Embryology

Gametogenesis

Dr. Saeednia

Primordial germ cells (PGCs)

- Development begins with Fertilization
- Sperm & Oocyte (gametes) unite to form zygote
- Gametes are derived from PGCs
- PGCs formed in second week from epiblast
- Move to wall of yolk sac

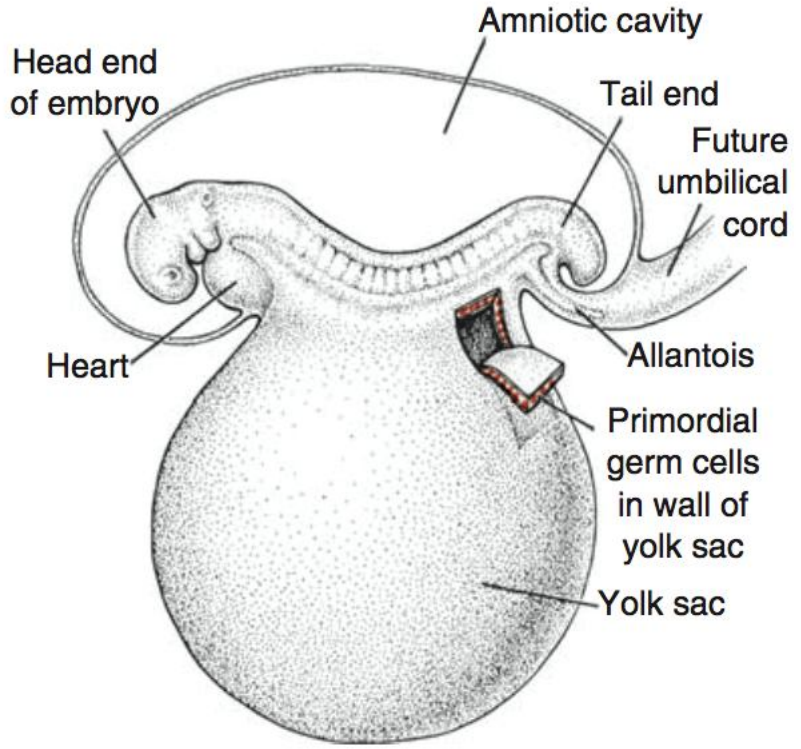


Figure 2.1 An embryo at the end of the third week, showing the position of PGCs in the wall of the yolk sac, close to the attachment of the future umbilical cord. From this location, these cells migrate to the developing gonad.

- In 4th week migrate from yolk sac to developing gonads
- By the end of 5th week they arrived to developing gonads
- Mitotic division increase their number during their migration
- In preparation for fertilization Gametogenesis (Meiosis & differentiation)

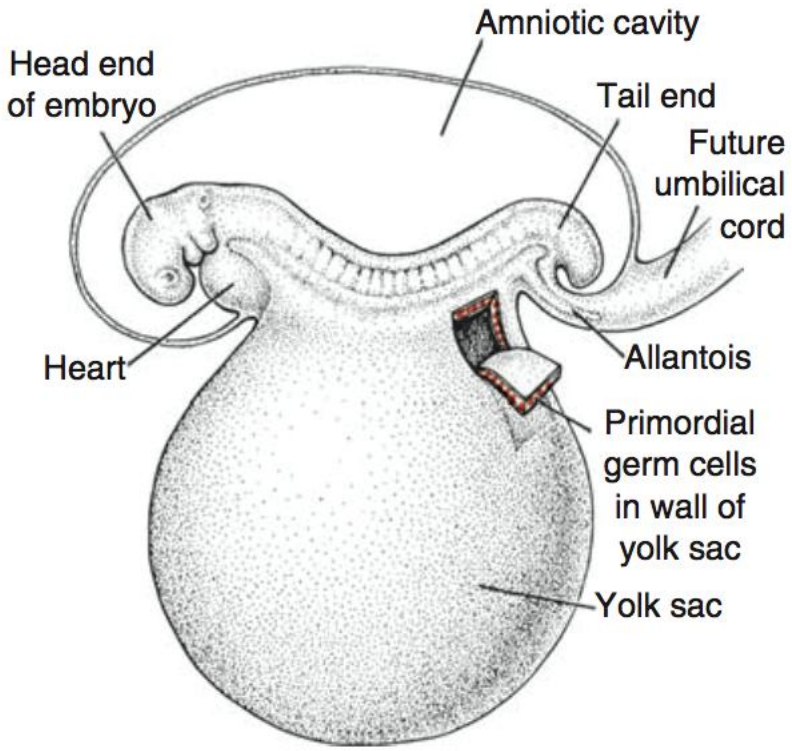


Figure 2.1 An embryo at the end of the third week, showing the position of PGCs in the wall of the yolk sac, close to the attachment of the future umbilical cord. From this location, these cells migrate to the developing gonad.

Clinical Correlates

Primordial Germ Cells and Teratomas

Teratomas are tumors of disputed origin that often contain a variety of tissues, such as bone, hair, muscle, gut epithelia, and others. It is thought that these tumors arise from pluripotent stem cells that can differentiate into any of the three germ layers or their derivatives. Some evidence suggests that PGCs that have strayed from their normal migratory paths could be responsible for some of these tumors (Fig. 2.2). Another source may be epiblast cells that give rise to all three germ layers during gastrulation (See Fig. 5.9, p. 58 and p. 59).

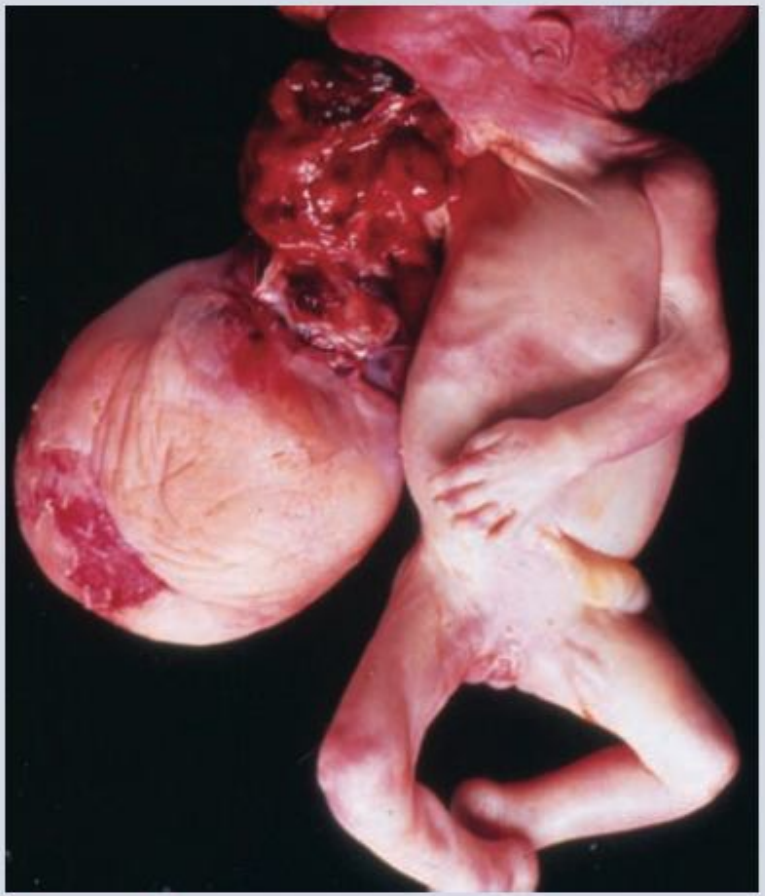


Figure 2.2 Oropharnyngeal teratoma. These tumors may arise from PGCs or from epiblast cells (see Chapter 5), both of which are pluripotent. Tissues within the tumors include derivatives of all three germ layers and may include gut, bone, skin, teeth, and so forth.

The chromosome theory of inheritance

- ***Traits of a new individual by inherited genes from the father and & mother.***
- Humans genome 23,000 genes
- 46 chromosomes
- ***linked genes*** (Genes on the same chromosome tend to be inherited together)
- ***In somatic cells 23 homologous pairs***
- 22 pairs are ***autosomes***
- one pair of ***sex chromosomes***
- XX & XY
- ***One chromosome of each pair*** is derived from the maternal gamete, the oocyte, and one from the paternal gamete, the sperm
- ***each gamete contains a haploid number of 23 chromosomes***
- ***fertilization restores the diploid number of 46***

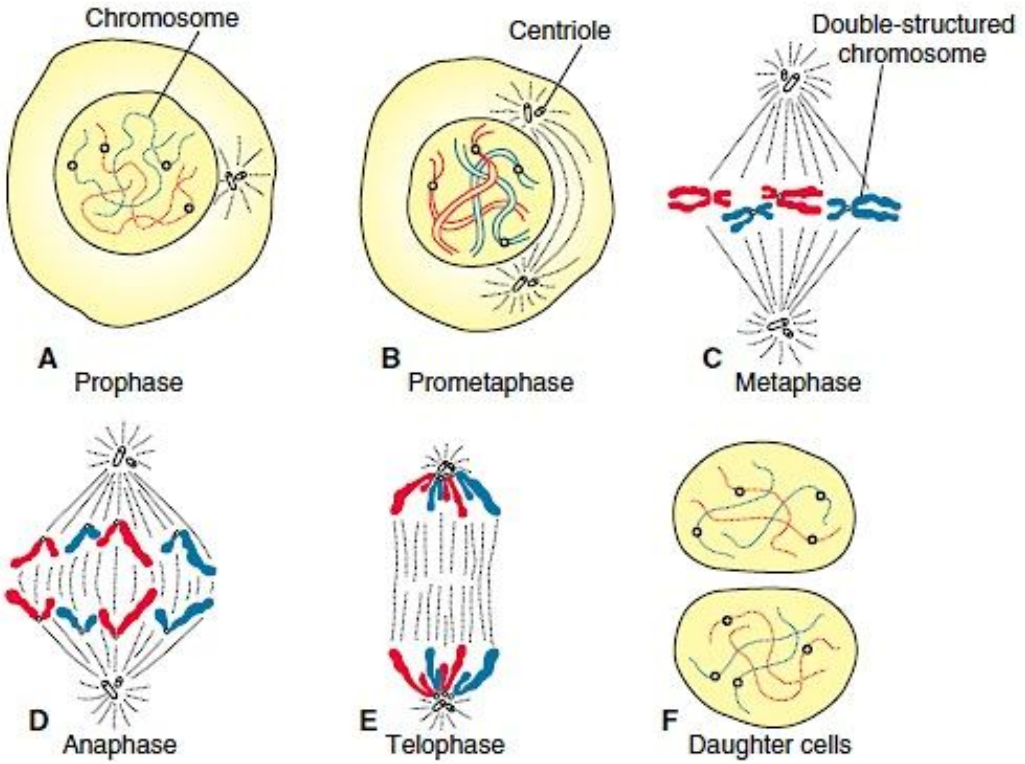
Mitosis

Before a cell enters mitosis, each **chromosome replicates its deoxyribonucleic acid (DNA)**

During this replication phase, **chromosomes are extremely long**

Prophase: the chromosomes begin to coil, contract, and condense. Each chromosome now consists of two parallel subunits, chromatids, that are joined at a narrow region common to both called the centromere

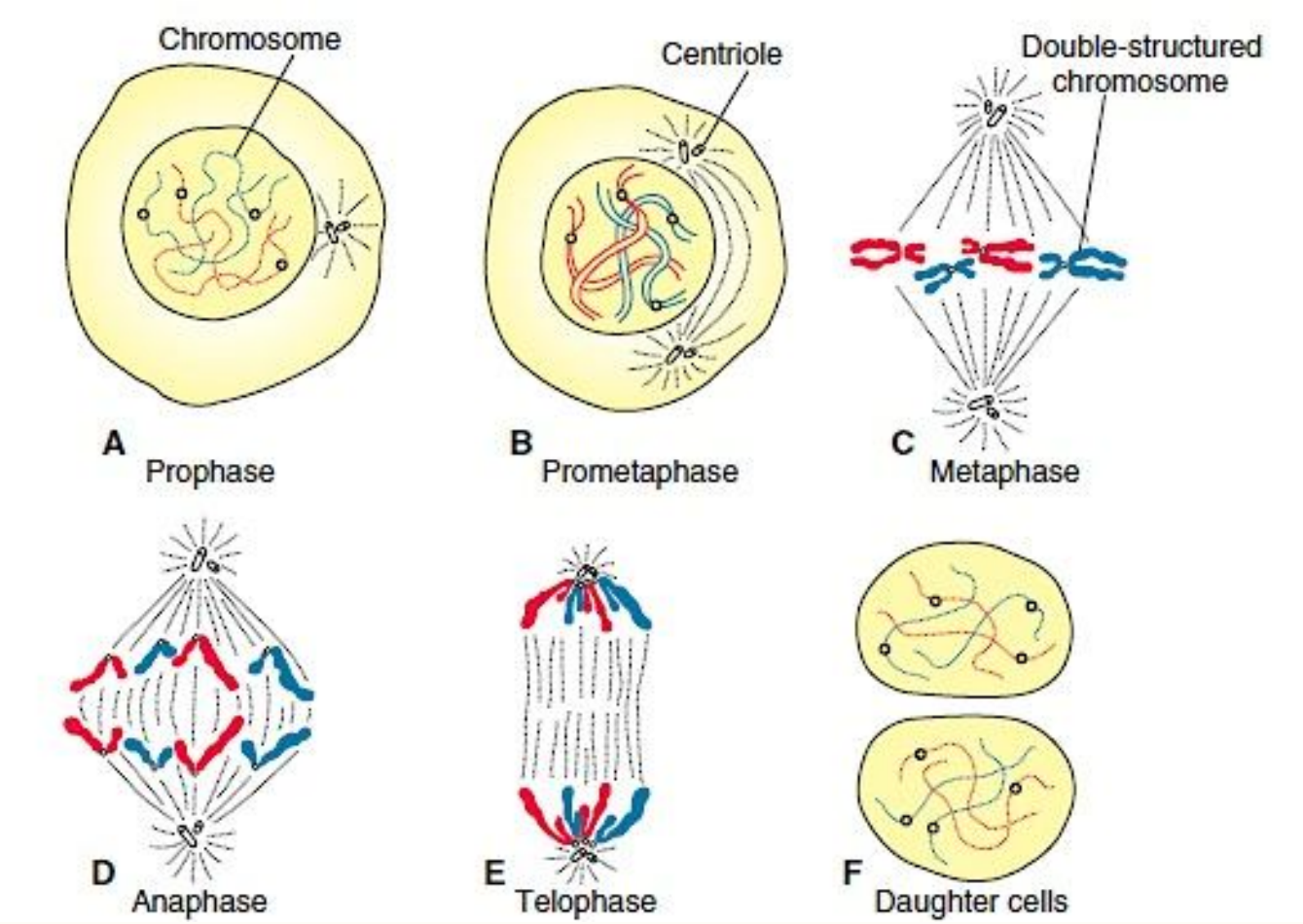
prometaphase : the chromatids become distinguishable



Metaphase : the chromosomes line up in the equatorial plane, and their doubled structure is clearly visible . Each is attached by microtubules extending from the centromere to the centriole, forming the mitotic spindle

Anaphase: the centromere of each chromosome divides, followed by migration of chromatids to opposite poles of the spindle

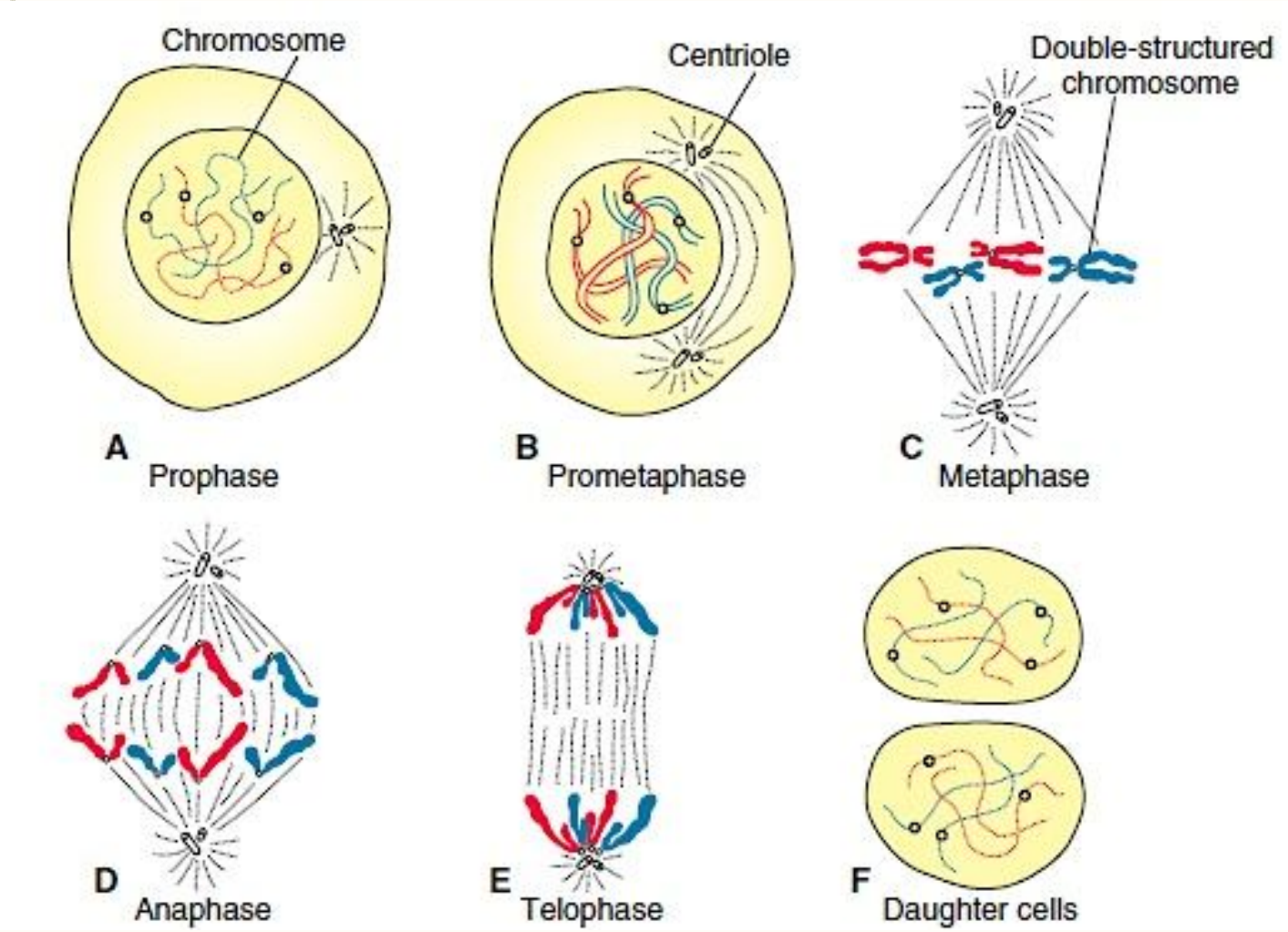
Mitosis



Mitosis

Telophase: chromosomes uncoil and lengthen, the nuclear envelope reforms, and the cytoplasm divides

Each daughter cell receives <u>half of all doubled chromosome</u> material and thus maintains <u>the same number of chromosomes as the mother cell.</u>

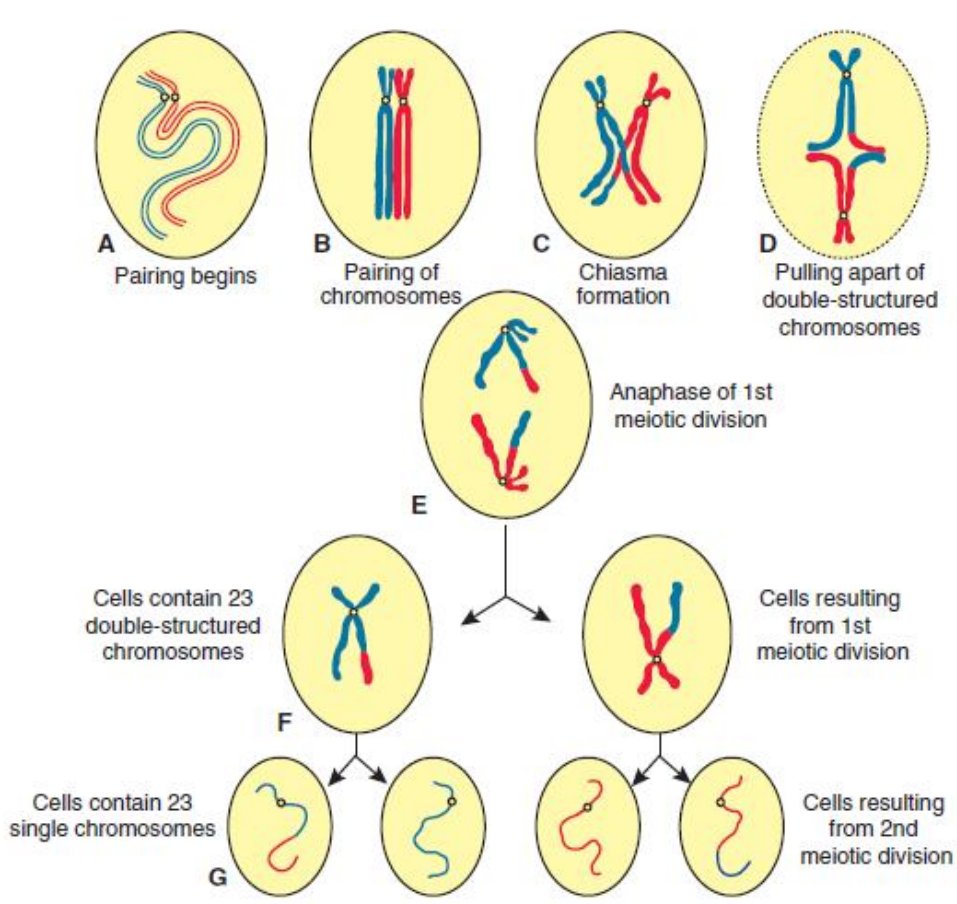


Meiosis is the cell division that takes place in the germ cells to generate male and female gametes

Meiosis requires two cell divisions, **meiosis I and meiosis II**, to reduce the number of chromosomes to the haploid number of 23

at the beginning of meiosis I replicate their DNA

Meiosis

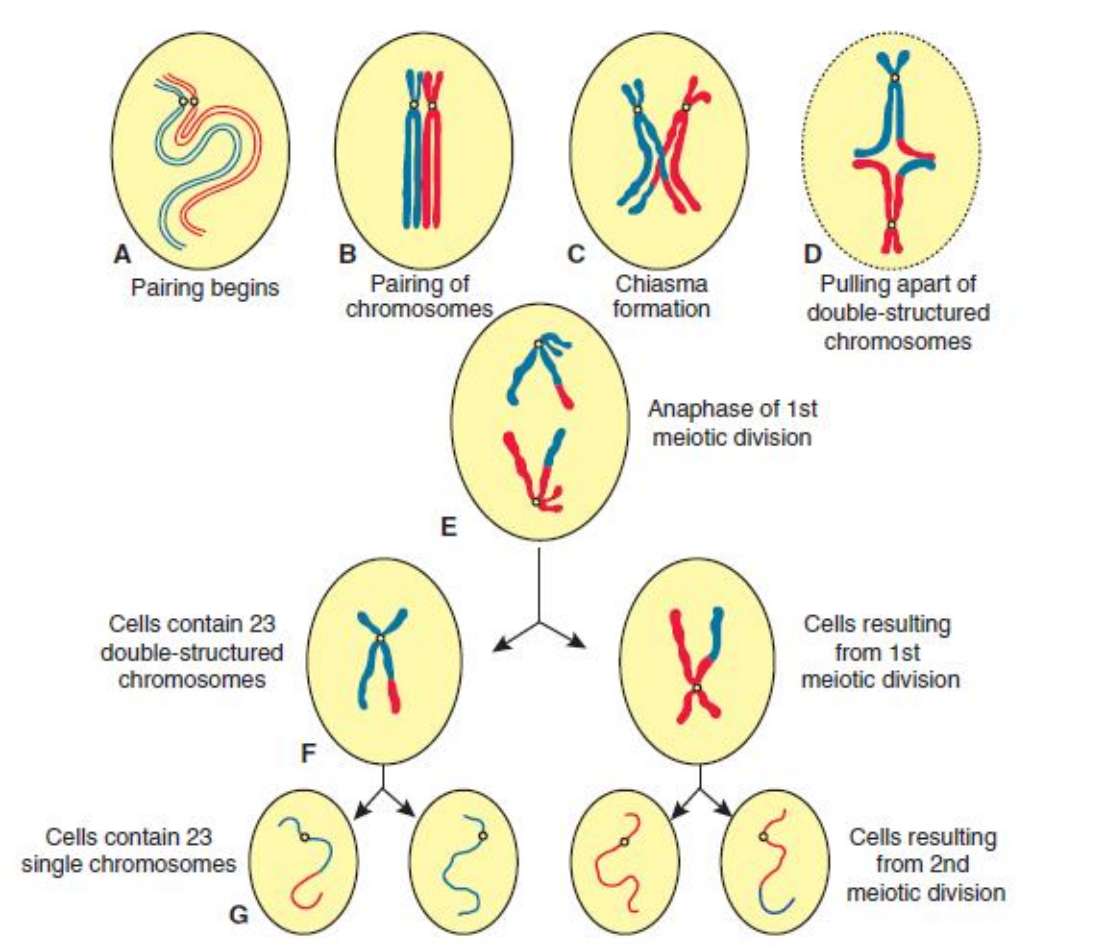


homologous chromosomes then align them- selves in pairs, a process **called synapsis**

Homologous pairs then separate into two daughter cells, thereby reducing the chromosome number from diploid to haploid

meiosis II separates sister chromatids. Each gamete then contains 23 chromosomes

Meiosis



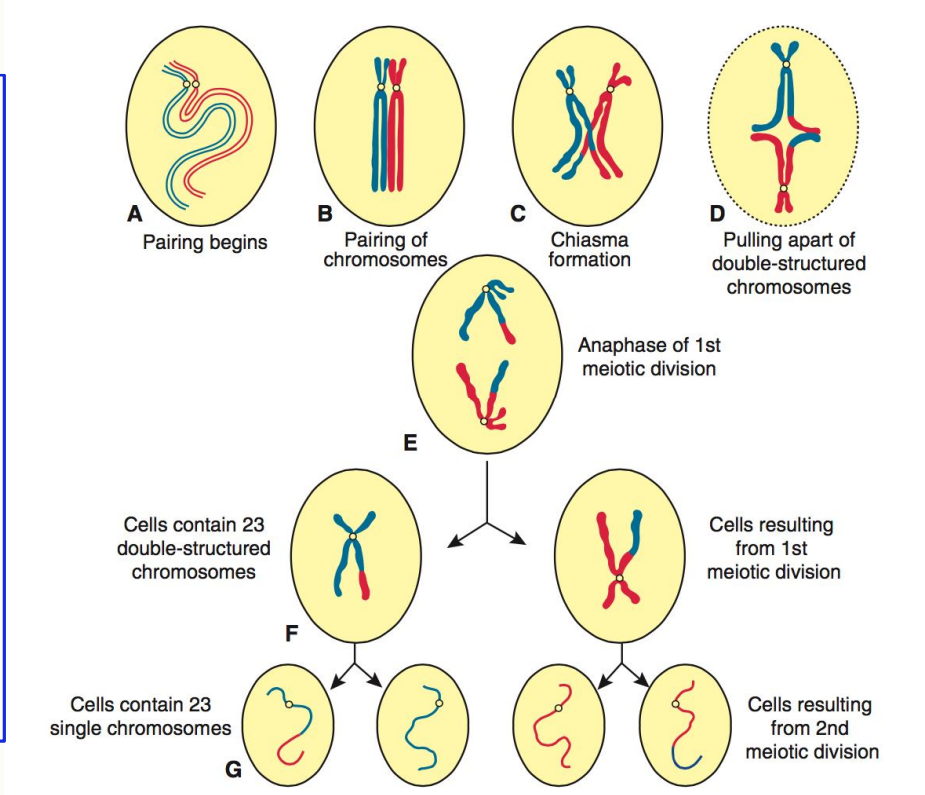
Crossovers, critical events in meiosis I, are the interchange of chromatid segments between paired homologous chromosomes

As separation occurs, points of interchange are temporarily united and form an X-like structure, a chiasma

As a result of meiotic divisions:

- **Genetic variability** is enhanced through

- crossover, which redistributes genetic material
- random distribution of homologous chromosomes to the daughter cells
- Each germ cell contains a haploid number of chromosomes, so that at fertilization the diploid number of 46 is restore



Polar Bodies

Also during meiosis, one primary oocyte gives rise to four daughter cells, each with 22 plus 1 X chromosomes (Fig. 2.5*A*). Only one of these develops into a mature gamete, however, the oocyte; the other three, the **polar bodies,** receive little cytoplasm and degenerate during subsequent development. Similarly, one primary spermatocyte gives rise to four daughter cells, two with 22 plus 1 X chromosomes and two with 22 plus 1 Y chromosomes (Fig. 2.5*B*). In contrast to oocyte formation, however, all four develop into mature gametes.

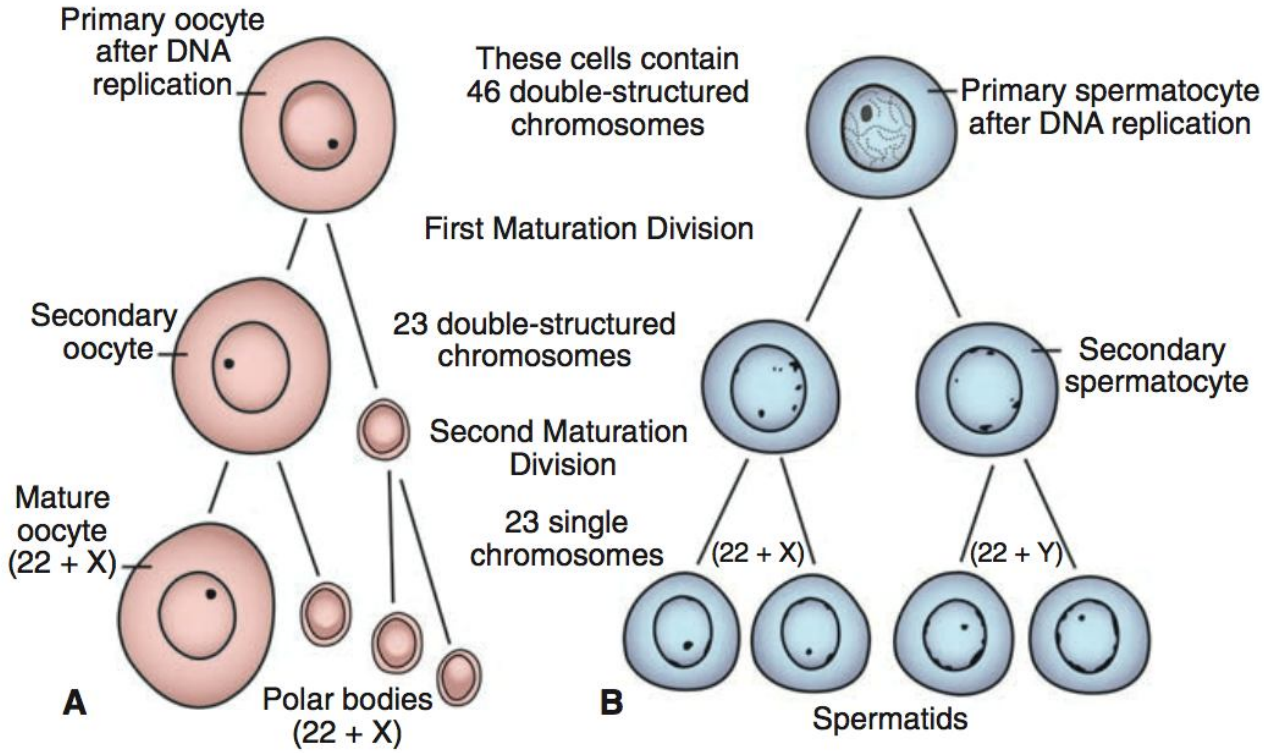
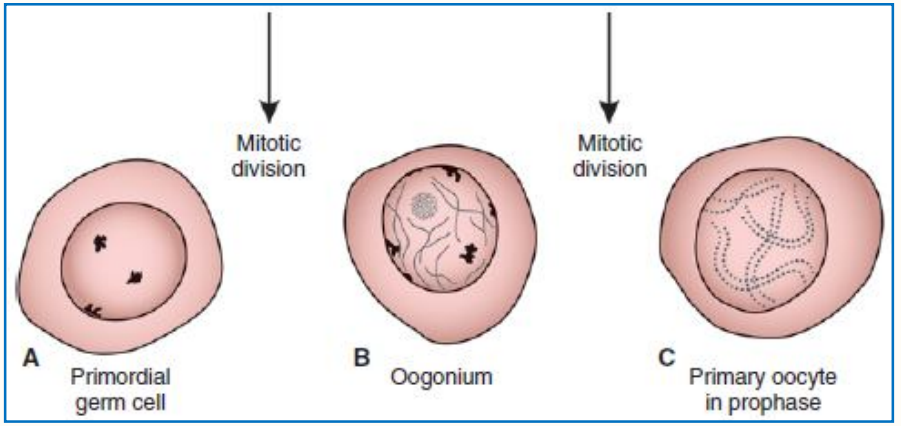


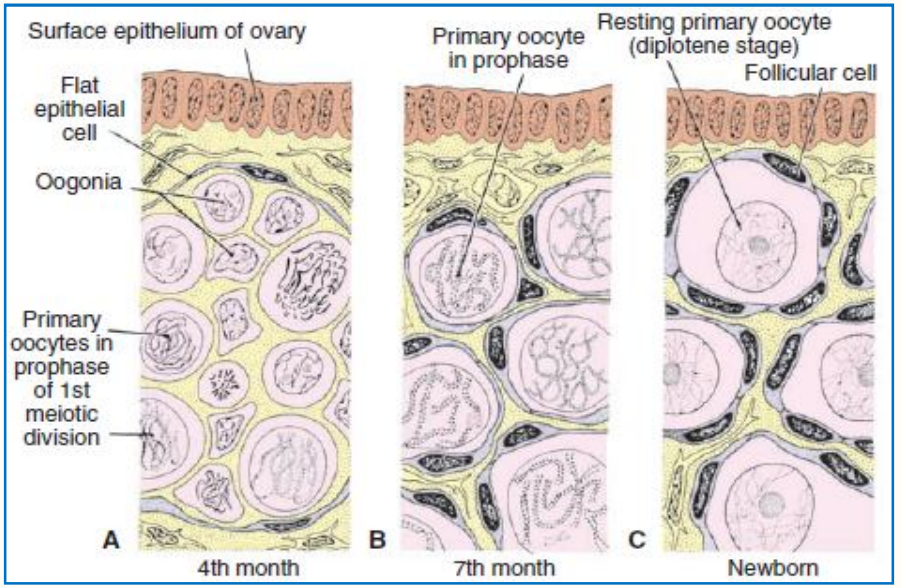
Figure 2.5 Events occurring during the first and second maturation divisions. **A.** The primitive female germ cell (primary oocyte) produces only one mature gamete, the mature oocyte. **B.** The primitive male germ cell (primary spermatocyte) produces four spermatids, all of which develop into spermatozoa.

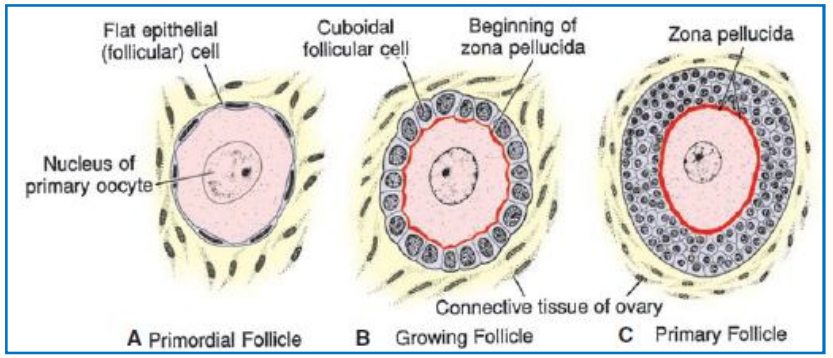
Oogenesis

Maturation of Oocytes Begins Before Birth

- PGCs have arrived to gonad
- Differentiate to oogonia
- Mitosis
- end of 3rd month Oogonia Arranged in clusters
- Cluster surround by layer of **flat epithelial cells that called follicular cell**
- **Follicular cell originated from surface epithelium covering the ovary**
- **Some oogonia** differentiate to **primary oocyte**
- **5th month** 7 million oogonia
- **7th month** majority of oogonia & primary oocyte **degenerated**
- primary oocyte duplicated DNA
- primary oocyte Enter Prophase Meiosis I







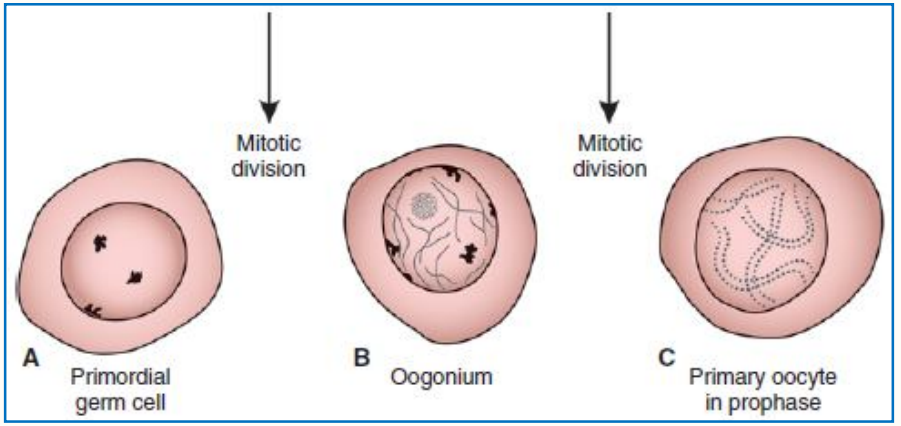
Oogenesis

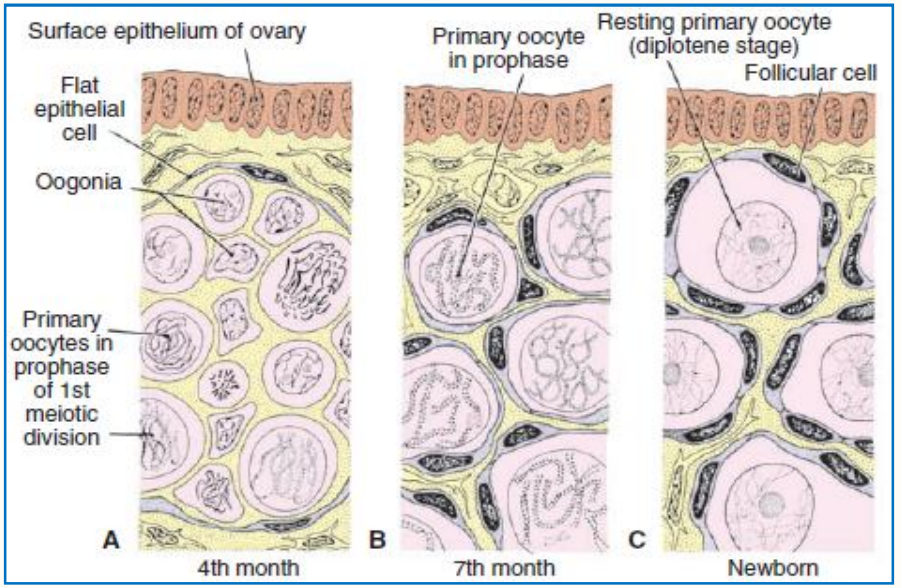
Maturation of Oocytes Begins Before Birth

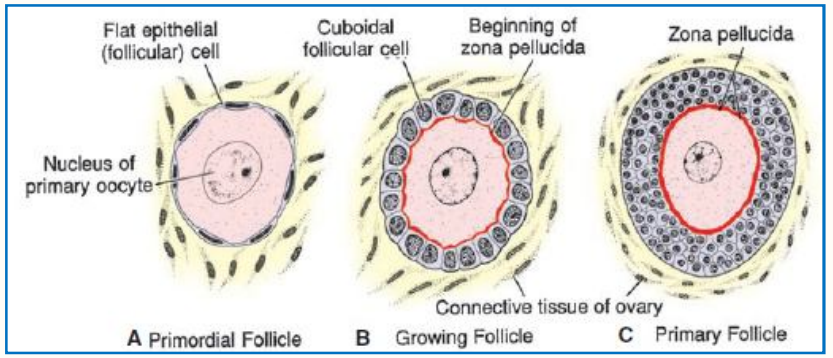
- All surviving primary oocyte enter prophase of miosis1
- Most of them surrounded by flat follicular epithelium that called **primordial follicle**
- **Primordial follicle :** A primary oocyte, together with its surrounding flat epithelial cells
- **Primary oocyte enter Diplotene stage of prophase meiosis I**

➢Follicular cells secrete Oocyte maturation inhibition (OMI)

➢600000-800000 follicles at birth
➢400000 at puberty
➢500 released in fertility period

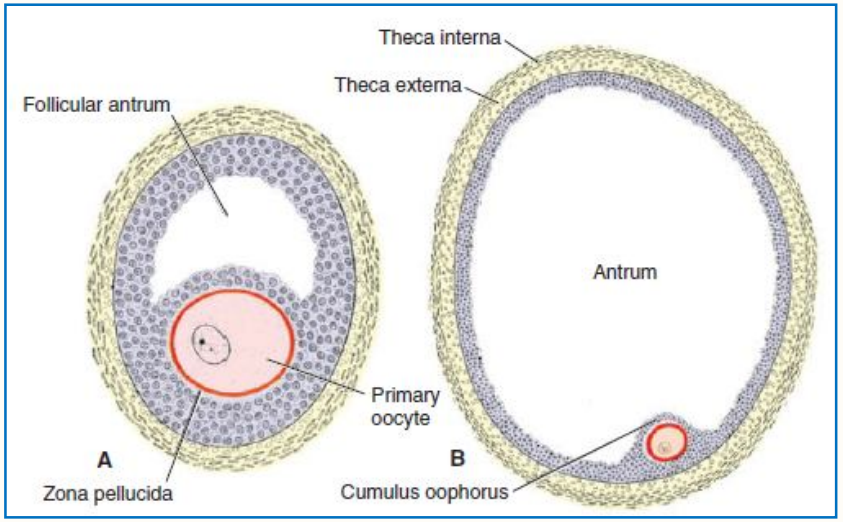


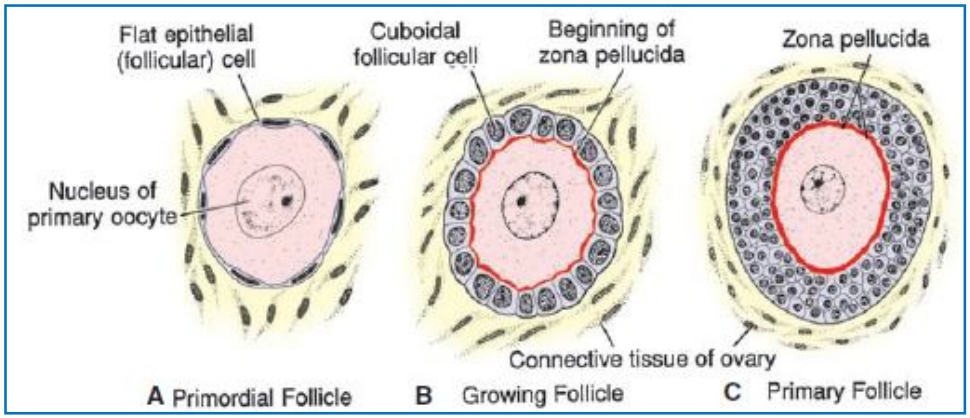




Maturation of Oocytes Continues at Puberty

- In each cycle 15-20 follicle
- follicular cells change from flat to cuboidal
- **and**
- proliferate to produce a stratified epithelium of **granulosa cells**
- the unit is called a **primary follicle**
- surrounding ovarian connective tissue (stromal cells) that form the **theca folliculi** / Theca interna - Theca externa

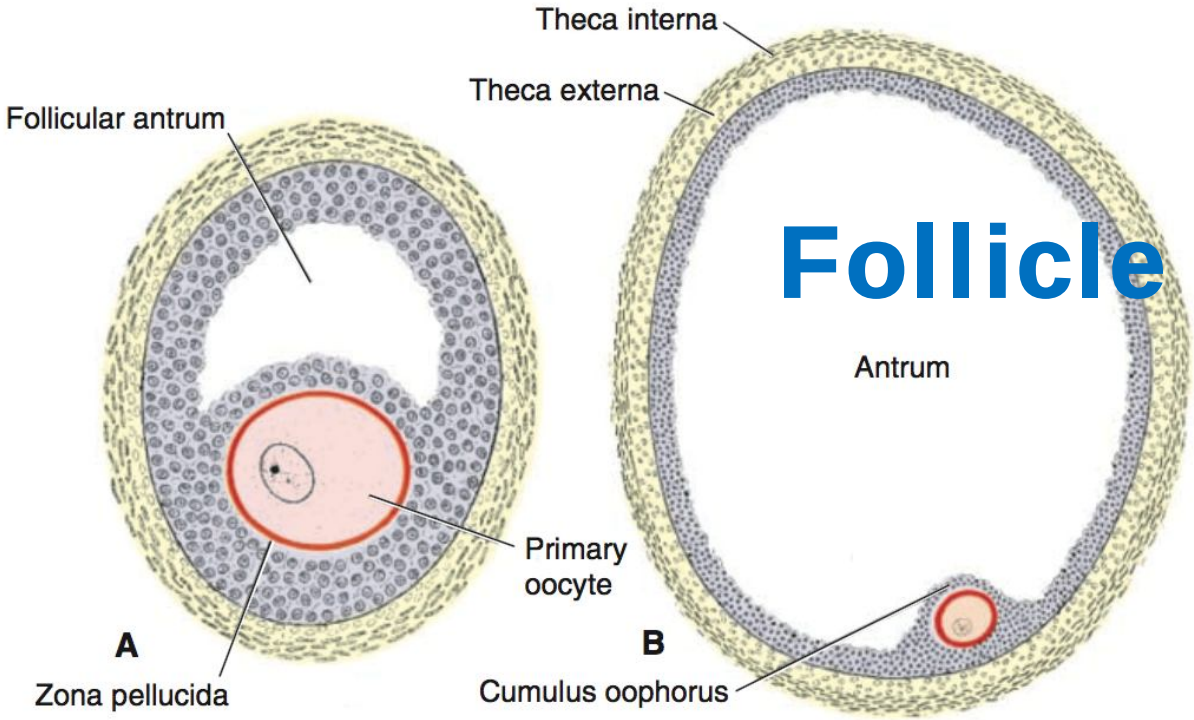




❖granulosa cells and the oocyte secrete a layer of glycoproteins on the surface of the oocyte, forming the **zona pellucida**

❖Multilayers of granulosa cells
❖Antrum formation / **Cumulus oophorus** / antral or **vesicular stage** (longest stage / **secondary folliculi**)

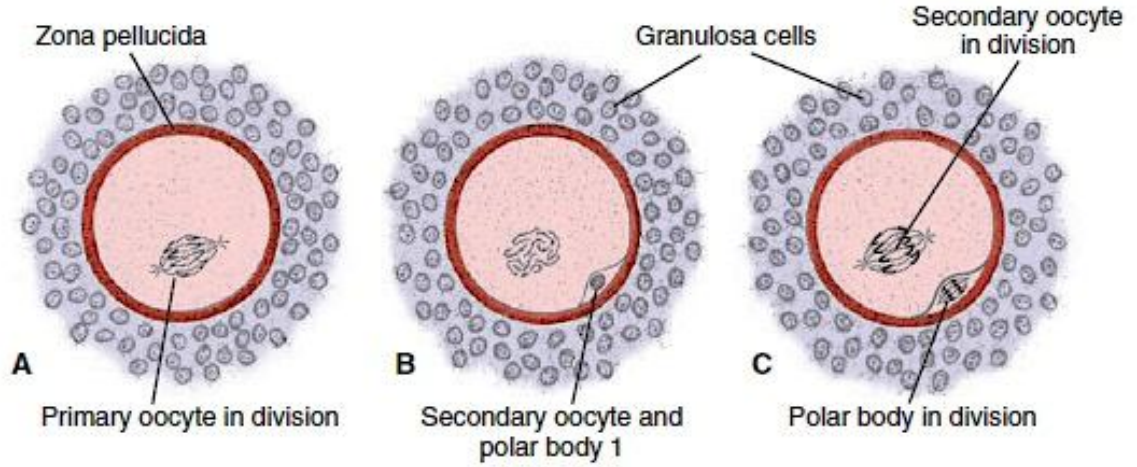
❖**Graffian follicle** or mature vesicular follicle / tertiary folliculi
❖**theca interna** = steroid secretion & rich in blood vessels
❖**theca externa** = merges with the ovarian connective tissue



Follicle maturation

Follicle maturation

- With each ovarian cycle,
- a number of follicles begin to develop,
- **When the secondary follicle is mature,**
- **surge in luteinizing hormone (LH)** induces the pre ovulatory growth phase
- **Meiosis I is completed**
- **Secondary oocyte**, receives most of the cytoplasm;
- first polar body, receives practically none
- **Cell enters meiosis II but arrests in metaphase approximately 3 hours before ovulation**
- **Meiosis II is completed after fertilization**



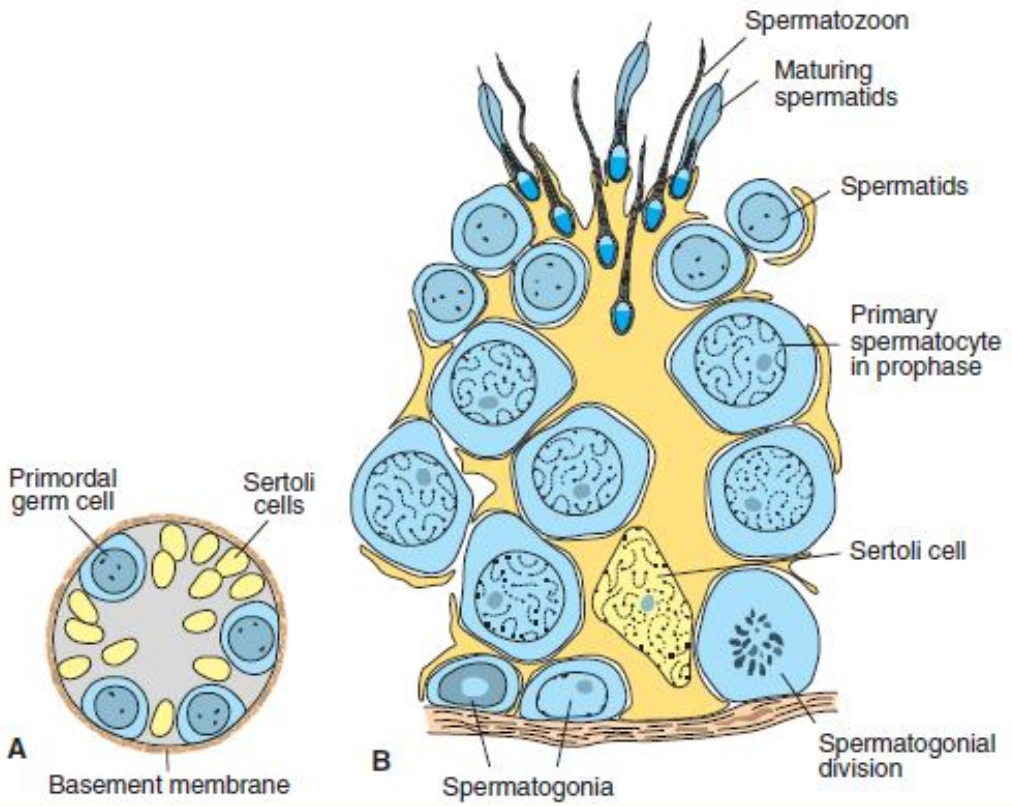
Spermatogenesis

Maturation of Sperm Begins at Puberty

- Spermatogonia to spermatozoid
- At male birth, germ cells in the sex cords of the testis
- Large, pale cells surrounded by supporting cells
- Supporting cells, are derived from the surface epithelium of the gonad
- sustentacular cells, or Sertoli cells

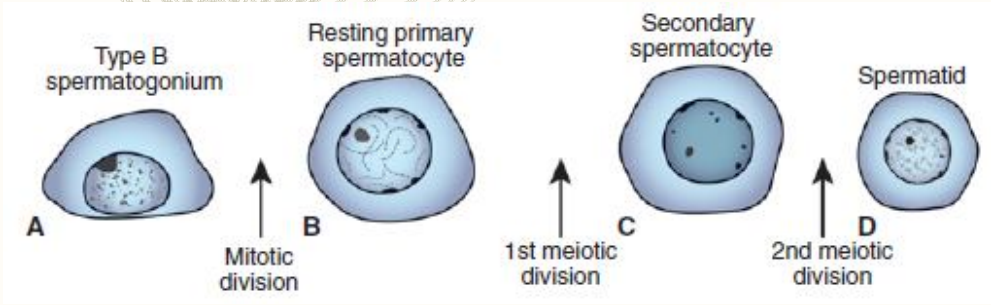
Shortly before puberty

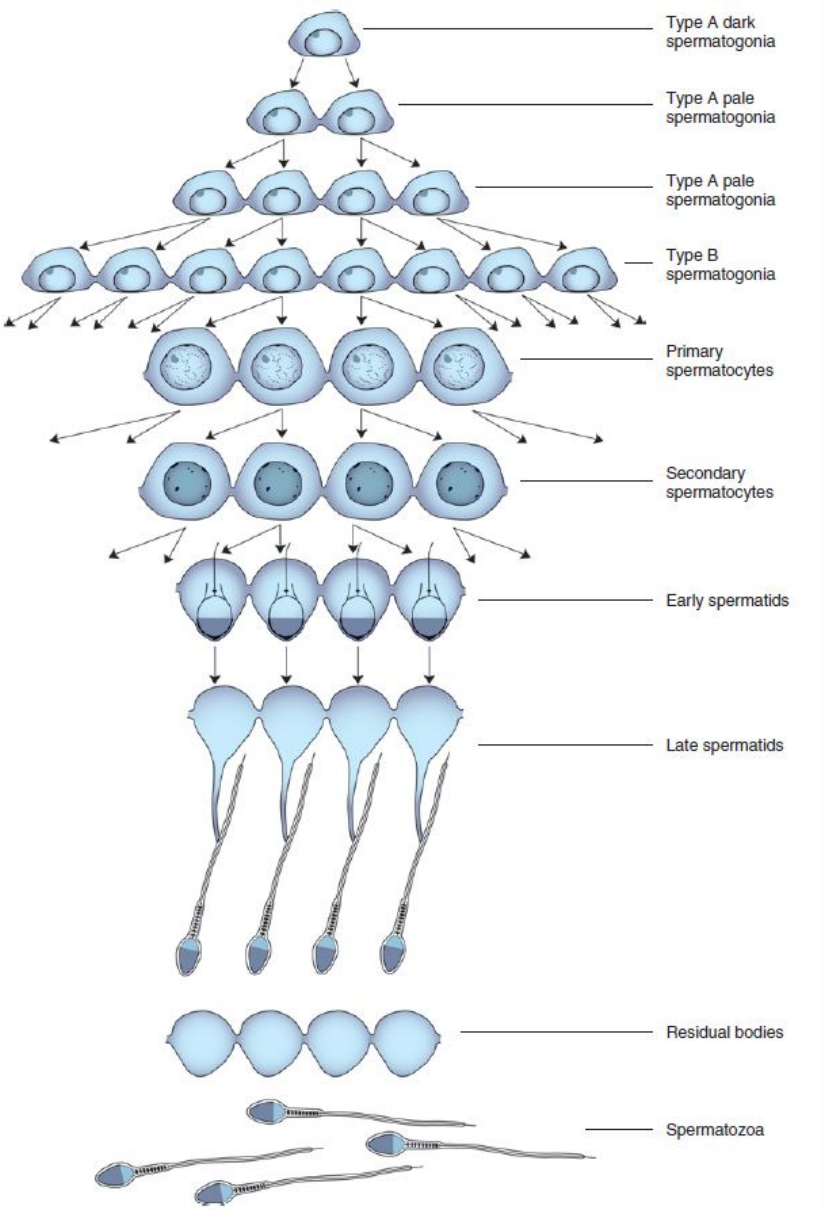
- the sex cords become the seminiferous Tubules
- **PGCs give rise to spermatogonial stem cells.**
- type A spermatogonia / mitosis division
- type B spermatogonia
- primary spermatocytes



Spermatogenesis

- Primery spermatocytes enter a prolonged prophase (22 days)
- **Secondary spermatocytes** / at the end of miosis I
- **spermatids formation** / at the end of miosis II / haploid 23 chromosome
- incomplete cytokinesis
- remain embedded in deep recesses of Sertoli cells
- ***Sertoli cells:***
- support and protect the germ cells
- participate in their nutrition
- assist in the release of mature spermatozoa





Point:

Spermatogenesis is regulated by LH production by the pituitary gland

LH binds to receptors on Leydig cells and stimulates testosterone production

testosterone binds to Sertoli cells to promote spermatogenesis

Follicle-stimulating hormone (FSH) is also essential because its binding to Sertoli cells

stimulates testicular fluid production and synthesis of intracellular androgen receptor proteins

Spermiogenesis

– ***spermatids into spermatozoa***

changes include:

– (1) formation of the acrosome,

– (2) condensation of the nucleus;

– (3) formation of neck, middle piece, and tail;

– (4) shedding of most of the cytoplasm

– In humans, 74 days, daily 300 million sperm

– obtain full motility in the epididymis

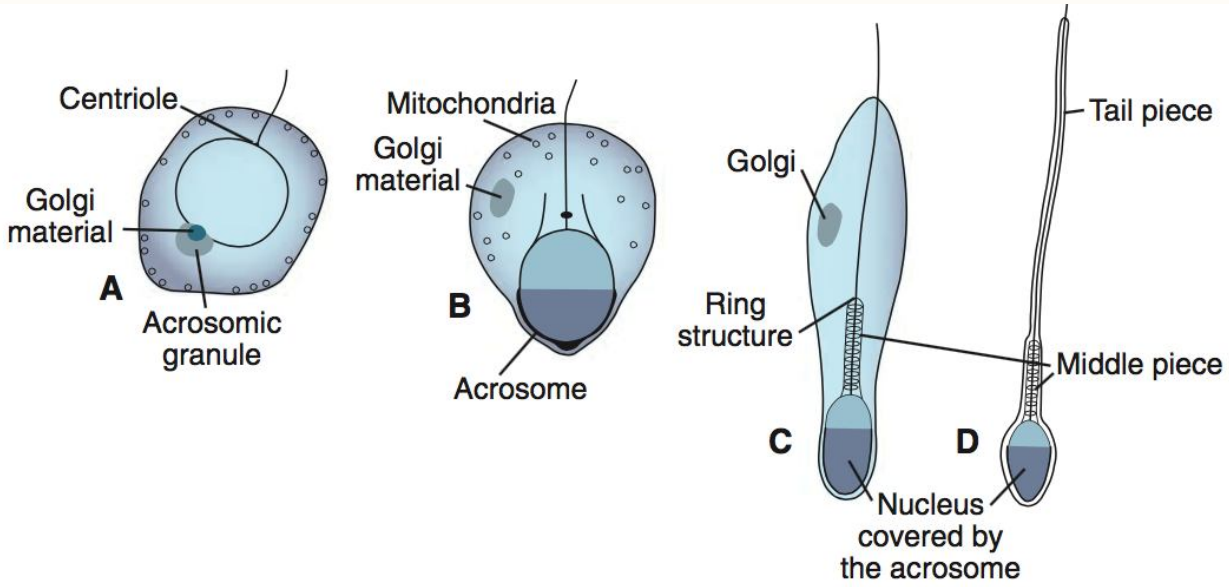


Figure 2.24 Important stages in transformation of the human spermatid into the spermatozoon.

Clinical Correlates

Abnormal Gametes

In humans and in most mammals, one ovarian follicle occasionally contains two or three clearly distinguishable primary oocytes (Fig. 2.25*A*). Although these oocytes may give rise to twins or triplets, they usually degenerate before reaching maturity. In rare cases, one primary oocyte contains two or even three nuclei (Fig. 2.25*B*). Such binucleated or trinucleated oocytes die before reaching maturity.

In contrast to atypical oocytes, abnormal spermatozoa are seen frequently, and up to 10% of all spermatozoa have observable defects. The head or the tail may be abnormal, spermatozoa may be giants or dwarfs, and sometimes they are joined (Fig. 2.25*C*). Sperm with morphologic abnormalities lack normal motility and probably do not fertilize oocytes

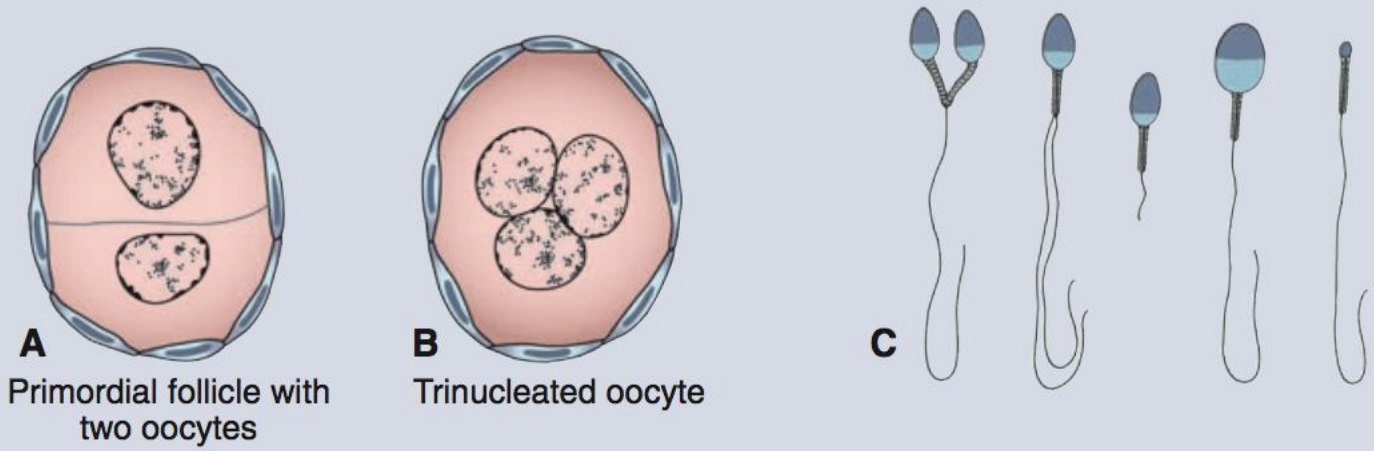


Figure 2.25 Abnormal germ cells. **A.** Primordial follicle with two oocytes. **B.** Trinucleated oocyte. **C.** Various types of abnormal spermatozoa.

Birth defects & spontaneous abortion

chromosomal & genetic factors

– ***Numerical***

– ***Structural***

25% of conceptuses have a major chromosomal abnormalities

– Turner s.

– Triploidy

– Trisomy 16

birth defects

– 10% (chromosomal abnormalities)

– 8% (gene mutation)

Numerical abnormality

Human somatic cell

- 46 chromosomes & diploid(2n)

Human gamete

- 23 chromosomes & haploid(n)

- Euploid
- Aneuploid : Trisomy / Monosomy
- Nondisjunction
- Translocation (13,14,15,21,22)

Down syndrome

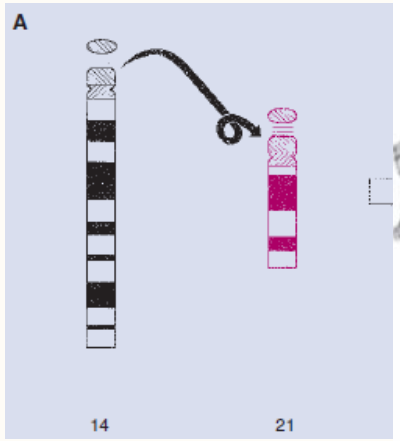
Trisomy 21

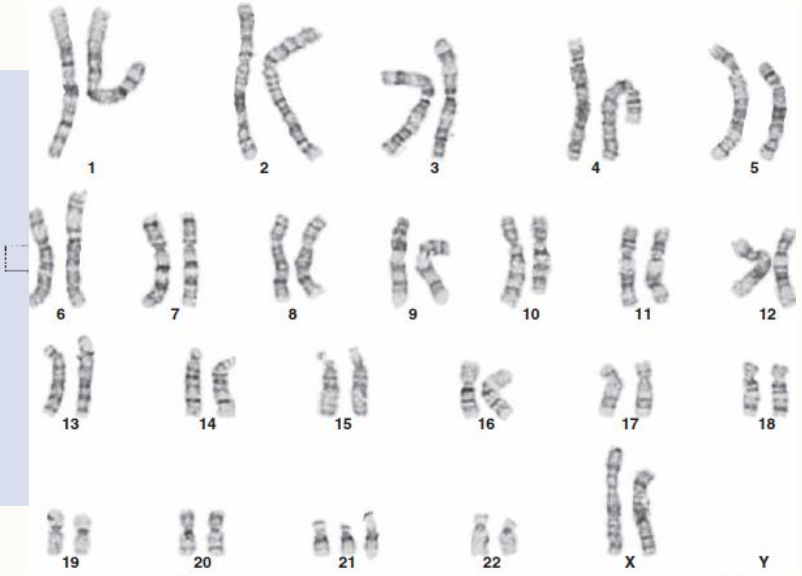
Children features

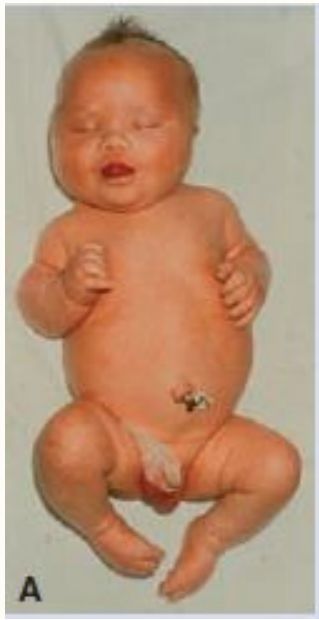
- Growth retardation / Intellectual disability
- Craniofacial abnormalities / Flat faces
- Small ears / Cardiac defects
- Hypotonia / Leukemia
- Infections / Thyroid dysfunctions
- Premature aging / Alzheimer

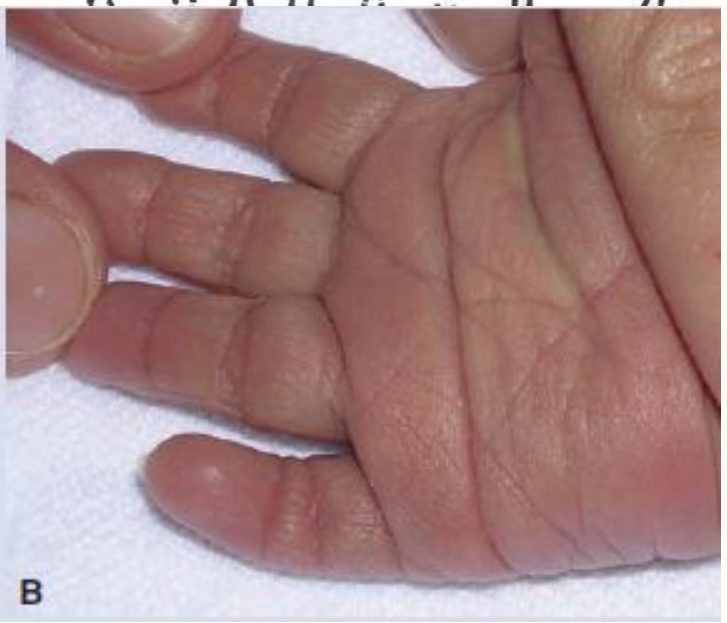
- 95% meiotic nodisjunction
- 75% maternal
- 4% translocation 21 with 13,14,15
- 1% mosaism in mitosis

- 1 in 2000 mothers age under 25 years
- 1 in 300 mothers age 35 years
- 1 in 100 mothers age 40 years









Trisomy 18

- Intllectual disability
- Congenital heart defect
- Low-set ears
- Fingers & hands flection
- Micrognathia
- Renal anomaly
- Syndactyly
- Skeletal system malformations

- 1 in 5000
- 85% lost between 10 weeks of gestation & term
- Those born alive die by 2month age
- 5% live beyond 1 year

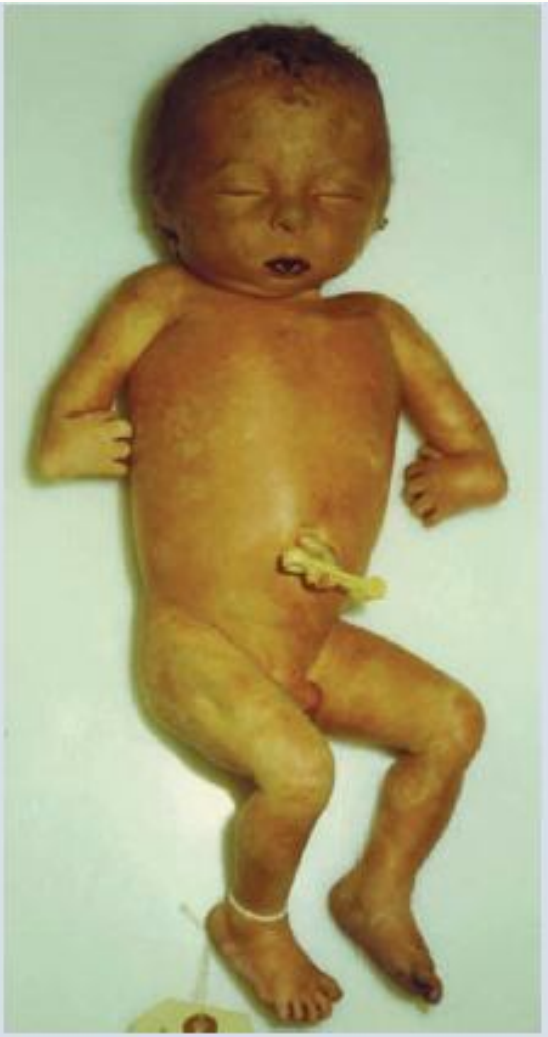


Figure 2.10 Child with trisomy 18. Note the low-set ears, small mouth, deficient mandible (micrognathia), flexion of the hands, and absent and/or hypoplasia of the radius and ulna.

Trisomy 13

- Intllectual disability
- Holoprosencephaly
- Congenital heart defect
- Deafness
- Cleft lip & palate
- Eye defects (microphthalmia, anophthalmia, cloboma)
- 1 in 20000 live birth
- 90% die in first month
- 5% live beyond 1 year

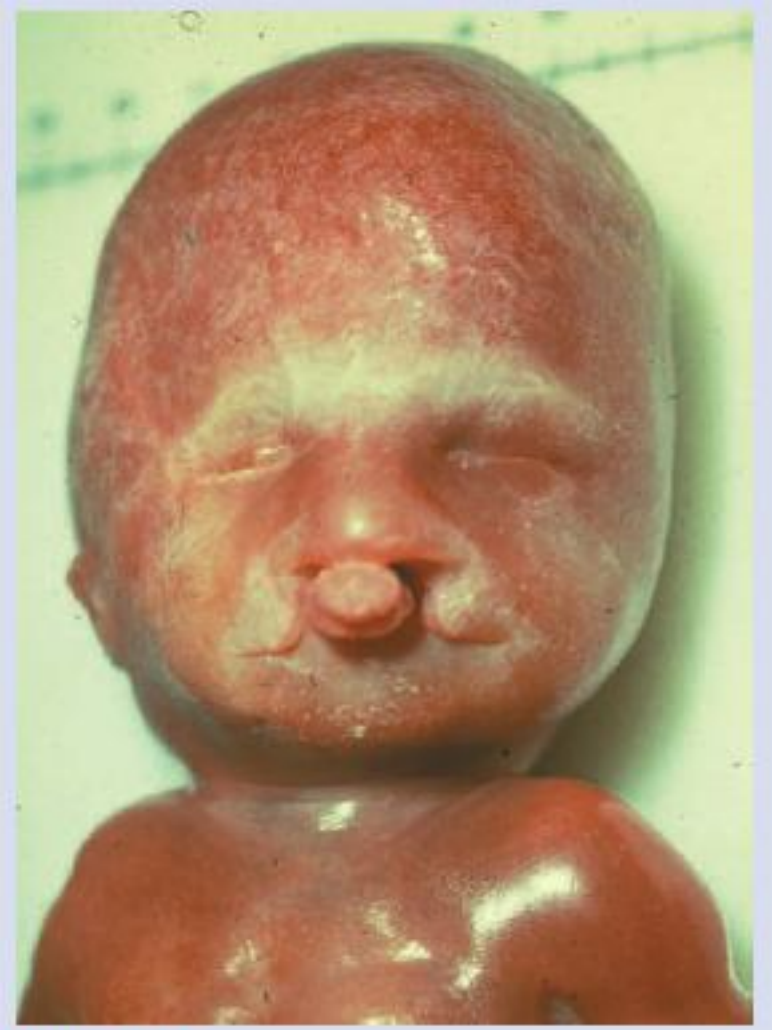


Figure 2.11 Child with trisomy 13. Note the bilateral cleft lip, the sloping forehead, and anophthalmia.

Klinefelter syndrome

- In male
- XXY
- XX nondisjunction

- Strility
- Testicular atrophy
- Seminiferous tubule hyalinization
- Gynecomastia

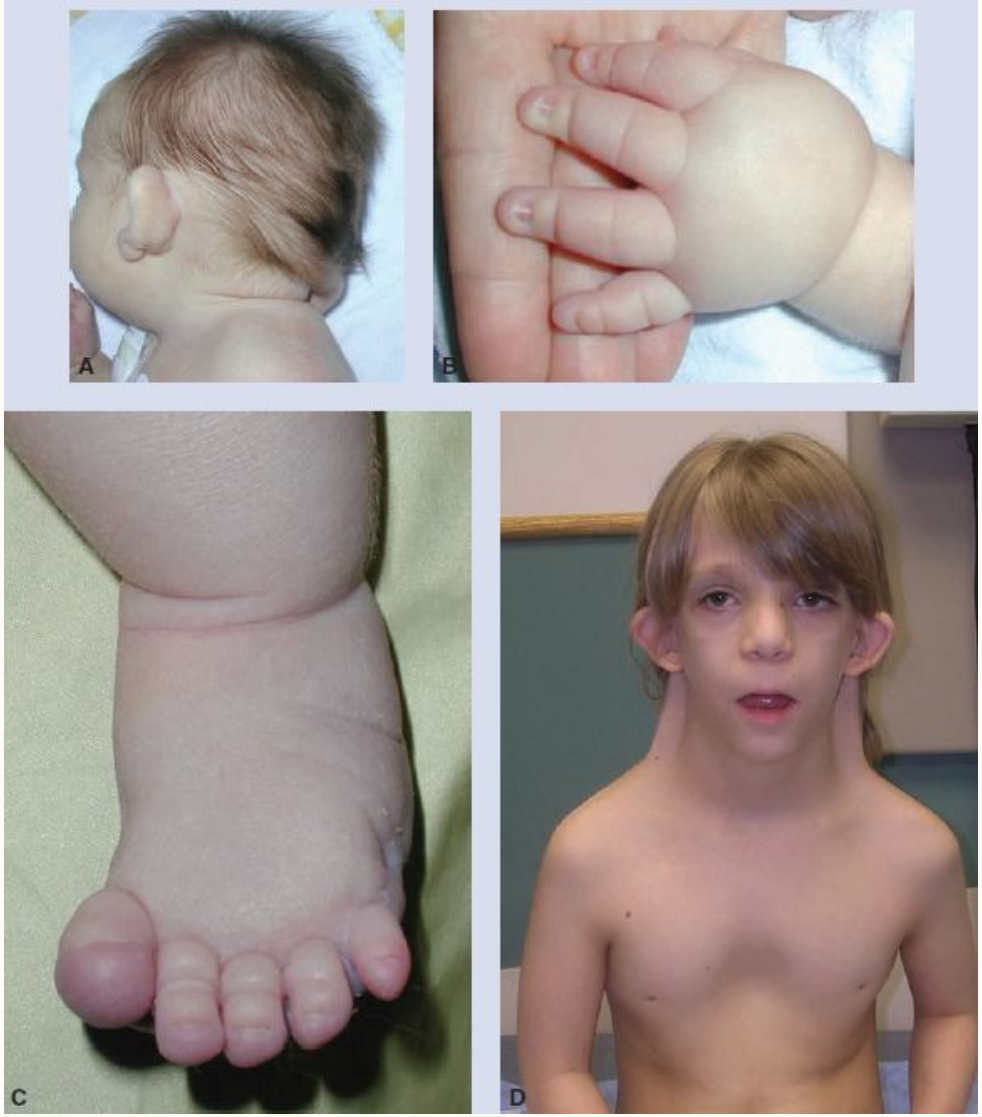
- Bar body (80%)
- 1 in 500 males

- Detect by amniosynthesis

Turner syndrome

- 45 X
- Monosomy
- 98% spontaneous aborted

- Female appearance
- Absence of ovaries (Gonadal dysgenesis)
- short stature
- Webbed neck
- Extremity lymphedema
- skeletal deformation
- Broad chest
- Widely spaced nipple
- 55% meiosis nondisjunction
- 80% in male gamete
- Mitosis nondisjunction & mosaism



Triple X syndrome

TRIPLE X SYNDROME Patients with **triple X syndrome (47, XXX)** often go undiagnosed because of their mild physical features. However, these girls frequently have problems with speech and self-esteem. They have two sex chromatin bodies in their cells.

Structural chromosome abnormalities

- Chromosome breakage
- Environmental factors

Virruses

Radiation

Drugs

Partial Deletion

Short arm of chromosome 5(cry-du-chat syndrome)

Children features

- Cat-like cry
- Microcephaly
- Intllectual disability
- Congenital heart disease

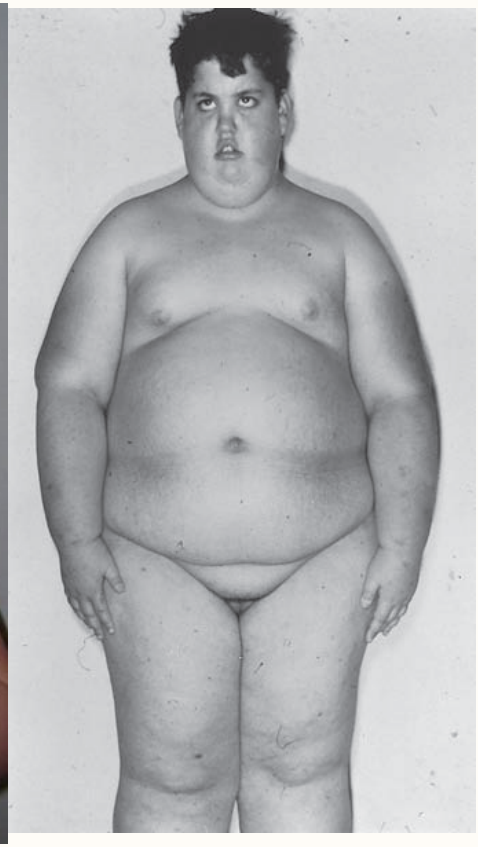
Microdeletion

- Contiguous genes
- Microdeletion or contiguous syndrome
- Detect by FISH
- 15q11-15q13
- Maternal (angelman syndrome)
- Children features
- Intellectual disability / Cannot speak
- poor motor development
- Unprovoked & prolonged period of laughter

- Paternal (prader willi syndrome)
- Children features
- Hypotonia / Obesity / Intellectual disability / Hypogonadism / Undecendant testis

Genomic imprinting

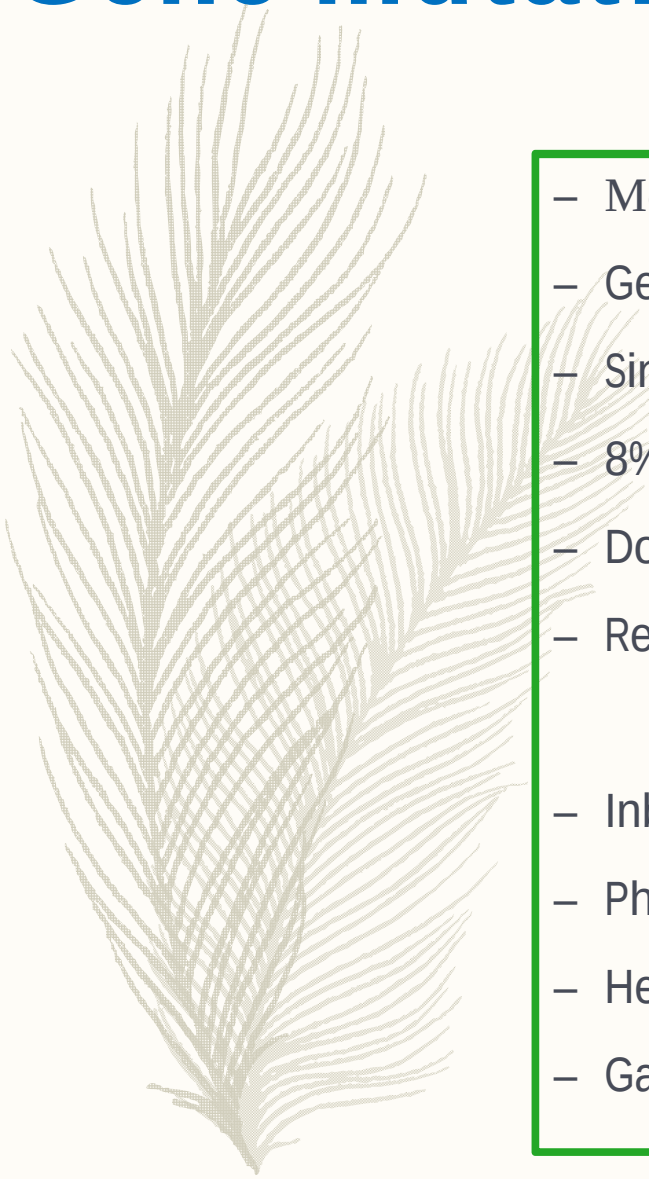
- Miller-dicker syndrom
- Lissencephaly
- Developmental delay
- Seizures
- Cardiac & facial abnormalities
- 17p13



Fragile sites

- CGG repeats
- Fragile X syndrome
- Xq27
- 200 repeat near promoter instead of 6-54 repeats
- Children features
- Intellectual disability
- Large ear
- Prominent jaw
- Large testes
- 1 in 5000
- The second cause of intellectual disability after down syndrome

Gene mutations



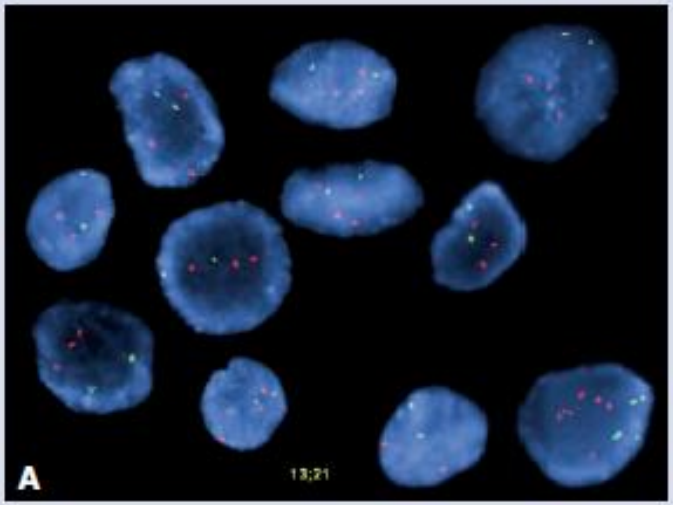
- Mendelian pattern
- Gene Structural & functional change
- Single gene mutation
- 8% of all human abnormalities
- Dominant mutation
- Recessive mutation

- Inborn errors of metabolism
- Phenylketonuria
- Hemocystinuria
- Galactosemia

Diagnostic techniques for identifying genetic abnormalities

- Cytogenetic analysis
- Giemsa stained
- High resolution metaphase banding technique

- FISH
- microarrays



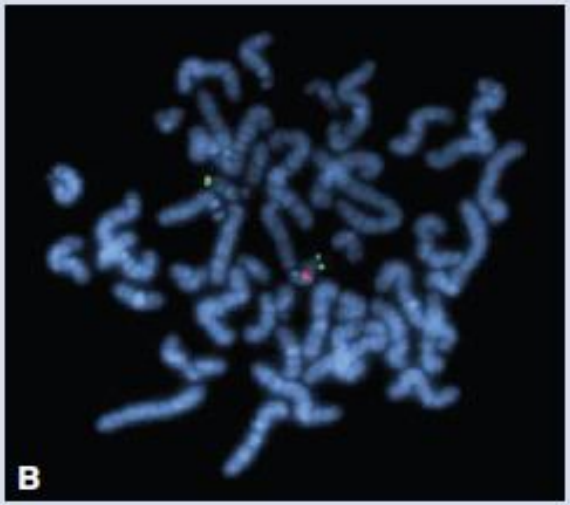


Figure 2.15 **A.** FISH, using a probe for chromosome 21 (*red dots*). Note that there are three red dots in each cell, indicating trisomy 21 (Down syndrome). The *green dots* represent a control probe for chromosome 13. Two cells are superimposed on the lower right, giving the impression of the presence of multiple probes. **B.** FISH analysis of 22q11 deletion syndrome. The green signals identify chromosome 22; the red signal represents FISH probe N25, which is in the q11 region. It is present on only one of the pairs of chromosome 22 indicating the other has the 22q11 deletion.