Sex Determination and Development of Reproductive Organs

- **Sex determination**
  - The $SRY^+$ gene is necessary and probably sufficient for testis development
  - The earliest sexual difference appears in the gonad
- Genital duct development
- External genitalia development
- Synthesis and action of steroid hormones
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- Hormonal control of postnatal sexual development
In many species, adult males and females differ not only in their reproductive organs but also in other traits, including size, weaponry, and ornaments.

In red deer, males are considerably larger and seasonally produce large antlers, which they use for fighting.
Figure 16.1: Genotypic sex determination in mammals.

Males have two sexually dimorphic chromosomes, designated X and Y, while females have two X chromosomes. “A” stands for one complete set of non-sex chromosomes, or autosomes. Thus, males produce two types of sperm, with karyotypes AX and AY. This system generates a sex ratio of 0.5, as long as XA and YA sperm have equal chances at fertilization, and provided that AAXX and AAXY embryos are equally viable.
<table>
<thead>
<tr>
<th>Sex Chromosome Status</th>
<th>Human Phenotype</th>
<th>Mouse Phenotype</th>
<th>Drosophila Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>XO</td>
<td>Sterile female*</td>
<td>Fertile female</td>
<td>Sterile male</td>
</tr>
<tr>
<td>XX</td>
<td>Normal female</td>
<td>Normal female</td>
<td>Normal female</td>
</tr>
<tr>
<td>XXX</td>
<td>Fertile female</td>
<td>Unknown</td>
<td>Sterile female</td>
</tr>
<tr>
<td>XY</td>
<td>Normal male</td>
<td>Normal male</td>
<td>Normal male</td>
</tr>
<tr>
<td>XXXY</td>
<td>Sterile male†</td>
<td>Sterile male</td>
<td>Fertile female</td>
</tr>
<tr>
<td>XYY</td>
<td>Fertile male</td>
<td>Semisterile male</td>
<td>Fertile male</td>
</tr>
</tbody>
</table>

* Turner’s syndrome.
† Klinefelter’s syndrome.

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Figure 16.2: Generation of sex-reversed humans by rare X-Y recombination in male meiosis.

The top diagrams show one chromatid each from the X chromosome and from the Y chromosome during meiotic prophase.

If the exchanged Y chromosome fragment contains the testis-determining factor (TDF), then the crossover generates an X-like chromosome (X’) containing TDF and a Y-like chromosome (Y’) lacking TDF.

If sperm with such chromosomes fertilize then the resulting zygotes will develop into sex-reversed XX’ males and XY’ females, respectively.
Figure S16.b: Human Y chromosome near the pseudoautosomal boundary

The scale at the top indicates the distance in kb from the boundary towards the centromere. The acronyms refer to cloned marker sequences used as probes in Southern blots of DNA from sex-reversed XX’ males.
Figure S16.c: Method for generating transgenic mice by microinjecting the cloned transgene into one pronucleus of a fertilized egg.
### Table 26.4 Analysis of Mouse Embryos Injected with an Sry1 Transgene

The embryos were assayed for the presence of sex chromatin (Barr body), the Sry<sup>+</sup> transgene, the Zfy<sup>+</sup> gene (located on the normal Y chromosome), and the phenotypic sex (testis cords). Among eight chromosomal females (XX karyotype) transgenic for Sry<sup>+</sup>, two were phenotypic males, while six were phenotypic females. ND = not determined.

<table>
<thead>
<tr>
<th>Number of Embryos</th>
<th>Sex Chromatin</th>
<th>Sry&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Zfy&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Deduced Karyotype</th>
<th>Transgenic</th>
<th>Phenotypic Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>+</td>
<td>−</td>
<td>−/ND</td>
<td>XX</td>
<td>−</td>
<td>o</td>
</tr>
<tr>
<td>27</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>XY</td>
<td>ND</td>
<td>o</td>
</tr>
<tr>
<td>58</td>
<td>−</td>
<td>ND</td>
<td>ND</td>
<td>XY</td>
<td>ND</td>
<td>o</td>
</tr>
<tr>
<td>2</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>XO</td>
<td>−</td>
<td>o</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>XX</td>
<td>+*</td>
<td>o</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>XX</td>
<td>+</td>
<td>o</td>
</tr>
</tbody>
</table>

* In four of these cases, the transgene may not have been present in all cells.

Y-linked human genes
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After the indifferent stage, a genetic hierarchy controlled by \( Sry^+ \) causes the development of the indifferent gonad into a testis, a process called *primary sex differentiation*.

<table>
<thead>
<tr>
<th>Chromosomes</th>
<th>Genes controlling primary sex differentiation</th>
<th>Hormones controlling secondary sex differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>\textcolor{teal}{SRY}^+</td>
<td>Testosterone</td>
</tr>
<tr>
<td>X</td>
<td>\textcolor{blue}{Dax-1}^+</td>
<td>Anti-Müllerian hormone</td>
</tr>
<tr>
<td>A</td>
<td>\textcolor{teal}{Sox-9}^+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>\textcolor{blue}{Wnt-4}^+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>\textcolor{blue}{Amh}^+</td>
<td></td>
</tr>
</tbody>
</table>

- \textcolor{teal}{Active gene}
- \textcolor{blue}{Inactive gene}

- No Testosterone
- No anti-Müllerian hormone
Figure 16.3: Primary sex differentiation in the human embryo

All diagrams show transverse sections. (a) Indifferent gonad during 6th week of gestation. (b) Ovary during 7th week. Cortical portions of primary sex cords form follicles. (c) Testis during 8th week. Medullary portions of primitive sex cords form testis cords.
Figure 16.4: Seminiferous tubule in mammalian testis

(a) schematic drawing of testis
(b) photograph showing tubules in cross section
(c) drawing of segment outlined in part (b)
Figure 16.5: Human oocyte development in the ovary

b: total ovary  
a: follicle during antrum formation  
c: mature follicle, inset shows oocyte.  
d: photograph of a monkey oocyte during antrum formation. The zona pellucida appears dark in this preparation.
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The immigrating primordial germ cells are surrounded by proliferating gonadal epithelial cells to form primitive sex cords. The mesonephric (Wolffian) and paramesonephric ducts are both in place. The former functions as part of the embryonic kidney.
Figure 16.6: Genital duct development in the human female.

(a) Fourth month of gestation. Both Müllerian and Wolffian ducts are in place. 
(b) At birth, the proximal portion of each Müllerian duct has formed an oviduct. The distal portions of both Müllerian ducts have fused to form uterus and upper vagina. The Wolffian duct has degenerated.
Figure 16.7: Genital duct development in the human male

(a) Fourth month of gestation. The proximal portion of the Wolffian duct is embedded in the mesonephros.
(b) After the descent of the testis, the mesonephric tubules have become efferent tubules. The Wolffian duct has formed the epididymis, ductus deferens, and seminal vesicle. The Müllerian duct has degenerated except for a small rudiment.
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The genital tubercle forms either the corpora cavernosa of the penis or all of the clitoris.

The urogenital groove becomes either the urethra or the vestibule of the vagina.

The urethral folds form either the corpus spongiosum of the penis or the labia minora.

The genital swellings give rise to either the scrotum or the labia majora.
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Testosterone is synthesized via progesterone from cholesterol.

In the presence of the enzyme aromatase, testosterone is converted into estrogen.

In the presence of $5\alpha$-reductase, testosterone is converted to $5\alpha$-dihydrotestosterone.
The target cells of steroid hormones have receptor proteins to which the hormones bind. The receptors of many steroids are located in the cytoplasm. The hormone-receptor complex enters the nucleus, where it binds to enhancer steroid response elements associated with many target genes. Together with other transcription factors, the steroid receptors activate or inhibit transcription.
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Figure 16.10: Somatic sexual development in mammals
Primary (gonadal) sex differentiation depends on the $Sry^+$ gene, whereas secondary sex differentiation is controlled by sex hormones.
Genetic Disorders Interfering with Secondary Sex Differentiation

- **Congenital adrenal hyperplasia (CAH)** – based on loss-of-function alleles for enzymes converting progesterone to metabolic steroids. Leads to elevated testosterone and masculinisation in females.

- **Androgen insensitivity** – loss of function in gene for androgen receptor. Allows development of female external genitalia and female secondary sex characteristics in males with normal $SRY^+$ and (non-descended) testes.

- **Guevedoces (penis at 12 years of age)** – based on autosomal recessive alleles for 5-α-reductase, which metabolizes testosterone to DHT. Affects only males.
**Figure S16.e: Congenital Adrenal Hyperplasia**

This baby girl shows mild enlargement of the clitoris and fused urogenital folds.
Androgen Insensitivity

Individuals with this disorder have normal XY chromosomes except for a mutation in the gene for the androgen receptor. They have (non-descended) testes and produce androgens, but their cells cannot respond. By default, and in response to estrogen produced in their adrenal glands, they develop female external genitalia and female secondary sex characteristics.
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