Meiosis

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The set of two successive cell divisions that serve to separate homologous chromosome pairs and thus reduce the total number of chromosomes by half. The meiotic process includes two sequential nuclear divisions that must occur prior to the formation of gametes (sperm and eggs). The major purpose of meiosis is the precise reduction in the number of chromosomes by one-half, so a diploid cell can create haploid gametes. To accomplish this reduction, a single cell undergoes two meiotic divisions to produce four daughter cells, each with half the original chromosome complement. The nonmeiotic (or somatic) cells of humans, for instance, have 46 individual chromosomes, or 23 pairs of homologous chromosomes. However, following meiosis, human eggs or sperm have only 23 chromosomes, one member of each pair. Reducing the number of chromosomes in the gametes to 23 allows the fusion of an egg with a sperm (fertilization) to result in an embryo with the requisite 46 chromosomes. Meiosis is therefore a critical component of sexual reproduction. *See also:* GAMETOGENESIS.

Chromosome behavior

For example, consider an organism that contains only two pairs of chromosomes (**Fig. 1**). The chromosomes in each of these pairs are referred to individually as homologs; one is derived from the father of the organism and the other from the mother. Both homologs carry the same array of genes. As the cell begins meiosis, each chromosome has already duplicated its DNA and carries two identical copies of the DNA molecule. These are visible as two lateral parts, called sister chromatids, which are connected by a centromere.

The basic events of meiosis are actually quite simple. Homologous pairs of chromosomes are first identified and matched. This process, which occurs only in the first of the two meiotic divisions, is called pairing. The matched pairs are then physically interlocked by recombination, which is also known as exchange or crossing-over. After recombination, the homologous chromosomes separate from each other, and at the first meiotic division are partitioned into different nuclei. The second meiotic division begins with half of the original number of chromosomes. During this second meiotic division, the sister chromatids of each chromosome separate and migrate to different daughter cells. *See also:* CHROMOSOME.

The patterns by which genes are inherited are determined by the movement of the chromosomes during the two meiotic divisions. It is a fundamental tenet of Mendelian inheritance that each individual carries two copies of each gene, one derived from its father and one from its mother. Moreover, each of that individual's gametes will carry only one copy of that gene, which is chosen at random. The process by which the two copies of a given gene are distributed into separate gametes is referred to as segregation. Thus, if an individual is heterozygous at

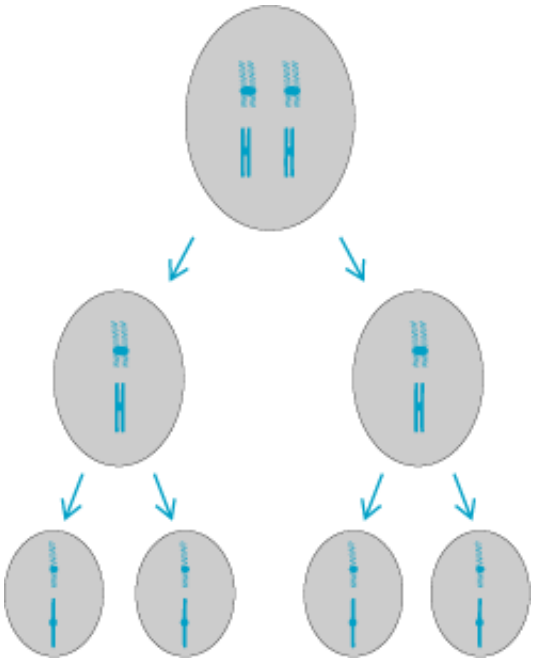

Fig. 1 **Simplified view of the two meiotic divisions.**

the *A* gene for two different alleles, *A* and *a*, his or her gametes will be equally likely to carry the *A* allele or the *a* allele, but never both or neither. The fact that homologous chromosomes, and thus homologous genes, segregate to opposite poles at the first meiotic division explains this principle of inheritance. *See also:* CELL CYCLE.

Mendel's law of independent assortment states that the segregation of two different gene pairs occurs at random with respect to each other. Thus, for an individual of the genotype *AaBb*, the gametes *AB, Ab, aB*, and *ab* will be formed with equal frequency. This result can be easily understood if the *A* and *B* genes lie on different chromosomes (**Fig. 2**). Because the chromosome pair bearing the *A* gene orients independently of the homolog pair bearing the *B* gene, *AB* ↔ *ab* segregations are as likely as *Ab* ↔ *aB* segregations. Cases where independent assortment does not occur (an effect called linkage) can be understood as resulting from situations where the two gene pairs lie at different positions on the same pair of homologous chromosomes. *See also:* ALLELE; GENE; MENDELISM.

Meiotic divisions

The two meiotic divisions may be divided into a number of distinct stages. Meiotic prophase refers to the period after the last cycle of DNA replication, during which time homologous chromosomes pair and recombine. The end of prophase is signaled by the breakdown of the nuclear envelope, and the association of the paired chromosomes with the meiotic spindle. The spindle is made up of microtubules that, with associated motor proteins, mediate chromosome movement. In some cases (such as human sperm formation), the spindle is

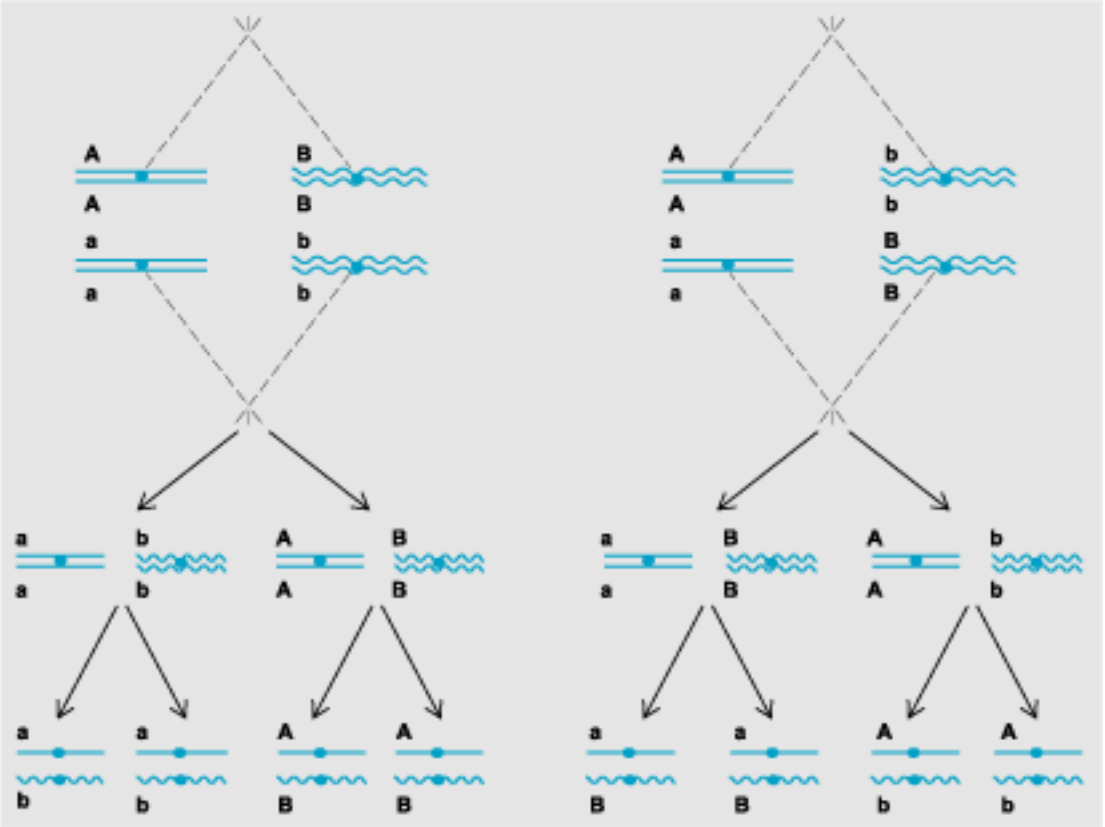

Fig. 2 **Behavior of chromosomes at the first meiotic division explains independent assortment.**

already formed at the point of nuclear envelope breakdown, and the chromosomes then attach to it. In other systems (such as human female meiosis), the chromosomes themselves organize the spindle.

Metaphase I is the period before the first division during which pairs of interlocked homologous chromosomes, called bivalents, line up on the middle of the meiotic spindle. The chromosomes are primarily (but not exclusively) attached to the spindle by their centromeres such that the centromere of one homolog is attached to spindle fibers emanating from one pole, and the centromere of its partner is attached to spindle fibers from the other pole (**Fig. 3**). The bivalents are physically held together by structures referred to as chiasmata that are the result of meiotic recombination events. In most meiotic systems, meiosis will not continue until all of the homolog pairs are properly oriented at the middle of the spindle, the metaphase plate. It is important to remember that the orientation of each pair of homologs on the spindle occurs in a random fashion, such that the paternally derived homolog of one bivalent may point toward one pole of the spindle, while the maternally derived homolog in the adjacent bivalent is oriented toward the same pole.

Anaphase I refers to the point at which homologous chromosome pairs separate and move to opposite poles. This is accomplished by the release of chiasmata. Although the sister chromatids remain attached around their

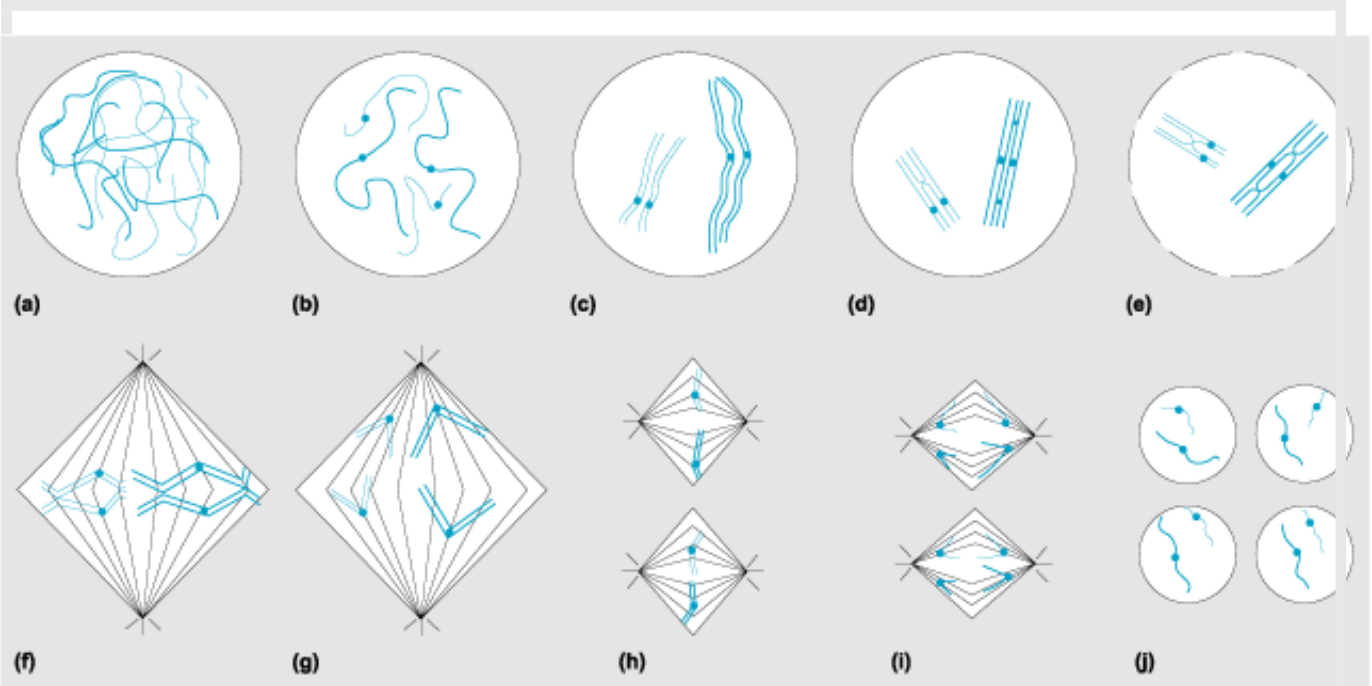

Fig. 3 Stages of meiosis. (*a*) Premeiotic interphase. (*b*) Leptotene (note the appearance of individualized chromosomes). (*c*) Zygotene (signified by the alignment of homologs). (*d*) Pachytene (the chromosomes making up each bivalent are intimately aligned). (*e*) Diplotene/diakinesis. (*f*) Metaphase I. (*g*) Anaphase I. (*h*) Metaphase II. (*i*) Anaphase II. (*j*) Telophase II.

centromeres, they release each other along the arms of the chromosome, allowing chiasmata to be resolved. Depending on the organism, there may or may not be a true telophase, or a time in which nuclei reform. In most organisms, the first cell division occurs after the completion of anaphase I.

Following the completion of the first meiotic division, the chromosomes align themselves on a new pair of spindles, with their sister chromatids oriented toward opposite poles. The stage at which each chromosome is so aligned is referred to as metaphase II. In some, but not all, organisms, metaphase II is preceded by a brief prophase II. DNA replication does not occur during prophase II; each chromosome still consists of the two sister chromatids. Nor are there opportunities for pairing or recombination at this stage due to the prior separation of homologs at anaphase I.

The start of anaphase II is signaled by the separation of sister centromeres, and the movement of the two sister chromatids to opposite poles. At telophase II, the sisters have reached opposite poles and the nuclei begin to reform. The second cell division usually occurs at this time. Thus, at the end of the second meiotic division, there will be four daughter cells, each with a single copy of each chromosome.

Details of meiotic prophase

Because pairing and recombination occur during the first meiotic prophase, much attention has been focused on this stage of the process. The prophase of the first meiotic division is subdivided into five stages: leptotene, zygotene, pachytene, diplotene, and diakinesis. Homolog recognition, alignment, and synapsis occur during leptotene and zygotene. In the leptotene, an initial phase of chromosome individualization, initial homolog alignments are made. By zygotene, homologous chromosomes have become associated at various points along their length. These associations facilitate a more intimate pairing that results in the homologous chromosomes lying abreast of a tracklike structure called the synaptonemal complex.

The beginning of pachytene is signaled by the completion of a continuous synaptonemal complex running the full length of each bivalent. During diplotene, the attractive forces that mediated homologous pairing disappear, and the homologs begin to repel each other. Luckily, homologs virtually always recombine, and those recombination events can be seen as chiasmata that tether the homologs together. In some organisms, those rare chromosome pairs that have failed to undergo recombination will fly apart prematurely from each other at this stage. The final stage in meiotic prophase is diakinesis, during which the homologs shorten and condense in preparation for nuclear division.

Mechanisms of pairing

Recent models of meiotic pairing suggest that homologous chromosomes initially undergo multiple interactions at many sites along their lengths, and often at their tips. These interactions are the result of several types of homology—finding mechanisms which serve to bring the chromosomes into alignment. However, these associations are apparently weak and transient, and must be stabilized early in meiotic prophase by one of two mechanisms. In the yeast *Saccharomyces cerevisiae*, these pairings can apparently be locked in by the initiation of recombination. The formation of recombination intermediates appears to be fully sufficient to ensure segregation even in genetic backgrounds in which synapsis and synaptonemal complex formation do not occur. In contrast, recombination is delayed in many higher organisms and its completion appears to require the formation of the synaptonemal complex. In these higher organisms, it is synaptonemal complex formation during zygotene that appears to maintain chromosome pairing during the processes of chromatin compaction and chromosome movement which accompany the progression of meiotic prophase.

The mature synaptonemal complex is a tripartite structure consisting of two lateral elements that flank the chromosomes, and a central element, and running the full length of each bivalent (**Fig. 4**). It is believed that the synaptonemal complex is essential for both synapsis and sister chromatid cohesion, and that proteins involved in maintaining sister chromatid cohesion (known as cohesins) are a major component of the synaptonemal complex itself.

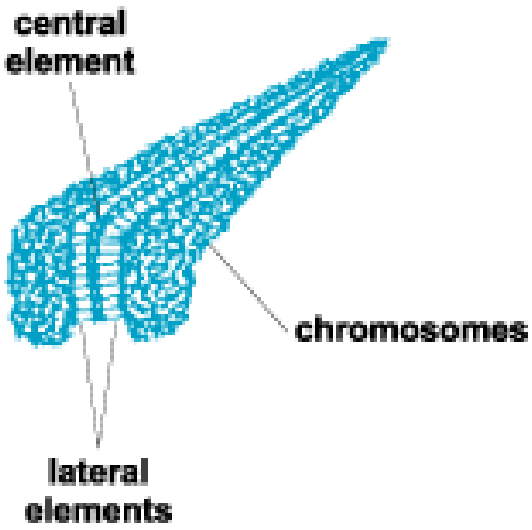

Fig. 4 Synaptonemal complex.

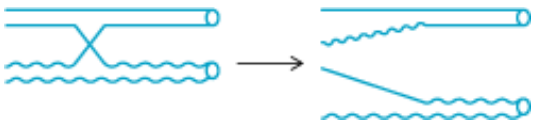

Fig. 5 Recombination involves the physical interchange of genetic material between two nonsister chromatids.

Mechanisms of recombination

Meiotic recombination involves the physical interchange of DNA molecules between the two homologous chromosomes, thus allowing the creation of new combinations of alleles for genes located on that pair of chromosomes. Mechanistically, recombination occurs between homologous chromosomes, and involves the precise breakage and rejoining of two nonsister chromatids. The result is the formation of two recombinant chromatids, each of which carries information from both of the original homologs (**Fig. 5**).

The actual mechanism of recombination involves a complex series of cutting and rejoining of homologous DNA. The initial event appears to be the controlled cleavage of one of the two nonsister chromatids to create a double-strand break, in which both phosphodiester backbones of the double-helical DNA molecule are cleaved. The initial break is then extended to create a gap. Sequences adjacent to the gap seek out identical regions of DNA sequence on the homolog, and then use the homolog as a template to replace the DNA base pairs removed during gap formation. As a result of this process, the two DNA molecules exchange strands at two closely linked sites and create a structure referred to as a double Holliday intermediate. The resolution of this intermediate can either create a pair of recombinant chromatids or simply result in a short region of DNA from one chromatid being inserted into the other as a result of the gap-filling process. This latter event is called gene conversion.

The number and position of recombination events is very precisely controlled. Exchange occurs only in the gene-rich euchromatin that makes up most of the chromosome arms, never in the heterochromatin that surrounds the centromeres. Moreover, as a result of a process known as interference, the occurrence of one exchange in a given chromosomal region greatly decreases the probability of a second exchange in that region. *See also:* DEOXYRIBONUCLEIC ACID (DNA); RECOMBINATION (GENETICS).

Function of genetic recombination

Recent studies have indicated that failures of meiotic chromosome segregation in many organisms, including humans, may arise by a common mechanism. In these organisms, the absence or misplacement of exchange events along the length of a bivalent greatly increases the probability of failed segregation at anaphase I. For certain chromosomes (such as human chromosome 21 and the *Drosophila* X chromosome), exchange events that occur in the distal or most proximal regions of the chromosome frequently result in segregation errors at metaphase I.

Recombination events

The cytological manifestation of an exchange event is a chiasma. Chiasmata can be visualized at diplotene–diakinesis as sites on the bivalent in which two nonsister chromatids appear to cross over from one homolog to the other. Because the sister chromatids display tight cohesion during meiotic prophase and metaphase I, chiasmata hold the paired chromosomes together and thus commit the two centromeres that are physically linked by the exchange to orient to opposite poles of the spindle. Once the two centromeres have oriented toward opposite poles, the chiasmata also function to halt the progression of the homologous centromeres toward opposite poles, thus holding the properly oriented bivalent at the metaphase plate. This represents a stable position in which the bivalent will remain until anaphase I.

Linkage (recombination mapping)

Recombination can occur anywhere within the euchromatin, but never occurs within the heterochromatin. For two genes on the same chromosome, recombination can be detected by the creation of new combinations of alleles. Consider the case of an *AaBb* double heterozygote, where the *A* and *B* genes lie on the same chromosome arm. In this instance, the *A* and *B* alleles lie on one homolog and the *a* and *b* alleles lie on the other. In the absence of recombination, only *AB* and *ab* gametes can be produced. However, recombination allows the production of *aB* and *Ab* gametes, and the frequency of such gametes will be proportional to the frequency of recombination (**Fig. 6**).

To a rough approximation, the farther apart two genes are on a given chromosome, the more likely it is that a recombination event will occur between them. Since virtually all homolog pairs undergo at least one recombination event per arm at each meiosis (and the longer chromosome arms may experience three to five

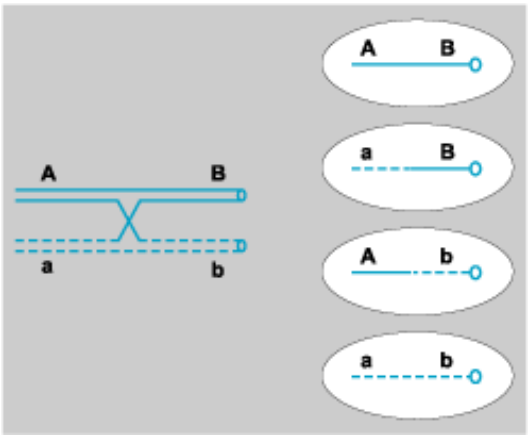

Fig. 6 **Recombination leading to linkage.**

exchanges), the probability that two genes far apart on a given arm will have at least one recombination event occurring between them is quite high. In contrast, genes lying close to each other will recombine only very rarely. Thus, by determining how often recombination occurs between various pairs of genes, geneticists can build linkage maps and order the position of genes along a given chromosome. *See also:* LINKAGE (GENETICS).

Sex differences in meiosis

In human male meiosis, all four daughter cells of meiosis will go through a complicated cellular differentiation process called spermiogenesis to become mature functional sperm. In contrast, oogenesis results in only one of the four products of meiosis becoming an egg. The other three products donate their cytoplasm to the chosen oocyte, and then die. The oocyte then completes the cellular differentiation process to become a mature egg.

In human females, meiosis begins during fetal development. All of the oocytes (eggs) that a human female will possess in her lifetime are produced during fetal development, but these oocytes are arrested at the end of pachytene. Thus, all of the meiotic recombination that a human female will ever do is completed before she is born. These arrested oocytes remain quiescent until the girl enters puberty. At that point, a few oocytes are allowed to begin the maturation process during each menstrual cycle; usually only a single oocyte is ovulated per cycle. The ovulated egg completes anaphase I and then proceeds through meiosis until it arrests again at metaphase II. The completion of the second meiotic division is triggered only by fertilization.

Male meiosis begins at puberty and continues uninterrrupted throughout the life of the male. The stem cells that will produce male meiotic cells continue to divide throughout the male's life, constantly producing new populations of spermatocytes. Moreover, once meiosis is initiated in human spermatocytes, it usually proceeds without interruption to produce four daughter cells, all of which differentiate to become mature spermatids.

The molecular mechanisms that ensure meiotic segregation are also different in males and females. In human males, the meiotic spindle is organized by the centrosomes. The chromosomes then attach to the developing spindle after it is formed by the centrosomes. In females, the chromosomes themselves bind to the microtubules, and build the spindle from the inside out without the assistance of the centrosomes. The frequency and distribution of recombination events for each chromosome pair also differ between males and females. *See also:* OOGENESIS; SPERMATOGENESIS.

Errors of meiosis

The failure of two chromosomes to segregate properly is called nondisjunction. Nondisjunction occurs either because two homologs failed to pair and/or recombine or because of a failure of the cell to properly move the segregating chromosomes on the meiotic spindle. The result of nondisjunction is the production of gametes that are aneuploid, carrying the wrong number of chromosomes. When such a gamete is involved in a fertilization event, the resulting zygote is also aneuploid. Those cases where the embryo carries an extra copy of a given chromosome are said to be trisomic, while those that carry only one copy are said to be monosomic for that chromosome. Most aneuploid zygotes are not viable and result in early spontaneous abortion. There are no viable monosomies for the human autosomes; however, a few types of trisomic zygotes are capable of survival. These are trisomies for the sex chromosomes (XXX, XXY, XYY), trisomy 21 (Down syndrome), trisomy 18, and trisomy 13. *See also:* CROSSING-OVER (GENETICS).

Meiosis versus mitosis

The fundamental difference between meiosis and mitosis is that sister chromatids do not separate at the first meiotic division; rather, homologous chromosomes separate from each other with their sister chromatids still attached to each other. Although in some organisms some chromosome pairing does occur in mitotic cells, intimate synapsis along the entire length of chromosomes is usually restricted to meiotic cells. Recombination is frequent in most meiotic cells; however, it occurs only rarely in mitotic cells, usually as part of DNA repair events.

Most critically, DNA synthesis occurs only once within the two meiotic divisions, while there is a complete replication before every mitotic division. This allows mitosis to produce two genetically identical daughter cells, while meiosis produces four daughter cells, each with only one-half the number of chromosomes present prior to meiosis. *See also:* CELL DIVISION; GENETICS; MITOSIS.

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