Chapter 10

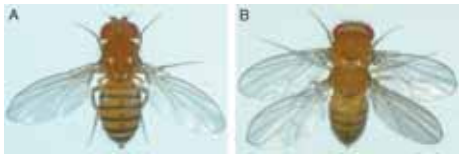
Cells Differentiate

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)
  - Vertebrate
    - Frogs, chicken, fish (zebrafish)
      - Develop in eggs outside the mother's body
    - Mouse
      - Identifying the gene function using genetically modified mice
      - Use information from other model systems



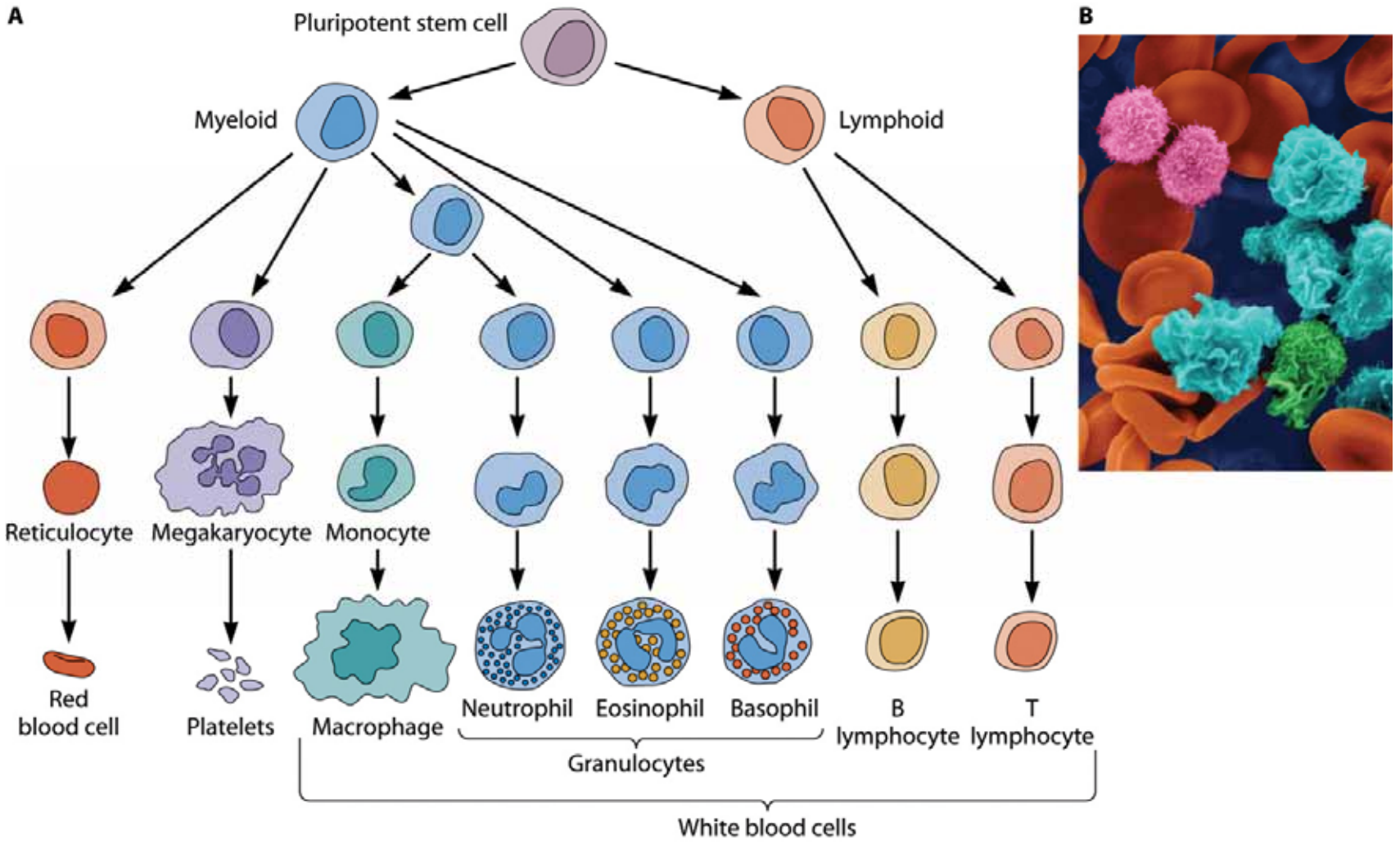
Fundamental Developmental Processes

- Development
  - Differentiation
    - Generation of different specialized kinds of cells from zygote (fertilized egg) of other precursor cells
      - Epithelial, liver, muscle etc
  - Morphogenesis
    - Creation of form and structure
      - Legs, eyes, wings, skin, organs, tissues, structures

Differentiation

- Totipotent
  - Fertilized egg : contains all the information to develop into all the type of cells
- Pluripotent
  - Can be developed into several different cell types
- Terminally differentiated
  - A cell with specialized properties of a particular cell type
  - Usually no reproduction
  - Stem cells: provide new terminally differentiated cells (blood cells, epithelial cells)

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

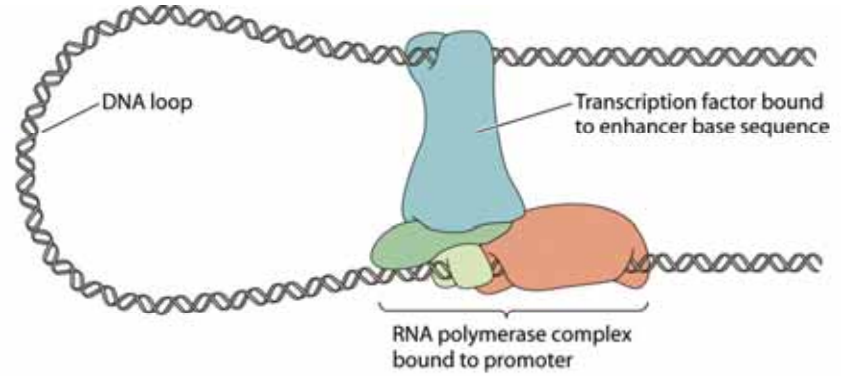
    → Formation of limb buds under the outer layer of embryo

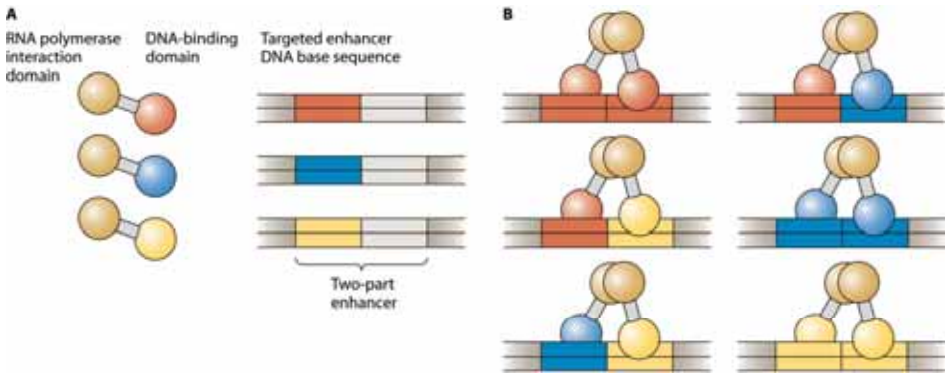
Morphogenesis

- Cell migration and fur pigmentation
  - No melanocytes in the hair follicle → white hair
  - Formed in the neural crest cells and migrate from the region of spinal cord
- Apoptosis in morphogenesis
  - Apoptosis: programmed cell death
  - Apoptosis in development
    - Webbed foot vs. nonwebbed foot
    - Development of sexual organs

Differential Gene Expression

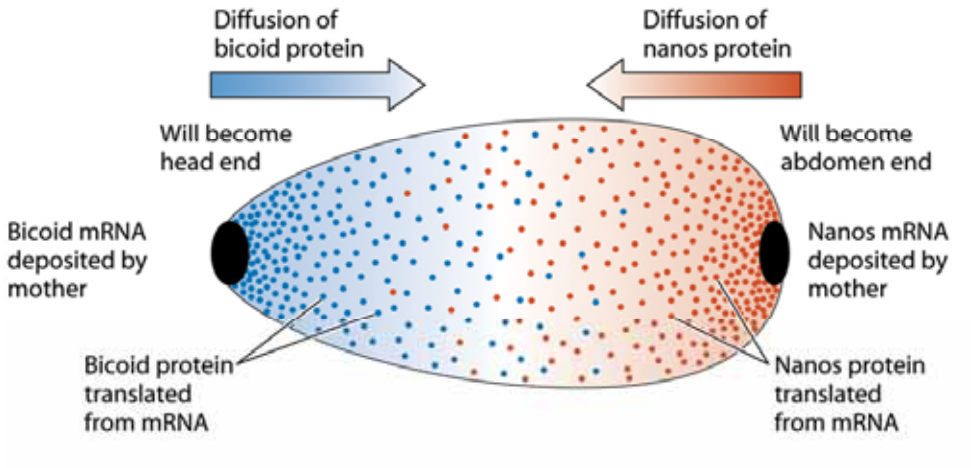
- Enhancer
  - Activate transcription
  - Far from the RNA polymerase binding site
  - Silencer: turn off transcription
- Transcription factors
  - Usually act as a complex with other proteins
  - Regulation of gene expression with smaller number of transcription factors





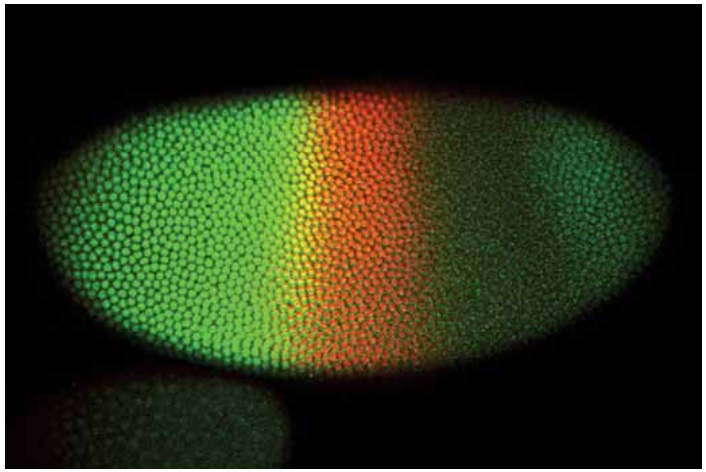
Determination of anterior-posterior body axis in fly

- Mutant fly embryos
  - Bicoid: embryo with two tails
  - 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 nonos upon fertilization
    - Bicoid end → head
    - Nanos end → tail



Determination of anterior-posterior body axis in fly

- Bicoid and nanods
  - Regulation of gene expression
    - Hunchback: required for development of thorax
      - Bicoid: activation of hunchback
      - Nanos: repression of hunchback
  - Divide the Drosophila embryo into segments
- Homologous genes in frog, chicken, zebrafish, mouse, and human



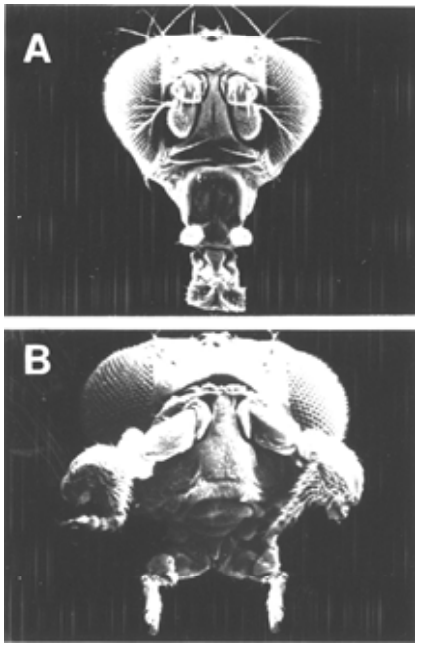
Green: hunchback

Red: Krupple

Yello: both

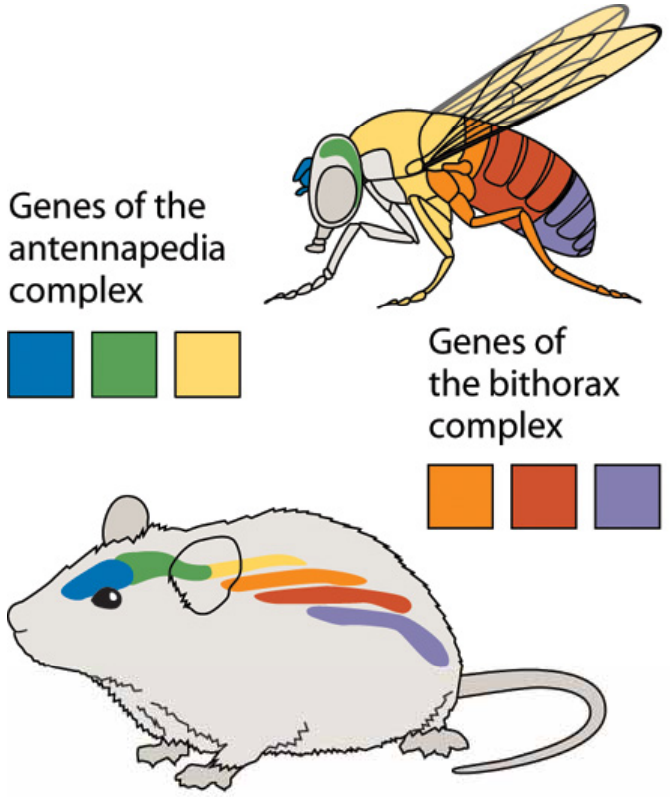
Homeotic Genes in Fly

- Hometic genes
  - Determination of the fates of the individual segments
- Bithoras 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
  - Controlling the development of the anterior part



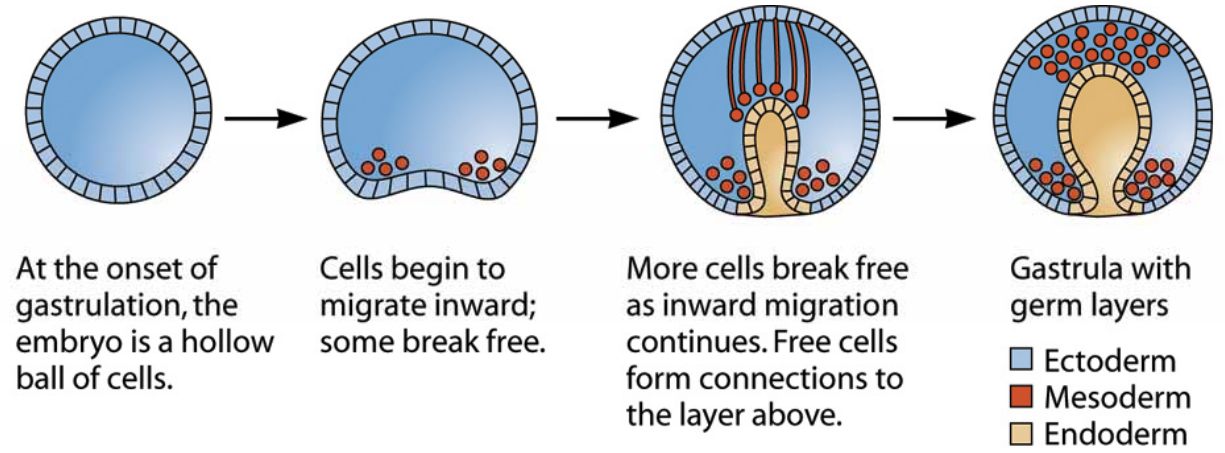
Homeotic Genes in Vertebrates

- Similar to drosophila homeotic genes
  - Mouse and human have 4 copies of bithorax and antennapedia cluster
  - DNA binding proteins
    - Homeodomain
    - Possibly regulated differential gene expression



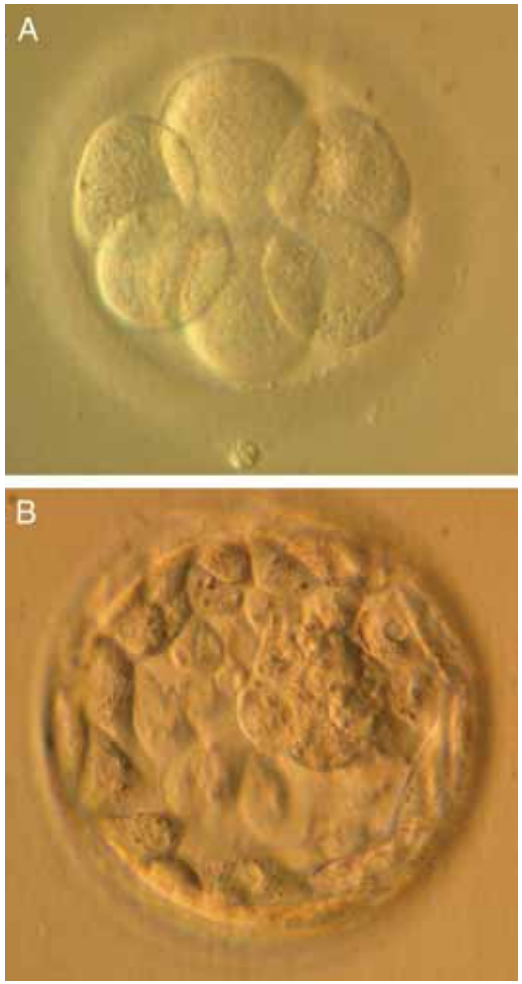
Early Development in Mammals

- Development in mammals
  - Rapid cell division of a fertilized egg
  - Blastula: hollow ball shape
  - Gastrulation
    - Formation of thee 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



Development of Embryonic and Extraembryonic tissues

- Extraembryonic tissues
  - Fetal side of placenta
  - Membranes surrounding the fetus
- Blastocyst: 64-cell stage
  - 13 cell inner cell mass → embryo and extraembryonic membrane
  - Outer cell layer (trophoblast)
    - Implantation into the uterus
    - Formation of placenta



Totipotent Inner Cell Mass

- Monozygotic (identical) twins
  - Splitting of a single inner cell mass (totipotent) 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

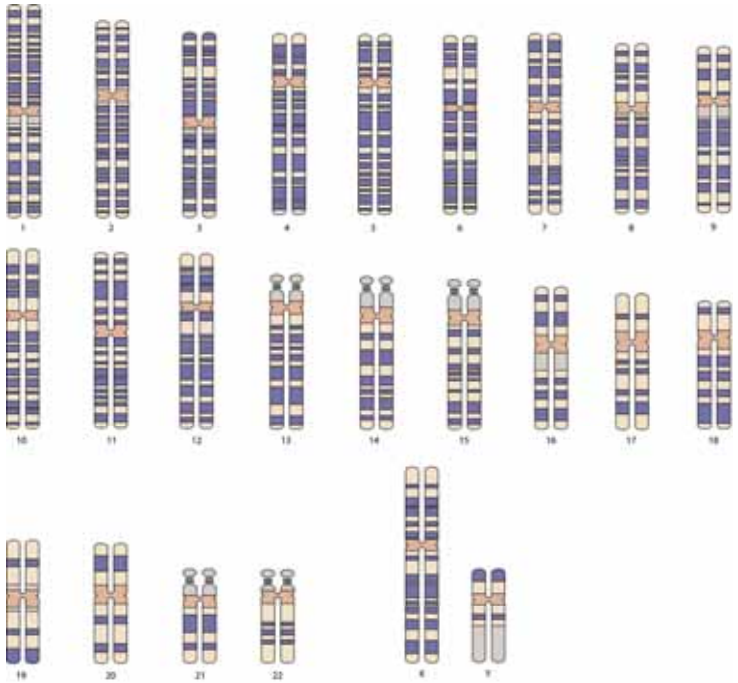
- Stem cell therapy for blood cells
  - Sickle-cell anemia, severe combined immune deficiency, leukemia, and lymphoma
  - Destroy own bone marrow and transplant donor’s bone marrow
  - Donor : with genetic match which can reduce graft-versus-host (GVH) disease
  - Use own stem cells : placental blood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

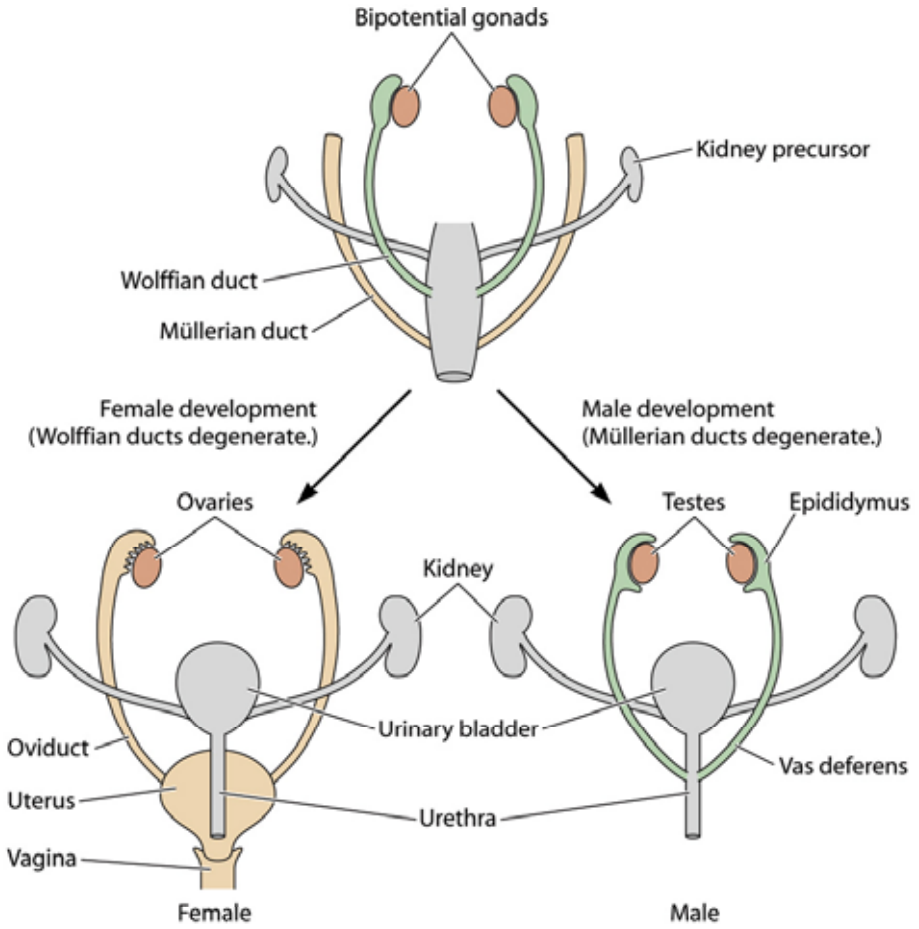
Primary Sex Determination

- 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

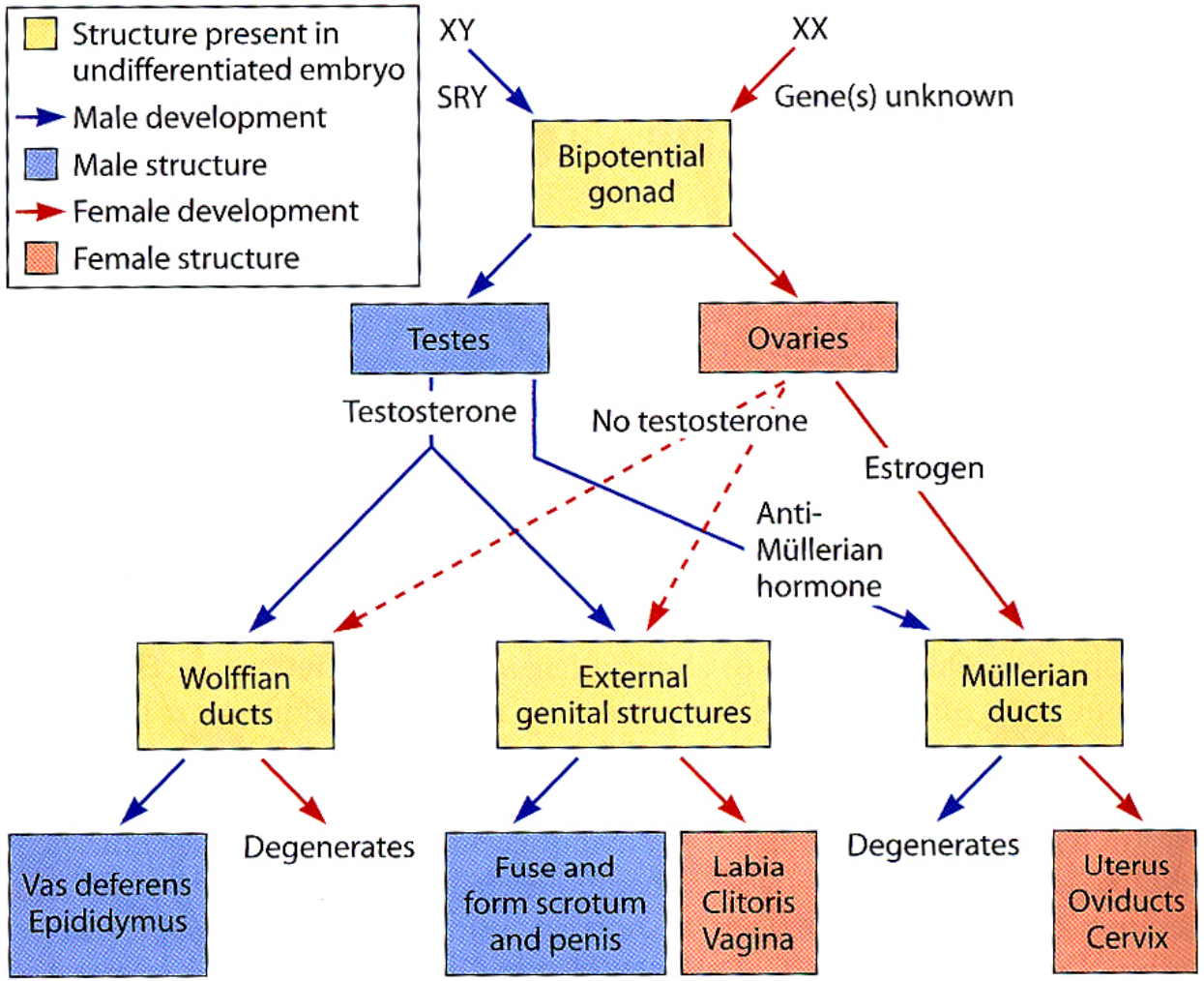
- Primordial gonadal structure : bipotential gonands
  - Mullerian and Wolffian ducts
- Female development
  - Degeneration of Wolffian ducts
  - Generation of ovaries and eggs
- Male development
  - Degeneration of Mullerian ducts
  - Generation of testes and sperms



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
- Withour 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) insensitivity : XY female
  - Mutation of the testosterone receptor in X chromosome
    - Testes formation because of SRY gene
    - Female external genital structures
- DHT deficiency
  - Testosterone converted into 5a-dihydrotestosterone in the fetal external genitalia
  - Mutation of the converting gene on chromosome2
  - → development of external genitalia at puberty
- CAH
  - No cortisol-synthesizing enzyme
  - Overproduction of testosterone and other androgens from adrenal gland
  - Male-like genital structure

Gender Identity

- Testosterone
  - Key factor in the development of sexual identity