INTERSEXES
Part 1
MALE AND FEMALE SEXUAL DIFFERENTIATION
- INTERSEXES

DISORDERS OF SEXUAL DIFFERENTIATION
Abnormalities of sexual differentiation - Intersex
INTERSEX

An individual in whom there is discordance between chromosomal, gonadal, internal genital, and phenotypic sex or the sex of rearing

INTERSEXUALITY:
Discordance between any two of the organic sex criteria

TRANSSEXUALITY:
Discordance between organic sex and psychological sex components
What is Intersex?

“Intersex” is a general term used for a variety of conditions in which a person is born with a reproductive or sexual anatomy that doesn’t seem to fit the typical definitions of female or male.

http://www.isna.org/faq/what_is_intersex
In other words...

Their bodies are neither wholly Female nor wholly Male
There are Hundreds of Different Intersex Conditions

- Congenital Adrenal Hyperplasia (CAH), Androgen Insensitivity Syndrome (AIS), Kleinfelter Syndrome, Persistent Mullerian Duct Syndrome, etc etc

- Different Problems
- Different Concerns
- Different Needs
- Different Treatment Required
Medical, Not Sexual or Gender

- Separate from Sexual Orientation
  - May be attracted to Males, Females, Both, Neither....

Each person’s experience of AIS is different but there are probably very few of us who don’t feel their sexuality isn’t affected by it in some way. It’s very difficult not to feel some degree of insecurity about your sexuality when your reproductive organs and/or genitals are different from the norm.

http://home.vicnet.net.au/~aissg/sexuality_relationships.htm

- Separate from Gender Identity
  - May self-Identify as Male, Female, 3rd Sex, “Other”

Unlike transsexualism and/or transgender where 100% of people have gender identity issues, only a small portion of people with intersex conditions (probably about 5-10%) have an issue with their gender.
Issues

- Health
- Psychological
- Social
- Sexual
- Gender
- Legal
- Privacy
- Ignorance
Health Issues

- Some conditions are life threatening
- Fertility is usually compromised
- Physical effects of childhood persecution (beatings, rape)
- Hormonal imbalances and mood swings
- Effect of “corrective” neonatal surgery
- May not be aware of condition
- Lack of awareness of surgical and hormonal therapeutic options
Gender Issues

- Many identify as female, and usually want to conceal their condition
- Many identify as male, and usually want to conceal their condition
- A few identify as Intersexed, a 3rd alternative, and are usually out and proud
- Some are just plain confused – questioning
- Some suffer from surgically-induced Transsexualism
Actual Example – Legal Issues

- UK birth certificate: M
- Australian Dept of Health: F
- UK passport: F
- Australian passport: DENIED
- Australian Tax Office: F
- Australian Electoral Office: F
- ACT Registrar of Births, Marriages, and Deaths: M
- Zurich insurance policy: M
- Westpac insurance policy: F
Issues of Ignorance

- Ignorance in Medical Service Providers
- Ignorance in the General Population
- Ignorance in the Government (Bureaucracy, Legislature, Judiciary)
- Ignorance in Academe
  - Philosophy: “gender is a social construct” vs. medical reality
  - Sociology: how many TS or IS people are there?
  - Medicine: what are the causative mechanisms?
- Ignorance in the GLBITQ lobby
- Ignorance amongst the Intersexed themselves
How to Help: Recommended Principles (IMHO)

- Empowerment of the student is the key
- Do NOT treat as per usual GLB situation
- Each case different
- Emphasise choice – we just provide the facilities, they choose their way forward
- Emphasise “it's OK to be straight” “it's OK to conceal” as well as “it's OK to be gay” and “it's OK to be out”
- Their way, not your way
Transsexuality vs. Intersexuality

His Honour, Justice Chisholm said obiter:

In my view the evidence demonstrates (at least on the balance of probabilities) that the characteristics of transsexuals are as much "biological" as those of people now thought of as intersex. The difference is essentially that we can readily observe or identify the genitals, chromosomes and gonads, but at present we are unable to detect or precisely identify the equally "biological" characteristics of the brain that are present in transsexuals.

What’s normal in a term newborn?

- **Female:**
  - Vaginal opening fully visible: 3-4 mm slit or stellate orifice with heaped-up mucosa
  - Clitoris width 2-6 mm
  - Absence of gonads in labia majora or inguinal region

- **Male:**
  - Urethra at tip of glans (may be inferred by a fully developed foreskin)
  - Penis of normal stretched length (2.5-5 cm) and diameter (0.9-1.3 cm)
  - Bilateral testes of normal size (8-14 mm) in the scrotal sacs
Ambiguous genitalia: what is it?

Evaluation of intersex problem required for:

1. Male-appearing genitalia with micropenis, mod/severe hypospadias, bilateral cryptorchidism, or two mild defects (e.g. mild hypospadias and unilateral cryptorchidism)

2. Female-appearing genitalia with posterior labial fusion, clitorimegaly, or a labial or inguinal mass
**Hypospadias and Epispadias**

- Abnormal site of external urethral meatal opening
- Due to malformation of the urethral groove and urethral canal
- Abnormal openings can either be on
  - Ventral surface of the penis - Hypospadias
  - Dorsal surface of the penis - Epispadias
- Commonly associated with
  - Failure of normal descent of the testes
  - Malformations of the urinary tract

**Clinical Significance:**

- If the abnormal opening is constricted - partial urinary obstruction
  > Cystitis > spread to the rest of urinary tract
- Are a possible causes of sterility in men
  - Orifice situated near the base of the penis > normal ejaculation and insemination are hampered or totally blocked
PROBLEMS WITH MALE DEVELOPMENT

- **Hypospadias:** In 1/300 boys the urethra doesn’t close all the way, or is opened on the body of the penis.
HYPOSPADIA
Basic concepts

- Fetal sex differentiation:
  - Occurs at 7-14 weeks’ fetal age only
  - Is innately female and does not require ovaries or estrogens
  - As a male requires:
    1. Sex-determining region of Y (SRY) gene
    2. Bilateral testes producing mullerian inhibiting substance (MIS/MIF/AMH) and testosterone
    3. 5α-reductase enzyme (external genitalia)
    4. Testosterone and dihydrotestosterone receptor (internal and external genitalia)
Human Gonadal Development and Differentiation

Genital ridge
- SF-1
- WT-1
- SOX-9
- SRY

Bipotential gonad
- SF-1
- SF-1
- SRY

Ovary
- DSS

Testis
- SF-1
- SF-1
- Leydig cells
- Sertoli cells

Follicular cells
- SF-1
- Theca cells

Follicles

Wolffian Duct
- Male int genit.
- Testosterone

Mullerian Duct
- Regression
- Female Internal Genitalia

Genit. Tub.
- Urogen. Sinus
- DHT
- Penis
- Prostate

Genital Tub.
- Urogenital Sinus
- DHT
- Penis
- Prostate

Male int genit.
- Testosterone

AMH

Mullerian Duct
- Regression
- Female Internal Genitalia
It’s a boy! (or..girl!)… maybe…

- Evaluation is a medical and psychosocial emergency
- Why?
  1. Diagnose CAH before an adrenal crisis
  2. Designate correct gender
  3. Correct problems early for correct body image and gender identity
  4. Provide genetic counseling for the future
  5. Identification of children at higher risk for gondal tumor
Sex differentiation

What makes us Male or Female?
Chromosomic Sex

The Sperm Decides The Genetic Sex

XY

X

Y

Sperm

XX

Chromosomes

XX

Ovum

X

X

Male XY gonad: Testis

Female XX gonad: Ovary

Fig. 29-1

KMc
karyotype
Chromosomal Sex

- Y Chromosome – SRY Gene – codes for the testis determining factor. In the absence of SRY there are no testes.
- X Chromosome – DSS – Double dose gene. Two DSS genes are required for the ovaries to be fully functional.
Chromosomic number

Full trisomy of an individual occurs when a chromosome fails to separate during gamete formation. This can result in an extra or missing chromosome in a sperm or egg cell. After fertilization, the resulting fetus has 47/45 chromosome instead of the typical 46.

Partial/mosaic

- A partial trisomy occurs when part of an extra chromosome is attached to one of the other chromosomes, or if one of the chromosomes has two copies of part of its chromosome.
- A mosaic trisomy is a condition where extra chromosomal material exists in only some of the organism's cells.
Sex chromosomes are special

- You cannot have any monosomy of any chromosome other than X and Y. (in those cases you can function just fine)

- Trisomies of sex chromosomes will be expressed mostly in the reproductive area; but not necessarily.
Bipotential Gonads

- In the presence of SRY – Testes
- In the absence of SRY – Ovary like
- Two doses of DSS needed to develop fully functioning ovaries.
BIPOTENTIAL GONAD

mesonephros

Wolffian duct

Müllerian duct

gonads

kidney

ureter

adrenal glands

ovary

oviduct

Müllerian duct

uterus

vagina

FEMALE

kidneys

ureters

urinary bladders

testis

epididymis

Wolffian duct

MALE
Brain

- Presence of androgens – Brain – Male
- Absence of androgens - Brain – Female
Genital Sex

The undifferentiated genital tubercle is identical in genetic males and females.

- glans area
- urethral fold
- urethral groove
- anal pit

Male development requires the androgen dihydrotestosterone.

Partial development (7 to 8 weeks old):
- Male
- Female development occurs in the absence of dihydrotestosterone.

- glans
- site of future origin of prepuce
- urethral fold
- urogenital groove
- lateral buttress (corpus or shaft)
- labio-scrotal swelling
- urethral folds partly fused
- anus
Genital Sex

Male
- urethral meatus
- glans penis
- prepuse
- shaft of penis
- scrotum

Female
- prepuse
- glans clitoridis
- urethral meatus
- labium minus
- labium majus

Fully developed (12 weeks old)

perianal tissue including anal sphincter
Brain Differentiation

- In the presence of SRY – Testes
- In the absence of SRY – Ovary like
- Two doses of DSS needed to develop fully functioning ovaries.
Brain Lateralization

corpus callosum

Right Brain Oriented Female  Left Brain Oriented Female

1.  10.1 cm²  4.5 cm²
2.  9.2 cm²  4.8 cm²

Right Brain Oriented Male  Left Brain Oriented Male
Size of the Anterior Commissure in the Brain

It is a fiber tract that is larger in its midsagittal area in women than in man
Brain – Sexual chemistry

Sexual Chemistry

Brain scans show heightened activity in the hypothalamus region of the brain, which regulates sexual activity, when subjects are exposed to a chemical released by the opposite sex. The subjects lack the activity in the hypothalamus when exposed to a chemical from their own sex.

**Female Brain Cutaway**
- Increased activity in hypothalamus

**Female Brain**: Women smelling androgen-like compound
- Increased activity in olfactory centers

**Male Brain Cutaway**
- Increased activity in hypothalamus

**Male Brain**: Men smelling estrogen-like compound

**Female Brain**: Women smelling estrogen-like compound

**Male Brain**: Men smelling androgen-like compound

SOURCE: Cell Press

THE WASHINGTON POST
Brain Differentiation Rats

Testosterone masculinizes and feminizes rat brain

Male pup

castration on day 1

+ testosterone

Exhibits male behaviours

Female pup

testosterone on day 1

+ estrogen

Exhibits female behaviours

Organizational effect of testosterone

Activational effect of testosterone and estrogen
Gender differentiation brain
What Makes Us Male or Female?

- Chromosomal Sex
- Gonadal Sex
- Genital Sex
- Brain Differentiation
In women, the ring finger and the index finger tend to be about the same length. But in men, the index finger is usually the shorter of the two digits.
Finger length correlates with the concentration of androgens in utero.
Chromosomal defects

XO – Turner

XXY - Klinefelter
Turner

Missing X Chromosome

Low hair line

- Short stature
- Low hairline
- Shield-shaped thorax
- Widely spaced nipples
- Shortened metacarpal IV
- Small finger nails
- Characteristic facial features
- Fold of skin
- Constriction of aorta
- Poor breast development
- Elbow deformity
- Rudimentary ovaries
- Gonadal streak (underdeveloped gonadal structures)
- Brown spots (nevi)
- No menstruation
Klinefelter syndrome

Extra X/Y Chromosome
Androgenized Genetic Female Child

Genetic Female: XX
External Genitalia exposed to Androgens during genital differentiation
Androgenized Genetic Female Child

- Progestin Induced Virilization – androgens given to mothers to prevent miscarriages.
- Congenital Adrenal Hyperplasia – need medical attention at birth.
- Some anticonvulsant drugs
- Pollutants?
Gender role preference behaviors in congenital adrenal hyperplasia patients

Girls with the adrenogenital syndrome show more male role behaviours than unaffected sisters.

- No interest in jewelry, make-up, and hairdo: significantly different
- Preference for functional clothing: significantly different
- Ambivalent with gender role, or desires to be boy: significantly different
- Always or completely tomboyish: significantly different

Percentage
Androgen Insensitivity Syndrome
5 alpha reductase deficiency is one of several conditions where girls are born with XY genes (the usual male pattern). It is not known how common 5 alpha reductase deficiency is, but it can run in families or it can be a chance event.

External genitalia female – testes present. Secondary Sex differentiation can include the growth of the clitoris (virilisation) and descending of the tests hirsutism.

In some parts of the world some girls born with this condition have changed to start living as a boy and man after puberty, but this is uncommon in Western Cultures.
Intersex

- True hermaphrodites: have both gonads
- Pseudo hermaphrodites: external genitalia does not match internal gonadal sex.
Gender Identity

- How a person perceives him/herself as male or female
- Feeling of Maleness/femaleness or an ambivalence between the two.
Gender Identity disorder

- Your concept of oneself (Male / Female) does not match genitalia
- Brain differentiation form of gender intersex?
"When you work with these kids, you see that they're not making a decision," he says. "They have always known. The sense of who one is--[boy or girl]--is a crucial existential aspect of humanity. It is powerful and inborn." The absence or presence of a penis is incidental. "The most important sex organ is the brain."
Normal Sex Differentiation

- Gender identity the result of the following determinants
  - Genetic sex
  - Gonadal sex
  - Internal & external genitalia
  - The secondary sexual characteristics that appear at puberty
  - The role assigned by society

- Four major steps which constitute normal sexual differentiation

  Fertilization and determination of genetic sex
  Formation of organs common to both sexes
  Gonadal differentiation
  Differentiation of the internal ducts and external genitalia
Normal Sexual Differentiation

Jost paradigm:

1. Establishment of chromosomal sex at fertilization
2. Development of the undifferentiated gonads into testes or ovaries
3. Differentiation of the internal ducts and external genitalia
Chromosomal Sex

- TDF was mapped to the most distal aspect of the Y-unique region of the short arm of the Y chromosome, adjacent to the pseudoautosomal boundary.

- $Sry$ is localized to the smallest region of the Y chromosome capable of inducing testicular differentiation in humans and in mice.

- $Sry$ appears to be capable of recognizing specific sites on DNA, and, by binding and producing bending of the DNA, it is able to activate downstream gene expression.
TDF candidates

- **ZFY** (zinc finger gene on Y chromosome) was excluded with certainty as a candidate for TDF when four individuals with testicular development were found to have inherited a fragment of the Y chromosome that did not include \textit{ZFY}

- **H-Y gene**: A number of women with 45,X gonadal dysgenesis were found to be H-Y antigen positive
Other Important Genes

- **WT-1**: originally isolated in experiments that identified an oncogene on chromosome 11 as being involved in the etiology of Wilms' tumor. Research on *WT-1* in the mouse suggests that it exerts its effects upstream of *SRY* and is likely to be necessary for commitment and maintenance of gonadal tissue.

- **SF-1**: a nuclear receptor, is expressed in all steroidogenic tissue and appears to be a regulator of müllerian inhibiting substance (MIS).

- **SOX-9 gene**: identified in patients with camptomelic dysplasia, a congenital disease of bone and cartilage formation that is often associated with XY sex reversal.
  - *SOX-9* HMG-box amino acid sequence has 71% similarity to that of *SRY*.
  - Expression of the gene in adults is greatest in the testes and is thought to be involved in gonadal differentiation.
Other Important Genes

- **DSS (DAX-1)** (dosage-sensitive sex reversal). Found in XY females with duplication of this gene
  - Suggests duplicated X chromosome causes XY sex reversal by expressing a double dose of the gene normally subject to X inactivation. Screening of XY females with a normal Sry gene detected a submicroscopic duplication designated DSS
  - Implicated in adrenal hypoplasia congenita

- **WNT4** (factor in ovarian pathway)
  - Thought to repress the biosynthesis of gonadal androgen in female mammals, therefore is suppresses male sexual differentiation (Hughes, NEJM, 351(8), Aug 19, 2004. 792-798)
Gonadal Stage of Differentiation

- During the first 6 weeks of embryonic development structures are bipotential in both 46,XY and 46,XX embryos.
- Migration of the germ cells begins in the 5th week of gestation through the mesentery to the medial ventral aspect of the urogenital ridge.
- \( SRY \) initiates the switch that induces the indifferent gonad toward testicular organogenesis.
  - In the absence of \( SRY \), ovarian organogenesis results.
- The differentiation of Sertoli cells is associated with the production of MIS, a glycoprotein encoded by a gene on the short arm of chromosome 19.
- Primordial cells of steroidogenic mesenchyme remain among the testicular cords and represent future Leydig cells, which differentiate at 8 to 9 weeks.
Gonadal Stage of Differentiation

- Duplicate copies of at least one X chromosomal locus is likely necessary for normal oviarian organogenesis
  - Dysgenetic ovaries in Turner's syndrome patients

- In embryonal ovaries, germ cells undergo intense mitotic proliferation and in the process exhaust their entire mitotic potential prenatally
  - a maximum endowment of 20 million cells by 20 weeks gestation
Gonadal Function

- The initial endocrine function of the fetal testes is the secretion of MIS by the Sertoli cells at 7 to 8 weeks' gestation.
- Testosterone secretion by the fetal testes is detectable shortly after the formation of Leydig cells in the interstitium at approximately 9 weeks' gestation.
  - Testosterone peaks at 13 weeks and then declines.
  - Testosterone enters target tissues by passive diffusion.
- DHT binds to the androgen receptor with greater affinity and stability than does testosterone.
  - The gene encoding the androgen receptor has been cloned and mapped to the X chromosome between the centromere and q13.
- Estrogen synthesis is detectable in the female embryo just after 8 weeks of gestation.
Defining Sex and Gender

Gender identity (Psychological sex)
Inner sense of owns maleness / femaleness.
- Sex of rearing
- Gender role

Sexual identity (Organic sex)
The biologic sexual differentiation
- Chromosomal sex
- Gonadal sex
- Internal genital sex
- External genital sex
- Hormonal sex
Human sexual differentiation

- Chromosom al sex
  - Gonadal sex
    - Internal genital sex
    - External genital sex

SEX ASSIGNMENT

- Sex of rearing
- Gender identity and role
Gonadal development
Gonadal development

SRY-gene (TDF)
Short arm of Y chromosome

Present
Receptors For H - Y antigen
TESTES

Bipotential Gonad

Absent
2 X chromosomes
OVARY
Undifferentiated Urogenital Tract

8 wks

Indifferent stage
- Gonad
- Mesonephros
- Müllerian duct
- Wolffian duct

Ovary
- Fallopian tube
- Uterus
- Vagina
- Female

10 wks

Epididymis
- Testis
- Vas deferens
- Seminal vesicle
- Prostate
- Male

10 wks

Undifferentiated External genitalia
### Differentiation Timeline

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<th>Internal Duct Structures</th>
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<th>Gestation Weeks</th>
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**FEMALE**

**MALE**

**Virilization**

**Testicular Descent**

**Phallic Growth**
Internal genital organs development
External genital organs development

Urogenital sinus

Male

Female

Genital swelling
Genital fold
Genital tubercle

Scrotal swelling
Phallus
Prepuce
Glans
Urethra
Scrotum

Anus
Urethral groove

Labial swelling
Hooded clitoris
Vaginal opening
Labia majora
Labia minora
Male development

TESTIS

Leydig cells
Sertoli cells

Testosterone

Wolffian duct

5α-reductase

DHT

Urogenital sinus

Male internal Genital organs

Male external genitalia

Mullerian inhibiting factor

Regression of Mullerian ducts
Female development

Neutral Development

OVARY

Urogenital sinus
- Female external genitalia
  - Lower part of vagina
  
  Absence of androgen exposure

Mullerian ducts
- Female internal genital Organs
  - Most of upper vagina
  - Cervix and uterus
  - Fallopian tubes
Normal Sex Differentiation

- Gender identity the result of the following determinants
  - Genetic sex
  - Gonadal sex
  - Internal & external genitalia
  - The secondary sexual characteristics that appear at puberty
  - The role assigned by society

- Four major steps which constitute normal sexual differentiation
  
  Fertilization and determination of genetic sex
  Formation of organs common to both sexes
  Gonadal differentiation
  Differentiation of the internal ducts and external genitalia
Fertilization and Determination of Genetic Sex

- Step 1 in sex differentiation: Determination of genetic sex

  Egg (23,X) + Sperm (23,X)=46,XX genetic female

  OR

  Egg (23,X) + Sperm (23, Y)=46, XY genetic male karyotype
Formation of Organs Common to Both Sexes

- The fertilized egg multiplies to form a large number of cells. Differentiation of the sex organs in this development.

At that stage, both 46,XX & 46,XY fetuses have similar sex organs, specifically:

- Gonadal ridges
- Internal ducts
- External genitalia
Internal reproductive organs
Gonadal Differentiation

- The important event in gonadal differentiation is of the gonadal ridge to become either an ovary or a testis

  - In males, the gonadal ridge develops into testes as a result of a product from a gene located on the Y chromosome
    - "Testis determining factor" (TDF)
      - Gonadal medullary region -> Sertoli cell
    - "Sex determining region of the Y chromosome" (SRY)

  - In females, the absence of SRY, due to the absence of a Y chromosome, permits the expression of other genes
    which will trigger the gonadal ridge to develop into ovaries
Gonadal Differentiation

- Pseudoautosomal region

- The distal ends of the short arms of the X and Y chromosomes

- During meiosis the homologous distal short arms of the X and Y chromosomes pairs, and interchange of genetic material occurs in autosomes

- Gene deletions in this area of the X chromosome (Xp22.3) are associated with various conditions such as short stature, mental retardation, X-linked ichthyosis, Kallmann’s syndrome.
Gonadal Differentiation

- Subsequent sexual differentiation requires direction by various genes with TDF
  - **SRY**: The Y chromosome sex determinants region
  - **SOX9**: An autosomal testis-determining gene
  - **DAX1**: A potential testis-suppressing gene on X-chromosome
  - **SF1**: The link between SRY and the male development pathway
  - **WT1**: necessary for normal renal and gonadal development
  - **WNT4**: A potential ovary-determining gene on an autosome
Gonadal Differentiation

- **SRY**
  - Sex determining region of the Y chromosome
  - Locate on the short arm of the Y chromosome
  - Transcription factor contains HMG (high-mobility group) box
    - a DNA binding domain => control of gene transcription

- Investigations of the DNA-binding properties of the protein of SRY in the promoter P450 aromatase (conversion of testosterone to estradiol that is down-regulated in the embryo) & anti-mullerian hormone (responsible for regression of the mullerian ducts)

- The expression of SRY in the tissue destined to become a gonad directs the cells of this gonadal primordium to differentiate as Sertoli cell
Gonadal Differentiation

- **SOX9**: An autosomal testis-determining gene
  (SRY-like box) genes are similar in sequence to *SRY*
  : an extra copy of *SOX9* develops males, even if they have no
  SRY gene – XX mice made transgenic for *SOX9* develop testes

- **SF1**: Steroidogenic factor, necessary to make the bipotential gonad
  Collaboration with *SOX9* → elevate levels of AMH transcription

- **Wnt4**: Activate *DAX1* expression
  Lack the *Wnt4* gene
  → Ovary fail to form properly, express testis specific markers
Postulated cascades leading to the formation of the sexual phenotypes.
Summary of key genetic events in early sex determination

- Migration of primordial germ cells to the urogenital ridge

- Differentiation of the bipotential gonadal tissue under the direction of \textit{WT-1} and \textit{SF-1}

- \textit{SRY} activation of male-specific genes, especially \textit{SOX9}, to produce the testes by cell proliferation, differentiation, migration and vascularization

- Ovarian differentiation by suppression of \textit{SOX9} through the activity of \textit{DAX1} and \textit{Wnt4}
Summary of the genetics of gonadal dysgenesis

- Gonadal streaks without germ cells in XX or XY (female phenotype):
  - Deficiencies in *WT-1* or *SF-1*

- Lack of testicular development in XY individuals, pure gonadal dysgenesis (female phenotype):
  - Deficiencies in *SRY* or *SOX9*

- Male phenotype in a 46,XX individual:
  - Presence of *SRY*

- Mixed gonadal dysgenesis in mosaics (varying phenotype):
  - Excess *DAX1*
Internal reproductive organs - Embryonic development

- **Urinary and genital tract**
  - Closely related, anatomically and embryologically
  - Embryologic urinary system -> important inductive influence on developing genital system
  - Anomalies in one system are often mirrored by anomalies in another system

- **Urinary system, internal reproductive organs & external genitalia**
  - Develop synchronously at an early embryologic age
Kidney, renal collecting system & ureters from nephrogenic cord
Mesonephric (Wolffian) duct

- Singular importance for the following reasons
  - Grows caudally in developing embryo to open an excretory channel into the primitive cloaca and outside world
  - Serves as starting point for development of the metanephros which becomes definitive kidney
  - Differentiates into the sexual duct system in male
  - Although regressing in female fetuses, inductive role in development of the paramesonephric or mullerian duct
Mullerian duct

- Paramesonephric or mullerian ducts - development
  - Form lateral to mesonephric ducts
  - Grow caudally and then medially to fuse in midline
  - Contact urogenital sinus in region of the post. urethra at slight thickening known as sinusal tubercle
Duct System Differentiation - Male

- **TDF**
  - Results in degeneration of gonadal cortex and differentiation of the medullary region of the gonad into Sertoli cells

- **Sertoli cells**
  - Secrete glycoprotein known as *anti-mullerian hormone (AMH)*
    - Regression of paramesonephric duct system in male embryo
    - Signal for differentiation of Leydig cells from the surrounding mesenchyme
Duct System Differentiation - Female fetus

- In the absence of TDF, medulla regresses and cortical sex cords break up into isolated cell clusters (-> primordial follicles)

- In the absence of AMH & testosterone
  - Mesonephric duct system degenerates
  - Then, paramesonephric duct system develops
    - Inf. fused portion
      - Uterovaginal canal  -> uterus and upper vagina
    - Cranial unfused portions
      - Open into celomc cavity (future peritoneal cavity)
      - Fallopian tubes
Anti-Müllerian Hormone

- A member of the transforming growth factor-β family
- Regression of Müllerian duct system in male embryo
- AMH has an inhibitory effect on oocyte meiosis
- Plays a role in the descent of the testes
- Inhibits surfactant accumulation in the lungs
- Proteolytic cleavage of AMH produces fragments that have the ability to inhibit growth of various tumor (a potential therapeutic application)
Duct System Differentiation

- **Leydig cells**
  - Produce testosterone & dihydrotestosterone with 5α-reductase

- **Testosterone**
  - Responsible for evolution of mesonephric duct system into vas deferens, epididymis, ejaculatory duct & seminal vesicle
  - At puberty, leads to spermatogenesis & changes in primary and secondary sex characteristics

- **DHT (dihydrotestosterone)**
  - Results in development of the male external genitalia, prostate and bulbourethral glands
External Genitalia Differentiation

- **In the female**, absence of androgens permits the external genitalia to remain feminine
  - The genital tubercle becomes the clitoris
  - The labioscrotal swellings → the labia majora
  - The urogenital folds → the labia minora

- **In the male**, fetal androgens from the testes masculinize the external genitalia
  - The genital tubercle grows to become the penis
  - The labioscrotal swellings fuse to form the scrotum
Summary of Normal Sex Differentiation

- Genetic sex is determined at fertilization.
- Testes develop in XY fetus, ovaries develop in XX fetus.
- XY fetus produces MIS and androgens and XX fetus does not.
- XY fetus develops Wolffian ducts and XX fetus develops Mullerian ducts.
- XY fetus masculinizes the female genitalia to make it male and the XX fetus retains female genitalia.
Psychosexual Differentiation

- **gender identity**: the identification of self as either male or female
- **gender role**: aspects of behavior in which males and females appear to differ
- **gender orientation**: choice of sexual partner (heterosexual, homosexual, or bisexual)
- **cognitive differences**
Psychosexual Differentiation

- Experience in patients with congenital adrenal hyperplasia (CAH) who were exposed prenatally to androgen and in patients reared in a sex opposite to their chromosomal or gonadal sex have provided evidence to indicate that gender identity is not merely a function of chromosomal complement or prenatal endocrine milieu.

- Strong evidence has accumulated for the impact of prenatal hormonal influences on sexually dimorphic behavior or gender role.

- Previously accepted dogma that children are psychosexually neutral at birth and capable of being environmentally oriented has been seriously challenged by those who support the concept of prenatal psychosexual differentiation.
CLASSIFICATION OF INTERSEXUALITY

1. Virilization of genitically female foetus
   Female pseudohermaphroditism

2. Incomplete masculinization of genitically male foetus
   Male pseudohermaphroditism (XY-FEMALE)

3. The presence of both ovarian and testicular tissue in the same individual
   True hermaphroditism

4. Chromosomal abnormality
   Mixed gonadal dysgenesis (45,X0 / 46,XY)
Disorders of fetal Endocrinology

**Incompletely masculinized males (male pseudohermaphroditism)**
Androgen insensitivity syndromes (androgen receptor abnormalities)
5α-Reductase deficiency
Testosterone biosynthesis defects
   - 3β-Hydroxysteroid dehydrogenase deficiency
   - 17α-Hydroxylase (P450c17) deficiency
   - 17β-Hydroxysteroid dehydrogenase deficiency
Congenital lipoid adrenal hyperplasia (StAR deficiency)
Gonadotropin-resistant testes
Anti-müllerian hormone deficiency
CLASSIFICATION OF INTERSEXUALITY

Disorders of Gonadal Development

Male pseudohermaphroditism

Primary gonadal defect – Swyer syndrome

True hermaphroditism

Gonadal dysgenesis
  Turner syndrome
  Mosaicism
  Normal karyotype — Noonan syndrome
How many children are born with intersex conditions?

- A conservative estimate is that 1 in 2000 children born will be affected by an intersex condition.
- 98% of affected babies are due to congenital adrenal hyperplasia.
FEMALE PSEUODOHERMAPHRODITISM

EXCESS FETAL ANDROGENS

Congenital adrenal hyperplasia
  21α-hydroxylase deficiency
  11β-hydroxylase deficiency
  3β-hydroxysteroid dehydrogenase deficiency

EXCESS MATERNAL ANDROGENS

Maternal androgen secreting tumors (ovary, adrenal)

Maternal ingestion of androgenic drugs
Female Pseudohermaphroditism

- 46,XX individuals with ovaries have a partially masculinized phenotype and ambiguous genitalia
- CAH is most common cause
- Uncommon etiologies:
  - Maternal ingestion of androgens
  - Virilizing tumors in the mother
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(Female Pseudohermaphroditism, 8th to 12th Fetal Week)
21-hydroxylase deficiency
congenital adrenal hyperplasia

Cholesterol
- Pregnenolone
- Progesterone
- 17-OH progesterone

21-hydroxylase
- Cortisol
- Androgens

Pituitary
- ACTH

Adrenal cortex
- Cortisol
- Androgens