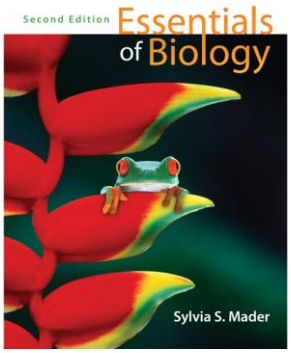
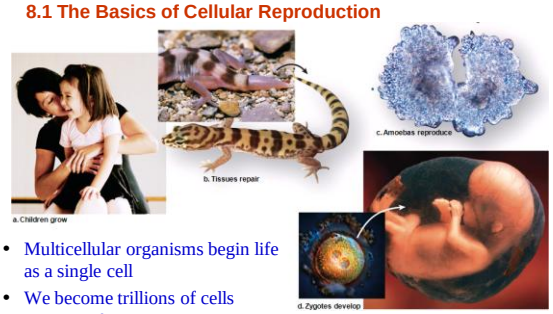


Essentials of Biology

Sylvia S. Mader

Chapter 8
Cellular Reproduction: Mitosis
Lecture Outline

8.1 The Basics of Cellular Reproduction



- Multicellular organisms begin life as a single cell
- We become trillions of cells because of cellular reproduction
- Continues as we grow and replace worn-out or damaged tissues

Figure 8.1 Cellular reproduction

Cellular Reproduction

- **Things that must happen before a cell divides:**

In the nucleus

1. _____

Cell organelles

2. _____

- **What must happen to the chromosomes during cell division?**

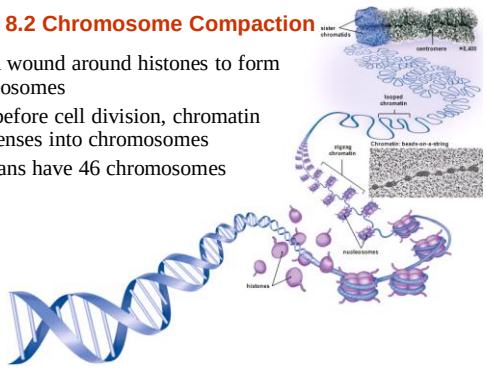
3. _____

- **What's a chromosome??**

- Chromatin
  - DNA and associated proteins have appearance of thin threads
- Chromosomes
  - DNA packaged into chromosomes
    - Thickened complex of DNA and proteins
    - Allows easier distribution to daughter cells

Figure 8.2 Chromosome Compaction

- DNA wound around histones to form nucleosomes
- Just before cell division, chromatin condenses into chromosomes
- Humans have 46 chromosomes



Replication of DNA

- Duplicated chromosomes composed of sister chromatids joined at centromere
  - **Each sister chromatid has identical DNA**

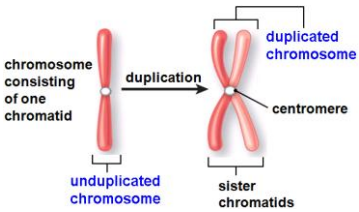
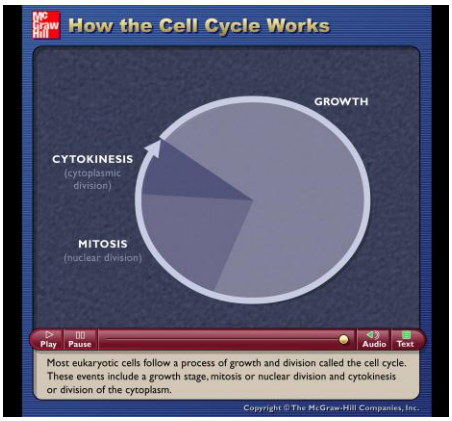


Figure 8.4

8.2 The Cell Cycle

- The orderly cycle from cell division to cell division
- Consists of 4 phases or stages….



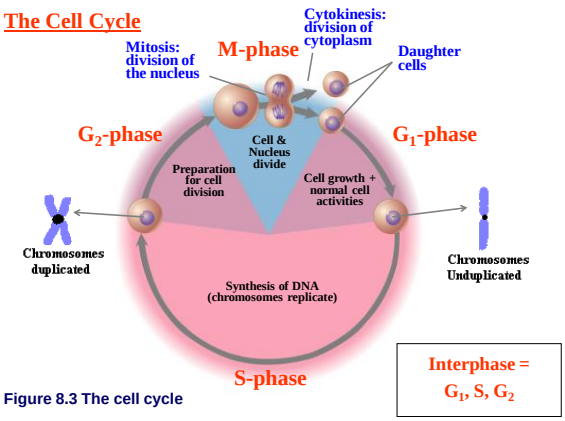


Figure 8.3 The cell cycle

The 3 Stages of Interphase

- **G_1 – stage before DNA replication**
  - Cell doubles organelles
  - Accumulates materials for DNA synthesis
  - Makes decision whether to divide or not
  - G_0 – arrested – does not go on to divide
- **S – DNA synthesis**
  - Results in each chromosome composed of two sister chromatids
- **G_2 – stage following DNA synthesis**
  - Synthesizes proteins needed for cell division

How long does G_1 Last?

G_1 can vary greatly

a. **Can last indefinitely**
   - e.g. Liver & kidney cells
b. **Can live months to years w/o dividing**
   - e.g. Nerve & muscle cells
   - Usually never divide (G_o)

8.3 Mitosis and cytokinesis

- Mitosis: Separates sister chromatids into 2 nuclei

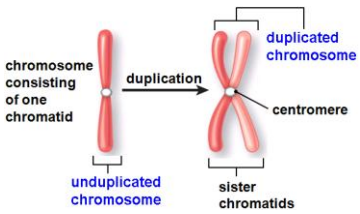
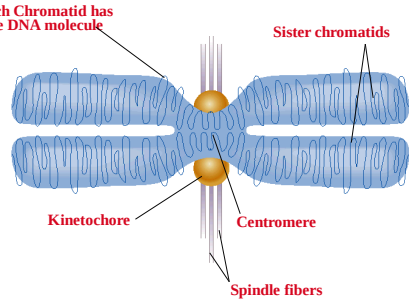


Figure 8.4 Overview of mitosis

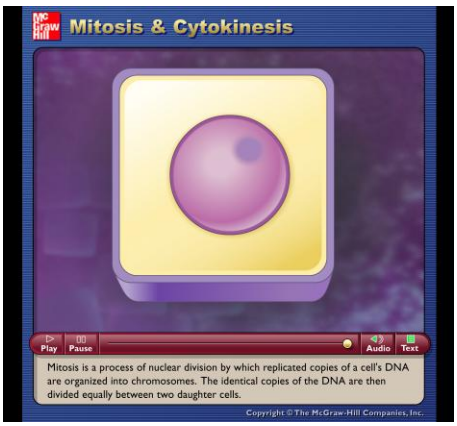
Sketch of a duplicated chromosome

1. How do sister chromatids compare genetically?
2. What happens to sister chromatids during mitosis?



Cell Division

- Cell division consists of two parts...
  - Division of nucleus (mitosis)
    - Creates two identical daughter nuclei
    - What needs to happen to the chromosomes….
      - Prior to mitosis?
      - During mitosis?
  - Division of cytoplasm (cytokinesis)
    - Creates to cells



- Mitosis is a continuous process
- Traditionally divided into 4 phases
  - Prophase
  - Metaphase
  - Anaphase
  - Telophase

Figure 8.5 Mitosis in a Plant Cell

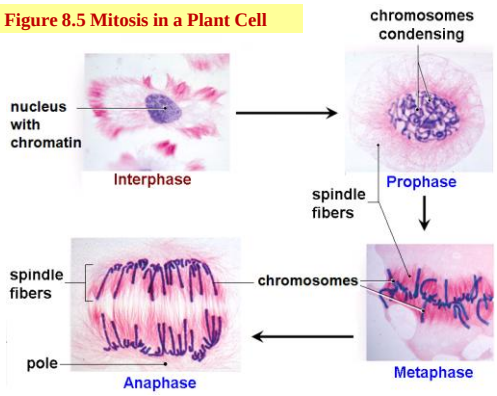
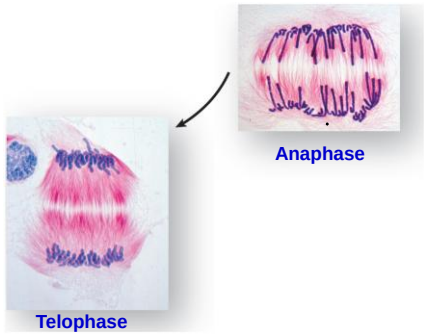


Figure 8.5 Mitosis in a plant cell (continued)



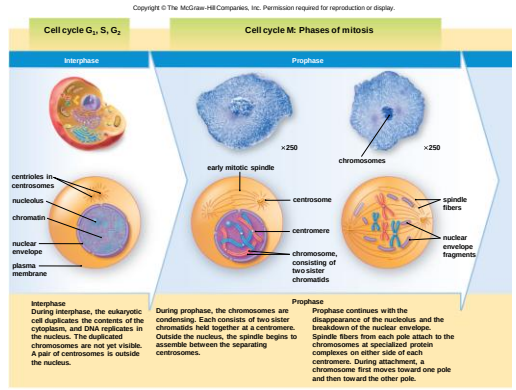


Figure 8.6 Phases of mitosis in animal cells

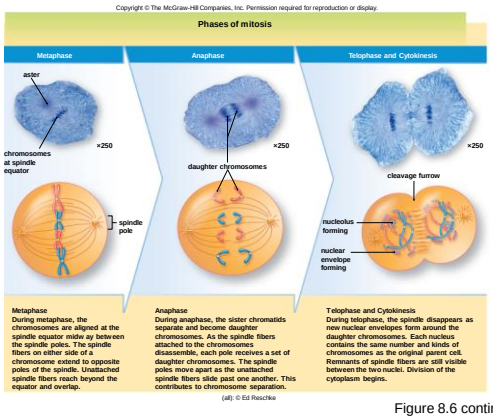
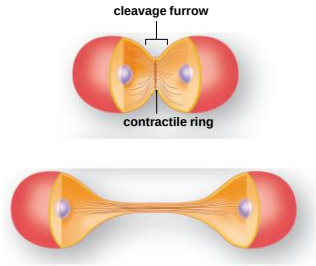


Figure 8.6 continued

Figure 8.7 Cytokinesis in animal cells

- Cleavage furrow forms as anaphase ends
  - **What prevents a cleavage furrow in plants?**
- Accompanies mitosis in most but not all cells
- **What is the result if Mitosis occurs *without* cytokinesis?**
  - **Muscle cells** in vertebrate animals
  - **Embryo sac** in flowering plants



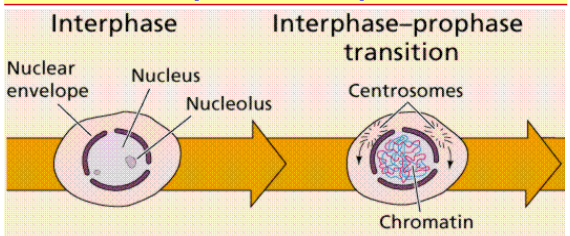
Modeling Mitosis w/ Pipe Cleaners for a cell with 3 pairs of Chromosomes

1. 3 pairs of chromosomes: 2n = 6
   - **Diploid Number ??**
   - **Haploid Number ??**
2. What does one pipe cleaner represent?
3. How do you represent a duplicated chromosome?
4. What do the colors represent?
5. What are Homologous chromosome?
6. What do the different sizes represent?

Modeling the Cell Cycle for a Cell containing 3 pairs of Chromosomes

- **Go through entire process: S → G2 → M → G1**
- **Ask each other these questions as you model mitosis**
  1. **How many molecules of DNA does one pipe cleaner represent?"**
  2. **What do two pipe cleaners twisted together represent?"**
  3. **What do the chromosomes look like from this organism just before the S phase?**
     - **How many chromosomes are present?**
  4. **What do the chromosomes look like from this organism just after the S phase?**
     - **How many chromosomes are present?**
  5. **What is happen in the cell during each phase of the cell cycle?**

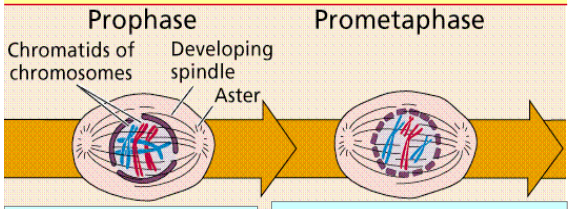
Interphase to Prophase



DNA is replicated in the nucleus

Chromatin begins to coil—makes it more compact

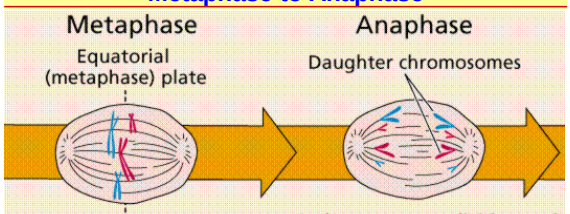
Prophase to Prometaphase



Chromatin continues to coil, making it more compact. Chromosomes are now visible: consist of identical, paired sister chromatids.

Nuclear envelope breaks down. Spindle fibers (microtubule proteins) attach to centromeres, resulting in movement of chromosomes.

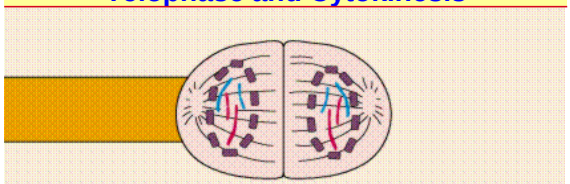
Metaphase to Anaphase



The duplicated centromere regions connecting paired chromatids become aligned in a plane atthe cell's equator

Each centromere divides, and the new chromosomes (each derived from one member of one of the sets of paired chromatids) begin to move toward the poles

Telophase and Cytokinesis

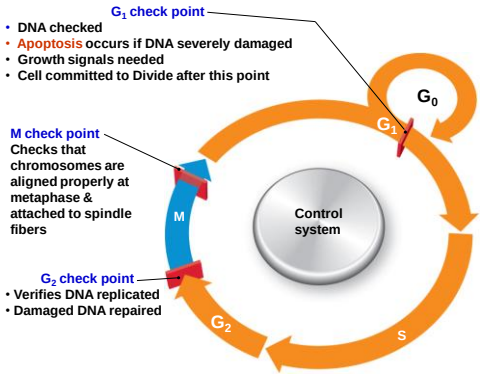


The separating chromosomes reach the poles. Telophase passes into the next interphase as the nuclear envelopes and nucleoli re-form and the chromatin becomes diffuse

8.4 The Cell Cycle Control System

- What is the consequence if the cell cycle is not controlled?
- Three Major Cell Cycle Checkpoints
  - G_1 checkpoint
  - G_2 checkpoint
  - Mitotic stage checkpoint

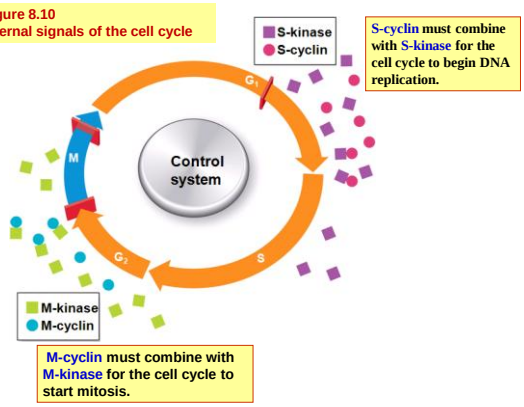
Figure 8.9 Major Cell cycle checkpoints



Control the Cell Cycle: Internal Signals

- **Signal** – a molecule that stimulates or inhibits an event
- External signals vs. Internal signals
- **Internal Signals**
  - **Kinases** removes a phosphate from ATP and add it to other molecules
  - **S-cyclin** must combine with **S-kinase** for S phase to occur (DNA replication)
  - **M-cyclin** must combine with **M-kinase** for mitosis to occur
- Cyclins are present only during certain stages of the cell cycle
- Destruction of cyclin at the appropriate time is necessary for normal cell cycle progression

Figure 8.10
Internal signals of the cell cycle



Control the Cell Cycle: External Signals

- **Epidermal growth factor (EGF)**
  - stimulates skin near an injury to finish cell cycle and repair injury
- **Estrogen** (a steroid hormone)
  - stimulates lining of the uterus to divide and prepare for egg implantation
- **Contact inhibition**
  - cells stop dividing when they touch.
- **Telomere Shortening**
  - Cells divide about 70 times and then become senescent or die
    - Senescent cells lack differentiation (i.e. lose normal function)
  - Due to shortening of telomeres
    - Telomere- repeating DNA sequence at end of chromosome

Apoptosis

- **Programmed cell death (cell suicide)**
  - **Remaining cell fragments engulfed by white blood cells**
  - **Unleashed by internal or external signals**
- **Benefits include…**
  - **Helps keep number of cells at appropriate level**
  - **Rids body of damaged or unneeded cells**
- **Normal part of growth and development**
  - **Tadpole tail**
  - **Webbing between human digits**
  - **Human lens**
  - **Peeling of skin after a sunburn**
  - **Menstruation in women**
  - **Metamorphosis in butterflies**

Figure 8.11 Apoptosis

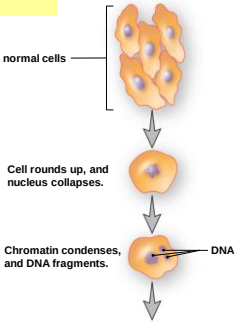
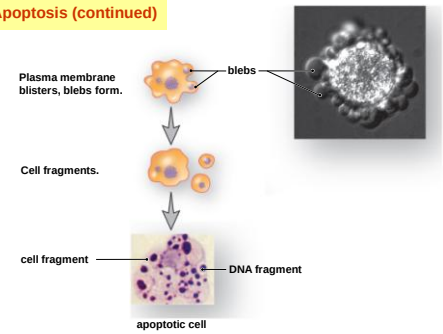


Figure 8.11 Apoptosis (continued)



8.5 Cell Cycle and Cancer

- Cell cycle regulated by signals that inhibit or promote cell cycle
  - Cancer may result from imbalance
- Cancer…
  - genetically dictated loss of cell cycle control
  - cancer cells cannot stop dividing
    - form a large mass of immortal cells
    - malignant tumor vs. benign tumor
- Cancerous cells arise in everyone!
  - Why doesn't everyone get cancer?

Obituary brings to light the tragedy of one local family

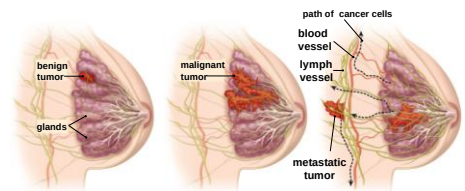
A letter to the Editor of the *Enumclaw Courier Herald*

Wednesday, March 9, 2005

Did anyone pay close attention to the obituary of Laura Ann Maples that appeared in last week's Courier-Herald? Laura is the daughter of a friend and former co-worker of mine, Elden Jones. Take another look at that obituary. This beautiful young lady died of breast cancer on Feb. 10, 2005, at the age of 39.

Figure 8.12 Development of Breast Cancer

Development of breast cancer and metastatic tumors



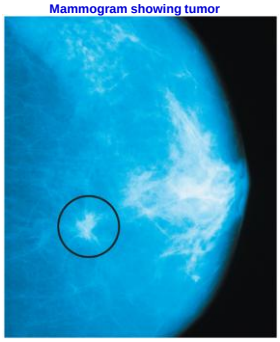
A *single cancer cell* grows into a tumor.

The tumor becomes malignant and invades nearby tissue.

Cancer cells travel (dotted arrows) through lymphatic (green) and blood (red) vessels, and metastatic tumors form.

Figure 8.12 Development of Breast Cancer (cont.)

Mammogram showing tumor



Brief Comparison of Normal vs. Cancer Cells

Table 12.1 | Normal Cells Compared to Cancer Cells

Normal Cells	Cancer Cells
Contact inhibition	No contact inhibition
Controlled growth	Uncontrolled growth (tumor)
Specialized cells	Nonspecialized cells
Normal chromosomes	Abnormal chromosomes
Undergo apoptosis	No apoptosis

Six Characteristics of Cancer Cells

1. No Contact inhibition
   - continue growing and moving when they touch other cells.
   - Pile up to form tumors
2. Metastasize
   - Cancer cells migrate to other parts of the body – the cancer spreads ⊗
3. Lack differentiation (i.e. non-specialized cells)
   - do not contribute to body function
4. Immortal – can divide and live forever!
   - Do not undergo apoptosis!
5. Angiogenesis
   - Secrete growth factor to cause blood vessels to grow into cancerous tissue. Significance?
6. Have Abnormal Nuclei
   - abnormal number of chromosomes

Contact Inhibition

1. Cells do not normally grow or divide when in contact w/ other Cells
   - E.g. Cultured cells in a petri dish divide until they form a layer one cell thick and then stop when make contact w/ other cells.
   - Called contact inhibition of cell growth
2. Cells may migrate in culture.
   - Stop moving when touch other cells due to contact inhibition of cell movement.

← Back

Normal Skin Cell Growth vs. Basal Cell Carcinoma

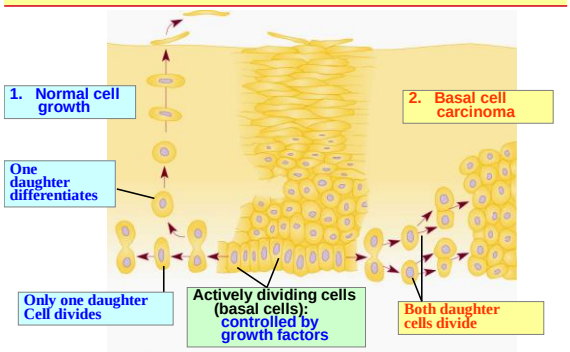


Figure 12.14 Development of Cancer

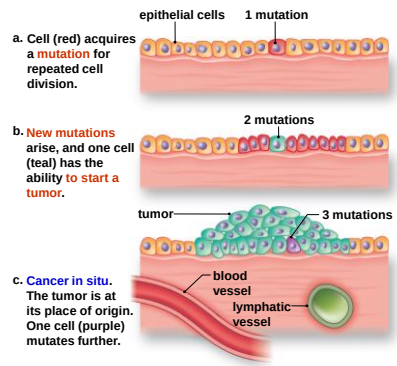
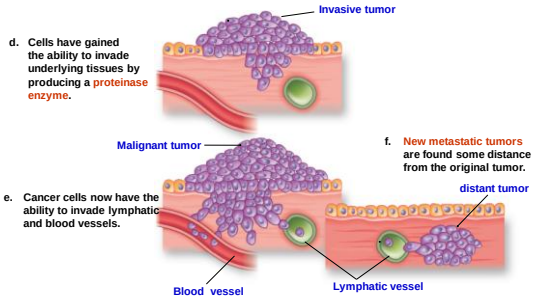


Figure 12.14 Development of Cancer (cont.)



Now….. Let's study the genes involved!

12.2 Cancer—A Loss of Genetic Control

- Cancer is a genetic disease.
- Takes years for cancer to develop. Why?
- Likelihood of cancer increases with age. Why?
- Requires mutations to genes that regulate the cell cycle.
- The major regulatory genes…
  - Growth Factor Genes (the "on switch" or "gas pedal")
    - Proto-oncogenes
    - Oncogenes
  - Tumor Suppressor Genes (the "off switch" or the "brakes")

Cancer: It's all in the Genes

1. ☺ Proto-oncogenes ☺ (like a gas pedal)
   - ☺ Normal genes that stimulate cell division
   - Inhibit apoptosis
   - Active in actively dividing tissues
     - ✓ e.g. skin, blood stem cells, hair follicle cells., etc.
   - Sometimes mutate into.....
2. ☹ Oncogenes ☹ (like a Camry's gas pedal??)
   - Constantly on – do not get turned off!
   - Over stimulate mitosis
   - Consequence??
   - Oncogenes are rarely inherited.....Why?

Figure 12.15 Regulation of the cell

- **Growth factor**
  - activates a cell-signaling pathway
- **Activated Signaling Protein**
  - Activates proto-oncogene
  - Stimulates cell division

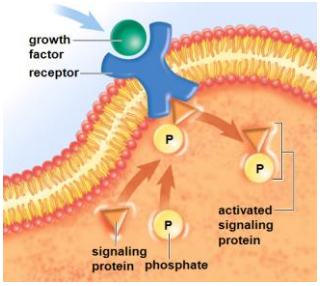
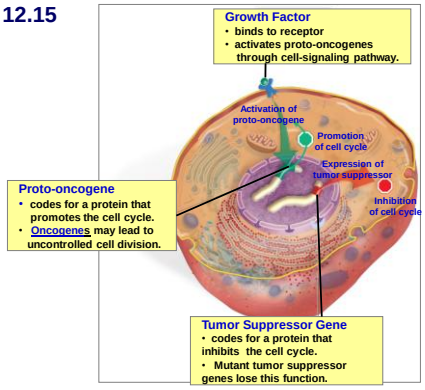


Figure 12.15



☺ Proto-Oncogenes can Mutate into Oncogenes ☹

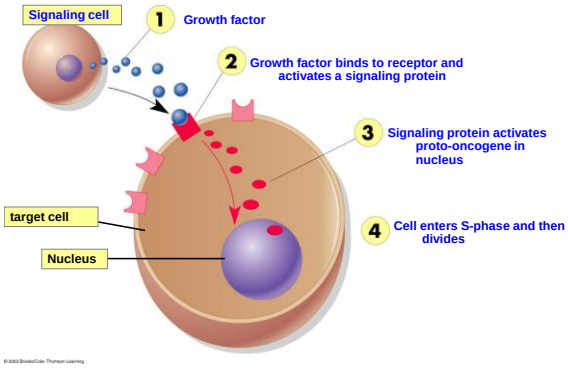
A common Example…

- ***Ras* proto-oncogenes ☺**
  - promote mitosis
  - Activated when growth-factor binds to a receptor.
- ***Ras* oncogenes ☹**
  - Permanently turned on
  - promote mitosis even when growth factors are not present.
  - Found in 20-30% of human cancers

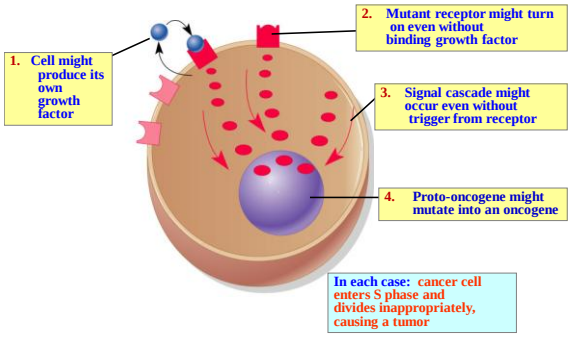
Growth Factors: Stimulate Cell Division

1. Chemical messengers produced in one part of the body, but effect cells elsewhere
2. Bind to Membrane Receptors, like a key fitting into a lock.
   - Stimulates a cell to divide by activating proto-oncogene
3. Each receptor binds to a different growth factor.
4. Different cell types are stimulated by different growth factors.

Growth control in a normal cell



Different ways to get faulty growth control in a cancer cell



Tumor Suppressor Genes

Tumor suppressor genes

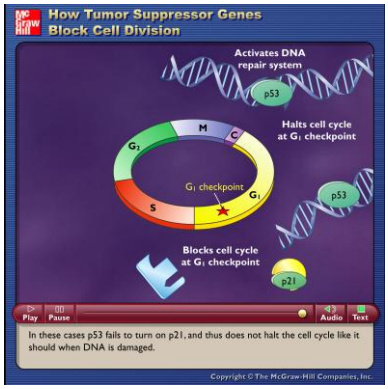
- Code for proteins that inhibit cell cycle
  - Like a car's _____??_____
- Prevent cells from dividing inappropriately
  - Stop cells from entering the S-phase
- Promote apoptosis in cells with damaged DNA

Mutant tumor suppressor gene

- Does not inhibit cell cycle nor promote apoptosis.
  - Significance??

P53 Gene—a Tumor Suppressor Gene

1. **p53 Gene → codes for p53 protein**
   - p53 protein stops the cell cycle in G_1
   - Half of all cancers involve a mutated p53 gene
2. One mutant Tumor Suppressor Gene does *not* cause cancer....Why?
   - How many p53 genes did you inherit? Why?
   - How many p53 genes need to mutate before a cell becomes cancerous? Why?



- **RB gene**
  - **Tumor suppressor gene**
  - Causes eye tumor: **retinoblastoma**
  - Usually only in one eye. Why?
    - How many RB gene mutations are needed?
  - If you inherit a mutated allele it's more likely to have tumors in both eyes. Why?
- **RET gene**
  - **Proto-oncogene** inherited in an autosomal dominant manner
  - Predisposition to thyroid cancer

Figure 12.18 Inherited retinoblastoma

Figure 12.17 Breast cancer can run in families.

BRCA 1
Breast Cancer Susceptibility Gene

1. **BRCA 1** is a Tumor Suppresser gene
2. If a women inherits BRCA 1 she has a
   a. **80 to 90%** chance of developing breast cancer
   b. **40 to 50%** chance of ovarian cancer.
   c. **Why aren't the percentages 100%?**
   d. **Why are the percentages much lower for the average woman?**

- Testing for these and other genes
  - Genetic are tests available for *BRCA* genes, *RET* gene and *RB* gene.
  - Genetic tests are also available for other types of mutated genes that help a physician diagnose cancer.
  - Test for the presence of telomerase

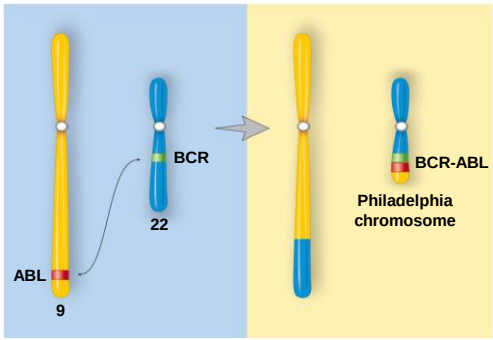
- **Cancer-causing alleles**
  - In 1990, DNA studies revealed the first gene allele associated with breast cancer was ***BRCA1.***
  - Later ***BRACA2*** discovered
  - Both alleles are **mutant tumor suppressor genes** that are inherited in an **autosomal recessive manner**.
  - If one mutated allele is inherited, a mutation in the other allele is required for the predisposition of cancer to increase.
  - Because the first mutated allele is inherited, it is present in all body cells.
  - **Cancer is more likely wherever the second mutation happens.**

- **Other genetic changes**
  - **Absence of telomere shortening**
    - Repeating DNA sequence at the end of the chromosomes
    - Promote chromosomal stability
    - Each time a cell divides the telomeres get shorter.
    - **Telomerase** rebuilds telomeres and is turned on in cancer cells.
      - **Telomerase gene is only active in what two kinds of cells?**
    - Cells can divide over and over again.

Chromosomal rearrangements may lead to cancer

- Translocation – portion of chromosome may break off and reattach to another chromosome.
- May disrupt genes that regulate cell cycle
- **Philadelphia chromosome: translocation between 9 and 22**
  - Causes nearly 95% of chronic myelogenous leukemia (CML), a bone marrow cancer

Figure 12.16
A translocation can create the Philadelphia chromosome.



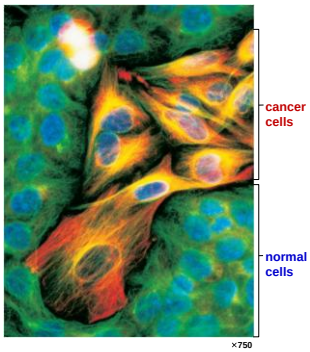
The Role of the Environment in Causing Cancer

1. Certain Viruses, toxins, or Radiation may lead to a p53 mutation
2. A 2nd p53 mutation may lead to <u>one</u> of the following cancers

Cancer of the....

Bladder, blood, brain, breast, colon, esophagus, liver, lung, spleen, thyroid, etc.

Figure 8.13 Cancer cells



- **Cancer treatment**
  - Either remove tumor or interfere with ability of cancer cells to reproduce
  - As rapidly dividing cells, they are susceptible to **radiation therapy** and **chemotherapy**
    - Damages DNA or some aspect of mitosis
    - Leads to side effects
  - **Hormone therapy** designed to prevent cells from receiving signals for continued growth and division

Therapeutic Strategies: Attack Actively Dividing Cells

- **Since cancer is uncontrolled cell division, all treatments involve the cell cycle.**
- **Phase-specific chemotherapies**
  1. **Prevent cells from entering S-phase**
  2. **Block the S-phase**
  3. **Block the M-phase (mitosis)**

Phase-specific Chemotherapies

1. **Prevent cells from entering the S-phase**
   - **Block Growth factor receptors on cell membrane with antibody (e.g. Herceptin)**
2. **Block the S phase**
   - **Methotrexate and other chemotherapeutic drugs block DNA synthesis**
3. **Block or stop mitosis**
   - **Taxol interferes with the movement of the chromosomes along spindle fibers**

Cells Affected by Chemotherapy

1. May affect all rapidly dividing cells
2. Which cells divide rapidly?
   a. **Hair follicle cells**
   b. **Skin cells**
   c. **Cells lining digestive tract**
   d. **Blood stem cells**
      - Divide to produce???

So.... What would be the side effects?

Side Effects of Chemotherapy

1. Lose hair
2. Wounds don't heal well
3. Destroy lining of digestive tract
   - nausea and severe bacterial infection
4. Decrease Blood cell Production
   - RBC's ➔ Anemia
   - WBC's ➔ decreased ability to fight infections and kill cancer cells

Summary of the Characteristics of Cancer Cells

1. **Immortal**
2. **Metastasize: Spread into other tissues**
3. **Not subject to contact inhibition**
4. **Have lost the genetic ability to stop dividing – mutations to...**
   - **Tumor Suppressor Genes (e.g. p53, BRCA1)**
   - **Growth factor Genes**
5. **Cancer is heritable: Cancer cells give rise to cancer cells**
6. **Are Dedifferentiated**
   - **less specialized than the cell it came from)**

- **Prevention of cancer**
  - **Protective diet**
    - Limit dietary fat (**concentrates artificial growth hormones**)
    - Weight loss can reduce cancer risk
      - **Fat cells produce estrogen** (a growth factor → increased risk of breast cancer
    - Eat plenty of fiber
      - Fiber speeds passage through digestive tract decrease risk of colon cancer
    - Increase consumption of foods rich in vitamins A and C
    - Avoid salt-cured or pickled foods (contain nitrites)
    - Include cabbage family members in the diet

Figure 8.14 The right diet helps prevent cancer

Prevention of cancer

- **Protective behaviors**
  - Avoid smoking – accounts for about 30% of all cancer deaths
  - Avoid sun exposure – major factor in development of most dangerous type of skin cancer, melanomas
  - Heavy drinkers prone to particular cancers
  - Exercise regularly
    - Stimulates production of **SOD** and **Catalase**
  - **Learn to recognize the warning signs of cancer**

Common Warning Signs of Cancer: C.A.U.T.I.O.N.

C - change in bowel or bladder habits

A - a sore that does not heal

U - unusual bleeding or discharge

T - thickening or lump in the breast or any part of the body

I - indigestion or difficulty swallowing

O - obvious change in a wart or mole

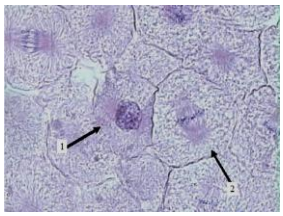
N - nagging cough or hoarseness

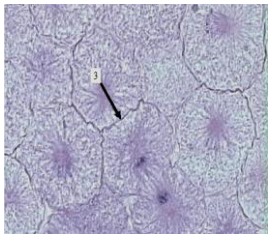
Mitosis and Meiosis Practice Problems

1. The phase of ***mitosis*** in which sister chromatids are separated is called
   A. prophase. B. metaphase.
   C. anaphase. D. telophase.
2. The phase of ***mitosis*** in which chromosomes condense is called
   A. prophase. B. metaphase.
   C. anaphase. D. telophase.
3. The phase of ***meiosis*** in which the nuclear membrane is dismantled is called
   A. prophase I. B. anaphase I.
   C. prophase II. D. metaphase II.
4. The phase of ***meiosis*** in which sister chromatids are separated is called
   A. metaphase I. B. anaphase I.
   C. anaphase II. D. metaphase I
5. Most of the problems with chromosome numbers in cells are a result of
   A. alcohol. B. U.V. light
   C. non-disjunction. D. mitosis
6. List four differences between mitosis and meiosis.
7. Cite two ways that allow for genetic variation in an organism from meiosis.

Mitosis Practice Problems

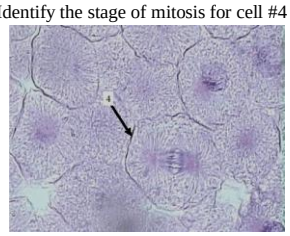
1. Identify the stage of mitosis for cell #1 below.
2. Identify the stage of mitosis for cell #2 below.
3. Identify the stage of mitosis for cell #3 below.
4. Identify the stage of mitosis for cell #4 below.





Mitosis Practice Problems

1. Identify the stage of mitosis for cell #4 below.



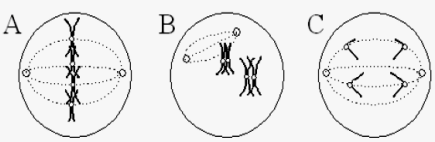
2. A diploid cell is one that
   a. has two homologues of each chromosome.
   b. is designated by the symbol 2n.
   c. has chromosomes found in pairs.
   d. All of the above

Mitosis and Meiosis Practice Problems

1. During ***anaphase of mitosis*** in humans or other diploid organisms, how many chromatids does each chromosome have as they move toward the poles?
2. During ***anaphase I of meiosis***, how many chromatids does each chromosome have as they move toward the poles?
3. During ***anaphase II of meiosis***, how many chromatids does each chromosome have as they move toward the poles?.
4. A student is simulating ***meiosis 1*** with chromosomes that are red long and yellow long; red short and yellow short. Why would you not expect to find both red long and yellow long in one resulting daughter cell?
5. If there are 13 pairs of homologous chromosomes in a pre-sperm cell, how many chromosomes are there in a sperm? How many chromatids?

Mitosis and Meiosis Practice Problems

Below are three dividing cells. Assuming that all three cells come from the same species, use the fir below each cell to tell whether this is mitosis, meiosis I, or meiosis II and the second blank to tell wh of mitosis or meiosis the cell is in.

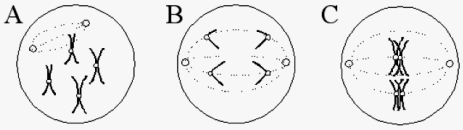


division: _____ _____ _____

stage: _____ _____ _____

Mitosis and Meiosis Practice Problems

The figure below shows three cells in the process of division. If no additional information is given, can you tell what kind of division is occurring? Fill in the first blank under each cell with mitosis, meiosis I, or meiosis II. If there is more than one possibility, list all of them. Then fill in the second blank to indicate the stage (phase) of mitosis or meiosis that this cell is in.

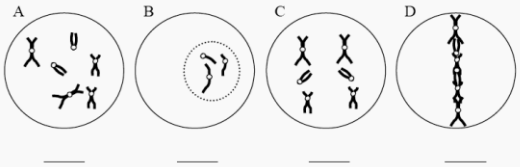


division: _____ _____ _____

stage: _____ _____ _____

Mitosis and Meiosis Practice Problems

5. The cells below come from the same organism and are in the process of cell divison:



_____ _____ _____ _____

a. What is N for this organism?
b. Circle the letter of each cell that could be either a germ cell or a gamete.
c. In the blank below each cell, place one of the following letters: **I** for **I**nterphase, **P** for **P**rophase, **M** for **M**etaphase, **A** for **A**naphase or **T** for **T**elophase.

Control of Cell Cycle and Cancer Practice Problems

- What role do each of the following play in controlling the cell cycle and in cancer?
  1. Proto-oncogenes
  2. Oncogenes
  3. Tumor Suppressor genes
  4. Growth factors
  5. p53 gene
  6. BRCA 1 gene