Embryology

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Part 1:
General Embryology

- **Chapter 1** (Introduction to Molecular Regulation and Signaling)
- **Chapter 2** (Gametogenesis: Conversion of Germ Cells into Male and Female)
- **Chapter 3** (First Week of Development: Ovulation to Implantation)
- **Chapter 4** (Second Week of Development: Bilaminar Germ Disc)
- **Chapter 5** (Third Week of Development: Trilaminar Germ Disc)
- **Chapter 6** (Third to Eighth Weeks: The Embryonic Period)
- **Chapter 7** (Third Month to Birth: The Fetus and Placenta)
- **Chapter 8** (Birth Defects and Prenatal Diagnosis)

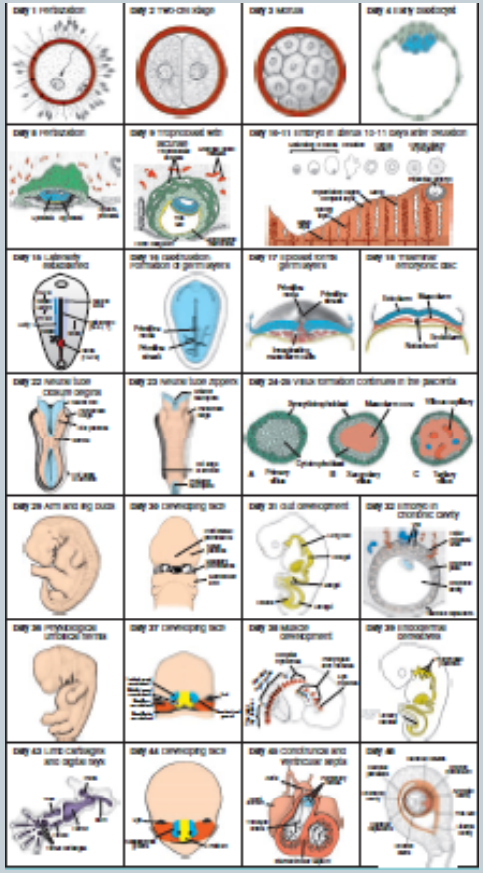
Part 2:
Systems-Based Embryology

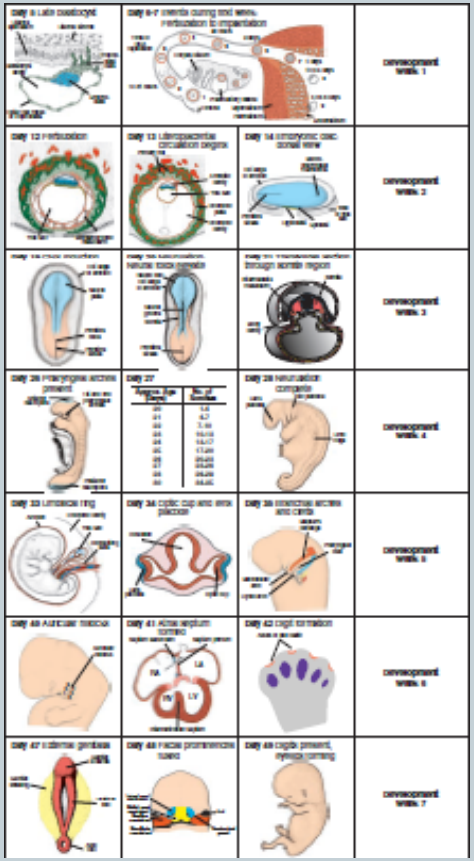
?????

Embryology
Clinical Relevance & Historical Perspective

- *developmental process* From a single cell to a baby in 9 months

Investigations of
- molecular,
- Cellular
- structural factors

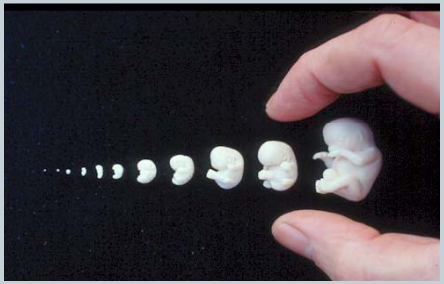


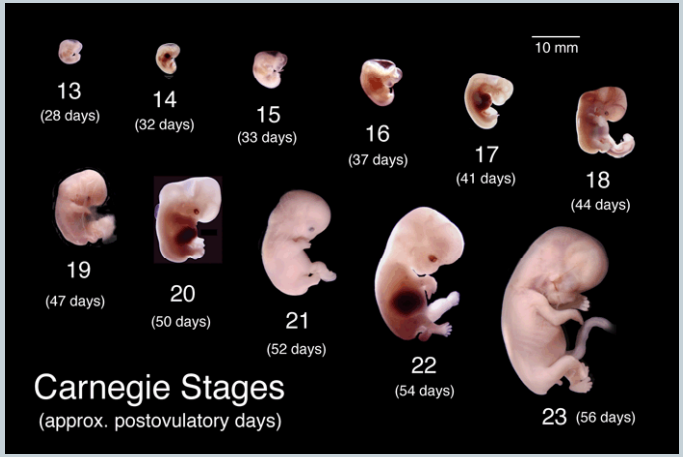


History

embryogenesis (organogenesis)

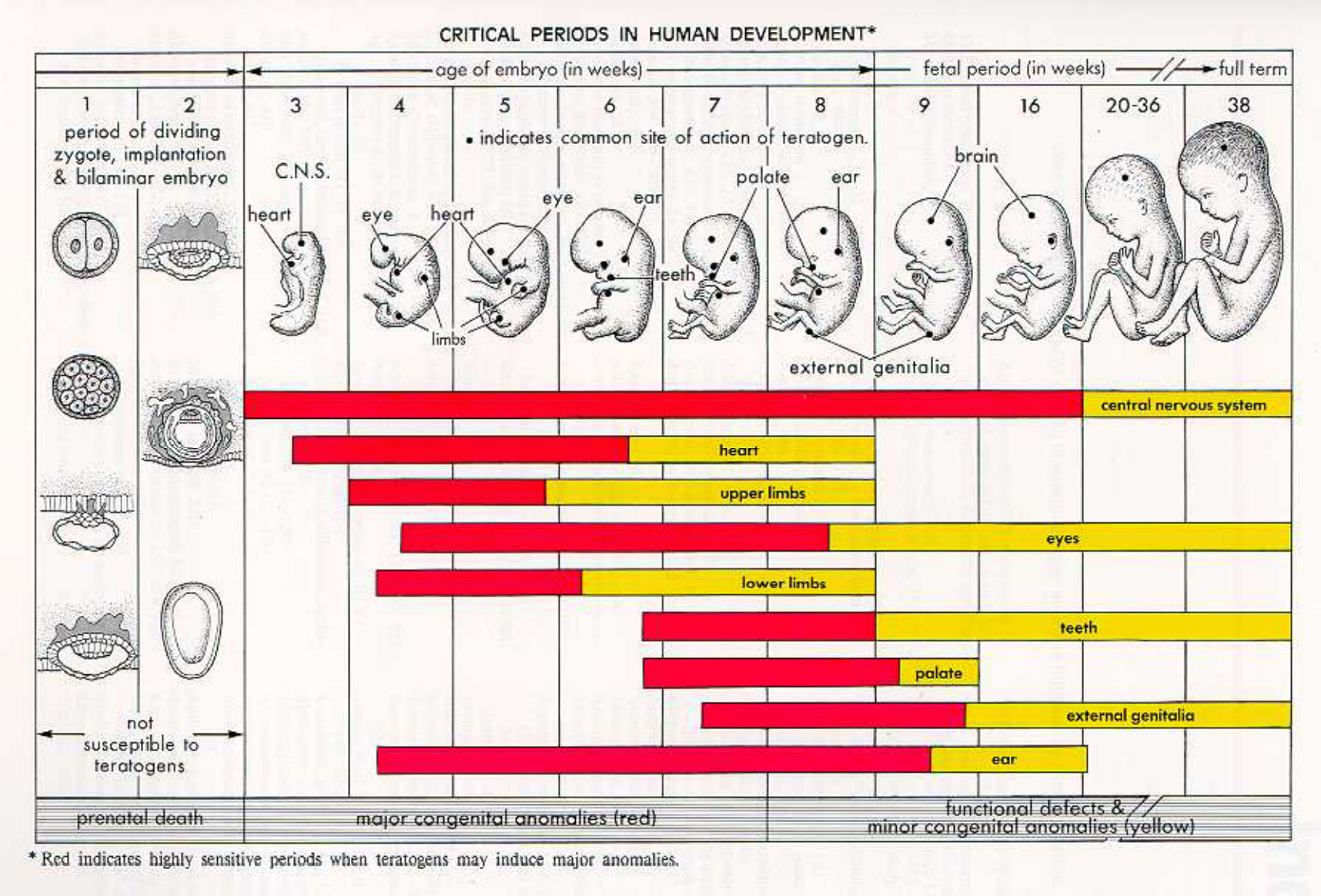
- The progressing from a single cell through the period of establishing organ primordia
- the first 8 weeks of human development



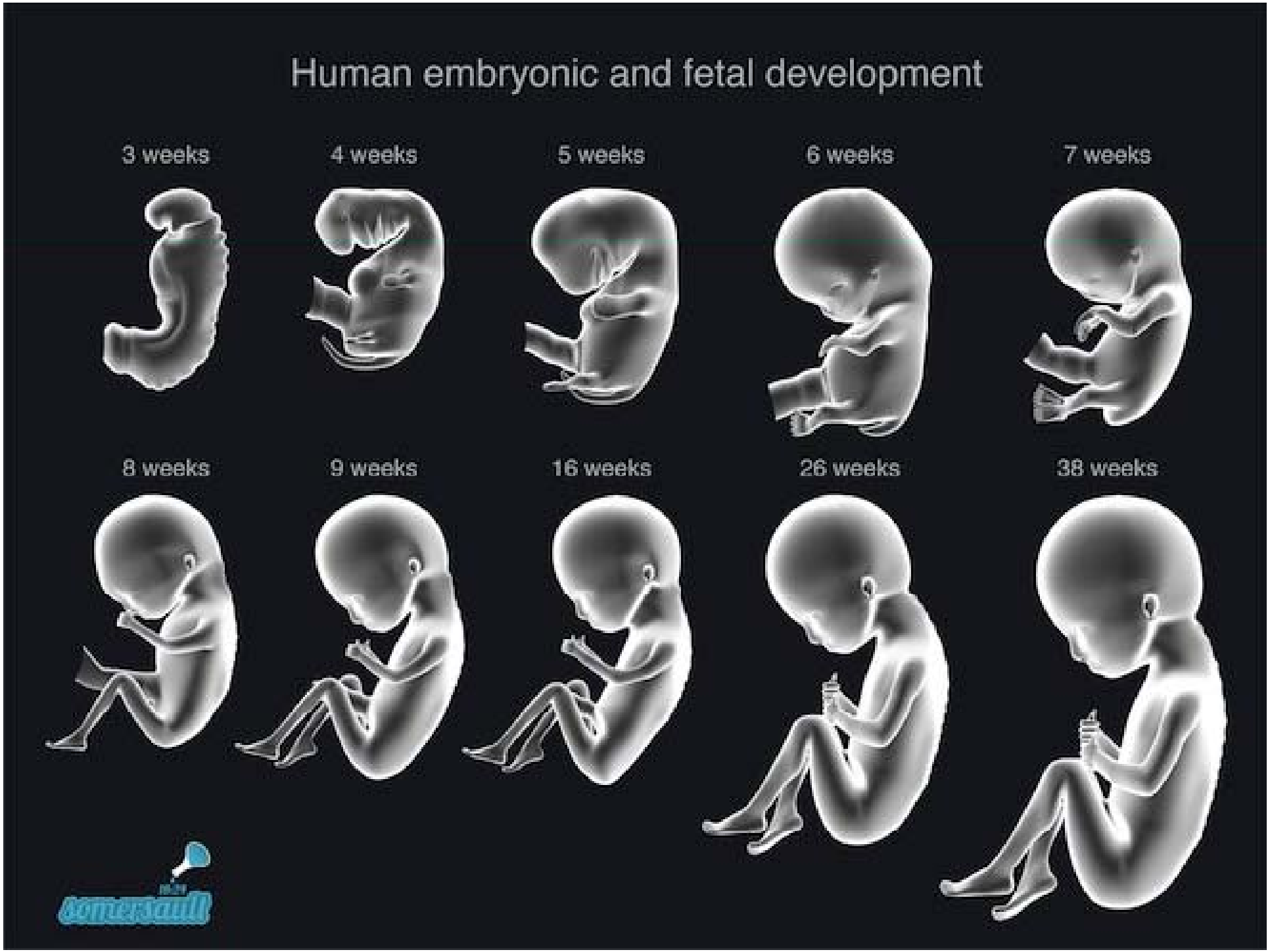


fetal period

- a time when differentiation continues
- period from 9th week until birth
- the fetus grows & gains weight



* Red indicates highly sensitive periods when teratogens may induce major anomalies.


Human embryonic and fetal development
3 weeks
4 weeks
5 weeks
6 weeks
7 weeks
8 weeks
9 weeks
16 weeks
26 weeks
38 weeks

History

- Early anatomical investigations
- Advances in optical equipment and dissection techniques
- Comparative and evolutionary studies among species
- Comparative studies between offspring with birth defects & organisms with normal developmental patterns

Teratology

20th century

- Experimental embryology
- observations of embryos from tunicates that contained pigmented
- living cells staining & follow their fates using vital dyes

History

- **1960s, radioactive labels & autoradiographic techniques**

- **creation of chickquail chimeras**

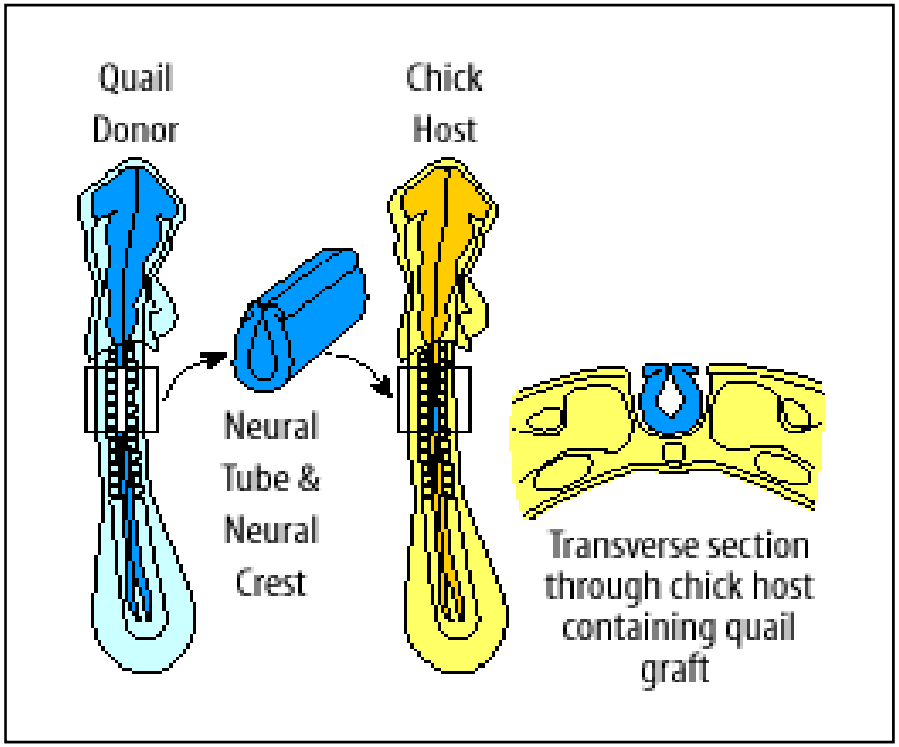
quail cells with unique pattern of heterochromatin were grafted

into chick embryos at early stages of development

Histological observations & determination of the quail cells fates

antibodies specific to quail cell antigens

valuable information about the origins of different organs & tissues


Quail
Donor
Chick
Host
Neural
Tube &
Neural
Crest
Transverse section
through chick host
containing quail
graft

History

- **Tissues signaling**

Grafting experiments

1. the primitive node grafting
   a second body axis induction

2. developing limb buds,(posterior axial border)

digits duplication

zone of polarizing activity (ZPA)

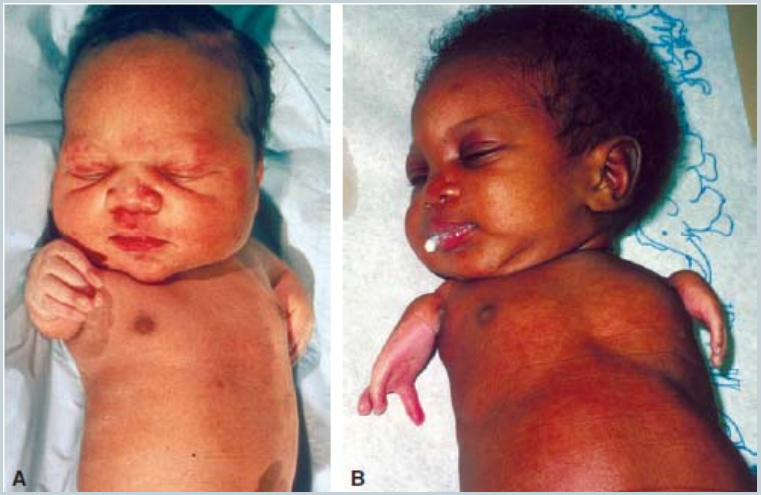
sonic hedgehog (SHH)

Experimental duplication of the ZPA results in mirror image digit formation

History

- **thalidomide**

Antinauseant & sedative
High range of birth defects
limbs abnormalities
ameli or phocomelia



- W. Lenz and W. McBride

conceptus was vulnerable to **maternal factors that crossed the placenta**

- **Using animal model**

Environmental factors
Drugs

History

- **molecular approaches**

Study normal & abnormal development

cells identifying using:

- reporter genes,
- fluorescent probes
- other marking techniques

ability to map cell fates

- **techniques for altering gene expression**

knockout

knock-in

antisense technologies

Embryology
Clinical Relevance & Historical Perspective

- Provide knowledge essential for creating health care strategies for better reproductive outcomes.

better understanding of embryology has resulted in:

1. new techniques for prenatal diagnoses & treatments
2. therapeutic procedures to circumvent problems with infertility
3. to prevent birth defects (the leading cause of infant mortality)

Molecular Regulation & Signaling

- Molecular biology

- Sequencing the human genome
- 23000 genes
- the one-gene–one protein hypothesis disproved

Gene expression is regulated at several levels:

(1) different genes may be transcribed

(2) DNA transcribed from a gene may be selectively processed to regulate which RNAs reach the cytoplasm to become mRNAs

(3) mRNAs may be selectively translated

(4) proteins made from the mRNAs may be differentially modified

GENE TRANSCRIPTION

- Gene is a complex of DNA & proteins (mostly histones) called **chromatin**
- **Nucleosome** basic unit of chromatin structure

Nucleosome:

- octamer of **histone proteins**
- 140 DNA bp

- Nucleosomes clusters by **linker DNA &** H1 histones

- **heterochromatin.**
- **euchromatin.**

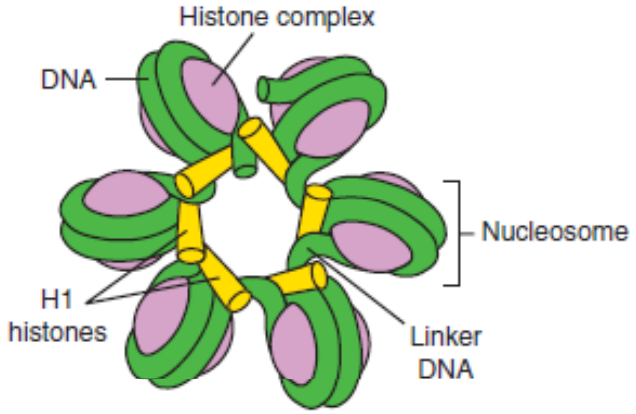


Figure 1.1 Drawing showing nucleosomes that form the basic unit of chromatin. Each nucleosome consists of an octamer of histone proteins and approximately 140 base pairs of DNA. Nucleosomes are joined into clusters by linker DNA and other histone proteins.

Gene structure

- **exons,** translated into proteins,
- **introns,** between exons & are not transcribed into proteins

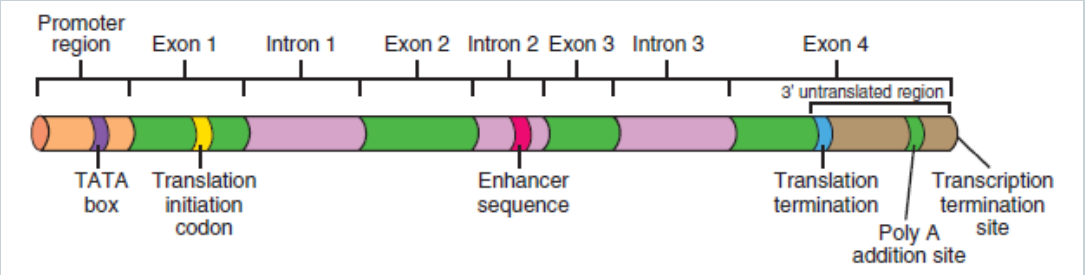
a typical gene includes:

- a **promoter region**

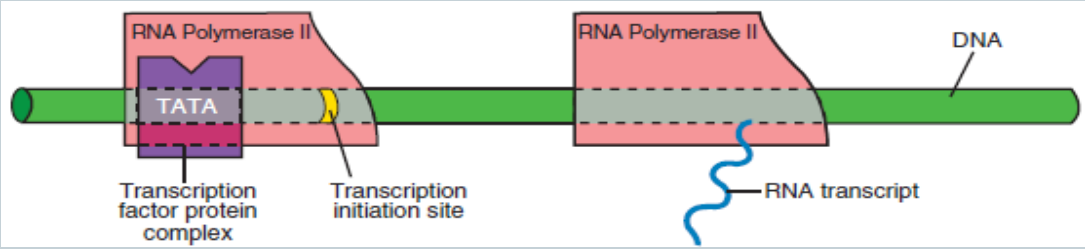
that RNA polymerase binding site (TATA box)

- a **transcription initiation site**
- **a translation initiation site**
- a **translation termination codon**
- **a 3′ untranslated region**

(the poly A addition site)



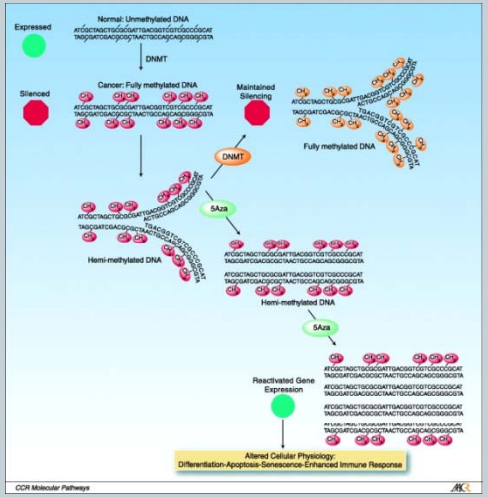
- Transcription factors
- Enhancers
- silencers



DNA Methylation

- **Represses Transcription**
- **X chromosome inactivation**

(muscle & blood cell)



- genomic **imprinting**
- 40 to 60 human genes are imprinted
- methylation patterns are established during spermatogenesis & Oogenesis

Methylation silences DNA by:

- inhibiting binding of transcription factors
- Altering histone binding & stabilization of nucleosomes and tightly coiled

- **nuclear RNA (nRNA) or *premessenger RNA (***The initial transcript***)**

introns that are removed **(spliced out)** movement from the nucleus to the cytoplasm

- **alternative splicing (**Cells produce different proteins from a single gene)

spliceosomes

- **small nuclear RNAs (snRNAs)**
- **proteins that recognize specific** splice sites at the 5′ or the 3′ ends of the nRNA

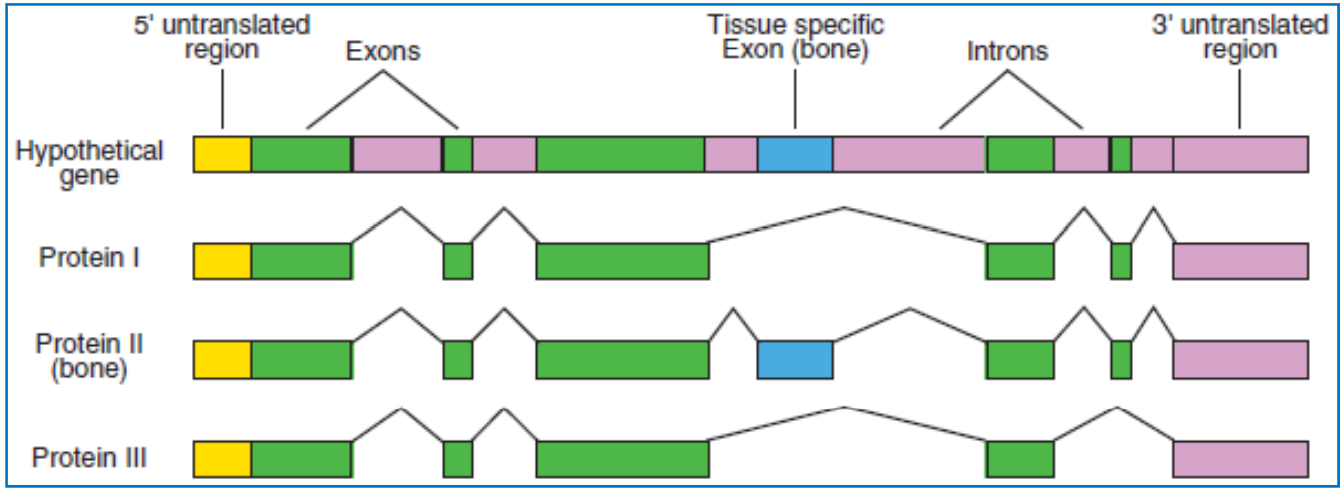
- **splicing isoforms (also called splice variants** or **alternative splice forms)**
- opportunity for different cells to use the same gene to make proteins specific for that cell type.

isoforms of the *WT1 gene* have different functions in gonadal versus kidney development

- **post-translational modifications** (affect its function)

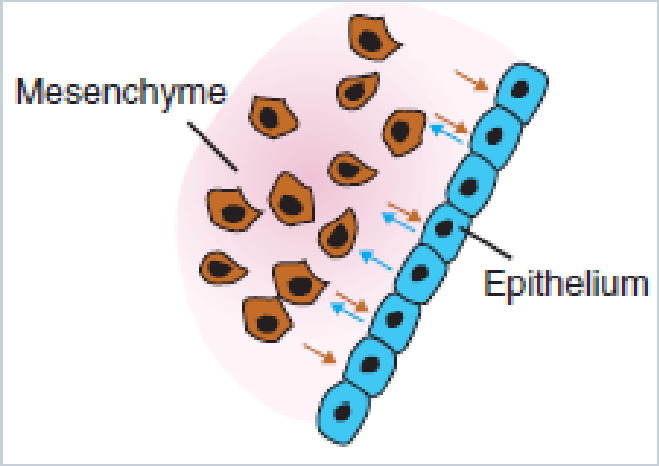
cleavage or phosphorylation to become active

only 23,000 genes exist, but number of proteins five times more



Induction & Organ Formation

- **Induction**
- **Inducer** (signal)
- **responder**
- **Competence & competence factor**



inductive interactions

epithelial– mesenchymal Interactions

Epithelial cells (tubes or sheets) mesenchymal cells (fibroblasts dispersed in ECM

- gut endoderm and surrounding mesenchyme (liver & pancreas)
- limb mesenchyme with overlying ectoderm (epithelium limb outgrowth & differentiation
- endoderm of the ureteric bud and mesenchyme from the metanephric blastema nephrons in the kidney

Inductive interactions between two epithelium

- lens formation by epithelium of the optic cup

- **crosstalk between the two tissues or cell**

Cell Signaling

- **paracrine interactions**

Diffusible factors

GDFs

- **Juxtacrine interactions**

Undiffusable factors

Paracrine signaling

- **paracrine interactions**

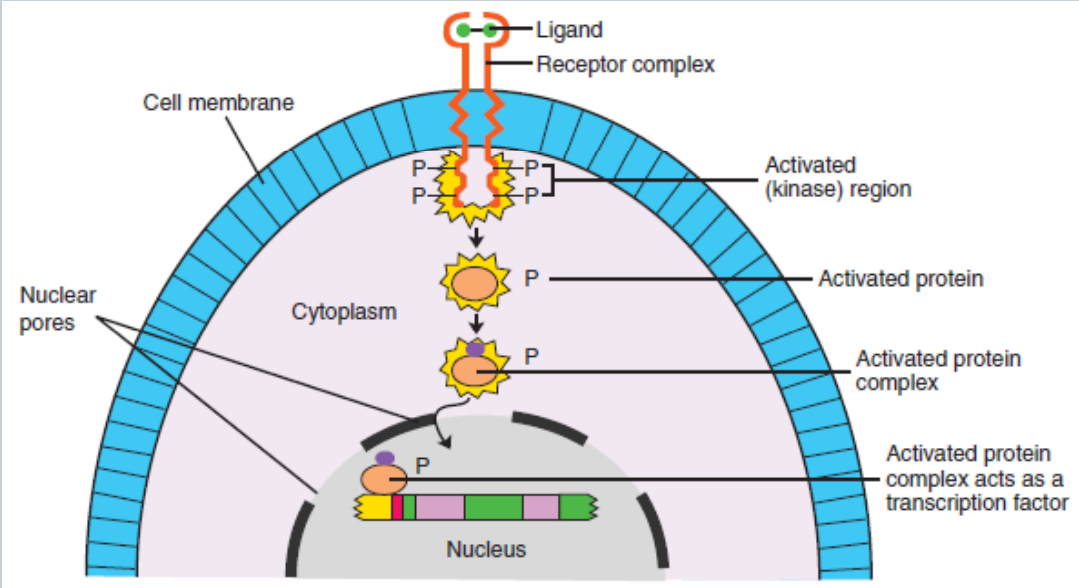
signal transduction pathways

- **signaling molecule (the ligand) and a receptor**
- **The receptor**

extracellular Domain , a transmembrane domain, a cytoplasmic domain

- Ligand-receptor : conformational change & cytoplasmic domain activation
- Enzymatic activity
- a **kinase activation**
- ATP & proteins phosphorylation cascade
- **transcription factor activation**

hedgehog signaling



Juxtacrine Signaling

- **No diffusable factors**

(1)

A protein on one cell surface interacts with a receptor on an adjacent cell

- **Notch pathway**
- Notch receptor protein (receptor)binds to cells that have Delta, Serrate, or Jagged proteins (ligand)

In:

- **neuronal differentiation,**
- **blood vessel specification**
- **somite segmentation**

(2)

- Ligands in ECM
- ECM contains large molecules

Collagen
proteoglycans (chondroitin sulfates, hyaluronic acid, etc.)
Glycoproteins (fibronectin and laminin)

Integrins"integrate" matrix molecules with a cell's **cytoskeletal machinery (actin microfilaments)**
integrins induce gene expression and regulate differentiation as in the case of chondrocyte that must be linked to the matrix to form cartilage

(3)

- signals transmission by **gap junctions**
- cells to act in concert.

Paracrine Signaling Factors

- **growth and differentiation factors (GDFs)**

- The 4 groups of GDFs include:

1. **Fibroblast growth factor (FGF)** FGF Receptor
   angiogenesis, axon growth, and mesoderm differentiation

2. **WNT**
   (the segment polarity gene, *wingless*& receptors members of frizzled family proteins)
   regulating limb patterning, midbrain development, somite & urogenital differentiation

3. **Hedgehog**
   3hedgehog genes (Desert, Indian, sonichedgehog) hedgehog family receptor is Patched that bind to smoothened pr.
   limb patterning, neural tube induction and patterning, somite differentiation, gut regionalization

4. **Transforming growth factor-b (TGF-β)**
   TGF- βs, BMPs, activin family, the Müllerian inhibiting factor (MIF, anti-Müllerian hormone)
   TGF- β in extracellular matrix formation & epithelial branching that occurs in lung, kidney, & salivary gland development
   BMP family induces bone formation and is involved in regulating cell division, cell death (apoptosis), & cell migration

- **neurotransmitters**

Serotonin as a ligand for G protein–coupled receptors
cell proliferation & migration, establishing laterality, gastrulation, heart development
Norepinephrine in apoptosis (programmed cell death) in the interdigital spaces and in other cell types