

Androgen Insensitivity Syndrome ^[1]

By: Drago, Mary Keywords: [sexual development](#) ^[2] [Hermaphrodite](#) ^[3]

Androgen Insensitivity Syndrome (AIS) is a human disorder in which an individual's genetic sex (genotype) differs from that individual's observable secondary sex characteristics (phenotypes). A [fetus](#) ^[4] with AIS is genetically male with a 46,XY genotype. The term 46,XY refers to the chromosomes found in most cells of the [fetus](#) ^[4]. Most cells have a total of 46 autosomes, or non-sex chromosomes, and a pair sex chromosomes, XX for genetic females, or XY for genetic males. Due to a defect on the androgen receptor gene (AR) located on the X chromosome, a [fetus](#) ^[4] with AIS cannot process male [sex hormones](#) ^[5] or [androgens](#) ^[6]. The effect on the [fetus](#) ^[4] is that, compared to genetically male fetuses without AIS, it doesn't develop normal male phenotypes. The resistance to [androgens](#) ^[6] affects all of the [fetus](#) ^[4]'s organs during embryonic development and during puberty. Although genetically male, persons with AIS can be socially raised as either female or male (sex-of-rearing) yet identify with a gender discordant with their sex-of-rearing. AIS and other states of intersexuality challenge physicians, scientists, and society to evaluate definitions of sex.

Although physicians and scientists studied intersexuality, or hermaphroditism, before the early 1900s, physicians used only an individual's gonads to determine an individual's sex. The individual was male if he had [testes](#) ^[7] and female if she had ovaries. Frank Rattray Lillie's studied [freemartin](#) ^[8] cattle in 1916 at the [University of Chicago](#) ^[9] in Chicago, Illinois, and he suggested that regardless of genetic sex, [hormones](#) ^[10] influence the development of sex characteristics, a process called [sex differentiation](#) ^[11]. Such characteristics include penises and prostates in males, and breasts and vaginas in females, but also include differences in hair, bones, and muscles between males and females. As scientists learned more about genetics, they determined sex according to an individual's chromosomes, gonads such as [testes](#) ^[7] in males or ovaries in females, and secondary sex characteristics such as breasts and hips and females, and facial hair and broader shoulders in males. Thus, any variation from the expected match between an individual's genetic sex, gonads, and secondary sex characteristics was termed hermaphroditism.

In 1876, Theodor Albrecht Edwin Klebs in Europe introduced a classification system that divided hermaphrodites into true hermaphrodites and pseudo-hermaphrodites based on their gonads. Hermaphroditism was classified into three categories: true hermaphrodite, male pseudo-hermaphrodite, or female pseudo-hermaphrodite. A true hermaphrodite was an individual who had one or more gonads which contained testicular and ovarian attributes, or an ovotestis. A female pseudo-hermaphrodite was genetically female and had ovaries, but exhibited male secondary sex characteristics. A male pseudo-hermaphrodite was genetically male and had [testes](#) ^[7], but exhibited female secondary sex characteristics.

AIS was grouped with other variations of sexual development as male pseudo-hermaphroditism until 1953. That year John McLean Morris a professor at the [Yale University](#) ^[12] School of Medicine and a doctor at the Yale-New Haven Medical Center in New Haven, Connecticut, published a paper in which he described eighty-two [humans](#) ^[13] with common features of a sex disorder, and he called the syndrome testicular feminization. Morris questioned whether the secondary sex manifestations of AIS patients resulted from [hormones](#) ^[10] or from the ability of organs in the body to respond to the [hormone](#) ^[14] stimulation. In 1957 Lawson Wilkins, a professor at [Johns Hopkins University](#) ^[15] in Baltimore, Maryland, published the results of his study, in which human male pseudo-hermaphrodites did not exhibit male secondary sex characteristics after androgen injections. Mary F. Lyon and Susan G. Hawkes at the [Medical Research Council](#) ^[16] Radiology Unit at Harwell, UK linked testicular feminization to the X chromosome in 1970 when they determined that a gene on the X chromosome caused complete androgen insensitivity in mice, the males of which could also have testicular feminization and thus served as a model for the human syndrom, and on which researchers could experiment.

In 2006 a group of fifty international experts introduced new nomenclature and classification for [humans](#) ^[13] states of intersexuality or hermaphroditism as disorders of sexual development. As scientists learned more about androgen resistance, they renamed the syndrome Androgen Insensitivity Syndrome. By the early decades of the twenty-first century, researchers located greater than 600 mutations of the AR (androgen receptor) gene on the human X chromosome.

Normal sex [differentiation](#) ^[11] requires interplay between the sex chromosomes and [hormones](#) ^[10]. The [egg](#) ^[17] and the [sperm](#) ^[18] each carry twenty-three chromosomes; the [egg](#) ^[17] provides only the X chromosome and [asperm](#) ^[18] can have either an X or a Y chromosome. At [fertilization](#) ^[19], the union of the [egg](#) ^[17] and the [sperm](#) ^[18] determines the genetic sex of the embryo as either female (46,XX) or male (46,XY). A few days after [gestation](#) ^[20], the gonadal ridge, precursor to [testes](#) ^[7] or ovaries, develops on an embryo. During the second month of [gestation](#) ^[20], all fetuses have both male (Wolffian) and female (Mullerian) internal sex ducts and their external genitalia appear female. In XY embryo, a gene on the Y chromosome called the sex-determining region (SRY) produces a protein that causes the bipotential gonads, formed from the gonadal ridge, to develop into [testes](#) ^[7]. Without the SRY gene, the bipotential gonads become ovaries. As the [testes](#) ^[7] develop, they secrete two [hormones](#) ^[10], Mullerian

Inhibiting Substance (MIS) and [androgens](#)^[6]. MIS inhibits the Mullerian ducts in an embryo from developing into [uterus](#)^[21], a [cervix](#)^[22], and [fallopian tubes](#)^[23]. Androgens released by the [testes](#)^[7] increase the growth of the Wolffian ducts, which then develop into the *vas deferens*, prostate gland, and seminal vesicles. Normally, in a genetic female, the absence of MIS and [androgens](#)^[6] permits the Mullerian ducts to develop into [fallopian tubes](#)^[23], a [cervix](#)^[22], and a [uterus](#)^[21]. Additionally, without [androgens](#)^[6] in a genetic female, the Wolffian ducts regress. As the [testes](#)^[7] continue to develop in an XY [fetus](#)^[4], testosterone released by the [testes](#)^[7] is converted to dihydrotestosterone (DHT), a [hormone](#)^[14] that masculinizes the external genitalia to become the penis and the scrotum.

Because the defect in the AR gene is linked to the X chromosome, all 46,XY embryos that have an X chromosome with a defective AR gene and a normal Y chromosome exhibit varying degrees of sex [differentiation](#)^[11]. Although most cases of AIS are in individuals with families that have had other individuals with AIS, scientists estimate that thirty percent of AIS cases result from spontaneous, or *de novo*, mutations to [AR genes](#)^[24]. AIS is classified into three categories based on the degree of altered sex [differentiation](#)^[11]: complete AIS (CAIS), partial AIS (PAIS), and mild AIS (MAIS).

In the early twenty-first century, doctors lacked precise figures for the number of infants born with CAIS, although 2012 estimates ranged from one in 20,400 to one in 99,100 per year. During development, an 46,XY embryo with CAIS cannot process the [androgens](#)^[6] produced by the [testes](#)^[7], but it responds to other [hormones](#)^[10]. As a result, the [testes](#)^[7] form and function during embryonic development. The [testes](#)^[7] secrete MIS, which causes the Mullerian ducts to regress, so the [uterus](#)^[21], [fallopian tubes](#)^[23], and the [cervix](#)^[22] do not develop. The Wolffian ducts don't respond to the [androgens](#)^[6] released by the [testes](#)^[7], and the ducts either regress or remain in a rudimentary form, but they do not develop into a prostate gland, *vas deferens*, or seminal vesicles. Unresponsive to the [androgens](#)^[6] testosterone and DHT, the external genitalia develop as they would in a normal 46,XX female. At birth, a 46,XY neonate has [testes](#)^[7] located in the abdomen, groin, or in the labia. The external genitalia are female. The [uterus](#)^[21], [fallopian tubes](#)^[23], and [cervix](#)^[22] are absent. The [vagina](#)^[25] is a closed-end tube, and is most often shorter than those of normal female neonates. Blood levels of testosterone and DHT may be above normal due to the lack of the negative feedback loop between the anterior [pituitary gland](#)^[26] and the blood level of [androgens](#)^[6], a feedback loop that normally keeps the level of [androgens](#)^[6] released by the [testes](#)^[7] in balance. Carl Richard Moore and Dorothy Price identified this negative feedback loop in 1932 when they were researchers at the [University of Chicago](#)^[9] in Chicago, Illinois.

Generally parents of a CAIS child rear the child as female. Nothing may indicate that the child has the syndrome until either a testis is found due to a hernia in the groin (inguinal hernia), or at puberty when the adolescent does not menstruate. Prior to puberty, approximately one percent of children have an inguinal hernia; however, eighty to ninety percent of persons with CAIS will develop an inguinal hernia in their lifetime if their [testes](#)^[7] are not removed. If the [testes](#)^[7] are not removed, testosterone levels remain high and the body biochemically converts testosterone to estrogens. Many physicians recommend removal of the [testes](#)^[7] prior to, or immediately following, the age of puberty due to an increased risk of [testicular cancer](#)^[27]. CAIS individuals develop breasts during puberty, while armpit and pubic hair is scant or missing, and they are infertile.

Embryos with PAIS have varying degrees of sex [differentiation](#)^[11], depending on the level of resistance to [androgens](#)^[6]. Neonates can exhibit external sex characteristics that resemble those of normal females or of normal males. These characteristics range from predominantly female external genitalia with an enlarged clitoris and partial fusion of the labia, to those of predominantly male external genitalia consisting of a small penis, a urethral opening on the underside of the penis instead of at the tip, and one or both [testes](#)^[7] undescended into the scrotum. Those structures that develop from the Wolffian ducts, such as the *vas deferens*, prostate gland, and seminal vesicles, may be partially or fully developed. Parents generally raise PAIS children as a member of the sex concordant with the child's external genitalia. At puberty, breasts develop, but the size of the penis does not increase significantly. The [testes](#)^[7] may also develop cancer at puberty, therefore most physicians recommend removal of the [testes](#)^[7]. Persons with PAIS are infertile. Due to the secrecy that often surrounds a diagnosis of PAIS, there are no figures about its prevalence.

In infants born with MAIS, parents often raise the children as male, as those infants exhibit mild alteration of normal male genitalia. Frequently, these alterations are undeveloped genitalia, the urethral opening may be on the underside of the penis, or the scrotum may not be completely fused. At puberty, however, breasts develop, the voice does not lower, and little sexual hair develops. The adult may also be impotent, but not all adults with the MAIS are infertile, because the formation of [spermatozoa](#)^[28], or spermatogenesis, can be normal.

Some ethical issues surround the medical treatment of children with AIS. In the 1950s many physicians followed the recommendations of John Money, a professor at [Johns Hopkins University](#)^[15] in Baltimore, Maryland, who stated that people identified with the sex their parents reared them as, and that any anatomical anomalies should be corrected early in a child's life. As a result, surgery was the predominant method of treating children with AIS. Internationally, surgeons and families commonly did not disclose the surgeries or the syndrome to the children. Because a child with complete androgen insensitivity syndrome has secondary sex characteristics that appear female, the first indication of the syndrome during the child's life was either when she developed a hernia or did not menstruate at puberty. Surgeons then removed the [testes](#)^[7] and may have told the child that they removed her ovaries. Surgeons also removed the [testes](#)^[7] of children with either partial or mild AIS, but frequently performed other surgeries based on the child's exhibited secondary sex characteristics. In many cases, surgeons altered the genitalia to resemble female secondary sex characteristics.

As adults, many of the children who were born with AIS in the years since Money's recommendation reported in support groups such as the Intersex Society of North America (ISNA) headquartered in California or the Androgen Insensitivity Syndrome Support Group, which has twenty-five national locations, that the secrecy surrounding the diagnosis made them feel abnormal. Without surgery, many also faced social stigma because of their anatomy. Many adults with AIS also declared that surgical corrections to their genitalia were inappropriate and unnecessary. For some, the sex characteristics created for them do not match the gender that they identify with. For some children born with AIS, treatments didn't include anatomical surgeries other than the removal of the [testes](#)^[7] to prevent [testicular cancer](#)^[27]. While ISNA states that the [testes](#)^[7] should be removed, they recommend that the surgery be delayed until puberty has begun. Another medical treatment for CAIS individuals is [estrogen](#)^[29] therapy. In a family with history of AIS, DNA testing has detected fetuses with AIS. Doctors can identify fetuses whose external genitalia does not match their genetic sex. To do so, doctors use [ultrasound](#)^[30] to view the [fetus](#)^[4] in the [womb](#)^[31], and they use either sampling of the placental tissue (chorionic villi sampling) or sampling of amniotic fluid (amniocentesis) to obtain cells that will reveal the genetic sex of the [fetus](#)^[4].

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