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Intersex And Androgen Insensitivity Syndrome

Androgen Insensitivity Syndrome (AIS) is one of a number of biological intersex conditions. Intersex is a variant from the usual embryological development of the reproductive tract, often determined by a known genetic mutation. It is a condition that affects the development of the reproductive and genital organs.

What is Intersex?

Sometimes, a child is born with genitalia which cannot be classified as either female or male. A genetically female child (with XX chromosomes[1]) may be born with external genitalia which appear to be those of a normal male or a genetically male child (with XY chromosomes) may be born with external genitalia that look feminine. In very rare cases, a child may be born with both female and male genitalia. Because these conditions are in a sense 'in-between' the two sexes, they are collectively referred to as 'intersex'.

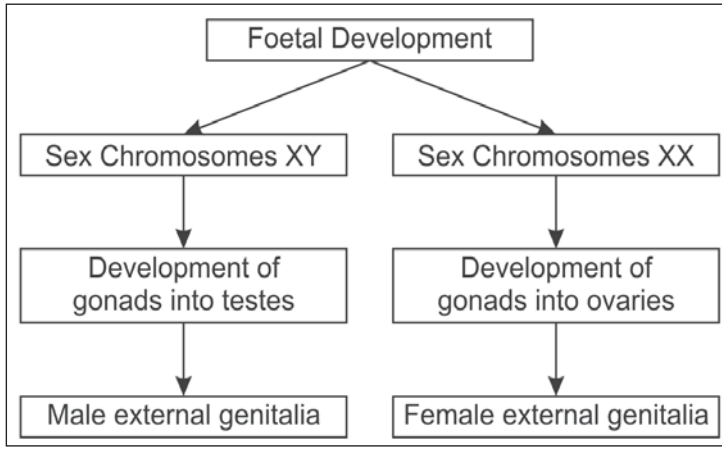
[1] The XX or XY sex determination system is the most familiar system, as it is found in human beings, most other mammals, as well as some insects. In the XY sex determination system, females have two of the same kind of sex chromosome (XX), while males have two distinct sex chromosomes (XY). The XY sex chromosomes are different in shape and size from each other, unlike the autosomes and are termed allosomes.

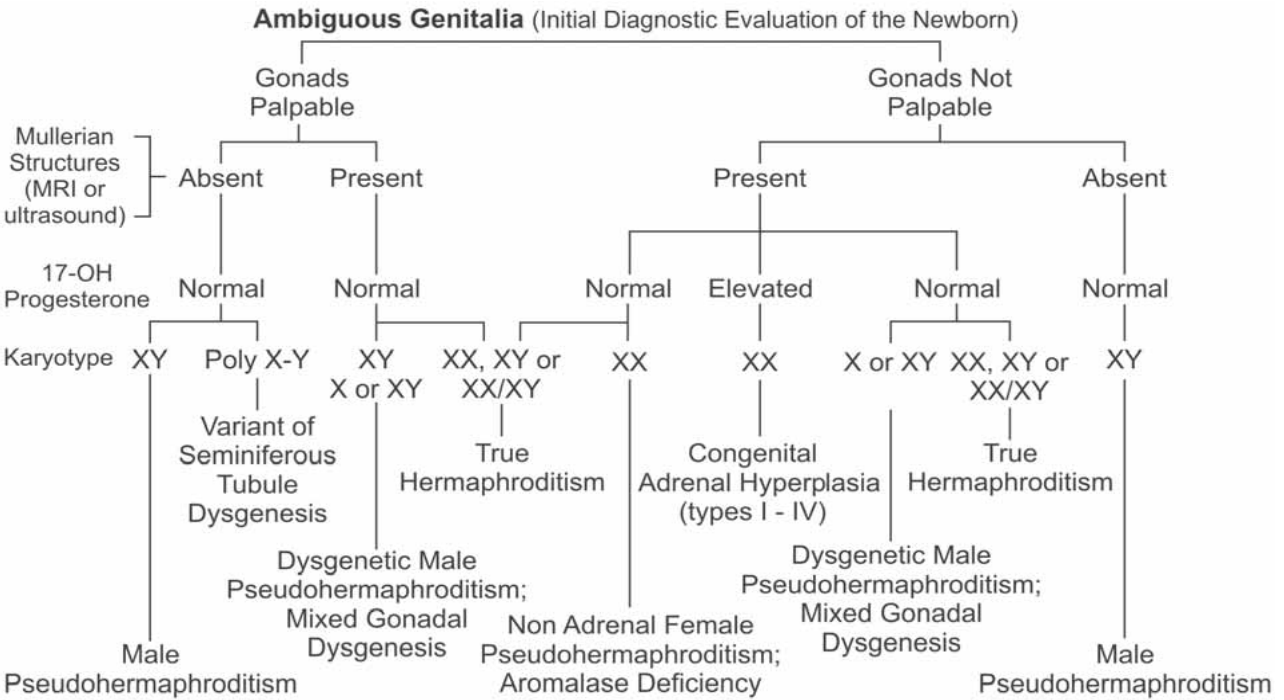
Intersex is the grey area between the sexes, where there is a significant presence of the characteristics of the opposite sex, in either a male or a female. This presence is significant enough to cause the sufferer to not desire to belong to either the male or female gender group or be classified as either gender, often at great cost and hardship to him/her.

Foetal Development and Gender Differentiation

The term 'intersex' refers to the elements of this entire alignment (the sex chromosomes, the gonads and the genitalia) and not just to the appearance of the external genitalia. A patient with the complete form of AIS (CAIS) or with Swyers Syndrome (XY Gonadal Dysgenesis) will always appear externally female (no ambiguity) but she is still intersexed because she has XY chromosomes and internal testes (testicular streak gonads in the case of Swyers) that are at odds with her external femaleness.

Normal Foetal Development





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Introduction to AIS

Male foetuses usually have a Y sex chromosome which initiates the formation of testes (and the suppression of female internal organ development) during gestation. Testes are the site of production of masculinising hormones (specially androgens) in large quantities.

Masculinisation is an active process; it needs the positive or active intervention of the male hormones in order to take place. If these male hormones are either absent or the tissues do not respond to them (as happens to differing degrees in the various forms of AIS), then the passive tendency is for the external genitals to differentiate into female external organs which are indistinguishable from those of normal girls, in the complete form of AIS.

This female physical development is not due to the presence and influence of female hormone oestrogen but to the ineffectiveness of androgens. In other words, the inherent trend for any foetus is to develop female external genitals and general body form, in the absence of the masculinising effects of male hormones.

Both male and female foetuses have at least one X sex chromosome, which contains a gene that gives their body tissues the capacity to recognise and react to androgens. At puberty, girls react to the relatively small quantity of androgens (that come mainly from their adrenal glands) by developing pubic and underarm hair and darkish pigmentation around the nipples.

People with AIS have a functioning Y sex chromosome (and therefore, no female internal organs) but an abnormality on the X sex chromosome that renders the body completely or partially incapable of recognising the androgens produced. In the case of CAIS, the external genital development takes a female form.

In the case of PAIS, the external genital appearance may lie anywhere along the spectrum from male to female. Other related conditions, resulting from changes on different chromosomes, also disrupt the normal pathway of androgen action, resulting again in a feminised phenotype (body form).

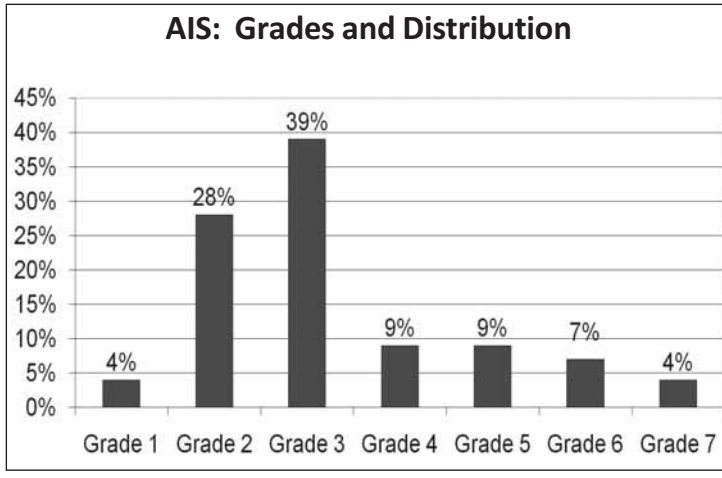
Thus, people with these 'XY conditions' may identify as female, intersexed or male.

AIS: Complete and Partial

There are two forms of the condition: Complete AIS (CAIS) where the tissues are completely insensitive to androgens and Partial AIS (PAIS) where the tissues are partially sensitive to varying degrees.

The condition is actually represented by a spectrum, with CAIS being a single entity at one end of a range of various PAIS manifestations. The scale runs from AIS Grade 1 to Grade 7 with increasing severity of androgen resistance - and hence decreasing masculinisation with increasing feminisation.

Most of the girls suffering from CAIS have completely normal female type external genitalia but they lack a uterus or upper vagina. This is known as CAIS,



technically AIS Grades 7 and 6. The remaining girls have PAIS, their outward genital appearance usually lying anywhere from almost completely female (AIS Grade 5, 4) through to almost completely male (AIS Grade 3 to 1).

At the CAIS end of the spectrum, the outward appearance is completely female (AIS Grades 6, 7) and the sex of rearing is invariably female. In PAIS, the outward genital appearance can lie anywhere from being almost completely female (AIS Grade 5), through mixed male/female, to completely male (Grade 1).[2] It has been suggested that slight androgen insensitivity might contribute to infertility in some otherwise normal men.

[2] Those with mild effective gynaecomastia are included among normal males, while barren and childless females are included among normal females.

Grades of PAIS

Before puberty, individuals with Grade 6 or 7 are indistinguishable. The term 'severe PAIS' is sometimes used to refer to Grades 5 and 6, to distinguish them from the lower grades of PAIS. In AIS Grades 5 and 4, the clitoris is enlarged. In Grade 5, there may be partial fusion of the labia majora (outer vaginal lips), in which the posterior (back) portion of the labia forms a web of tissue across the back part of the vaginal outlet. In Grade 4, this fusion extends further forward, covering both the vaginal opening and the true urethral opening. The cavity formed by the fused labia, through which urine is passed, is called a urogenital sinus.

In Grade 3 and the more masculinised form of Grade 4, the labia are completely fused, so that the urethral opening is at the base of the clitoris/penis. The fused labia may have a rugose or wrinkled appearance and form a bifid or double scrotum. The fusion is then more properly called 'labio-scrotal fusion'. The phallus has the appearance of a large clitoris or a small, bent penis, bound down in structures called 'chordee'. The chordee is formed from the same tissues that form the labia minora in the female and the frenulum of the penis and the tissues surrounding the urethra (corpus spongiosum) on the underside of the penis in the male. It is erroneously believed that the presence of chordee makes erections painful.

In Grade 2, the genital appearance is that of a male with hypospadias, i.e. with a urethral opening located somewhere on the underside of the penis.

AIS: Grades and Distribution

Grade	Conditon	Description	%
1	PAIS	Male genitals, infertility	4
2	PAIS	Male genitals but mildly 'under-masculinised', isolated hypospadias[3]	28
3	PAIS	Predominantly male genitals but more severely'under-masculinised' (perineal hypospadias, small penis, cryptorchidism i.e. undescended testes and/or bifid scrotum)	39
4	PAIS	Ambiguous genitals, severely 'under-masculinised' (phallic structure that is indeterminate between a penis and a clitoris)	9
5	PAIS	Essentially female genitals (including separate urethral and vaginal orifices, mild clitoromegaly i.e. enlarged clitoris)	9
6	PAIS	Female genitals with pubic/ underarm hair	7
7	CAIS	Female genitals with little or no pubic/underarm hair	4

[3] Hypospadia, in itself, is not an intersex condition but is a congenital condition of the penis.

Sex of Rearing in PAIS

The decision regarding the sex of rearing of a baby with PAIS should be made according to the individual's best interests and other factors such as sexual functioning, how the individual would feel about themselves need to be considered, preferably with less emphasis on surgery, even perhaps minimalising the need for surgery. Puberty is another issue that should be considered. While many would feel comfortable with a puberty that is concordant with the assigned gender of rearing, some would not and an understanding of the individual's wishes should take priority. The best approach is to explain the situation, let the patient decide what is best for them and offer the best choices available.

There are forms of PAIS with a male phenotype and minimal (Grade 2) or no (Grade 1) genital 'deformity'. In these cases, gender assignment is nearly always male and the androgen insensitivity is only detected at puberty when breast development (gynecomastia) occurs. The patient may be infertile.

Patients with AIS Grades 3-7 are always sterile, so potential fertility should not be a consideration. In PAIS Grade 3 (and some with Grade 4), there may be controversy about whether to raise the baby as a male or as a female. Patients with PAIS with Grade 5 and most with Grade 4 are too unresponsive to androgens to undergo masculinising puberty, either spontaneously or under the influence of exogenous hormones and cannot be masculinised surgically so as to function sexually as males. Like patients with CAIS, they will

undergo a spontaneous feminising puberty and should be raised as females.

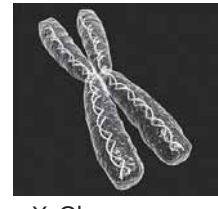
Genetics – Normal (non-AIS) Situation

In human somatic (non sex) cells there are normally 46 chromosomes made up of 23 pairs. Of these 46 chromosomes, 44 are called autosomes because they are not thought to determine gender. The other two are called sex chromosomes. Non-AIS males have a relatively large X and a small Y sex chromosome and normal females have two X sex chromosomes.

When the generative cells are formed in the body of an adult, these sex chromosomes become separated, so that a sperm carries either a single X or a single Y chromosome, while every egg carries a single X chromosome. At conception, the new embryo will be XX or XY, according to whether the egg, which is always X, was fertilised by an X or Y bearing sperm. Thus, the sperm controls the genetic sex of the child.

The genetic sex of a child is established at conception based on the 23rd pair of chromosomes it inherits.

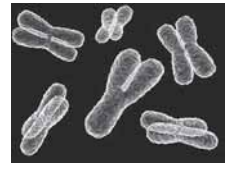
- A baby who inherits the X chromosome from the father is a genetic female (a pair of X chromosomes).



X Chromosome

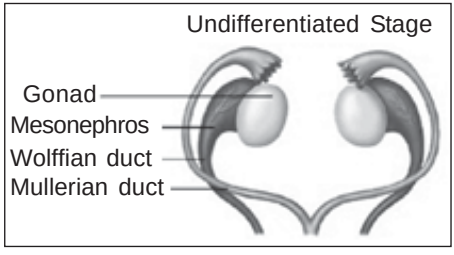
If the embryo is female (XX), then no testosterone is made. The Wolffian duct will degrade and the Mullerian duct

will develop into female sex organs. The female clitoris is the remnant of the Wolffian duct.


Y Chromosome

- A baby who inherits the Y chromosome from the father is a genetic male (one X and one Y chromosome).

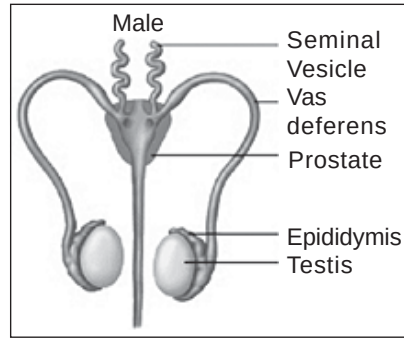
If the embryo is a male (XY chromosomes), then testosterone will stimulate the Wolffian duct to develop male sex organs and the Mullerian duct will degrade. The type of sex organs developed depends on the presence of the male hormone testosterone (in humans, the default sex is female).



During the first few weeks of foetus development, the baby's internal and external genital structures are the same, regardless of whether it is a boy or a girl.

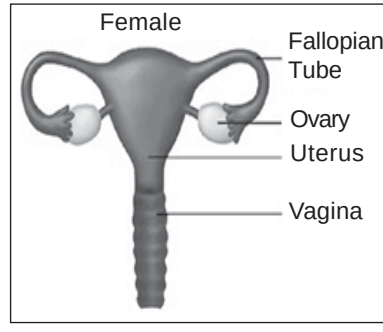
At this stage, they have two sets of organs: one that can develop into the female sex organs (Mullerian duct) and another that can develop into the male sex organs (Wolffian ducts).

The gonads will become ovaries or testicles, the phallus will become a clitoris or a penis and the genital folds will become labia or scrotum.



The SRY gene, on the short arm of the Y chromosome, initiates male sexual differentiation. The SRY influences the undifferentiated gonad to form testes, which produce the hormonal milieu that results in male sexual differentiation. Testosterone stimulates the Wolffian structures (epididymis, vas deferens and seminal vesicles) and Anti-Mullerian Hormone (AMH) suppresses the development of the Mullerian structures (fallopian tubes, uterus and upper vagina).

Testosterone converts to dihydrotestosterone in the skin of the external genitalia and masculinises the external genital structures. By 12 weeks, most of this male differentiation has occurred but they are still not completely formed. On ultrasound, the sex can be identified as early as the 16th to 18th week of pregnancy. The testicles remain inside the abdomen until late in the third trimester, when they usually descend into the scrotum.

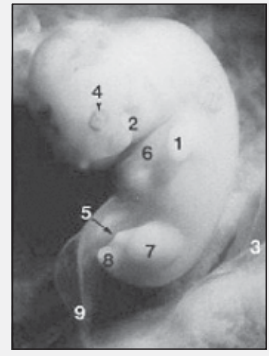


Female development will occur unless maleness is actively induced by the Y chromosome. If the embryo is female (XX), then no testosterone is made. The Wolffian duct

Genital changes in embryo development

(42 days / 6 weeks after fertilisation, around week 8 of pregnancy)

1. Buds of the arm
2. Arc branchial
3. Placenta membrane
4. Eye
5. Genital tuber*
6. Site of the heart
7. Bud of the leg
8. Tail
9. Umbilical cord



* At the 6th week, the site of the genitals is a small bud, called the genital tuber.

will degrade and the Mullerian duct will develop into female sex organs. In females, the gonads become ovaries. The uterus, cervix, fallopian tubes and vagina form, the labia develop and the phallus becomes a clitoris.

The lower part of the vagina is derived from a primitive structure called the urogenital sinus, which comes from the perineum. In males, the Mullerian ducts regress under the influence of a hormone, Mullerian Inhibitory Factor or MIF, secreted by the developing testes.

Embryology of a Foetus (AIS)

In AIS, although the testes fail to cause masculinisation of the external genitalia, they do produce sufficient MIF to suppress development of Fallopian tubes, uterus and upper vagina. The upper third of the vagina is invariably missing but the lower two-thirds may be fully

developed and sufficient for intercourse. In some cases the vagina may be even shorter, perhaps only a few centimeters or even just a 'dimple'.

Foetal Development – Abnormal (AIS) Situation

In the case of an AIS foetus, a Y-bearing sperm fertilises the egg (which is always X) and produces an XY embryo. Subsequently, in the early stage of foetal life, differentiation is as a male, with testes and the Mullerian ducts regressing. Once the testes are formed, they start to produce testosterone, which would normally cause the masculinisation of the body.

Until about 10 weeks of gestational age, male and female embryos appear identical in external anatomy. The same structures then begin to differentiate as male under the influence of testosterone or as female if the influence of testosterone is absent.

In the presence of intermediate amounts of androgens or in a condition of partial sensitivity to androgens, the external genitals will develop in an in-between way. In PAIS, the external genitalia can therefore be ambiguous, i.e. intermediate in structure between male and female. Note that the structure of ambiguous external genitalia can be the same, whether the genetic sex and the sex of the gonads is male or female. The structure of


Underdeveloped Genitalia

the external genitals does not provide a way to determine whether the condition is PAIS or some other intersex condition.

Unfortunately, by the time the androgen insensitivity becomes evident, the internal reproductive organs have already progressed partially down the male route and the MIF from the testes has already begun its work of destroying the primitive female internal organs. The testes remain in a 'frozen', i.e. partially developed male state and the development of the internal female organs cannot be reactivated.

The undescended testes can result in an inguinal hernia in infancy and this is when AIS may be diagnosed in an apparently female child (about 50% of cases). Otherwise, in the rest of cases, CAIS may not be discovered until puberty, when there is a failure to menstruate, known as primary amenorrhoea.

CAIS - Physical Manifestations

They should be observed in light of the following:

- Female body shape
- Large breasts with juvenile nipples
- Absent/scanty axillary and pubic hair
- No temporal hair recession (balding)
- Female external genitalia with small labia
- Blind-ending vagina
- Absent or rudimentary internal genitalia
- Gonads consistent histologically with cryptorchid testes
- Hyperplasia of interstitial cells - adenoma
- Testes produce androgen

- Increased gonadotrophins
- No ovaries, fallopian tubes or uterus

Pubic and Underarm (Axillary) Hair in AIS

Often, the pubic hair in individuals with CAIS is reported as 'scanty' or 'sparse' and it is unclear whether the hair that is present is anything more than the vellus down (which is not androgen dependent) similar to that found elsewhere on the body in both sexes, at all ages. True sexual hair - the longer, coarser, darker terminal hair characteristic of adult pubic and axillary regions - results from androgenic stimulation of hair follicles. The term 'pubic hair' should therefore, be confined to hair that is truly androgenic in nature, however sparse or abundant and its distribution should be described in terms of Tanner Staging (next page).

Some individuals, considered in infancy to have the complete form of AIS, develop sexual hair at puberty, sometimes of the density and distribution seen in normal postpubertal, 46XX females. The presence of true pubic hair, even in an AIS individual with an entirely female phenotype, must be regarded as evidence for some degree of androgen responsiveness and that such individuals are considered to have a severe form of PAIS (Grade 6) rather than CAIS (Grade 7).

Changes at Puberty

Body Changes

Although androgens are often called 'male hormones' and oestrogens are often called 'female hormones', both types of hormones are present in males and

Tanner Staging – Sexual Development in Girls
Sexual development in girls occurs in predictable stages. J M Tanner divided the visible changes of puberty into 5 stages in 1962, which occur in a very specific sequence, known as 'The Tanner Stages'.

It begins with thelarche (breast development), then adrenarche (pubic hair development), then a growth spurt (quick increase in height) and finally menarche (onset of menses) occurs.

Stage	Breasts	Pubic Hair
1	Preadolescent breasts with elevation of the papilla only.	None.
2	Breast buds develop and areolar diameter enlarges.	Sparse growth of long, slightly pigmented, straight or minimally curled hair that grows primarily along the labia.
3	Further enlargement of the breast and areola without any separation of their contours.	Hair becomes darker and curlier.
4	The areola and papilla project to form a secondary mound above the level of the breast.	Adult type pubic hair covers an area smaller than in the adult extend onto the thighs.
5	Breasts look like mature female breasts; the areola has recessed to the general contour of the breast.	The hair is adult in quantity and type and extends on to the thighs.

females, just varying in ratio. In normal males, the body produces androgens and a smaller amount of oestrogens. In fact, the richest natural source of oestrone (one type of oestrogen) is the testes of the stallion. Similarly, normal females produce male as well as female hormones. In AIS, the testicular oestrogen is secreted in a non-cyclical manner and not cyclically as in the menstruating female. Girls with AIS are particularly sensitive to oestrogens because of lack of the counter effect of androgens.

Although the body is insensitive to androgens, it is very responsive to oestrogens and is affected by the small amount of oestradiol (an oestrogen) produced by the testes, oestrone produced from testosterone in fat tissue or oestrogen replacement therapy.

The body develops even further in a feminine direction, causing the body appearance to perfectly resemble an XX female, with female breast development. Hence, it is sometimes stated that girls with AIS have a body form that is 'voluptuously female', i.e. with very adequate breast development and that the skin maintains a good condition, not being prone to acne (which is linked to the effects of male hormones).

However, since there is no uterus and no ovaries, there is no possibility of menstruation or conceiving. Although a vagina of sorts may be present as mentioned earlier, it is usually no more than a short blind pocket and may require lengthening if intercourse is to be made possible.

Growth - General

It is often stated that girls with AIS are taller than average. Contrary to this belief, individuals with Complete Androgen Insensitivity Syndrome are phenotypic females with 'normal female appearance'. Their growth in stature and body proportions is normal but there are some observations indicating that they might be taller than normal females. AIS girls tend to have a masculine skeleton and the size of their teeth is closer to that of men than of women. They have elongated limbs and large hands and feet.

However, some of these observations might have been made at a time when the practice of early gonadectomy and HRT was not so common and thus did not present a possible externally applied growth regulating factor.

Growth - Role of Oestrogens

Normal male pubertal growth spurt can be quite satisfactorily explained by the combined action of testosterone and growth hormone but the mechanisms involved in the female growth spurt are not completely understood. Oestrogens were formerly considered of minor importance and in the growth of girls, more influence was attributed to androgens from the adrenal glands. However , studies suggest that in normal girls, the pubertal growth spurt results from the effects of oestrogens rather than adrenal androgens. This leads to the conclusion that in AIS, the following changes take place:

- a spontaneous pubertal growth spurt takes place,
- the spurt velocity is equivalent to that of normal girls,

Eunuch Intersex - The Truth

A hermaphrodite is a mythical creature from ancient literature, one that supposedly has a complete working set of both male and female internal and external organs (such that the individual can, in theory, impregnate itself). This is not possible in humans. Medicine took over this literary term in the days before genetics was understood and employed it as a medical term, to refer to these individuals who have both ovarian and testicular tissue internally (an ovo-testis) and who, as a result, can have ambiguous external genitalia.

- it starts at an appropriate chronological age for girls (i.e. earlier than in normal boys),
- bone maturation (i.e. closure of the long bones and hence mature height) corresponds to that of normal boys rather than normal girls.

Presumably, these observations were in the absence of any HRT and therefore in spite of plasma oestrogen concentrations that would tend to be lower (due to lack of ovarian oestrogens) than in normal girls of the same age.

Growth - Role of Y Chromosome

It is presumed that genes on the Y chromosome have an effect on growth, independent of hormonal changes, as shown by increased growth in boys with an extra Y chromosome. In AIS, the XY karyotype (chromosomes) will result in excessive final height in relation to the female phenotype. The body shape (having accounted

for size differences) of 46 XY females does not deviate much from that of normal females but 46 XY females tend to be larger in all body measurements, although with a tendency to a slimmer body.

It may be concluded that the Y chromosome has a direct influence on growth but the greater height in normal males may indicate that an additive or inductive action of androgens is also necessary for the completion of body growth in normal males. Also, the body shape in 46 XY females is under the control of oestrogens and is not affected by the Y chromosome.