Cell Division

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At the molecular or submicroscopic level DNA can be regarded as the basic template that provides a blueprint for the formation and maintenance of an organism. DNA is packaged into chromosomes and at a very simple level these can be considered as being made up of tightly coiled long chains of genes. Unlike DNA, chromosomes can be visualizes during cell division using a light microscope, under which they appear as thread-like structures or "colored bodies".

Chromosomes are the factors that distinguish one species from another and that enable transmission of genetic information from one generation to the next. Their behavior at somatic cell division in *mitosis* provides a means of ensuring that each daughter cell retains its own complete genetic complement. Similarly, their behavior during gamete formation in *meiosis* enables each mature ovum and sperm to contain a unique single set of parental genes. Chromosomes are quite literally the vehicles that facilitate reproduction and the maintenance of a species[1].

The genetic material of eukaryotes is distributed among multiple chromosomes. Many eukaryotes have two copies of each type of chromosome in their nuclei, so their chromosome complement is said to be **diploid**, or 2N. Diploid eukaryotes are produced by the fusion of two **gametes**, one from the female parent and one from the male parent. The fusion produces a diploid **zygote**, which then undergoes embryological development. Each gamete has only one set of chromosomes and is said to be **haploid** (N). The complete complement of genetic information in a haploid chromosome set is called the **genome**.

In diploids, the members of a chromosome pair are called **homologous chromosomes**; each individual member of a pair is called a **homolog**. Homologous chromosomes are usually identical with respect to the arrangement of genes they contain and with respect to their visible structure; they are inherited from each parent. Chromosomes of different pairs that are unpaired are called nonhomologous chromosomes[2].

Cell Division (Mitosis and Meiosis)

A. Mitosis

It is the type of division in which a cell with 46 chromosomes produces two daughter cells, each of which also has 46 chromosomes[3].

1. ***Somatic cells*** undergo mitosis to produce genetically identical progeny.
2. ***Germ cells*** also undergo mitosis to increase their numbers within the gonads before the onset of meiosis.

Although mitosis is a continuous dynamic process, for purposes of description this segment of the cell cycle is divided into four stages (Figure 1):

a. At the conclusion of interphase, mitotic ***prophase*** begins with the condensation of the chromosomes into filaments that are visible under the light microscope.
b. In ***metaphase***, the chromosomes contract completely and move to the center of the cell. Spindle fibers extend from the kinetochore at the centromere of each chromosome to two centrioles located in opposite poles of the cell.
c. In ***anaphase***, the centromere of each chromosome divides, and the sister chromatids separate, becoming two daughter chromosomes that begin to move to the poles of the cell.
d. In ***telophase***, the daughter chromosomes reach the poles of the cell and begin to decondense into fibers of interphase chromatin. The cytoplasm divides, and nuclear membranes form again. At the completion of this process, ***interphase*** begins in the daughter cells. These cells have the same chromosomal and genetic composition as the original cells.

The Cell Cycle

The period between successive mitoses is known as **the interphase** of the cell cycle[1, 3]. In the rapidly dividing cells this lasts for between 16 and 24 h (Figure 2).

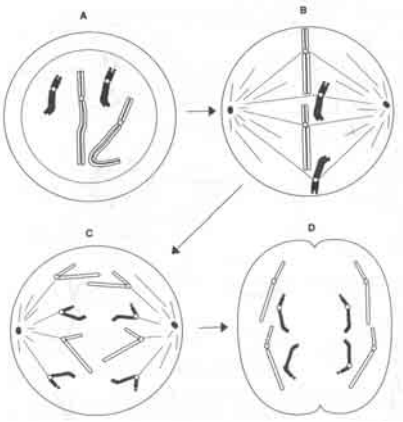

Figure 1. Mitosis.
(A) Prophase; (B) Metaphase; (C) Anaphase; (D) Telophase.

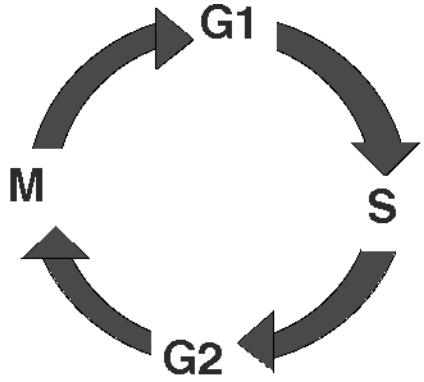

Figure 2. Stages of the cell cycle.
G1 and G2 are the first and second "resting" stages of interphase. S is the stage of DNA replication. M = mitosis

a. The interphase commences with **G1 phase (**Gap 1) during which the chromosomes become thin and extended. This phase of the cycle is very variable in length and is responsible for the variation in generation time between different cell populations. Cells which have stopped dividing, such as neurons, usually arrest in this phase and are said to have entered a non-cyclic stage known as G0.
b. The G1 phase is followed by the **S phase** (S = synthesis) when DNA replication occurs and the chromatin of each chromosome is replicated. This results in the formation of two chromatids which give each chromosome its characteristic X-shaped configuration. Usually homologous pairs of chromosomes replicate in synchrony. However, one of the X chromosomes is always late replicating. This is the inactive X chromosome which forms the sex chromatin, or the so-called Barr body, which can be visualized in interphase in female somatic cells.
c. Interphase is completed by a relatively short **G2 phase** during which the chromosomes begin to condense in preparation for the next mitotic division.

The entire cell cycle is thus the sequence of phases G1 → S → G2 → mitosis, which is repeated for each replicating somatic cell.

B. Meiosis

It is the type of cell division by which diploid gametic precursors produce haploid gametes. These meiotic products have 23 chromosomes rather than the 46 chromosomes that are typically present in somatic cells.

Meiosis is preceded by one round of DNA synthesis and consists of two special cell divisions (Figure 3).

a. The first meiotic division, meiosis I, is called reduction division because it reduces the chromosome number from 46 to 23[1, 4].

1. **Prophase I:** At the beginning of meiosis I prophase (prophase I), each chromosome has completed replication and consists of two sister chromatids attached at the centromere. Homologous chromosomes pair, and with the exception of the X and Y chromosomes in male meiosis, exchange of homologous segments occurs between non-sister chromatids, that is, chromatids from each of the pair of homologous chromosomes. This exchange of homologous segments between chromatids occurs as a result of a process known as crossing over or recombination. During prophase I in the male, pairing occurs between homologous segments of

the X and Y chromosomes at the tip of their short arms, with this portion of each chromosome being known as ***the pseudoautosomal region***.

2. **In metaphase I**: the nuclear membrane disappears and the bivalents align on a plane in the center of the cell. A spindle connects the centromeres to centrioles in opposite poles of the cell.
3. **In anaphase I**: the homologous chromosomes comprising each bivalent separate from each other and move to opposite poles of the cell.
4. During **telophase I**: Each set of haploid chromosomes has now separated completely to opposite ends of the cell, which cleaves into two new daughter gametes, so-called *secondary spermatocytes or oocytes.*

b. The second meiotic division, meiosis II, is preceded by a brief interphase in which DNA synthesis does not occur[3, 5].

1. Meiosis II is similar to mitosis in that the chromosomes, each consisting of two sister chromatids attached at the centromere, align on a central plane in the cell, a spindle forms, the centromeres split, and the daughter chromosomes move to opposite poles of the cell.
2. The essential difference is that in meiosis II there are only 23 chromosomes in the original cell and in each of the daughter cells, whereas in mitosis there are 46.

Meiosis differs from mitosis in the following ways:

a. Meiosis occurs only in germ cells; mitosis occurs in all somatic cells as well as in germ cells before they enter their final stages of development.
b. Meiosis consists of two sequential cell divisions; mitosis occurs in a single division.
c. Pairing of homologous chromosomes occurs in meiosis but not in mitosis.
d. Recombination between homologous chromosomes is a regular feature of meiosis but not of mitosis.
e. Meiosis results in a reduction of the chromosome number from 46 to 23. Mitosis produces two daughter cells with 46 chromosomes, the same number that was present in the original cell[3].

Gametogenesis

It is the formation of the ova or sperm. In males, the process is called spermatogenesi***s***; in females, it is called oogenesi***s.*** The process of gametogenesis shows fundamental differences in males and females (Figure 4 and Table 1). These have quite distinct clinical consequences if errors occur.

A. Spermatogenesis

It begins to occur in the seminiferous tubules of the testes at the time of puberty and continues throughout life[2]..

a. Mitotic germ cell precursors called spermatogonia produce primary spermatocytes, each of which undergoes meiosis I to produce two secondary spermatocytes.
b. Each secondary spermatocyte undergoes meiosis II to form two spermatids, which mature without further division to form sperm.
c. The production of mature sperm from a spermatogonium takes about 60-65 days.

Spermatogenesis is a continuous process involving many mitotic divisions, so that mature spermatozoa produced by a man of 50 years or older could well have undergone several hundred mitotic divisions. The observed paternal age effect for new dominant mutations is consistent with the concept that many mutations arise as a consequence of DNA copy errors occurring during mitosis.

B. Oogenesis

It differs in several important ways from spermatogenesis. Mature ova develop from oogonia by a complex series of intermediate steps[1, 3]:

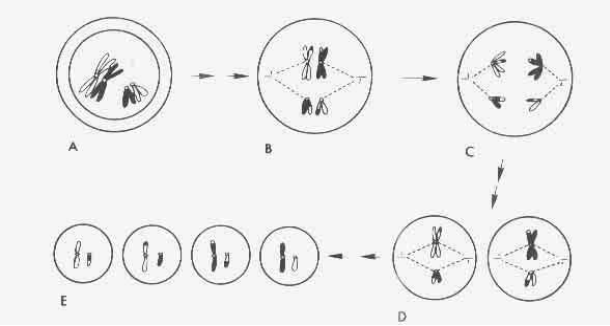

Figure 3. The major events in meiosis. (A) Prophase I; (B) Metaphase I; (C) Anaphase I; (D) Metaphase II; (E) Haploid products of meiosis.

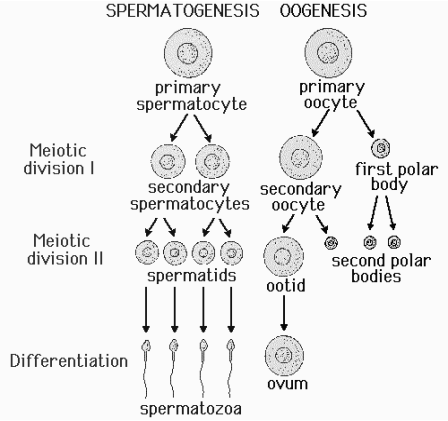

Figure 4. Stages of oogenesis and spermatogenesis.

a. Oogonia themselves originate from primordial germ cells by a process involving 20-30 mitotic divisions that occur during the first few months of embryonic life.
b. By the completion of embryogenesis at 3 months of intrauterine life, the oogonia have begun to mature into primary oocytes that start to undergo meiosis.
c. At birth all of the primary oocytes have entered a phase of maturation arrest, known as dictyotene, in which they remain suspended until meiosis I is completed at the time of ovulation, when a single secondary oocyte is formed.
d. This receives most of the cytoplasm. The other daughter cell from the first meiotic division consists largely of a nucleus and is known as a polar body.
e. Meiosis II then commences, during which fertilization can occur. This second meiotic division results in the formation of a further polar body.

It is probable that the very lengthy interval between the onset of meiosis and its eventual completion, up to 50 years later, accounts for the well-documented increased incidence of chromosome abnormalities in the offspring of older mothers. The accumulating effects of wear and tear on the primary oocyte during the dictyotene phase probably damage the cell's spindle formation and repair mechanisms, thereby predisposing to non-disjunction.

Table 1. Differences in gametogenesis in male and female[1].

	Male	Female
Commences	Puberty	Early embryonic life
Duration	60-65 days	10-50 years
Numbers of mitoses in gamete formation	30-500	20-30
Gamete production per meiosis	4 spermatids	1 ovum + 3 polar bodies
Gamete production per ejaculate	100-200 million cycle	1 ovum per menstrual cycle

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