genital ducts and enlarged adrenals were noted. The adrenals were characterized by cortical cells filled with lipid material consisting of cholesterol and cholesterol esters. Because of the adrenal findings, the patient's disorder was termed congenital lipoid adrenal hyperplasia. Most of the patients subsequently described with this disorder have died in adrenal crisis in early infancy, due to inadequate glucocorticoid and mineralocorticoid production. However, a few patients have survived early childhood. Today, with early diagnosis and rapid institution of treatment, the prognosis for survival and continued growth and development of these infants is good.

The biosynthetic defect in congenital lipoid adrenal hyperplasia involves the side chain cleavage converting cholesterol to pregnenolone. At least three enzymes are involved in the conversion: 20α-hydroxylase, 22α-hydroxylase, and 20α,22α-desmolase. In 1971, Degenhart et al. reported a patient with biochemical evidence for deficiency of the
enzyme cholesterol 20α-hydroxylase. Theoretically, a deficiency of any of the three enzymes of the cholesterol desmolase group, resulting in an impairment in production of all three classes of steroids, should result in the same phenotypic appearance and adrenal pathology. The severe ambiguity of the external genitalia in the male with congenital lipoid adrenal hyperplasia suggests that the enzymatic defect is present in the testes, as well as the adrenal. Female infants with this disorder have normal genital development.

2. 3β-HSD Deficiency. This disorder, as in cholesterol desmolase deficiency, results in decreased synthesis of all three classes of adrenal steroids with impaired secretion of aldosterone, cortisol, and testosterone. Males are incompletely virilized and those with more severe enzyme deficiency are seen in early infancy in adrenal crisis. Females with 3β-HSD deficiency may have normal female external genitalia or minimal clitoral enlargement, due to elevated levels of dehydroepiandrosterone (DHEA) which is a weak androgen. DHEA is not a sufficiently strong androgen to masculinize completely the external genitalia in the male.

The 3β-HSD enzyme level in the testes, adrenal, and liver may be under different control with resultant varying degrees of enzymatic deficiency in different organs. In some cases, the testes have been less severely affected than the adrenal with resultant onset of virilization during puberty. Breast development during puberty may occur with this form of male pseudohermaphroditism. It has been suggested that inadequate testosterone production during fetal life fails to suppress the breast anlage, and hence, at puberty gynecomastia occurs. Long-term survival, without hormonal treatment, is possible in cases in which the enzyme deficiency is less severe.

3. 17-OHase Deficiency. A deficiency of 17-OHase will result in a decrease in cortisol production and androgen production. Genetic males are born with ambiguous genitalia, while females with this defect have hypogonadism which appears at puberty. Prominent breast development may be the only secondary sex characteristic occurring in males at puberty. Patients with 17-OHase deficiency have increased ACTH secretion as a result of impaired cortisol production. The increased ACTH leads to an increase in the production of corticosterone, a weak glucocorticoid, and deoxycorticosterone (DOC), a mineralocorticoid. Hypertension, accompanied by hypokalemic alkalosis is frequently present in this syndrome and results from the increased DOC production. The increased DOC results in sodium retention and plasma volume expansion. Plasma renin activity is suppressed and aldosterone production is decreased. Urinary 17KS levels are low. Treatment with glucocorticoids suppresses the elevated levels of DOC, which results in correction of the elevated blood pressure and hypokalemic alkalosis.

4. 17,20-Desmolase Deficiency. In 1972, Zachman et al first reported 17,20-desmolase deficiency in three related patients, two first cousins and a maternal "aunt." These individuals were all genetic males with ambiguous genitalia. Testes were found to be located intra-abdominally or in the inguinal canal, but spermatogenesis was absent. Biochemical testing showed elevated urinary pregnenolone, one of the metabolites of 17-OH pregnenolone, in the base line state. HCG and ACTH stimulation resulted in further elevation of the pregnenolone. In contrast, testosterone and DHEA production did not increase appreciably following these stimulation tests, consistent with the postulated site of enzymatic deficiency. A 46,XY phenotypic female, unrelated to the three cases reported by Zachmann et al, has also been documented to have 17,20-desmolase deficiency. In contrast to the previously described cases of Zachmann et al, in this individual gynecomastia developed at puberty.

5. 17β-HSD Deficiency. Another cause of male pseudohermaphroditism that results in decreased testosterone production is 17-hydroxysteroid dehydrogenase (17β-HSD) deficiency. In this disorder there is an impaired conversion of Δ4-androstenedione to testosterone in the testes. The conversion of estrone to estradiol is also impaired, but usually to a lesser degree. The Δ4-androstenedione/testosterone ratio measured in the peripheral blood and in the testicular venous effluent is elevated. Serum testosterone values are usually low, although some patients have low normal levels. The 17β-HSD defect appears to be only expressed in the gonads and, therefore, cannot be diagnosed after castration.

Most genetic males with 17β-HSD deficiency are extremely undervirilized and at birth a female sex assignment is made. The diagnosis is usually made at puberty, when signs of virilization become evident. The genetic males with this disorder have "clitoral" hypertrophy. Testes are usually found in the inguinal canal or in the labioscrotal folds. Spermatogenesis is absent and the Leydig cells are hyperplastic. The vaginal pouch is blind ending and Müllerian duct structures are absent. However, Wolffian duct differentiation is present. During puberty, gynecomastia may develop in the face of progressive virilization. The gynecomastia is thought to be due to the increased gonadal Δ4-androstenedione and estrone secretion during puberty. These hormones are peripherally converted to testosterone and estradiol. Due to the virilization that may occur at puberty, those patients who have been reared as females require castration in the prepubertal period and estrogen replacement at adolescence for breast development.

DISORDERS OF TESTOSTERONE METABOLISM

5α-Reductase Deficiency

Thus far, 5α-reductase deficiency is the only disorder of testosterone metabolism that has been clearly established to be a cause of male pseudohermaphroditism. 5α-Reductase deficiency, characterized by impaired conversion of testosterone (T) to dehydrotestosterone (DHT), has been described by several in-
vestigators. Individuals with this disorder have impairment of 5α-reduction of glucocorticoids, as well as androgens, but only the deficient 5α-reduction of testosterone appears to be of physiologic importance. The disorder is transmitted by an autosomal recessive gene. Affected female infants with this disorder are normal. As a result of the impaired production of DHT, the affected male is seen neonatally, with a small clitoris-like phallus. The urethral opening is at the base of the phallus and a urogenital sinus is present. In a few cases, separate urethral and vaginal openings are present. The vaginal pouch is blind ending. The testes are located intraabdominally, in the inguinal canals or in the labioscrotal folds. Wolffian structures are present and well developed, but Mullerian structures are absent (Fig 3). During puberty, males with this disorder virilize. The phallus enlarges and lengthens. The testes enlarge and descend into the labioscrotal folds. A male muscular body habitus develops along with voice deepening and the occurrence of erections. The ejaculates may contain a normal number of sperm. Others have reported decreased 5α-reductase activity in skin fibroblasts derived from genital skin, as well as nongenital skin. Others have reported that 5α-reductase deficiency is demonstrated only in fibroblasts from genital skin. There is one report of patients with male pseudohermaphroditism who have evidence of normal circulating testosterone and dihydrotestosterone, but who have evidence of 5α-reductase deficiency when in vitro studies are performed on samples of genital skin. This finding is in contrast to the serum hormonal findings reported in the large kindred studies of Imperato-McGinley and colleagues and Saenger et al. It is possible that different forms of the deficiency of 5α-reductase may exist. Evidence for enzyme heterogeneity in this disorder has been documented. There have been patients in whom the 5α-reductase enzyme has normal stability, but decreased affinity for the substrate, testosterone. In contrast, there are other patients who possess a 5α-reductase enzyme that is characterized by essentially normal affinity for its steroid substrate, but is grossly unstable.

In addition to serum hormone determinations and skin fibroblast studies, examination of the ratio of 5α/5β urinary testosterone and glucocorticoid metabolites can be helpful in the diagnosis of 5α-reductase deficiency. Additional diagnostic studies include the infusion of radioactive-labeled testosterone to determine the in vivo capacity to convert T to DHT.

Binding of 3H-DHT to cytosol receptors of skin fibroblasts is normal in patients with 5α-reductase deficiency. Hence, this syndrome is a result of a defect in testosterone metabolism and not in androgen binding. Of interest is the clinical observation that DHT-propionate treatment in these patients causes enlargement of the prostate, beard growth, and acne, thus further supporting the contention that the defect in this disorder is not one of impaired androgen binding.

Currently, it is recommended that when this disorder is diagnosed in infancy, gender assignment should be based on the infant’s phenotype. If a female sex assignment is made, castration is indicated and should be performed before puberty, to avoid virilization.

DISORDERS OF ANDROGEN RECEPTORS

Testicular Feminization Syndrome—Complete and Incomplete Forms

Testicular feminization is thought to be the most common form of male pseudohermaphroditism and is a result of abnormal androgen receptors. Testicular feminization ranks
third, after gonadal dysgenesis and congenital absence of the vagina, as a cause of primary amenorrhea. It accounts for 10% of patients with primary amenorrhea.14

In complete testicular feminization a phenotypic female usually comes to medical attention for evaluation of primary amenorrhea in the postpubertal period, or for evaluation of an inguinal hernia in the prepubertal period. Breast development and the general habitus and distribution of body fat are female in character. Axillary and pubic hair are scanty or absent. The external genitalia are unambiguously female. The clitoris is normal and the vagina is short and blind ending. Internal genitalia are absent except for testes which may be located intra-abdominally, in the inguinal canal, or in the labia majora. Occasionally remnants of the Müllerian or Wolffian ducts are present.15 In prepubertal children, histologic study of the testes documents findings similar to those seen in undescended testes in normal males. Adults have small seminiferous tubules that consist mostly of Sertoli cells, few spermatogenia, absent spermatzoa, and hyperplastic Leydig cells.3 The chromosomal constitution is 46,XY, and there is frequently a history of similarly affected family members. The gene for the disorder is X-linked.16 Approximately one third of these patients have negative family histories and are presumed to represent new mutations.

Approximately 10% of patients with testicular feminization have the incomplete form of this disorder. In the incomplete form, ambiguity of the external genitalia is present at birth and virilization and feminization may occur at puberty. These patients may have partial fusion of the labioscrotal folds and a variable degree of clitoromegaly. The vagina is short and blind ending. In contrast to the complete form of testicular feminization, some Wolffian duct derivatives are usually present. In most cases of incomplete testicular feminization the family history is unremarkable. There have been no reported families in which the complete and incomplete forms have occurred together.16

Serum testosterone levels in patients with both the complete and incomplete form of testicular feminization are normal or slightly elevated compared with normal male values.13 Further, the formation of DHT is unimpaired in this syndrome. It has been suggested that the increased rate of testosterone production is secondary to the higher mean serum level of LH (luteinizing hormone) found in these individuals. The elevated level of LH is thought to be due to defective feedback regulation caused by resistance to the action of androgens at the hypothalamic-pituitary level. The enhanced LH secretion also results in increased estrogen production by the testes. Both the peripheral conversion of the elevated testosterone to estrogen and the enhanced testicular secretion of estrogen result in unopposed elevated serum estrogen levels, and account for the feminization that occurs in puberty.3,16

Abnormalities of the androgen receptors are the cause of androgen resistance in testicular feminization. Recent evidence has suggested that at least two different molecular abnormalities of the androgen receptors can cause this syndrome: an unstable receptor or a lack of binding. Unstable receptors are associated with both the complete and incomplete form of testicular feminization. However, a lack of binding has only been found in patients with the complete form.16

A serious complication in testicular feminization is the development of a testicular neoplasm. It has been estimated that before age 25 years, the rate of neoplasia is 3.6%.50 The risk increases to 20% to 30% by the age 40 to 50 years.3,13 Therefore, it is recommended that castration be performed in all patients with testicular feminization. However, the recommended time of the operation is different for patients with the complete or incomplete forms. The patient with the complete form will feminize normally during puberty and as the risk of neoplasia is low at this age, castration is recommended after puberty is completed. Patients with the incomplete form virilize at puberty. Hence, gonadectomy is recommended before puberty. All castrated patients with testicular feminization require estrogen treatment during puberty and in the postpubertal period. In a few patients, vaginal development is inadequate to allow for normal sexual function. In such cases, either operative or nonoperative techniques may be used to increase the depth of the vagina. Psychosocial studies have demonstrated normal female gender identity and behavior in these patients.16

OTHER UNCLASSIFIED FORMS OF MALE PSEUDOHERMAPHRODITISM

By definition, any genetic male with evidence of incomplete virilization of the genitalia has a form of male pseudohermaphroditism. Hence, such abnormalities as hypospadias and micropenis can be considered forms of male pseudohermaphroditism. Hypospadias occurs as an isolated finding in approximately 8.2 cases per 1,000 live male births.51 The exact etiology of most cases of hypospadias is uncertain. The ingestion of progesterational agents during pregnancy has been suggested as a possible cause of hypospadias.52 In the majority of cases, in which there is no history of exposure to teratogens during pregnancy, the recurrence risk of hypospadias, after the birth of one affected child, is 7% to 10%.3,13

Hypospadias may occur in complex syndromes, such as in the autosomal recessive Smith-Lemli-Opitz syndrome (microcephaly, ptosis, mental retardation, and hypospadias). Additional penile anomalies, such as epispadias or absence of the penis may also occur as isolated anomalies or in syndromes.3,3 Micropenis, in the presence of otherwise normal male external genitalia, may be due to a variety of endocrine causes.13 Because of the risk of hypoglycemia in panhypopituitarism, one cause of micropenis, this condition must be considered in any male neonate who has isolated micropenis.

There are many additional causes of male pseudohermaphroditism such as agonadism, Leydig cell agenesis, and the syndrome of persist-
Pseudohermaphroditism

The relative frequencies of many of the different forms of male pseudohermaphroditism have been reported previously. Our institution’s experience with the evaluation of patients with male pseudohermaphroditism over an eight-year period (1969–1977) is summarized in the Table. Of note is that eight of the 46 patients we evaluated had normal 46,XY chromosomal complement (Table). The presence of a cervix indicates that the infant probably has a form of female pseudohermaphroditism, true hermaphroditism, or gonadal dysgenesis. A careful search for the presence of other somatic anomalies is of great importance in the examination of the neonate. The presence of somatic anomalies associated with Ullrich-Turner syndrome, occurring in conjunction with genital ambiguity, strongly suggest 45,X/46XY mosaicism.

In the newborn period the physician must bear in mind that the patient may be at risk for the development of an adrenal crisis until the diagnosis of one of the forms of adrenal hyperplasia, associated with the impairment of glucocorticoid and mineralocorticoid production and ambiguous genitalia, is ruled out. Hence, the most common form of congenital adrenal hyperplasia, 21-hydroxylase deficiency, either of the salt-losing or simple virilizing form, should be considered in an infant with ambiguous genitalia. Deficiency of 21-hydroxylase (21-OHase) is associated with female pseudohermaphroditism, whereas male newborns with this disorder usually appear normal at birth. Deficiency of 11β-hydroxylase (11β-OHase), which is much less common than 21-OHase deficiency, is also associated with female pseudohermaphroditism. As in 21-OHase deficiency, male neonates with 11β-OHase deficiency have normal genitalia. Salt wasting is classically not a feature of 11β-OHase deficiency, but rather

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Results of Evaluation of Male Pseudohermaphrodites Studied at NYH-CMC from 1969–1977 (46 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclassifiable* (8)</td>
<td>Complete testicular feminization (7)</td>
</tr>
<tr>
<td>Mixed gonadal dysgenesis (6)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol desmolase deficiency (1)</td>
<td></td>
</tr>
<tr>
<td>17-Hydroxysteroid dehydrogenase deficiency (1)</td>
<td></td>
</tr>
<tr>
<td>5α-Reductase deficiency (2)</td>
<td></td>
</tr>
<tr>
<td>Androgen receptor defect† (3)</td>
<td></td>
</tr>
<tr>
<td>Multiple congenital anomalies associated with normal 46,XY chromosomal complement (4)</td>
<td></td>
</tr>
<tr>
<td>Klinefelter (47,XXY) associated with normal testosterone response to HCG‡ (1)</td>
<td></td>
</tr>
<tr>
<td>Sex chromosome abnormalities associated with low testosterone response to HCG‡ (3):</td>
<td></td>
</tr>
<tr>
<td>46 ‘X’ Y with abnormal ‘X’-bilateral cryptorchidism with Leydig cell agenesis;</td>
<td></td>
</tr>
<tr>
<td>49XXXXY-Klinefelter variant with unilateral cryptorchidism;</td>
<td></td>
</tr>
<tr>
<td>46,XY/47, XY + ring chromosome-multiple congenital anomalies</td>
<td></td>
</tr>
<tr>
<td>Low testosterone response to HCG‡ without clearly demonstrable enzymatic deficiency; normal 46,XY chromosomal complement (9):</td>
<td></td>
</tr>
<tr>
<td>Bilateral or unilateral cryptorchidism (7)</td>
<td></td>
</tr>
<tr>
<td>Bilaterally descended testes (2)</td>
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<tr>
<td>Hypopituitarism (1)</td>
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* Normal 46,XY chromosomal complement, normal adrenal and testicular steroidogenesis, and positive nitrogen retention in response to testosterone treatment.
† Normal endogenous androgen production with lack of nitrogen retention in response to exogenous testosterone.
‡ HCG: 5,000 units given intramuscularly for three days.

Management of Patient with Male Pseudohermaphroditism

The management of the patient who has under-virilized or ambiguous genitalia, is in part, dependent upon the age of presentation. A newborn with ambiguous genitalia represents a medical emergency and requires immediate attention and investigation. It is recommended that such a neonate be referred to a major medical center, where resources necessary for performing sophisticated diagnostic studies and medical personnel with expertise in dealing with the problem of genital ambiguity, are available.

When examining a newborn with ambiguous genitalia, it is usually not possible to distinguish between male and female pseudohermaphroditism on the basis of the appearance of the external genitalia (Fig 4). However, gonads that have descended to labial, scrotal, or inguinal regions are almost always testes. An evaluation of the internal organs will additionally be helpful to delineate the diagnosis. A rectal examination should be performed in an attempt to palpate a uterine cervix. It should be noted that the presence of Müllerian derivatives in an infant with ambiguous genitalia excludes most forms of male pseudohermaphroditism, except for the cytogenetic forms resulting in gonadal dysgenesis. Hence, the presence of a cervix indicates that the infant probably has a form of female pseudohermaphroditism, true hermaphroditism, or gonadal dysgenesis. A careful search for the presence of other somatic anomalies is of great importance in the examination of the neonate. The presence of somatic anomalies associated with Ullrich-Turner syndrome, occurring in conjunction with genital ambiguity, strongly suggest 45,X/46XY mosaicism.
hypertension may be present and is attributed to elevation of deoxycorticosterone resulting from accumulation of precursors proximal to the enzymatic block. Deficiency of 3β-HSD as discussed above, is another form of congenital adrenal hyperplasia which may present with virilization of the female neonate and under-virilization of the male neonate. Depending on the degree of enzymatic impairment, frank salt wasting and hypocortisolemia may occur in the newborn period. Other less common forms of congenital adrenal hyperplasia, congenital lipoid adrenal hyperplasia and 17-OHase deficiency, should also be considered in the differential diagnosis of a neonate with genital ambiguity, as these disorders are also associated with adrenal insufficiency. Serial serum and urinary electrolytes should be followed in all neonates with genital ambiguity in the event that a salt-wasting form of congenital adrenal hyperplasia exists. Careful attention to the general medical status of the neonate is imperative. Appropriate hormonal tests, obtained to assess adrenal as well as gonadal function will be useful for diagnosing congenital adrenal hyperplasia, and detecting other causes of impaired testosterone biosynthesis, should they exist. These tests include base line serum and urine androgens, mineralocorticoids and glucocorticoids, as well as serum 17-hydroxyprogesterone levels. Determination of urinary 17KS, 17OHCs, pregnanetriol and aldosterone levels should also be performed. (Measurement of serum 17-hydroxyprogesterone is recommended as this hormone is elevated in 21-OHase deficiency). An ACTH or Cortrosyn stimulation test may also be performed to assess adrenal function further. An HCG stimulation test to assess gonadal function more carefully is necessary in most cases of male pseudohemaphroditism to define the etiology of the genital ambiguity.

While closely observing the neonate with ambiguous genitalia and pursuing hormonal studies, the issue of gender assignment must be addressed. This issue is of critical nature, and sensitivity to the concerns of the patient’s relatives is imperative. It is prudent to delay gender assignment until sufficient data are available to allow for the determination of the optimal sex assignment. The results of the buccal smear can be obtained within 24 hours, but a chromosome study should be initiated at the same time in all patients with ambiguous genitalia. The results of many of the critical diagnostic hormonal tests, discussed above, can be available within a week. Radiologic studies, including genitourinaryograms and ultrasonography, can be used in some cases, to define the internal genitalia in the neonatal period. Once the critical data required for making an accurate diagnosis are available, a panel of experts should determine the sex of rearing. Consideration as to whether puberty will conform to the sex of assignment and of the patient’s potential for normal sexual functioning and fertility is critical in the determination of gender assignment. If reconstructive surgery of the external genitalia is necessary, it should be initiated sometime before the age of 2½ years. Additional reconstructive surgery (ie, vaginoplasty) may be required in later years. Gonadectomy prior to adolescence may be indicated to avoid pubertal virilization in certain cases of male pseudohemaphroditism in which a female gender assignment has been made (eg, incomplete testicular feminization). In those forms of male pseudohemaphroditism associated with an increased risk of testicular neoplasm, gonadectomy is also indicated (ie, both forms of testicular feminization and all forms of gonadal dysgenesis associated with the presence of Y chromosomal material).

The above recommendations for evaluation of the newborn with ambiguous genitalia are shown in Fig 5. For patients with ambiguous genitalia who are beyond early infancy and adolescents with pubertal failure, prompt medical attention and evaluation, in a manner similar to that outlined for the neonate, are also required. A severe form of adrenal insufficiency, however, is essentially ruled out by later presentation, although milder forms must still be considered and investigation of adrenal function, along with gonadal function, is warranted.
Pseudohermaphroditism

It is apparent that male pseudohermaphroditism may be due to a variety of etiologies, only some of which are well understood. The diagnosis and management of male pseudohermaphroditism, and the need to characterize more thoroughly the nature of the developmental abnormalities, present a continued challenge to the medical community.

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tions. J Clin Endocrinol Metab 38:612, 1974

Fig 5 Evaluation of neonate with ambiguous genitalia.
EDUCATIONAL OBJECTIVE

79. Appropriate understanding of the management of a child with bladder paralysis (81/82).

Bladder Paralysis with Myelomeningocele


The urologic management of children born with myelodysplasia has three goals: (1) the preservation of renal function; (2) the control of urinary infection; and (3) the development of appropriate urinary continence for age.

The introduction of clean intermittent catheterization (CIC) in 1972 by Lapides has proven to be a superior method of bladder drainage. CIC can be started in the neonatal period. Children with normal intelligence are able to catheterize themselves from the age of 6 to 7 years. Continence can be achieved in most children on CIC but the presence of vesicoureteral reflux in the absence of vesicoureteral reflux. In order to assure that this procedure is safe, cystography should be performed and post-expression residual urine volumes should be measured. The procedure is definitely dangerous in the presence of vesicoureteral reflux when high intravesical pressures are transmitted directly to the kidney during bladder expression. (C. Uy)
Male Pseudohermaphroditism
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