Chapter 10

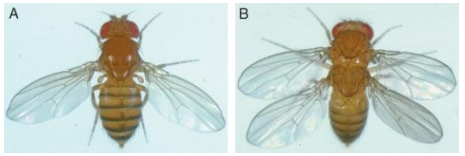
Cells Differentiate

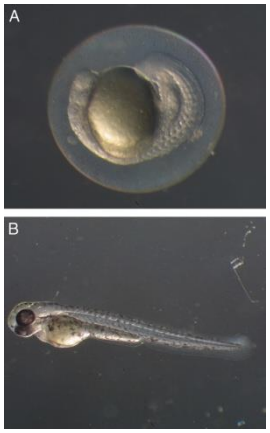
Developmental Biology

- Development
  - The process of transformation from fertilized egg to adult
- History of developmental biology
  - Until 20th century : Observation
  - 20th century : Identification of underlying mechanism using genetics and molecular biology

Developmental Biology

- Model systems
  - Fruit fly (*Drosophila melanogaster*)
    - Small, a short life cycle, well characterized, many mutant strains
    - Thomas H. Morgan
  - Nematode worm (*Caenorhabditis elegans*)
    - Sydney Brenner (1965, UK)
      - Trace the lineage of all the cells (<1000 cells)
  - Vertebrate
    - Frogs, chicken, fish (zebrafish)
      - Develop in eggs outside the mother's body
    - Mouse
      - Identifying the gene function using genetically modified mice





Fundamental Developmental Processes

- Development
  - Differentiation
    - Generation of different specialized kinds of cells from zygote (fertilized egg) or other precursor cells
      - Generate blood cells, muscle cells, neurons …
  - Morphogenesis
    - Creation of form and structure
      - Generate the shape of legs, eyes, wings, skin, organs, tissues, and structures

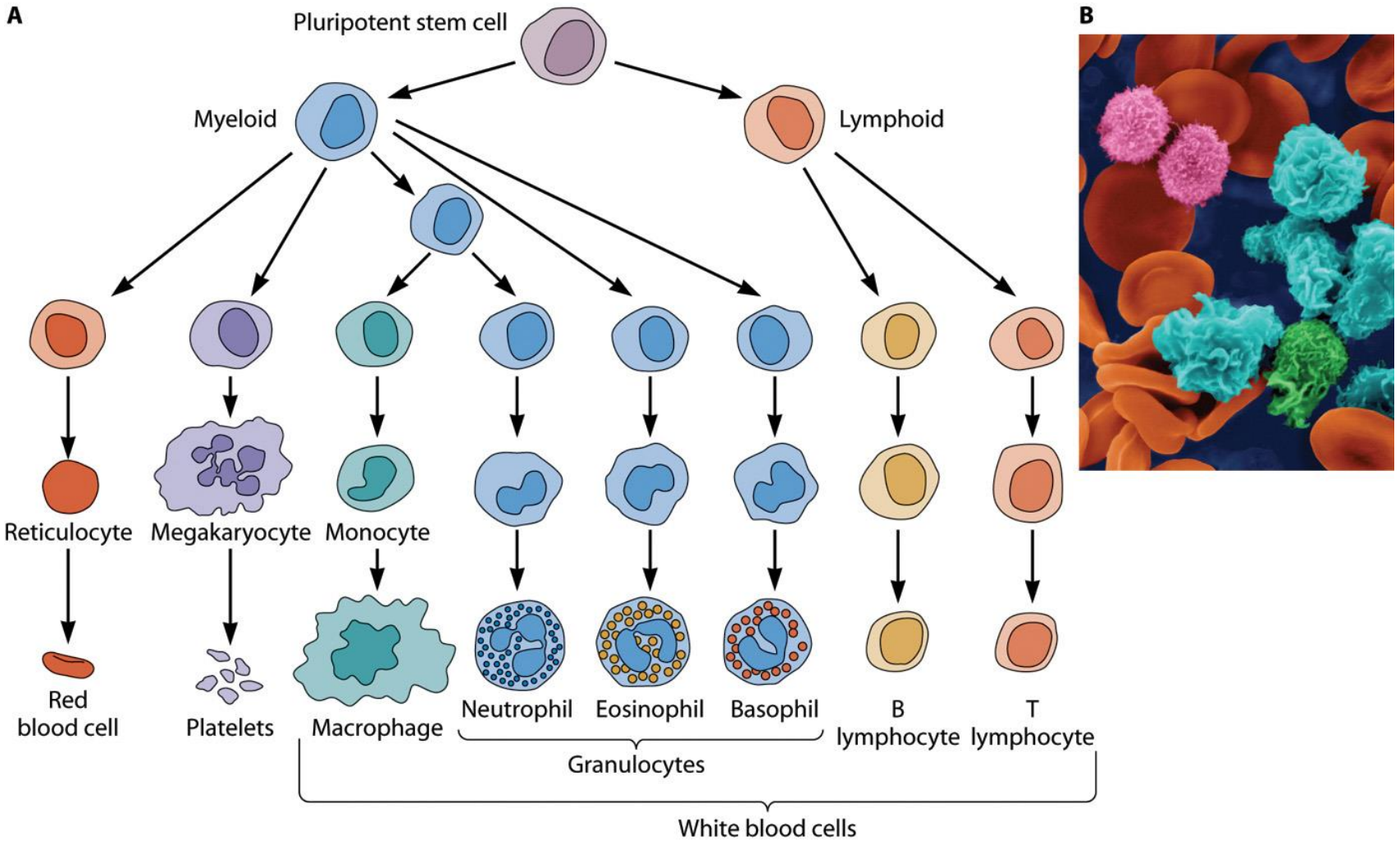
Differentiation

- Totipotent
  - Fertilized egg : contains all the information to develop into all the types of cells
- Pluripotent (multipotent)
  - Can be developed into several different, but not all, cell types
- Terminally (or fully) differentiated
  - A cell with specialized properties of a particular cell type
  - Usually no reproduction
- Stem cell
  - Less differentiated cell
  - Provide new terminally differentiated cells (blood cells, epithelial cells)

Totipotent, Pluripotent, Multipotent

- Totipotent cells can form all the cell types in a body, plus the extraembryonic, or placental, cells. Embryonic cells within the first couple of cell divisions after fertilization are the only cells that are totipotent.
- Pluripotent cells can give rise to all of the cell types that make up the body; embryonic stem cells are considered pluripotent.
- Multipotent cells can develop into more than one cell type, but are more limited than pluripotent cells; adult stem cells and cord blood stem cells are considered multipotent.

Differentiation of Blood Cells



Differentiated Cells

- Same set of genes
- Different expression pattern
  - Common expression of essential genes : housekeeping genes
  - Differential expression of cell-specific genes
  - Cellular differentiation is the process of turning on and off of specific genes

Table 10.1 Specialized products of differentiated cell types

Cell type	Specialized product	Specialized function
Keratinocyte (skin cell)	Keratin (protein)	Protection against abrasion and drying out
Erythrocyte (red blood cell)	Hemoglobin (protein)	Transport of oxygen
Melanocyte	Melanin (pigment)	Pigment production
Myocyte (muscle cell)	Actin and myosin (proteins)	Muscle contraction
Pancreatic islet cells	Insulin (peptide)	Regulation of glucose metabolism
Hepatocyte (liver cell)	Numerous enzymes (proteins)	Glycogen storage and breakdown; fatty acid synthesis; gluconeogenesis; other metabolic functions
Neuron (nerve cell)	Neurotransmitters (various)	Transmission of nerve signals

Morphogenesis

- Morphogenesis
  - Movement, migration, proliferation, and death of cells
  - Triggered by communication between cells
- Morphogenesis in vertebrate
  - Generation of neural tube → brain and spinal cord
    - Cells in the neural tube
      → migration and generate neural circuits
  - Formation of limbs
    - Migration of bone and muscle precursor cells
      → Formation of limb buds under the outer layer of embryo

Morphogenesis

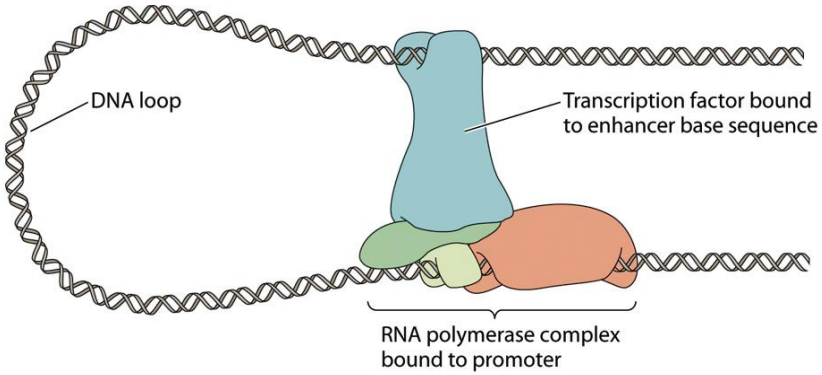
- Cell migration and fur pigmentation
  - Cells migrate outward from the region of spinal cord and differentiates into different types of cells including melanocytes.
  - No melanocytes in the hair follicle

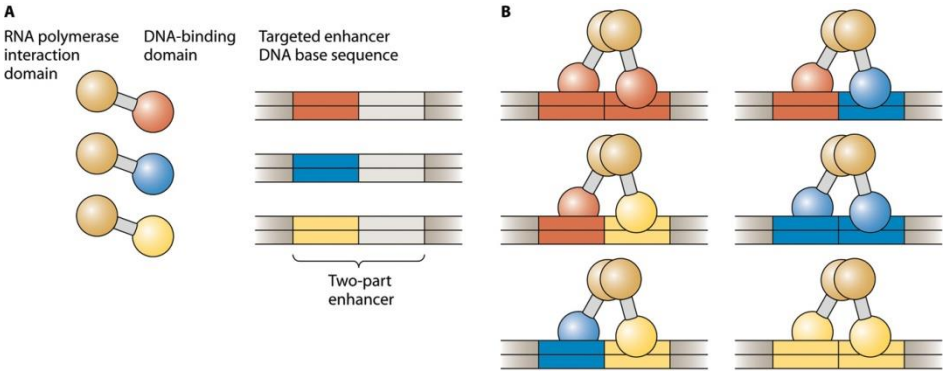
    → white hair

- Apoptosis in morphogenesis
  - Apoptosis: programmed cell death
  - Apoptosis in development
    - Webbed foot vs. nonwebbed foot
    - Development of male or female sexual organs

Differential Gene Expression

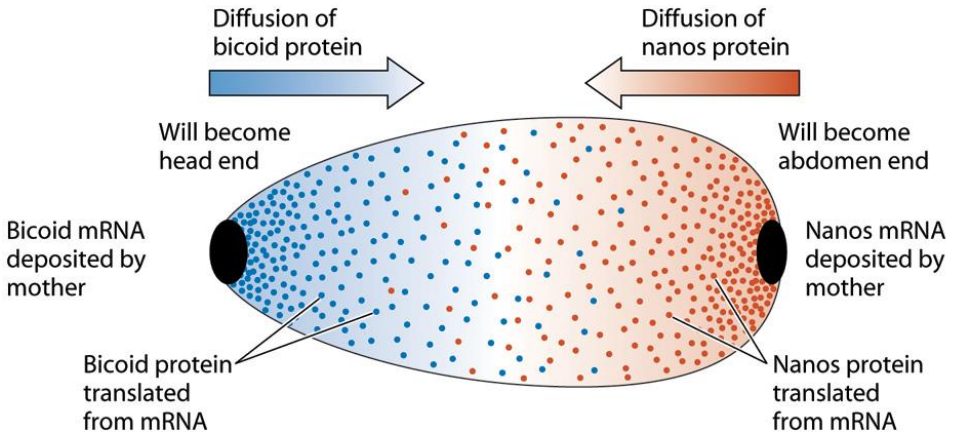
- Enhancer (base sequence)
  - Activate transcription
  - Far from the RNA polymerase binding site
- Silencer: turn off transcription
- Transcription factors
  - Usually act as a complex with other proteins
  - Regulation of gene expression with smaller number of transcription factors





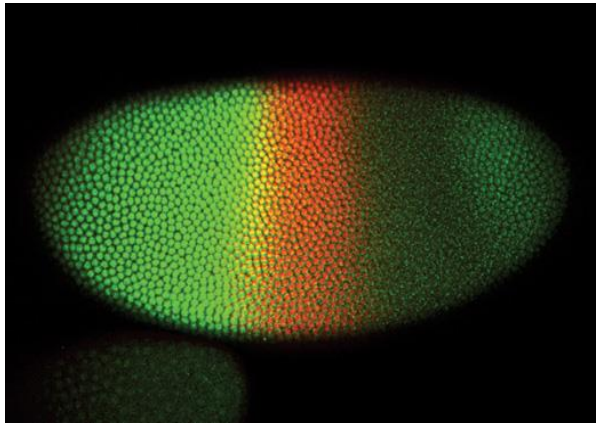
Determination of anterior-posterior body axis in fly

- Embryo produced by mutant fly
  - Mutant fly (mutation in bicoid) → embryo with two tails
  - Mutant fly (mutation in nanos) → embryo with two heads
- Establishment of body plan by maternal genes
  - Maternal cells deposit bicoid and nanos mRNA at the opposite ends of embryo during embryo formation
  - Concentration gradient of bicoid and nanos upon fertilization
    - Bicoid end → head
    - Nanos end → tail



Determination of anterior-posterior body axis in fly

- Hunchback: gene required for development of thorax
  - Regulation of gene expression by bicoid and nanos proteins
    - Bicoid: activation of hunchback
    - Nanos: repression of hunchback



Green: hunchback protein

Red: Krupple protein

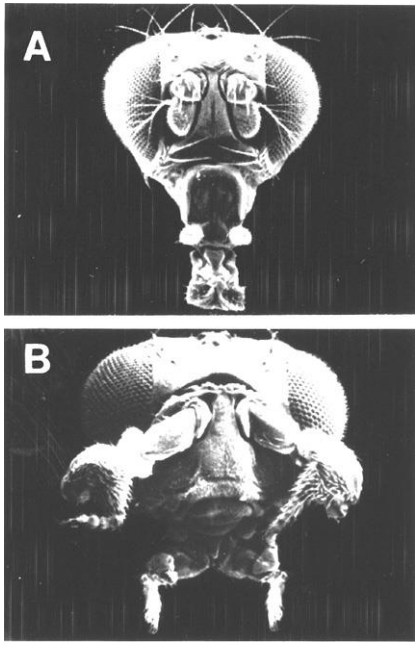
Yellow: both

- Genes turned on in the wake of the bicoid-nanos gradient divide the *Drosophila* embryo into segments
- Homologous genes in frog, chicken, zebrafish, mouse, and human

Homeotic Genes in Fly

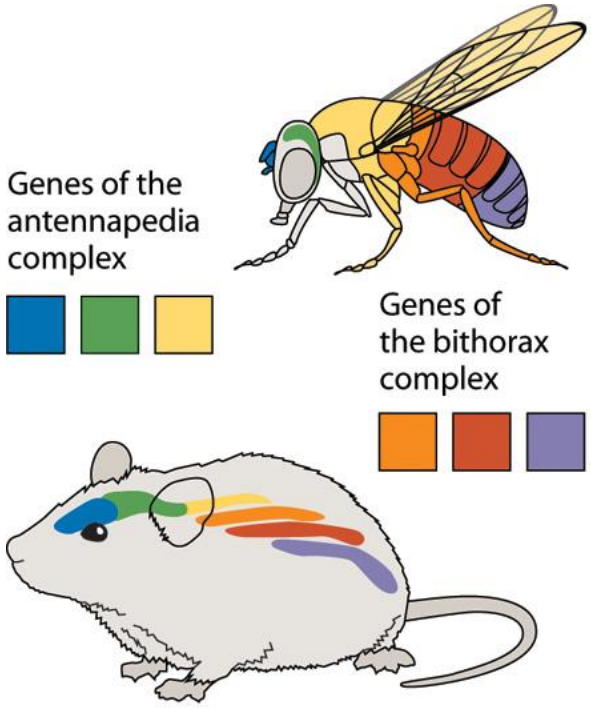
- Homeotic genes
  - The fates of the individual segments are controlled by an other family of genes: the homeotic genes
- Homeotic gene clusters
  - Bithorax complex
    - Controlling the development of the posterior half of the embryo
    - Gene arrangement on the chromosome is in the same order as the segments of the fly body they controls
  - Antennapedia complex
    - Controlling the development of the anterior part

A. Normal
B. Antennapedia



Homeotic Genes in Vertebrates

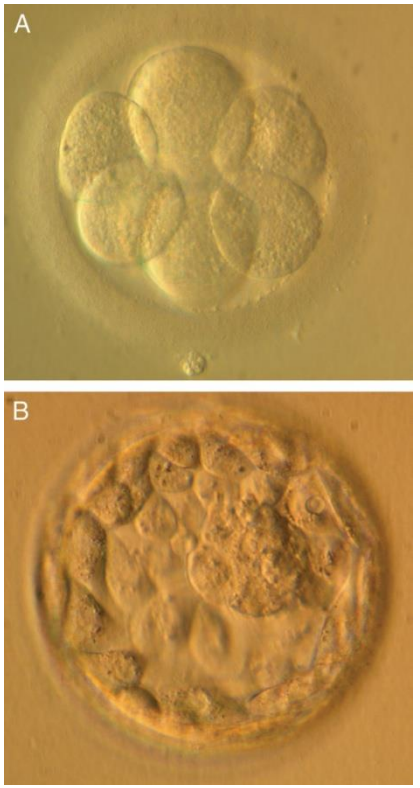
- Similar to *Drosophila* homeotic genes
- Instead of one bithorax cluster and one antennapedia cluster, mouse and human have 4 copies of each.
- The proteins encoded by homeotic genes have similar DNA binding domains, called the homeodomain.
- Homeotic genes would specify segment fate by turning different sets of genes on and off.



Early Cell Division and Implantation

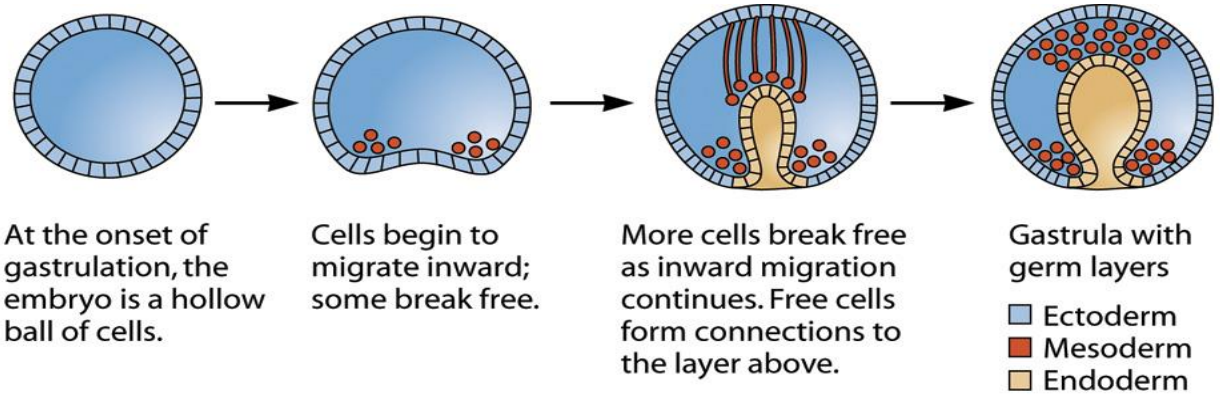
- Blastocyst: 64-cell stage
  - 13-cell inner cell mass
    → embryo, its yolk sac,
    and extraembryonic membrane
  - Trophoblast (outer cell layer)
    - The trophoblast cells form a fluid-filled ball with the inner cell mass.
    - The trophoblast cells will form the embryo's portion of placenta.
    - Implantation into the uterus
- Extraembryonic tissues
  - Fetal side of placenta
    +
  - Membranes surrounding the fetus
- After implantation, the cells of the inner cell mass undergo gastrulation.

A. 8-cell embryo
B. Blastocyst



Early Development in Mammals

- Rapid cell division of a fertilized egg
- A series of rapid cell division generates blastula (hollow ball shape).
- Gastrulation (The blastula undergoes a dramatic rearrangement.)
  - Formation of three germ layers
    - Ectoderm → outer layer of the skin and the nervous tissue
    - Endoderm → inner linings of the digestive organs and circulatory system
    - Mesoderm → muscle, bone, blood, and other internal organs and tissues



- Differentiation into specific tissues and organs
  - Homeotic genes

Pluripotent Inner Cell Mass

- Monozygotic (identical) twins
  - Splitting of a single inner cell mass (Pluripotent) into two or three independent embryos
- Chimeras
  - Mixture of inner cell masses of two embryos
- Embryonic stem (ES) cells
  - Cultured totipotent inner cell mass
  - ES cell line: originated from one blastocyst
  - Genetically modified ES cells → used to generate transgenic mouse
  - Induce to develop different cell types using growth factors
    → Stem cell therapy

Stem Cell Therapy In Action

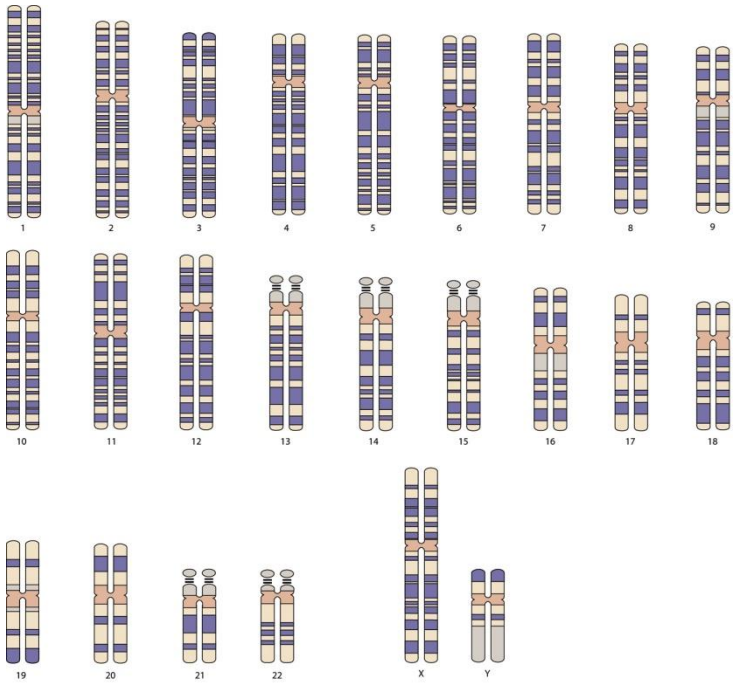
- Stem cell therapy for blood cells
  - Sickle-cell anemia, severe combined immune deficiency, leukemia, and lymphoma
  - Destroy own bone marrow and transplant donor's bone marrow
  - Donor : with genetic match which can reduce graft-versus-host (GVH) disease
  - Use own stem cells : placental blood cells

Sex Differentiation

- Primary sex determination
  - Determination of the gonads: ovaries or testes
    - Genetic
    - Environmental
      - Reptile ; depending on the temperature
- Secondary sex determination
  - Sexual phenotype outside the gonads
    - Male mammals: penis, seminal vesicles, prostate gland
    - Female mammals: vagina, cervix, uterus, oviducts, mammary glands
- Different from species to species

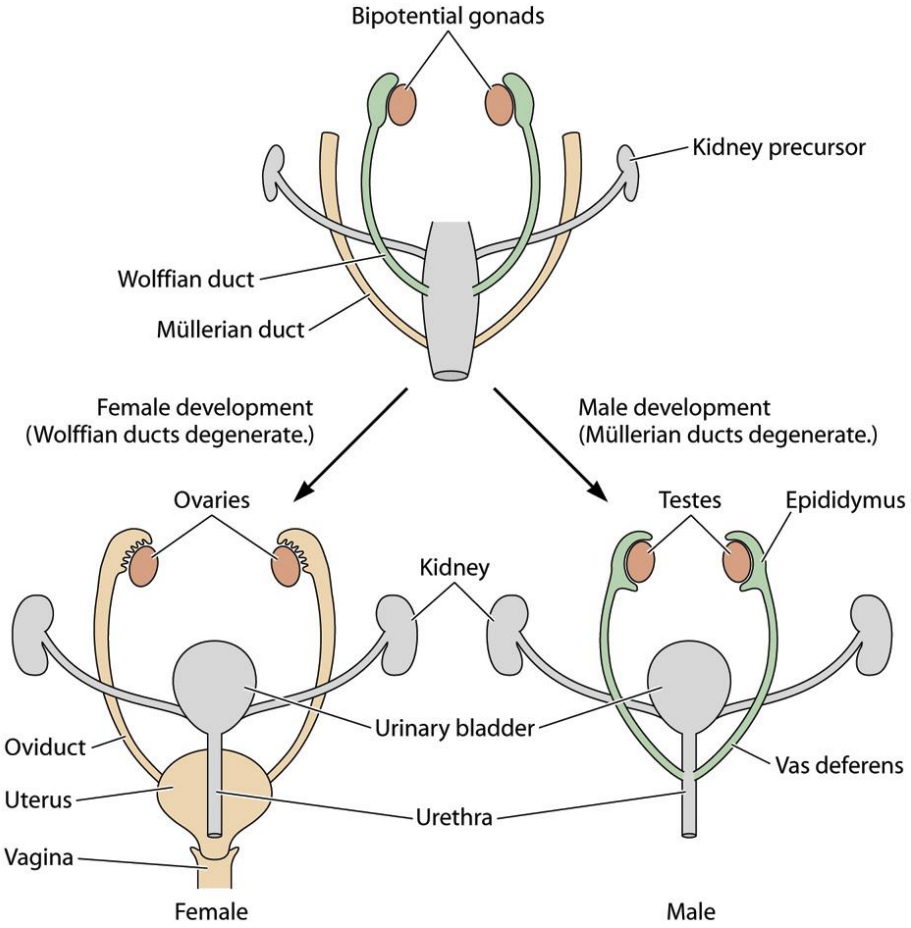
Primary Sex Determination

- 23 pairs of human chromosomes
  - Autosomes: 22 pairs (homologous chromosomes)
  - Sex chromosomes
    - Male: XY, Female: XX
    - X chromosome :1500 genes not related to gender development, essential for survival
    - Y chromosome: small, 100 genes
      - SRY: sex-determining region of the Y chromosome
      - Regulation of early gene expression



Sex Differentiation

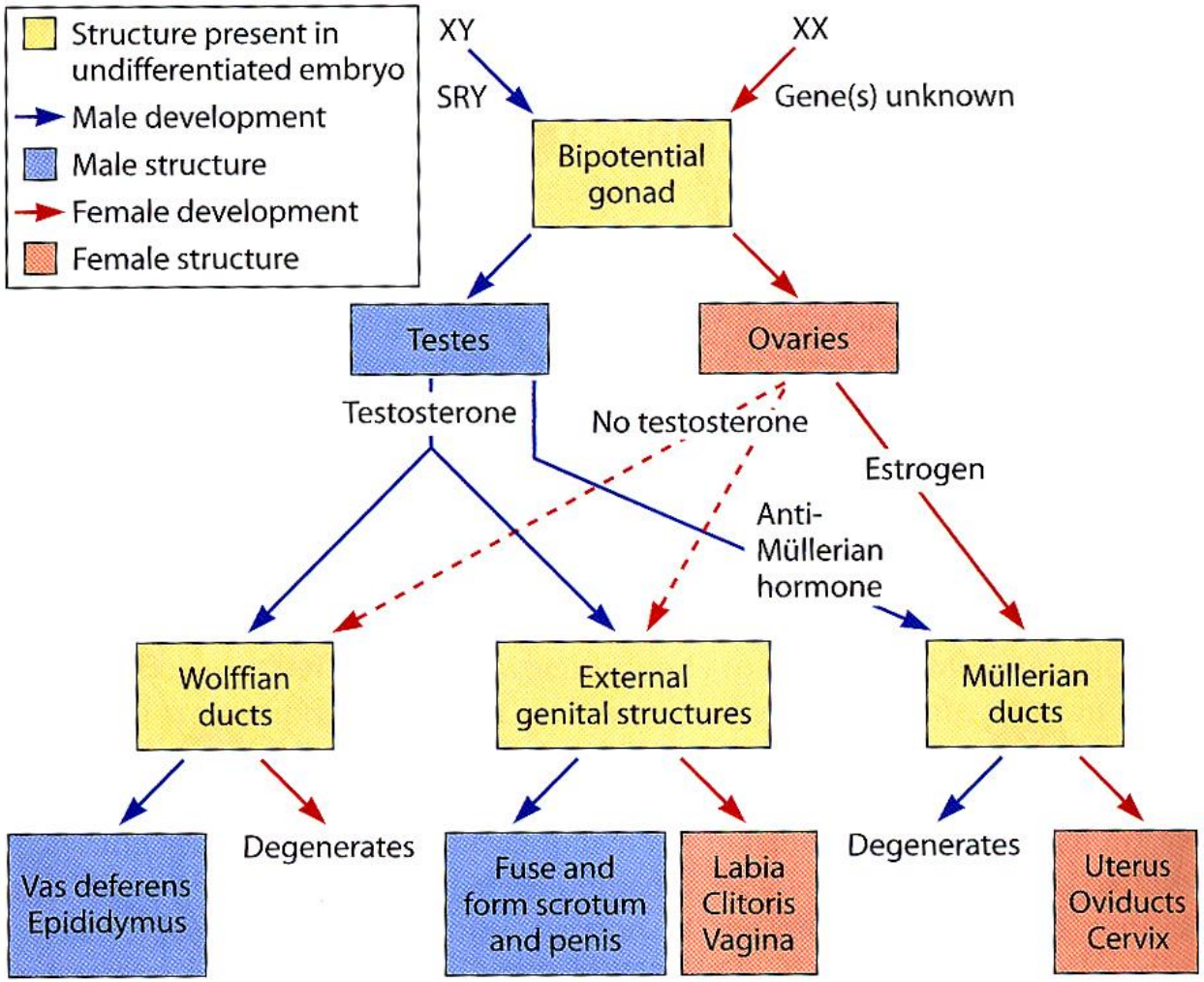
- Primordial gonadal structure : bipotential gonads
  - Mullerian and Wolffian ducts
- Female development
  - Degeneration of Wolffian ducts
  - Generation of ovaries and eggs
- Male development
  - Degeneration of Mullerian ducts
  - Generation of testes and sperms



Sex Differentiation

- With SRY
  - Expressed around week 7 of development
    - Stimulation of testes formation
  - Hormones secreted from testes
    - Anti Mullerian hormone (AMH)
    - Testosterone
      - Stimulate development of male sex organs
- Without SRY
  - Development of ovaries
  - Hormones secreted from ovaries
    - Estrogen
      - Generation of female sex organs
- Two X chromosomes are necessary for complete female sexual development
  - Turner's syndrome: one X, no Y chromosome

Sex Differentiation



Sex Hormones

- No strict female and male hormone
- Estradiol
  - Responsible for growth spurts of boys and girls at puberty
  - Conversion of testosterone to estradiol in the bone of boys
- Testosterone
  - Generated in the adrenal glands of the kidney and in the ovaries
  - Stimulation of the growth of mammary glands, uterus, and clitoris in rats
- Estrogen
  - Produced from the adrenal glands in both males and females
  - Necessary for complete development of the Wolffian ducts
  - Fertility in adult males
    - Water resorption during semen formation

Variations in Sex Development

- Androgen (male hormone secreted from testes) insensitivity: XY female
  - Androgen: 남성 호르몬의 작용을 나타내는 모든 물질을 일컫는 말
  - Mutation of the testosterone receptor in X chromosome
    - Testes formation because of SRY gene
    - Female external genital structures

Variations in Sex Development

- DHT deficiency
  - Testosterone converted into 5α-dihydrotestosterone (DHT) in the fetal external genitalia

    Testosterone → DHT

  - Mutation of the converting gene on chromosome 2
  - High concentration of testosterone at puberty
    → development of external genitalia at puberty
  - Common in a certain population in the Caribbean

Variations in Sex Development

- CAH (Congenital adrenal hyperplasia)
  - No cortisol-synthesizing enzyme
  - Cortisol precursor is same as androgen precursor.
  - Overproduction of testosterone and other androgens from adrenal gland
  - Female fetus → Male-like genital structure

Gender Identity

- Testosterone
  - Key factor in the development of sexual identity