

CHAPTER 11

11 THE CELL DIVISION CYCLE

11.1 Definition

Cell cycle is the period which begins when two new cells are formed by the division of parental cell and ends when one of the cells (daughter cells) then divide to form two new cells.

Three aspects of cell division (Eukaryotes and prokaryotes)

- i) Mitosis (nucleus division)
- ii) Cell division (cytokinesis or division of cytoplasm).
- iii) Interphase nucleus activities.

11.2 Cell cycle model (based on induction synchrony and selection synchrony techniques)

Induction synchrony technique of studying cell cycle.

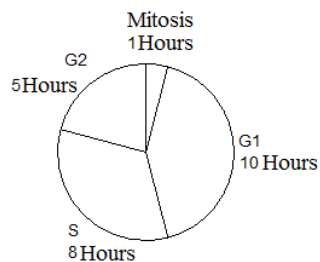
- i) Utilizes inhibitors to halt cell division at the same stage of cell division.
- ii) When inhibitors are removed, cell cycle continues from the same stage.
- iii) Example of inhibitor is excess Thymidine – this is referred to as Thymidine block technique.

Selection synchrony technique of studying cell cycle

- i) Cells in culture at the same stage of cell division are isolated and grown as separate population.

11.2.1 Stages of cell cycle in Eukaryotic cells

Stages of Cell division cycle (in Eukaryotes Cell)



Activities G1 (Gap 1) phase 10hrs

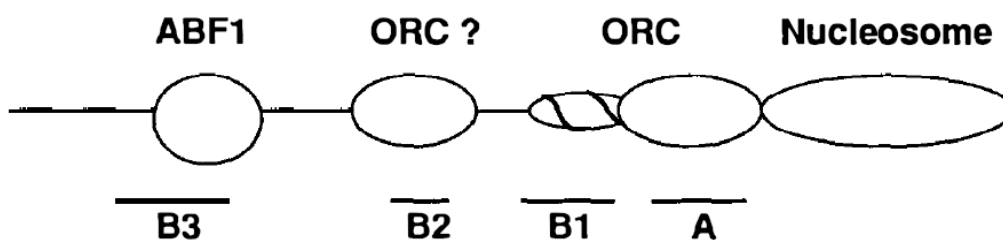
- i) The mRNA, tRNA and ribosomes are synthesized
- ii) Rapid growth of the nucleolus as new ribosomal materials are synthesized is realized
- iii) Synthesis of proteins e.g. proteins required replication and segregation of DNA
- iv) Change in morphology of the chromosome from condensed state in mitosis to extended state in interphase. This is due to transition to a lower level of coiling of the nucleosomes.
- v) Decision if cell is to proliferate or not is done here (cell prepare for DNA doubling and replication. The point at which this decision is to be made is called **restriction point or START**. After

biochemical event associated with restriction point occur, the cell is irreversibly programmed for DNA replication, interaction and consequent division.

- vi) Cells must grow to a certain mass (i.e. accumulate sufficient cellular proteins) before it commits itself to the rest of the cell cycle.
- vii) G1 is absent in some Eukaryotes e.g. slime mould (*Physarium polycephalum*) and fission yeast (*Schizosacharomyces pombe*).
- viii) Both Cyclin dependent Kinase (DDK) and Dbf4-dependent kinase (DDK) are down regulated, which allows origin licensing and prevents premature replication initiation

Activities S phase 8 hours

- i) Synthesis of DNA take place. DNA replication start at origin of replication which A/T rich as evidenced from yeast (*Sacharomyces cerevisiae*). These origins contain a 11bp consensus region. DNA sequences flanking Autonomous replicating sequences (ARS) play auxiliary role in replication.



- ii) The origin of replication contain two main domains, the AT-rich core sequence or domain A and Auxiliary domain B sequences. Domain B are stimulate ARS function. Domain B of the ARS has been found to have three subdomains (B3, B2and B1). ARS-binding protein Factor 1 (ABF1) binds on the B3 auxiliary sequence of ARS1(numeral 1 stands for the first replication controlling protein to be discovered). In yeast ABFI stimulate both DNA replication and transcription. Multi-protein origin recognition complex (ORC) bind to core sequence domain A and strongly influences functions of ARS1.
- iii) Mini-chromosome maintenance (MCM) proteins (a product of *MCM* gene is though to maintain the stability of mutiprotein complex within the origin of replication (over production of MCM lead to instability of replication).
- iv) There is DNA and chromosome division. Each chromosome and DNA of centromere replicate
- v) Chromatids are still held together by centromere
- vi) Coordination for duplicating the nucleosome organization to the Eukaryotic chromosome take place here.
- vii) Replication protein A (RPA) is a single strand DNA binding protein. Its function is to protect ssDNA from nucleases and control or DNA replication.
- viii) DNA unwinding element (DUE), an A/T-rich element and transcription factors bind to crease efficiency of initiation of DNA replication.
- ix) S-phase has initiator substance which directs DNA synthesis (cyclin-dependent kinases (CDK), Dbf4-dependent kinase (DDK) and the DNA damage checkpoint kinases).
- x) The duration of S-phase is determined by the rate (frequency) at which replicons form e.g. in young drosophila, the rate of replicon formation is higher than the rate in adult drosophila.
- xi) Areas rich in A and C bases tend to form replicons earlier than areas rich in A and T bases in S-phase.

- xii) Heterochromatic chromosome regions tend to be replicated relatively later than in euchromatic regions.
- xiii) Origin of replication / firing is also inhibited during the S phase when DNA damage or replication fork stalling activates the checkpoint kinases.
- xiv) To prevent double DNA replication, the DNA replication licensing factors disappear (and probably replication inhibition factors are produced)
- xv) At this time transcription is minimum

Activities G 2 phase 5 hours

- i) G2 check point takes place, and defective replicated chromosomes are blocked from entering mitosis.
- ii) Cell division cycle2 (*cdc2*) gene product is enhanced for promotion of mitosis
- iii) Chromosome begin to condense in preparation for mitosis..
- iv) RNA and protein are actively synthesized.
- v) Tubulin is one of the important proteins synthesized. Tubulin is a component of the mitotic spindle apparatus which are used to segregate the chromosomes into daughter cells during mitosis.
- vi) Activation of inducer maturation factor (MPF)

Mitosis – shortest phase of cell cycle 1hr (or 2hours).

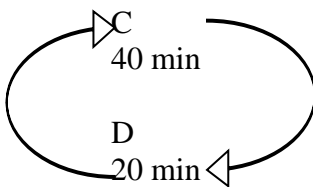
NB – events in S , G2 and M phases seem to take place at a fixed rate.

Importance of G1 and G2 in cell cycles

- i) Initiation of DNA synthesis appear to depend on events taking place in G1.
- ii) Events required for chromosome condensation and formation of mitotic spindles take place during G2.

11.2.2 Cell division in prokaryotes

Based on Cooper - Helmstetter model.



- i) Bacteria cells that divide within one hour, DNA replication is restricted to first 40 minutes (c) and (d) is 20 minutes.
- ii) In cells that divide more rapidly than one hour C and D phase begin to overlap.

Home work

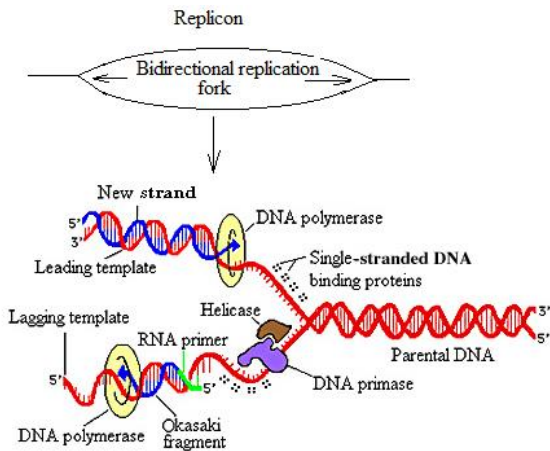
1.
 - i) Why do cells need energy.
 - ii) State the sources of energy to the cell.
 - iii) In what form is energy from foodstuff (protein , CHO and fat available to the cell)

2. State three ways in which the following can achieve movement.
 - i) Flagella - sperm cell, euglena, Trypanosoma.
 - ii) Cilia e.g. euplates, epithelium cells of man, sensory organ cells, Retina cells
 - iii) Cytoplasmic streaming (flow) e.g. amoeboid flow - amoeba, slime mould, protozoa, white blood cells (macrophages), plant cell.
3. Differentiate between Cilia and Flagella.

11.3 DNA Replication and cell cycle

Prokaryotic chromosome Replication.

- i) Bacterial chromosome DNA replicates once in about 40 minutes.
- ii) Replication is semi conservative.
- iii) Replication is bidirectional.



- iv) Bacterial replication contains a single replicon.
- v) Bacterial DNA measures about 1100 nm in circumference.
- vi) If a single replication takes 40 minutes, then the rate of replication is about 30nm per minute or 10,000 turns per minute.
- vii) To prevent stress or double helix molecules nuclear, make single strand breaks on DNA molecule permitting a more localized unwinding.
- viii) Breaks are later repaired by DNA ligase enzyme.
- ix) Replicating chromosome is thought to be closely associated with plasma membrane for enrichment e.g. nuclear region (nucleoid) in bacterial is associated with mesosomes (invagination of the plasma membrane).

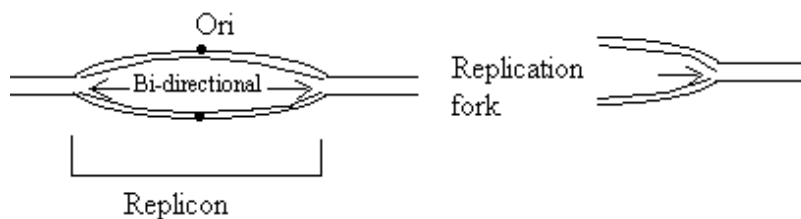
Factors that trigger initiation of DNA replication.

- i) Specific DNA sequence which a 850bp specific has been identified as the site of start of chromosomal DNA replication.
- ii) Some proteins have been implicated to trigger the start.

iii) These proteins only initiates the replication but are not necessary for elongation.

Eukaryotic chromosome Replication.

- i) Replication of Eukaryotic chromosome is complex because of:
 - a) Large volume of DNA
 - b) Disassembling and reassembling of nucleosomal organization of Eukaryotic chromatin at replication site.
- ii) Replication of Eukaryotic DNA is semi conservative (similar to prokaryotes).
- iii) Chromatids are newly replicated chromosomes but remain held (daughter chromatids) together by - centromere.
- iv) Eukaryotes have a multiple replication sites within each DNA molecules forming multiple replicons.
- v) Replication is bidirectional forming replication fork.



vi) When replication fork meet each other, DNA is spliced (joined) by DNA ligase to form new chromosomal DNA molecule.

Reasons of many Replicons

- i) Eukaryotic DNA is in more than one chromosome situation that demands more replicons.
- ii) Large amount of DNA in Eukaryotic chromosomes than in prokaryotic chromosomes.
- iii) Slow rate of DNA replication in Eukaryotes than in prokaryotes i.e about 0.5 nm/min in eukaryotes compared to 30 nm/min in prokaryotes (Bacteria).

Unwinding of DNA

- i) Catalysed by helicase enzyme.
- ii) Unwinding is very fast – about 100rpm.

Unwinding process in prokarytes

- i) Unwinding causes supercoiling on the replicon.
- ii) In bacteria enzymes topoisomerase I cleave the DNA strand to remove (reduce) supercoiling and reduce stress.
- iii) New bases are attached by complementary pairing and then joined upto each other lengthways by a new sugar phoshpate backbone.

- iv) Polymerisation - formation of new DNA chain.
- v) Polymerase enzymes (many) catalyse polymerisation.
- vi) In prokaryotes, there is double checking of added bases to ensure correct (accurate) addition.
- vii) Double check: a) if wrong base is added, DNA polymerase does not continue to add bases.
b) if wrong base is added, it is hydrolysed and removed and correct one is added.

NB – this way mutation is very rare in bacterial DNA. Error of base addition is 1 per 10^{10} bp.

To initiate DNA synthesis, RNA primers are synthesized by RNA polymerase, then DNA polymerase takes over to add bases to lengthen the chain.

Later, RNA primers are recognized by their ribose instead of deoxyribose backbone sugar and they are removed by RNase (Hydrolysis).

In Eukaryotes

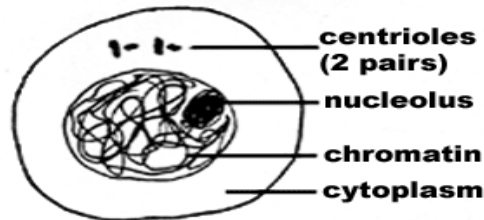
- i) Consist of many replicons
- ii) Supercoiling - it's not understood how it is removed.
- iii) Polymerisation is done by DNA polymerase.
- iv) RNA primer is required to initiate polymerization which is later hydrolyzed by RNase.
- v) Double check like the one found in Prokaryotic replication is missing but check for defects continue even after completion of replication.

NB – because of lack of check system, high rate of mutation is expected in Eukaryotes than in Prokaryotes. Replication is semi conservative and polymerization of bases is in 5 – 3 direction.

11.3 MITOSIS

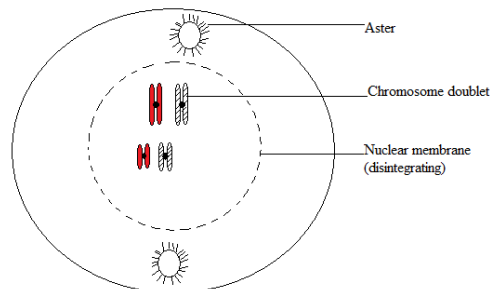
Events of cell mitosis

Interphase



- i) Chromosomes are extended and are not visible as different entities under light microscope.
 - ii) Are stretched out in the form of long chromatin threads swollen at intervals into visible chromatin granules.
 - iii) DNA divides.
 - iv) Accumulation of energy reservoirs.
 - v) Formation of cytoplasmic organelles – mitochondria, ribosomes, chloroplasts (in plants) e.t.c
- NB – Centrioles are found in animal cells and some primitive plants.

Prophase



- i) At start of prophase chromatids are elongated and are not visible under light microscope.
- ii) In late prophase chromatid fibres condense into distinct and visible chromosomes.
- iii) Chromatids remain joined by the centromere. Transcription of chromosomal DNA stops.
- iv) In animal cell, nucleoli disperse. In plant cell, it may disperse or remain as discrete entity.
- v) Assembly of mitotic spindles is initiated.
- vi) Cytoplasmic centrioles migrate to the opposite sides of the nucleus.

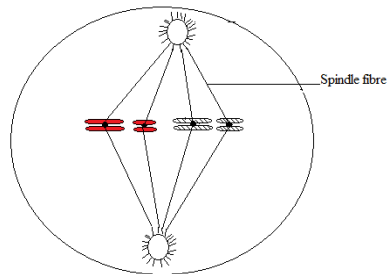
NB – centrioles contain microtubules.

- vii) Short microtubule radiate in all directions of the centrioles forming structures called asters.
- viii) Larger microtubules to form the spindle apparatus begin to assemble between the opposites pairs of centrioles.
- ix) Nuclear envelope breakdown (disappears) making the end of the prophase.

Metaphase

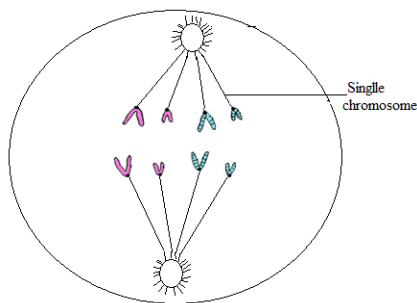
- i) Begins when the envelope has completely disappeared.

- ii) Nucleoplasm and have mixed with the cytoplasm.
- iii) Spindle fibres radiate from opposite sides of the cell to form spindle apparatus.
- NB – spindle fibres 25nm in diameter and consist of microtubules made of special protein called tubulin.
- iv) In animals, fungi and lower plants centriole located at each pole is involved in organising the spindle.
- v) higher plants do not have centrioles but do have spindle apparatus.
- vi) Spindles attach at the centromere of the chromosome.



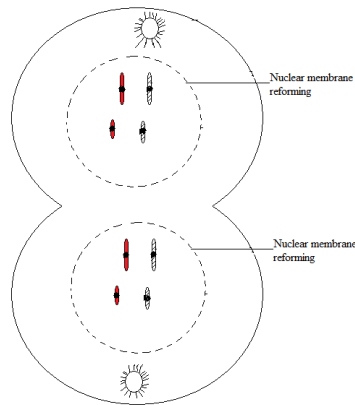
- vii) Chromosomes are aligned at the center of the cell or metaphase plate.
- viii) Centromere separates so that each chromatid has its own centromere.
- ix) One centromere is attached to microtubule coming from one pole and the other attached to the microtubule from the opposite pole.
- x) Chromatids are still condensed

Anaphase



- i) Sister chromatid pairs undergo disjunction (separation). Now the sister chromatids are called daughter chromosomes.
- ii) Daughter chromosomes move toward the poles.
- iii) Two centromeres of the sister chromatid move (migrate) toward the opposite poles of the cell.
- vi) Chromosomes assume their characteristic shapes, related to the location of the centromere along the length of the chromosome.

Telophase

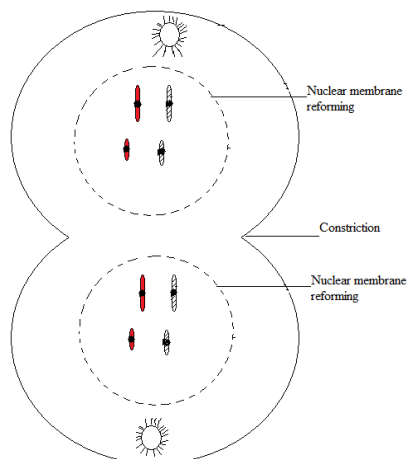


- i) Migration of daughter chromosomes to the opposite pole is completed.
- ii) The two sets of progeny chromosomes are assembled into two groups at opposite ends of the cell.
- iii) Chromosomes begin to uncoil and assume extended state characteristic of interphase.
- iv) Nuclear membrane forms.
- v) The spindle fibres disappear
- vi) Nucleoli reform.
- vii) The cell has two nuclei at this point.
- viii) DNA transcription resumes.

Cytokinesis

- i) Cytoplasm compartmentalizes the new nuclei into separate daughter cells and completes the mitotic cell division process.
- ii) Cytokinesis in animals
- iii) Constriction or furrow forms at the middle of the cell until the two daughter cells separate. Actin and myosin generate the forces for cleavage.

Cytokinesis in animals



Cytokinesis in plants cells

New cell membrane and cell wall (called cell plate) form between the two new nuclei.

11.4 MEIOSIS

Result to division diploid nucleus resulting to formation of haploid gametes (gametogenesis).

Analogous chromosome pair replicate once – undergo assortment - two meiotic division - haploid cells.

Two nucleus division

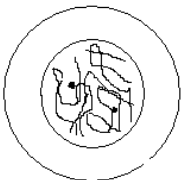
Meiosis I – result in reduction of number of chromosomes.

Meiosis II - result in separation of the chromatids.

Meiosis I

Prophase I

i) Leptonema (Leptotene)



- replication of chromosomes
- condensation of chromosomes have stopped and are visible.
- number of chromosomes equal that in diploid cells
- chomomeres appear (these are small thickened areas along the chromosome which give appearance of bead necklace)

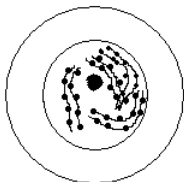
NB – once the cell enters Leptonema , it is committed for cell division.

ii) Zygonema(Zygotene)



- homologous chromosomes begin to pair in highly specific way and twist around one another. The two members are called homologs.
- synapsis – is this chromosome pairing.
- each synapsed set of homologous chromosome consist of four chromatids and is referred to as Tetrad.

iii) Pachynema (Pachytene) (meaning thick like)



- Nucleoli are pronounced
- Chromosomes become shorter and thicker.
- Chromosomes are intimately synapsed.
- Cross over takes place - physical exchange of chromosomes takes place.
- Crossing over can create new gene recombination in a chromatid.

NB – there is no loss or addition of genetic material to either chromosome since crossing over usually involves reciprocal exchanges.

- Crossing over results to formation of synaptonemal complex.

- Synaptonemal complex - is zipper-like structure involving four chromatids.

- Recombination / recombinant chromosome - is a chromosome which result from meiosis in a gene combination different from the original combination.

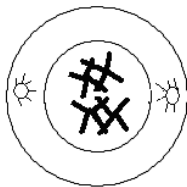
- Crossing over result to genetic recombination.

iv) Diplonema (Diplotene)



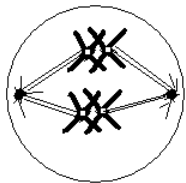
- chromosomes start to rebel one another and tend to move apart.
- chiasma (chiasmata - plural) forms.
- chiasma - this is a cross shaped structure formed in diplonema.
- NB - in most organisms , diplonema is followed quickly by remaining stages.
- in some animals e.g animal oocytes can remain in diplonema for a long time.

iv) Diakinesis



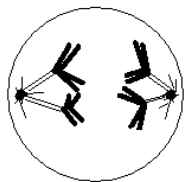
- chromatids of each tetrad are more condensed.
- chiasmata terminalise – they move down the chromosomes to the end.
- NB - chromosomes appear to be attached together at the tips .
- Nucleoli disappear and nuclear membrane begin to breakdown.

Metaphase I



- nuclear membrane has completely broken down.
- Nucleoli too has completely disappeared.
- Tetrad become aligned across the equatorial plane of the cell.
- Spindle fibres are completely formed.
- microtubules are attached to the centromere regions of the homologous.

Anaphase I



- chromosomes in each Tetrad separate.
- chromosomes homologous pairs (dyads) disjoin and migrate towards opposite poles.
- maternally and paternally deneved homologous are segregated (apart from chromosome parts exchanged during cross over process).
- the sister chromatids that segregate remain attached to each other at the

centromere.

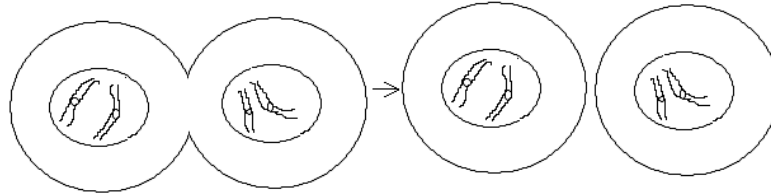
Telophase I



- varies in length among species.
- dynad complete their migration to the opposite poles of the cell.
- new nuclear membrane may form.
- Cytokinesis follow producing two cells each with one nucleus.
- in each nucleus the number of chromosomes are reduced to diploid.
- cell may enter interphase (interkinesis).

Cytokinesis

NB: In some organism this does not exist and cell quickly move to meiosis II. In others cytokinesis follow and nucleus membrane form before the meiosis II. The Meiosis I is called reduction division because it reduces the number of chromosomes by a one-half. The meiosis II is called equational division .

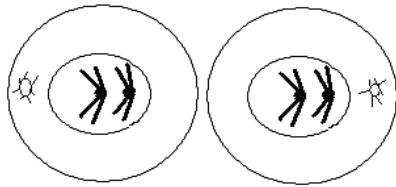


Meiosis II (second meiotic division)

- second meiotic division – similar to a mitotic division.

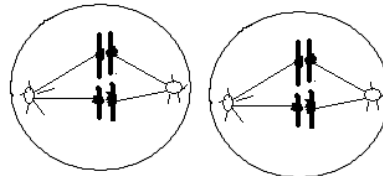
Prophase II

- Chromosome contraction takes place.
- NB – does not occur in all organisms.

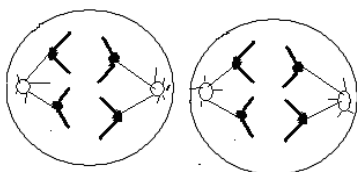


Metaphase II

- Centromere divides.
- Organisation of spindle apparatus which attach to the centromere.
- Centromere line up on the equator of the second division spindle.



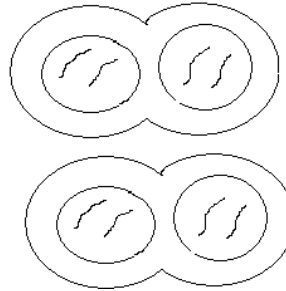
Anaphase II



- Centomere and chromatids are pulled to the opposite poles of the spindle.
- one sister chromatid of each pair goes to one pole while the other goes to the opposite pole.

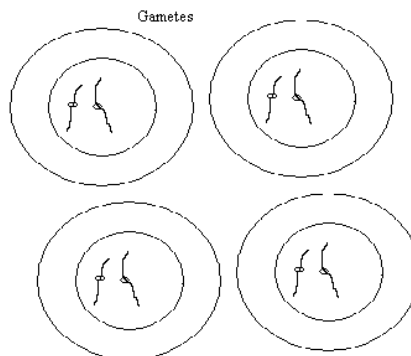
Telophase II

- Nuclear membrane forms around each set of chromosome.



Cytokinesis

- follow after telophase II
- chromosomes become extended in their interphase



NB - between Meiosis I and Meiosis II, there is no chromosome replication. Therefore, after Meiosis II there are four haploid cells from the original diploid cell.

Each of the four progeny cells has one chromosome from each homologous pair of chromosomes.

The chromosome in the four haploid cells are not exact copies of the original chromosomes because of the crossing over that occurs between chromosomes during pachynema of Meiosis I

Genetic significance of Meiosis.

1. Meiosis results to haploid cells - through fertilization, diploid state of the cells is restored .
2. During metaphase I of Meiosis each maternally and paternally derived chromosome has an equal chance of aligning on one side of the equatorial metaphase place. As a result , each nucleus generated by Meiosis will have a combination of maternal and paternal chromosomes
3. crossing over of chromosomes brings about variation in the final combination - this results into genetic recombination.

Question

1. Explain the usefulness of mitosis to a tea farmer
2. Discuss the utility of Mitosis in hybrid seed production
3. Bacteria has about one hour cell division cycle compared to 24 to 36hours division cycle in Eukaryotes. Explain the advantages of using bacteria in industrial production.
4. Using prophase I of cell division cycle explain the diversity of species.
5. Describe the importance of S-phase in cell division