Lecture 4C:
Cancer Terminology and Mechanisms
The Multistep Nature of Carcinogenesis
Metastasis
Grading and Staging of Cancer
Cancer Treatment
Risk Factors and Etiology

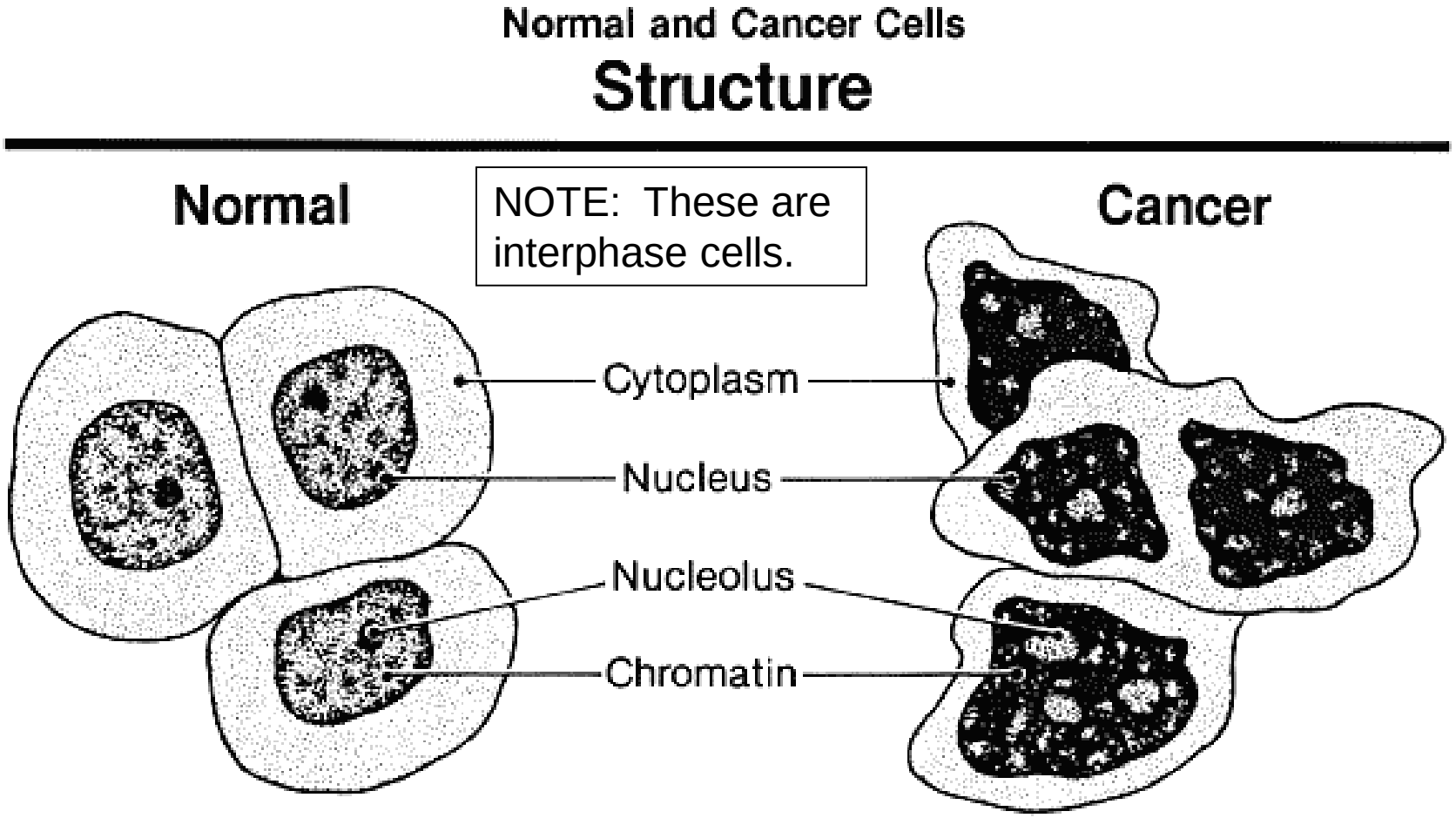
Cancer Terminology and Mechanisms

- **Neoplasia** means “new growth” and may be used interchangeably with the term “tumor”.
  - All of the cells in a tumor are produced (by mitosis) from a single “cell of origin”
- It is of critical importance to determine whether a tumor is benign or malignant.
- A **malignant** tumor is equivalent to cancer.
- A **benign** tumor is not cancerous.
- Cancer is the **second leading cause of death in the US** among both men and women. Cardiovascular disease is #1.
- Cancer is associated with the altered expression of cellular genes.
- Most cancers occur in **somatic cells** and thus are **not heritable**.

Cancer Terminology and Mechanisms

- A malignant tumor has the potential to kill the host if left untreated
  - A benign tumor does not, unless it blocks an airway or a blood vessel.
- Malignant tumors have “nomadic” cells. They **invade** adjacent tissues and may metastasize. Metastasis occurs when tumor cells enter lymphatic or blood vessels and travel to other parts of the body to invade distant tissues.
  - Benign tumors **do not invade** adjacent tissue or metastasize; most are encapsulated in connective tissue.
- Malignant tumor cells display **anaplasia**, an absence of tissue-specific differentiation (cell maturation). Differentiation occurs by turning some genes off and other genes on. When a gene is turned on, it means that it is transcribed and translated. Tumor cells are immature! They express (transcribe and translate) genes that they shouldn’t.
  - Benign tumor cells are generally normal, mature cells that undergo mitosis at a higher-than-normal rate.
- Histologically malignant tumors cells are characterized by large, darkly-staining nuclei and nucleoli. Multiple nuclei and nucleoli may be seen. The cytoplasm is sparse and may be either darker or lighter than normal in color.
  - Benign tumor cells closely resemble their cell type of origin (eg. skin, liver).
- Malignant tumors are **highly vascularized**, frequently have necrotic areas, and their cells are dysfunctional.
  - Benign tumors have **little vascularity**, rarely have necrotic areas, and often retain functions similar to those of the tissue of origin.

Cancer Terminology and Mechanisms



Cancer Terminology and Mechanisms

- Suffix –**oma** is used to indicate a **benign** tumor.
  - Lipoma-benign tumor in adipose tissue
  - Neuroma-benign tumor in neural tissue
  - Adenoma-benign tumor of glandular tissue
- **Exceptions to the "oma" suffix:**
- Lymphomas (lymphocytes), hepatomas(liver cells), melanomas (melanocytes of the skin) are highly malignant despite their –oma suffixes.
- **Carcinoma** denotes a **malignant** tumor of **epithelial** origin.
- **Sarcoma** denotes a **malignant** tumor of **mesenchymal** (connective tissue) origin.
- **Adenocarcinoma** denotes a **malignant** tumor of **glandular** tissue.
- **Leukemia** is the **malignant** growth of white blood cells.
- **90%** of human cancers are of epithelial origin. Epithelial tissue normally has the highest rate of mitosis of all tissue types.

Cancer Terminology and Mechanisms

- **Normal cells** proliferate (divide) only when:
  - Space is available.
  - Appropriate growth-stimulating signals are present.
- **Normal cells** proliferate according to a sequence of events:
  - **Growth factors** bind to growth factor receptors in cell membranes.
  - **Growth factor receptors** trigger cytoplasmic signaling molecules.
  - **Cytoplasmic signaling molecules** initiate pathways that transmit the "growth message" to the nucleus.
  - **Nuclear transcription factors** stimulate transcription of genes required for growth and cell division.
- **Normal cells** respond to signals that instruct them to undergo apoptosis.
- **Mutations are associated with cell division**. Gene mutations occur most often during DNA replication (S phase). Chromosomal defects (deletions, inversions, translocations, nondisjunction) are produced most often during anaphase of mitosis when the chromosomes are pulled away from the metaphase plate.

Cancer Terminology and Mechanisms

- Cancer cells exhibit **antisocial behavior**!
- They proliferate despite the lack of growth-initiating factors in their environment.
- They escape apoptosis signals and are capable of unlimited replication (immortality).
- They lose their differentiation (become less mature) and contribute little, if anything, to the functions of their tissue.
- They are genetically unstable. They accumulate new mutations at a higher rate than normal cells.
- They invade their local tissue, crowding neighboring cells and using more than their share of nutrients and oxygen.
- They invade adjacent tissues and may migrate to distant sites where they don’t belong (metastasis).

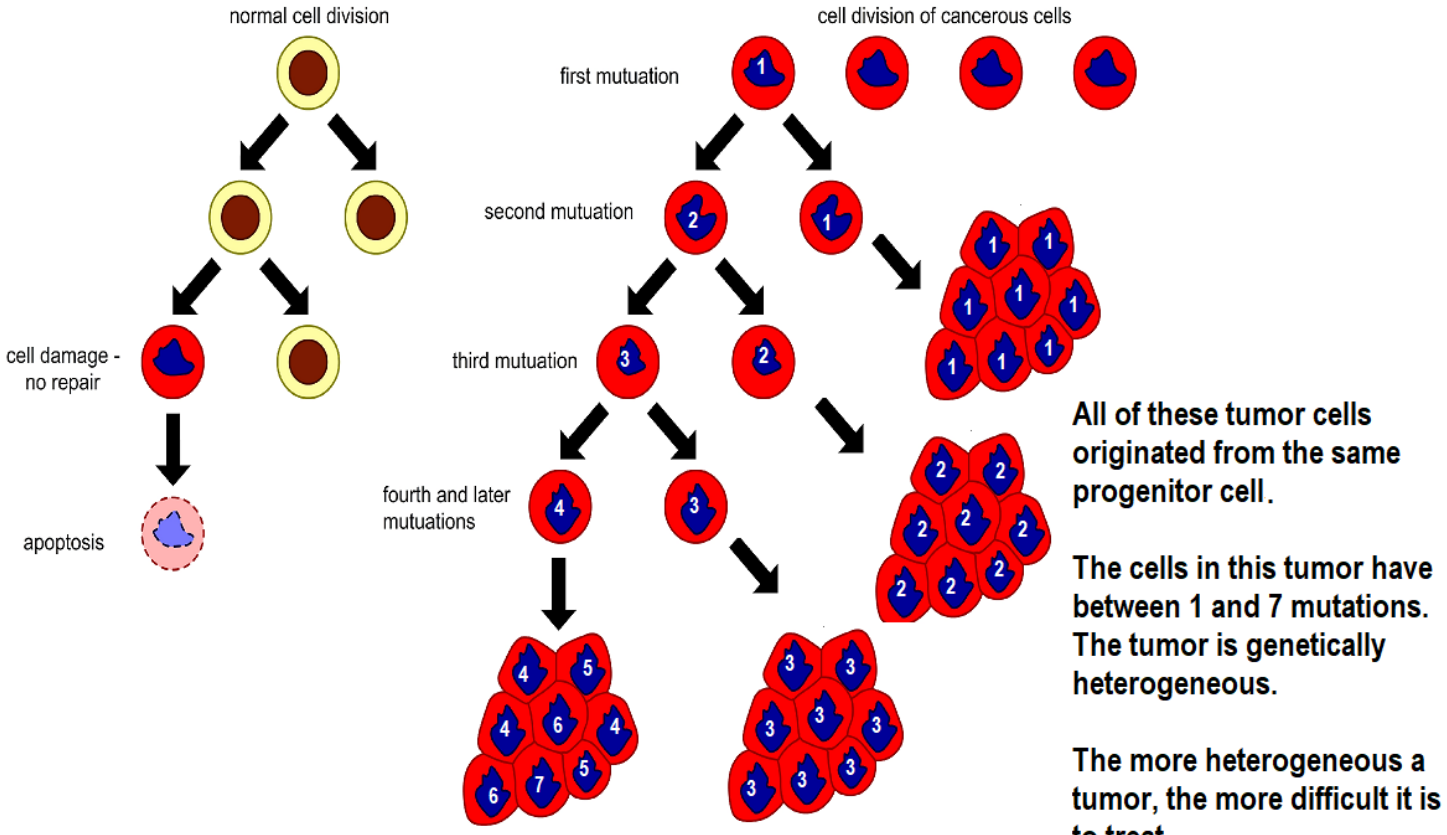
Cancer Terminology and Mechanisms

- Cancer is generally produced by **multiple** genetic changes (mutations) in a **somatic cell**. Two general categories of genes are associated with cancer:
  - **Proto-oncogene-A gene that promotes cancer when its expression increases or when it suddenly becomes expressed.**
  - **Tumor suppressor gene-a gene that promotes cancer when its expression decreases or ceases.**

Proto-oncogenes

- Oncogenes were the first tumor-associated genes to be discovered (in viral genomes).
- Over 100 have been described.
- A proto-oncogene is the **normal cellular counterpart** of an oncogene.

Cancer Terminology and Mechanisms



All of these tumor cells originated from the same progenitor cell.

The cells in this tumor have between 1 and 7 mutations. The tumor is genetically heterogeneous.

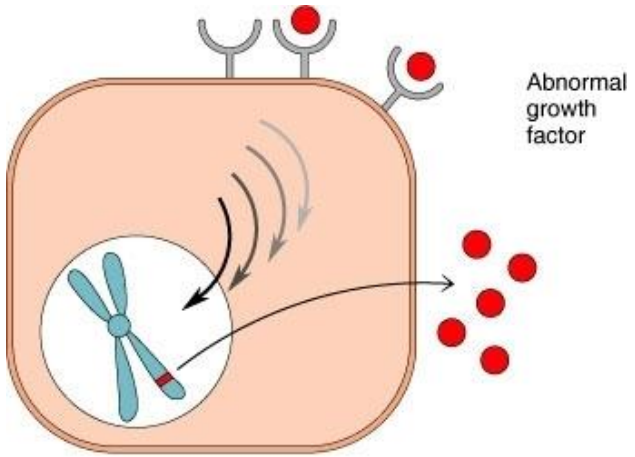
The more heterogeneous a tumor, the more difficult it is to treat.

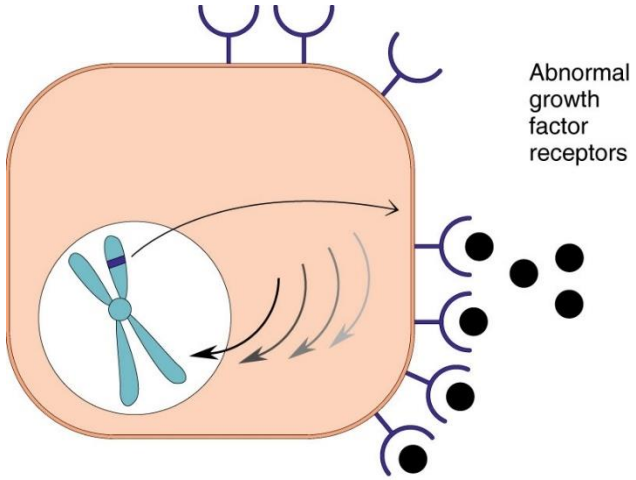
Cancer Terminology and Mechanisms

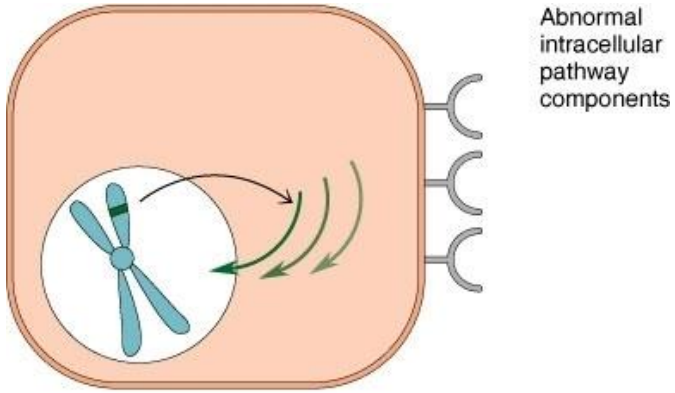
- There are four categories of proto-oncogenes:
  - **Growth factor genes**
  - **Growth factor receptor genes**
  - **Cytoplasmic signaling molecule genes**
  - **Nuclear transcription factor genes**
- **NOTE:** Proto-oncogenes exist for each of the four steps in the normal sequence of events leading to cell proliferation. Those steps are:
  - A **growth factor** is released by a cell into the extracellular space.
  - The growth factor binds to a **growth factor receptor** in the plasma membrane of the cell that will be signaled to divide.
  - Binding of growth factor to growth factor receptor transmits a signal through the membrane to initiate a **cytoplasmic biochemical pathway**.
  - The end product of the cytoplasmic pathway signals the nucleus of the cell to start producing **transcription factors**. (Transcription factors are required in order for the cell to begin transcribing the proteins necessary for cell division.)

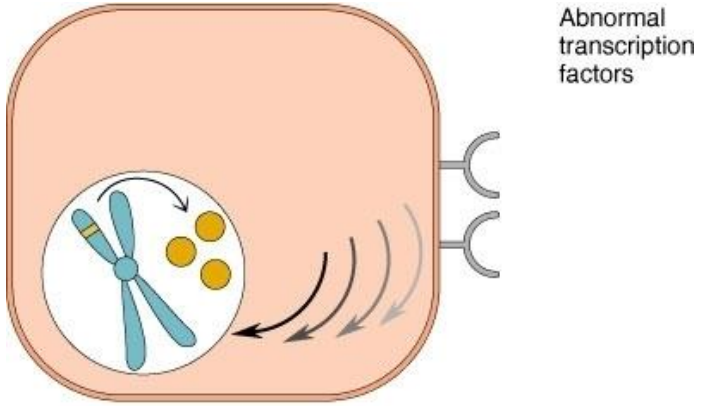
Cancer Terminology and Mechanisms

Oncogene Products:









Cancer Terminology and Mechanisms

- **Growth Factors:**
  - Small peptides that are made and secreted by cells into the extracellular space
  - Diffuse to nearby cells and interact with surface receptors to activate growth cascades
  - Some are growth-inhibiting factors
  - Mutation may cause a growth stimulating factor to become overactive or to bind too tightly to its receptor, causing cancer.
- **Examples of tumor-secreted growth factors:**
  - Platelet-derived growth factor (PDGF); commonly secreted by brain tumors and sarcomas
  - Fibroblast growth factor (FGF)
  - Transforming growth factor (TGF)
  - Epidermal growth factor (EGF)

Cancer Terminology and Mechanisms

- **Growth Factor Receptors:**
  - Transmembrane proteins
    - Growth factor-binding area is on the outside of the membrane
    - Enzyme-activating area is on the inside of the membrane
  - Highly specific in their binding of growth factors.
  - Mutation can lead to:
    - Expression of receptors that should not be present at all.
    - Excessive expression of a normally present receptor.
    - Receptors with an abnormally high affinity its growth factor.
    - Receptors that are activated in the absence of its growth factor.
- **Example: tumor-associated growth factor receptors**
  - Overexpression of human epidermal **growth factor receptor** type 2

    (**HER2**) occurs in about 25% of all breast cancers.

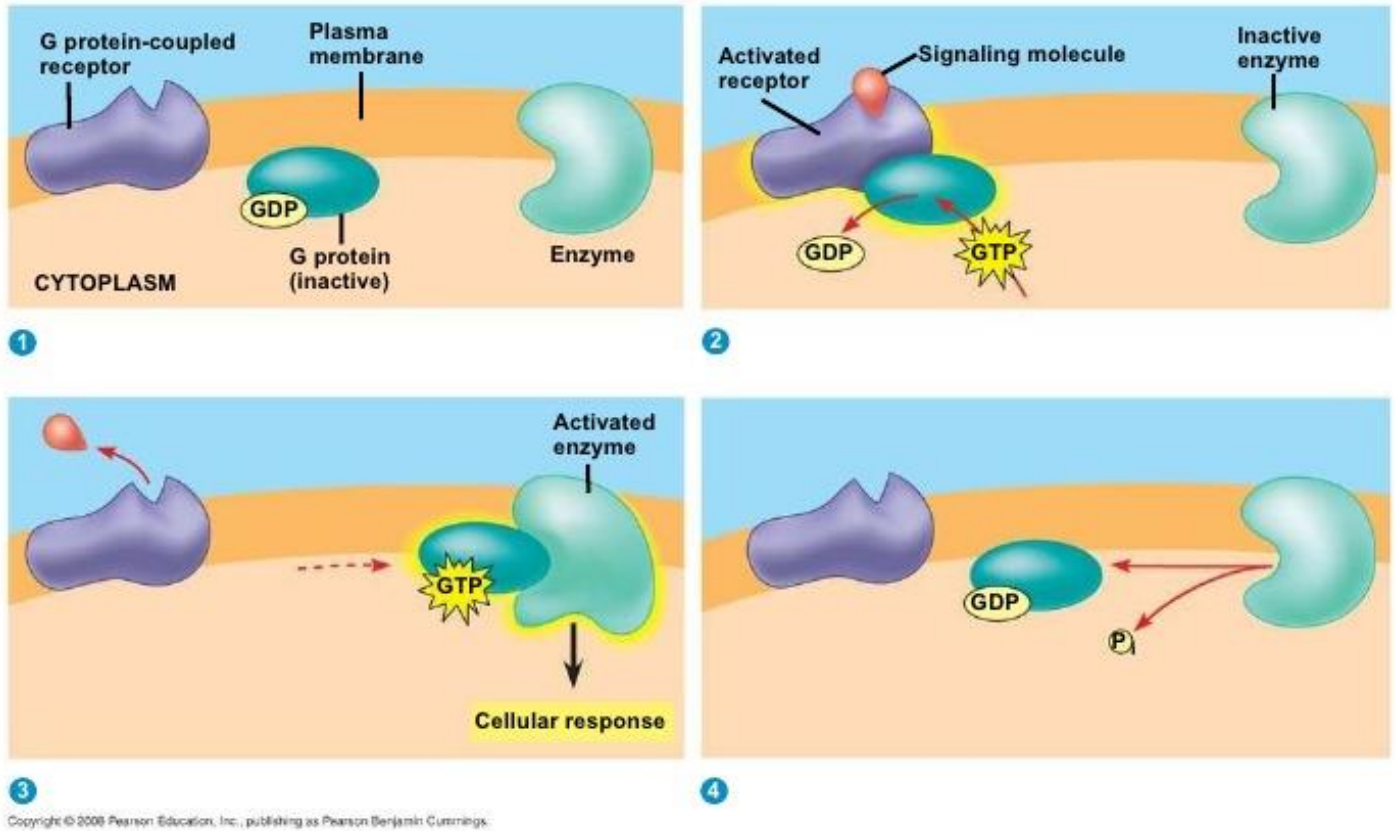
Cancer Terminology and Mechanisms

- **Cytoplasmic Signaling Molecules**
  - An oncogene that codes for excessive or abnormal cytoplasmic signaling components could cause activation of a cytoplasmic signaling pathway even though no signal was received at the cell surface.
- **Example: *ras* gene family**
  - The ***ras*** family of proto-oncogenes code for **G proteins**.
  - G proteins are activated when a ligand such as a growth factor binds to its receptor in the plasma membrane.
  - A G protein, when activated by bound GTP, transmit signals from a membrane receptor to a nearby membrane protein (usually an inactive enzyme) to cause its activation. The G protein then quickly hydrolyzes the GTP to GDP and Pi, turning itself off after a brief period.
  - *ras onco*genes can code for a G protein that is unable to hydrolyze GTP, so the G protein remains active and continually stimulates an enzyme that causes inappropriate cell division.
  - r*as* oncogenes occur in about 30% of all human cancers and is most-often the cause of **pancreatic cancer.**

Cancer Terminology and Mechanisms

Normal G Protein Function

Fig. 11-7b



Cancer Terminology and Mechanisms

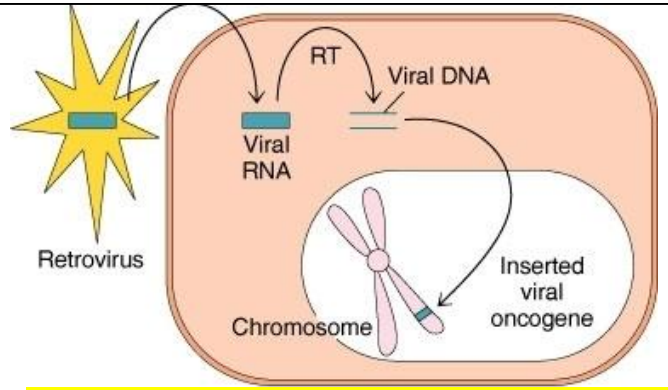
- **Transcription Factors**
  - Transcription factors are proteins that must assemble at the promoter region to begin transcription. Recall that the promotor region is where RNA polymerase binds to DNA.
  - Normally transcription factors are prevented from activity until signals cause their release.
  - Mutations in transcription factor genes may
    - Cause overproduction of transcription factors
    - Interfere with the mechanisms that normally keep transcription factors in check
    - Both situation could allow overproduction of proteins that stimulate cell division.
- **Examples of tumor-associated transcription factors**
  - *myc, jun,* and *fos* are examples of proto-oncogenes that code for transcription factors.
  - The myc proteins are associated with many cases of breast cancer and neuroblastoma.

Cancer Terminology and Mechanisms

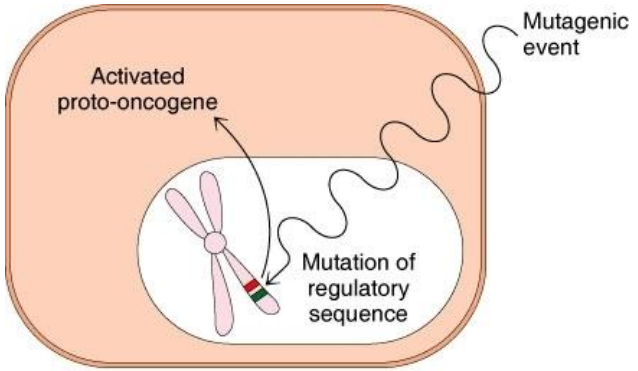
- **Four Ways Oncogenes and Proto-oncogenes Cause Cancer:**
  - 1. An oncogene is introduced into the host cell by a **retrovirus.**
    - A DNA copy of the oncogene is inserted into the host chromosome.
    - Insertion near a promoter may result in continuous transcription of the oncogene.
    - Viral oncogenes are not responsive to normal DNA transcription controls.
  - 2. A proto-oncogene within the cellular DNA incurs a mutation that changes its structure and function.
  - 3. A cellular DNA sequence that normally **regulates proto-oncogene expression** may become mutated.
  - 4. An error in chromosome replication called **gene amplification** may cause extra copies of a proto-oncogene. Multiple proto-oncogenes produce an oncogene-like situation.

Cancer Terminology and Mechanisms

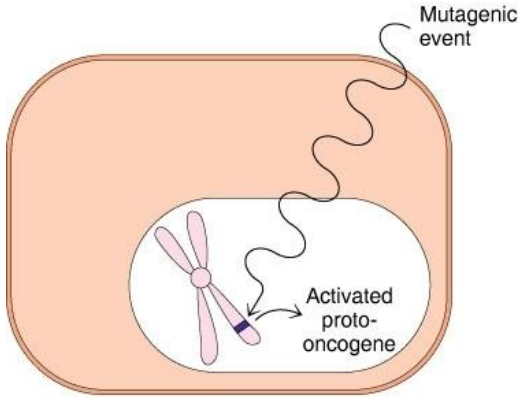
From Proto-oncogenes to Oncogenes: Four Modalities



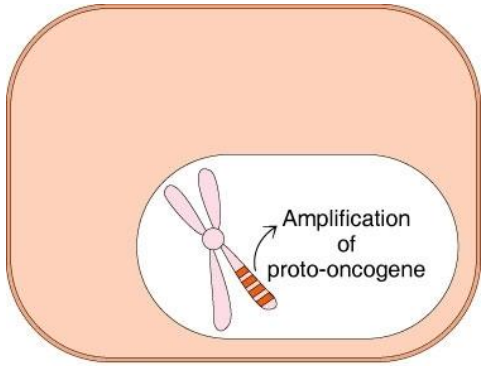
An oncogene is introduced by a retrovirus.



A gene that regulates a proto-oncogene is mutated.



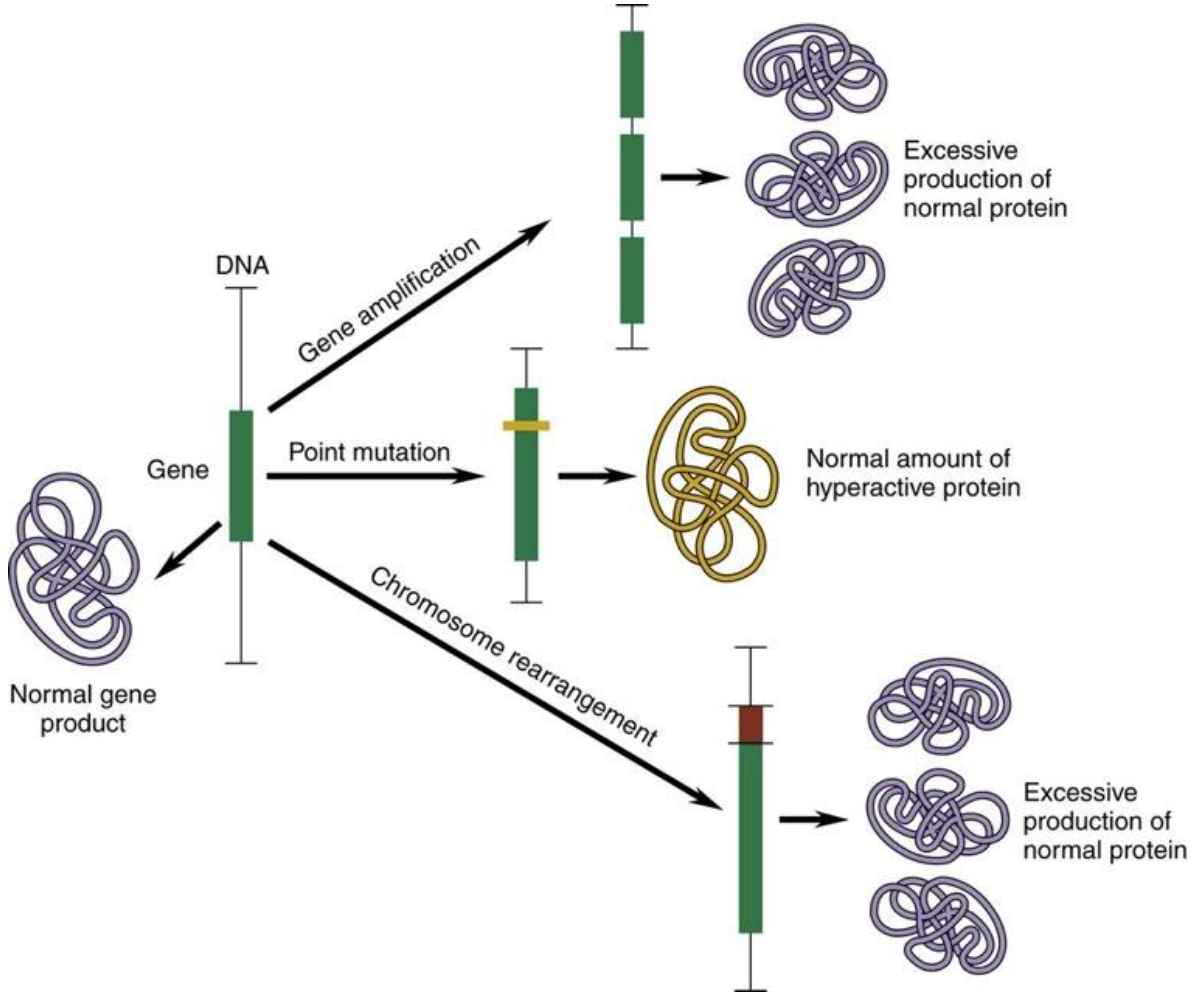
A proto-oncogene mutates to become an oncogene.



A proto-oncogene is amplified (many copies of it are produced).

Cancer Terminology and Mechanisms

A proto-oncogene can cause cancer if (1) its **normal** gene product is produced in **excess,** or (2) it is mutated and the resulting **abnormal** gene product is produced in **normal** amounts.

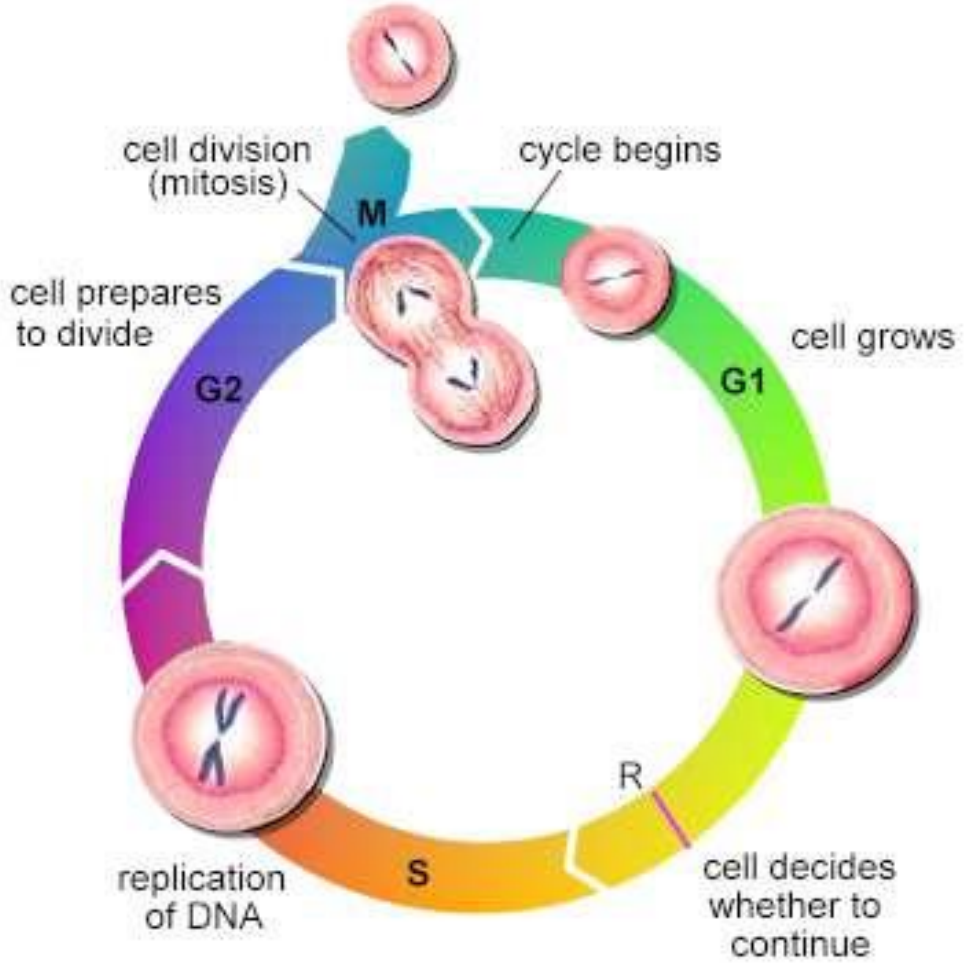


Cancer Terminology and Mechanisms

- **Tumor Suppressor Genes**
  - **The Rb Gene**
    - The Rb gene was the first tumor suppressor gene to be identified. It is associated with an eye cancer, **retinoblastoma.**
    - The **familial** (inherited) form of retinoblastoma is associated with a deletion in the portion of chromosome 13 that contains the Rb gene. Inheriting a single defective Rb allele predisposes an individual to retinoblastoma. If the other, normal Rb allele is mutated in a retinal cell, tumor formation begins.
    - The **sporadic** (non-heritable) form of the disease is due to a double mutational event in the DNA of a retinal cell.
  - **The Rb Gene Product**
    - Is called pRB; the "master brake" of the cell cycle
    - Normal pRB binds up transcription factors (particularly E2F).
    - It inhibits the transcription of genes that initiate the cell cycle.
    - In response to binding of a growth factor to a growth factor receptor, phosphorylation of pRB occurs. pRB then releases E2F and cell division procedes.
    - If pRB is absent or abnormal, there is no "master brake". Cells may become immortal causing cancer.
    - There is a 95% cure rate if the cancer is contained in just one eye.

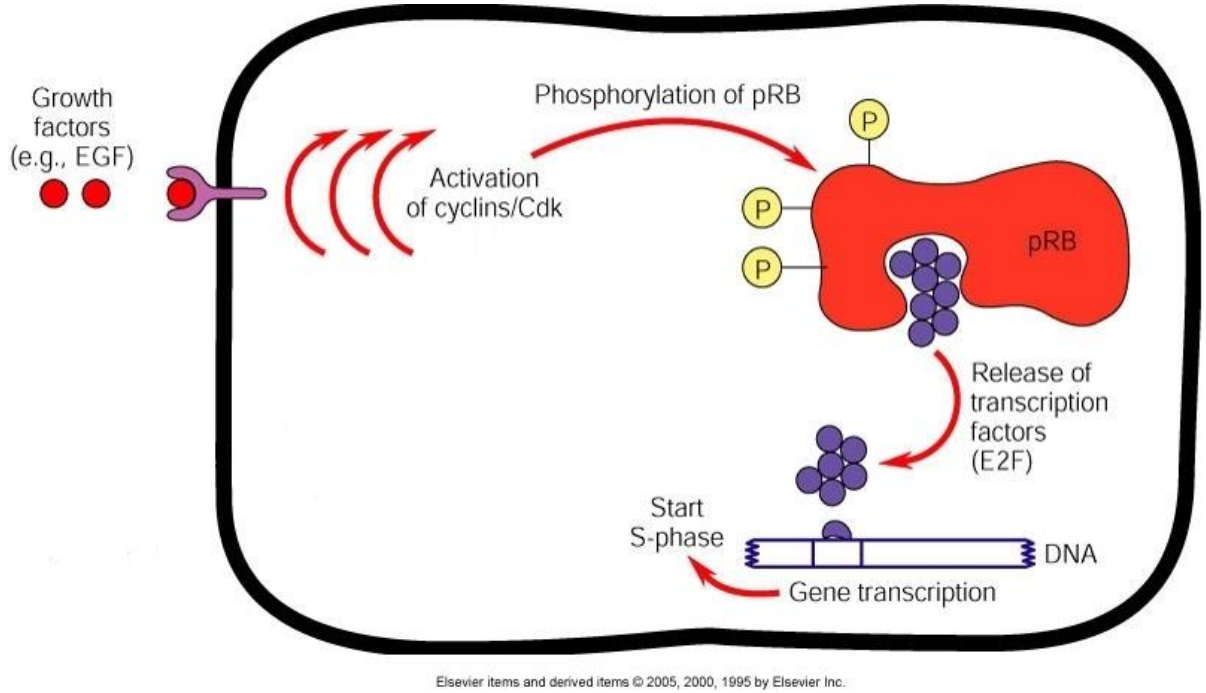
Cancer Terminology and Mechanisms

Remember the Cell Cycle?



Cancer Terminology and Mechanisms

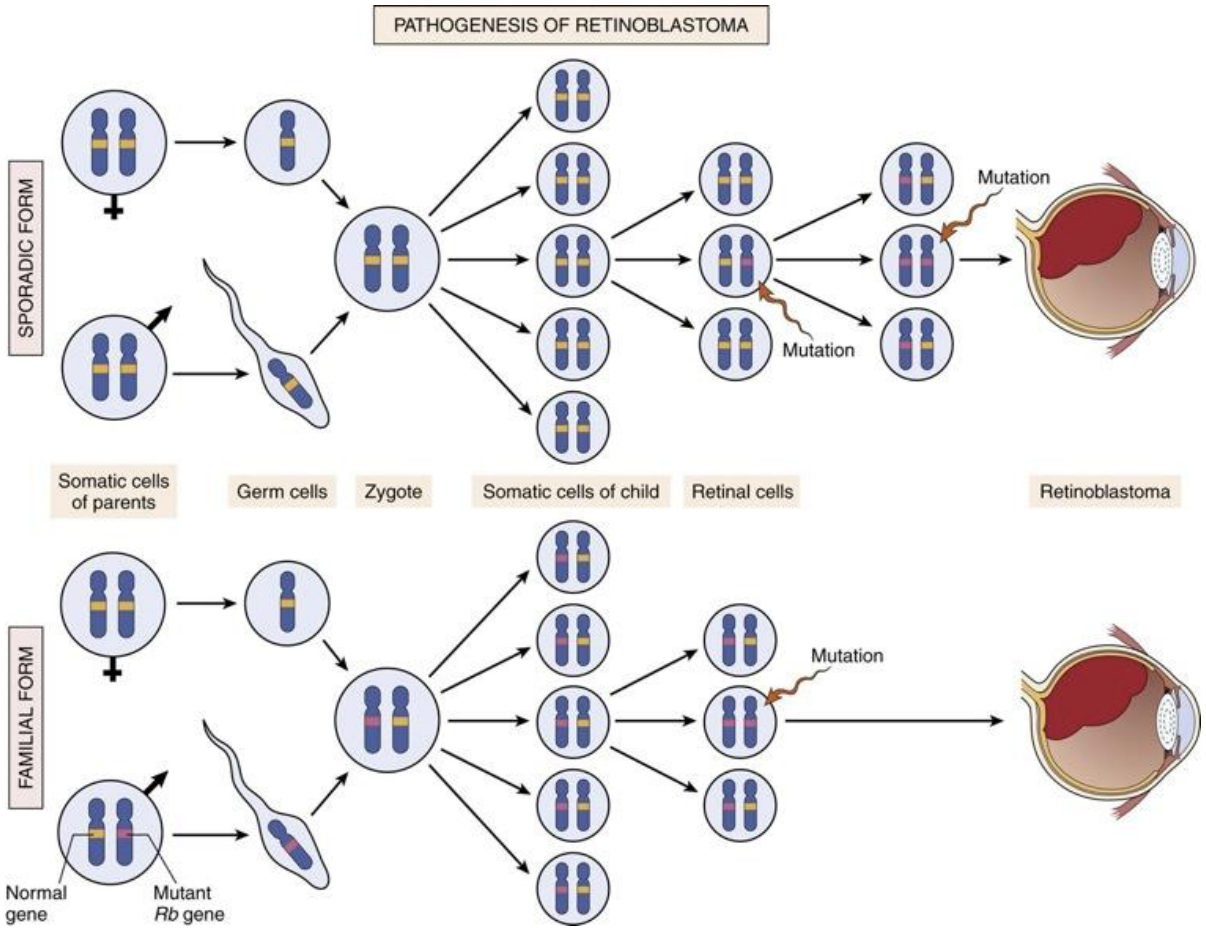
Normal pRB Function: pRB sequesters (binds up) transcription factors unless the cell is stimulated by a growth factor to enter the cell cycle. In that case transcription factors are released, and transcription of proteins required for S phase begins.



Cancer Terminology and Mechanisms

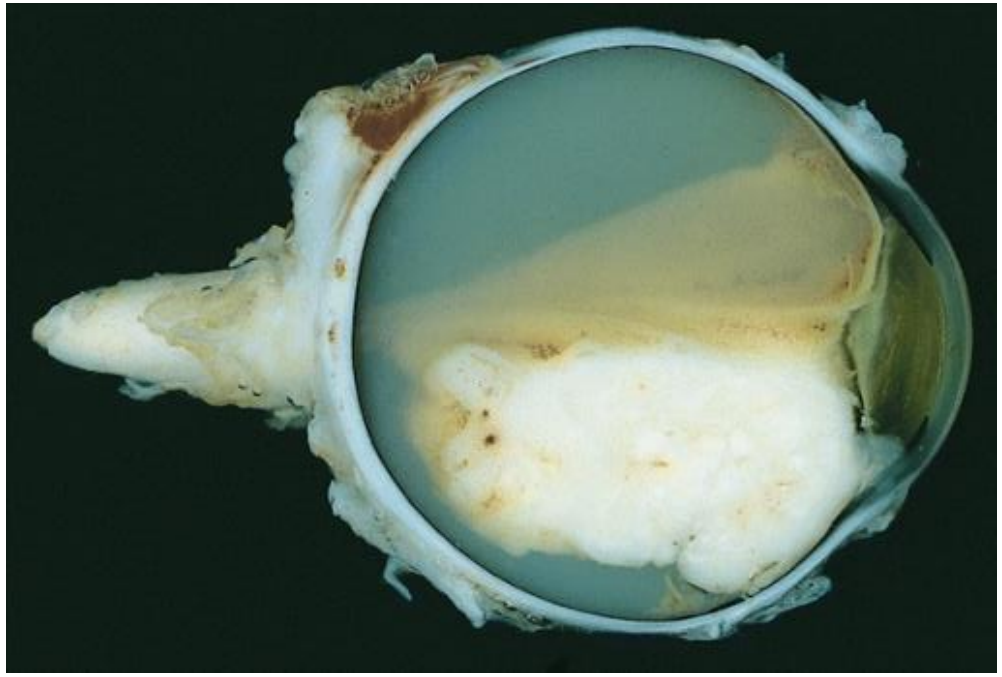
Retinoblastoma Sporadic Form:
2 somatic cell mutations

Retinoblastoma Inherited Form:
1 germ cell deletion on #13 plus
1 somatic cell mutation



Cancer Terminology and Mechanisms

Retinoblastoma



These tumors grow quickly and can be very disfiguring. See more Google Images, if you dare.

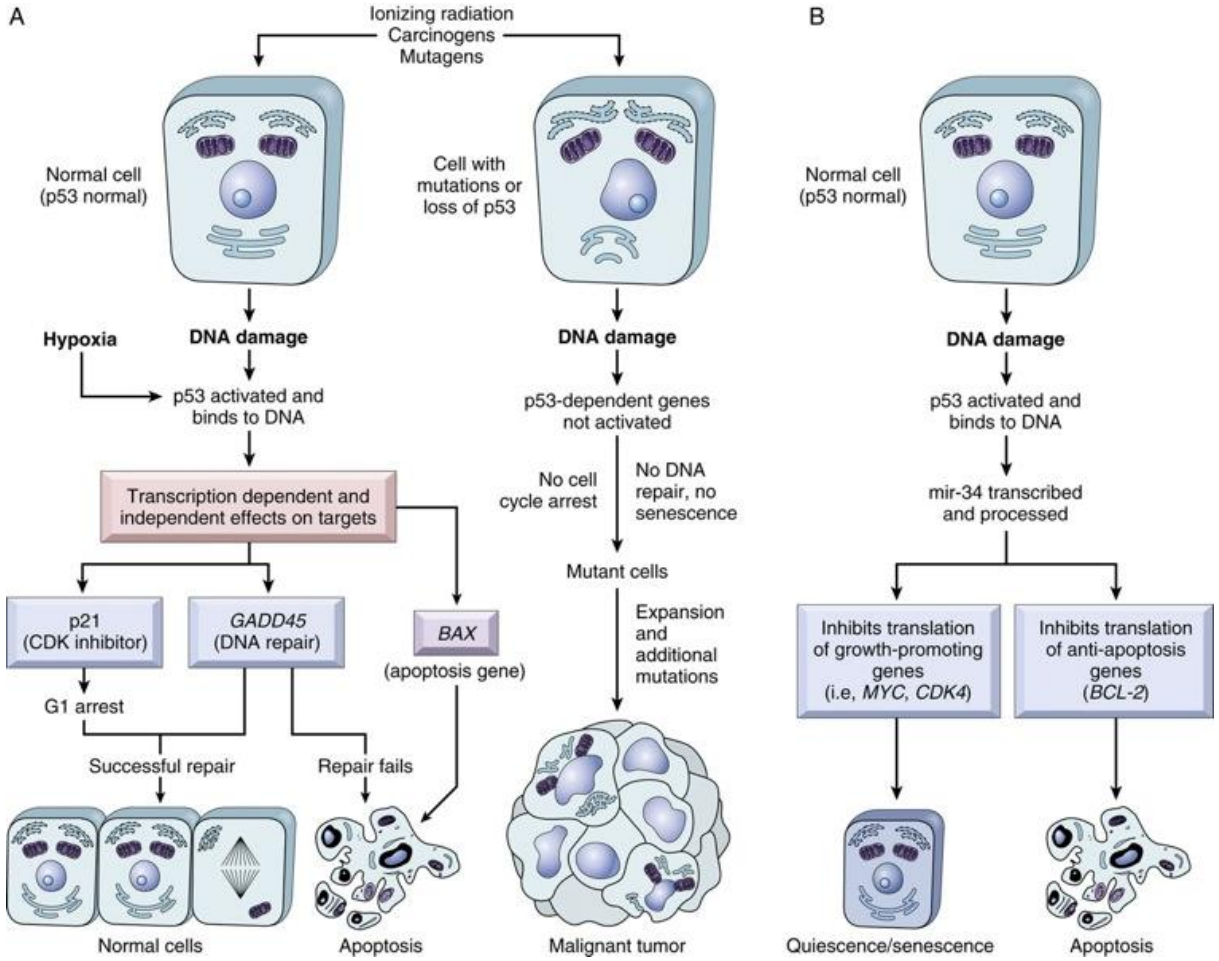
Cancer Terminology and Mechanisms

- **P53 Gene**
  - The most common tumor suppressor gene defect occurs in the P53 gene. It is located on chromosome #17.
  - Named because the molecular mass of its gene product is 53kd.
  - More than half of human tumors lack a functional P53 gene.
- **P53 Gene Product**
  - Normal p53 protein, like normal pRB, inhibits cell cycling.
  - Unlike pRB, p53 **accumulates** after cellular, particularly DNA, damage.
  - p53 binds to damaged DNA and stalls DNA synthesis, thus blocking the cell cycle at S Phase.
  - p53 accumulation serves as an **apoptosis** signal.
  - **Defective p53** allows genetically damaged and unstable cells to survive and replicate.
  - Cancer cells that lack functional p53 may be resistant to radiation and chemotherapy.

Cancer Terminology and Mechanisms

Normal p53 binds to damaged DNA leading to DNA repair, quiescence or apoptosis.

If p53 is abnormal or absent, cells with damaged DNA are allowed to divide possibly leading to cancer.



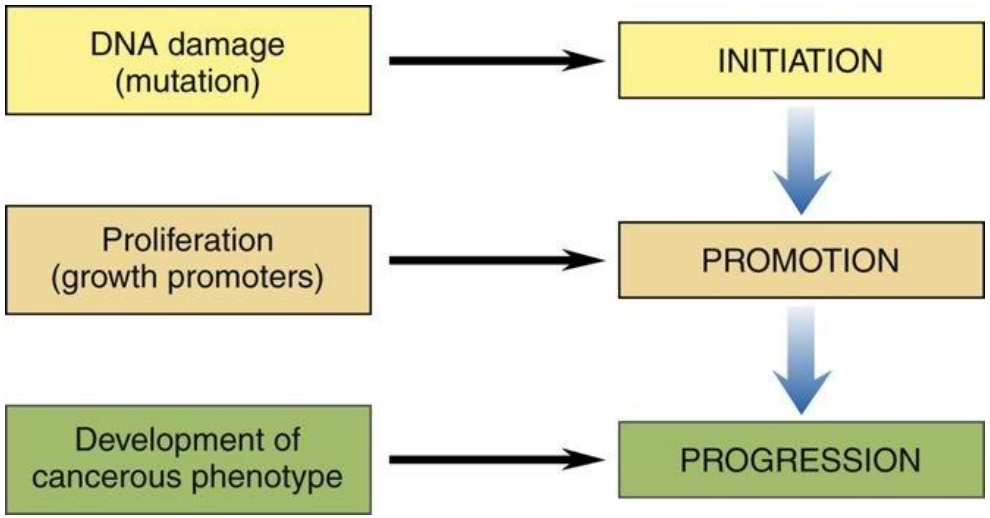
Cancer Terminology and Mechanisms

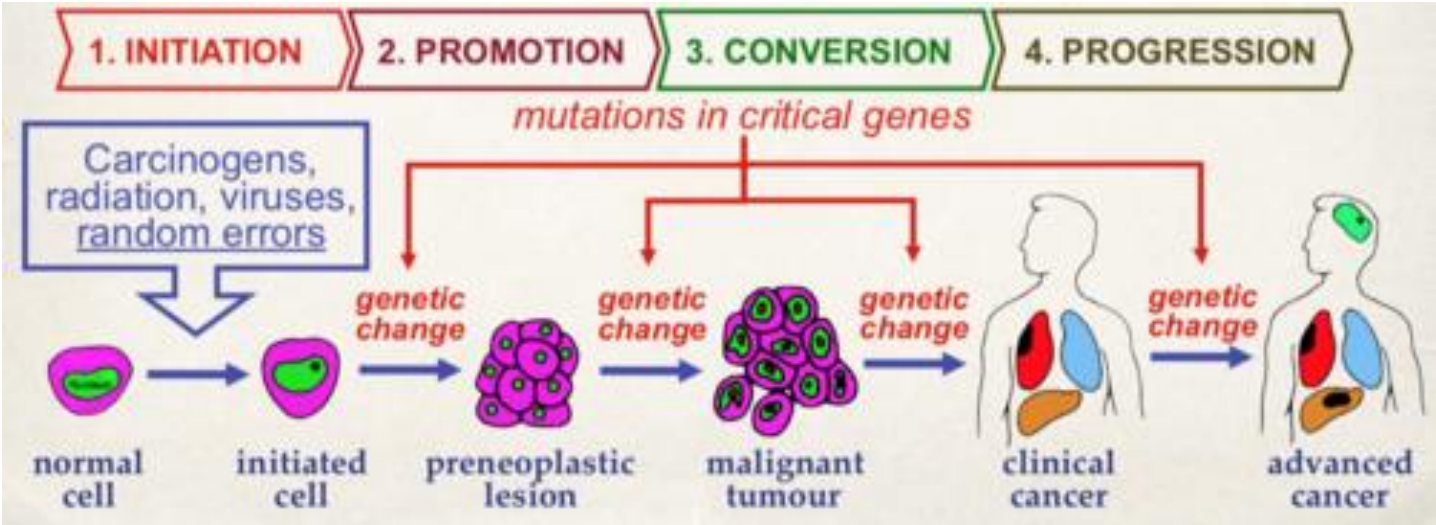
- **BRCA1 (on chromosome #13) and BRCA2 (on chromosome #17)** are autosomal tumor suppressor genes associated with inherited forms of breast cancer. Both gene products are important in DNA repair, particularly double-stranded breaks.
- Mutations in these genes interfere with a DNA repair process.
- Women with an inherited defect in the BRCA1 gene have about a 50% risk of breast cancer. There is an increased risk of ovarian cancer, as well.
- Age of onset of inherited breast cancer is earlier than the onset of non-inherited (sporadic).
- Prevalence of bilateral breast cancer is higher in inherited forms of breast cancer than in sporadic forms.
- Inherited forms of breast cancer account for **only 5%-10%** of all breast cancer cases.

The Multistep Nature of Carcinogenesis

- A single abnormal gene is usually NOT enough to induce conversion to full malignancy. A tumor develops from a single cell of origin that has a mutant gene. Then another cell in the tumor sustains a mutation, so it (and the cells it produces by mitosis) have two mutations. Then another cell in the tumor sustains a mutation, so it (and the cells it produces by mitosis) have three mutations. And so on.
- The cells in a malignant tumor are not genetically identical. They are genetically heterogeneous. That makes cancer difficult to treat.
- An interesting example is found in the synergy between the ras oncogene and the myc oncogene in tumor formation in rats.
  - An abnormal **ras gene** (codes for a cytoplasmic signaling protein) can cause cells to become anchorage independent, but it alone is not enough to cause tumor formation.
  - An abnormal **myc gene** (codes for a transcription factor) can cause cells to become immortal, but it alone is not enough to cause tumor formation.
  - The **combination** of an abnormal ras gene AND an abnormal myc gene IS enough to cause tumor formation.
- Theoretically, there are three steps in the development of cancer: initiation, promotion and progression.

The Multistep Nature of Carcinogenesis





The Multistep Nature of Carcinogenesis

Initiation (DNA Damage)

- Mutation activates a proto-oncogene or inactivates a tumor suppressor gene. This increases the rate of division in the cell of origin.
- The increased rate of cell division increases the probability of further mutation.
- Terminally differentiated tissues that have few stem cells and non-dividing cells (cardiac muscle or nervous tissue) are rarely cancerous. Epithelial tissue gives rise to cancer most often due to the high mitotic rate of its cells.
- Carcinogens are agents capable of inducing cancer.
  - Complete carcinogens
    - Initiate cancer by causing mutations
    - Promote cancer by stimulating proliferation.
  - Partial carcinogens
    - Capable of stimulating proliferation
    - Incapable of causing genetic damage (mutation) sufficient to initiate cancer
- Known carcinogens: uv and ionizing radiation, certain viruses, asbestos, and numerous chemicals (tobacco smoke)

The Multistep Nature of Carcinogenesis

Promotion (Proliferation)

- May involve the activation of another oncogene (mutation) or the inactivation of another tumor suppressor gene (mutation).
- Non-mutating factors may also be important: nutrition, infection, hormones.
  - The **greater the number of menstrual cycles** experienced, the higher the risk of **breast, ovarian, and uterine** cancer (**Estrogen** feeds those cancers.). Risk factors include:
    - Early menarche (first period), late menopause
    - Late first pregnancy or no pregnancy
    - Lack of breast feeding
  - **Tamoxifen** is an anti-estrogen agent used to treat breast cancer.
  - **Testosterone** is a growth factor for the **prostate** gland and a promoter for tumor formation in that tissue.

The Multistep Nature of Carcinogenesis

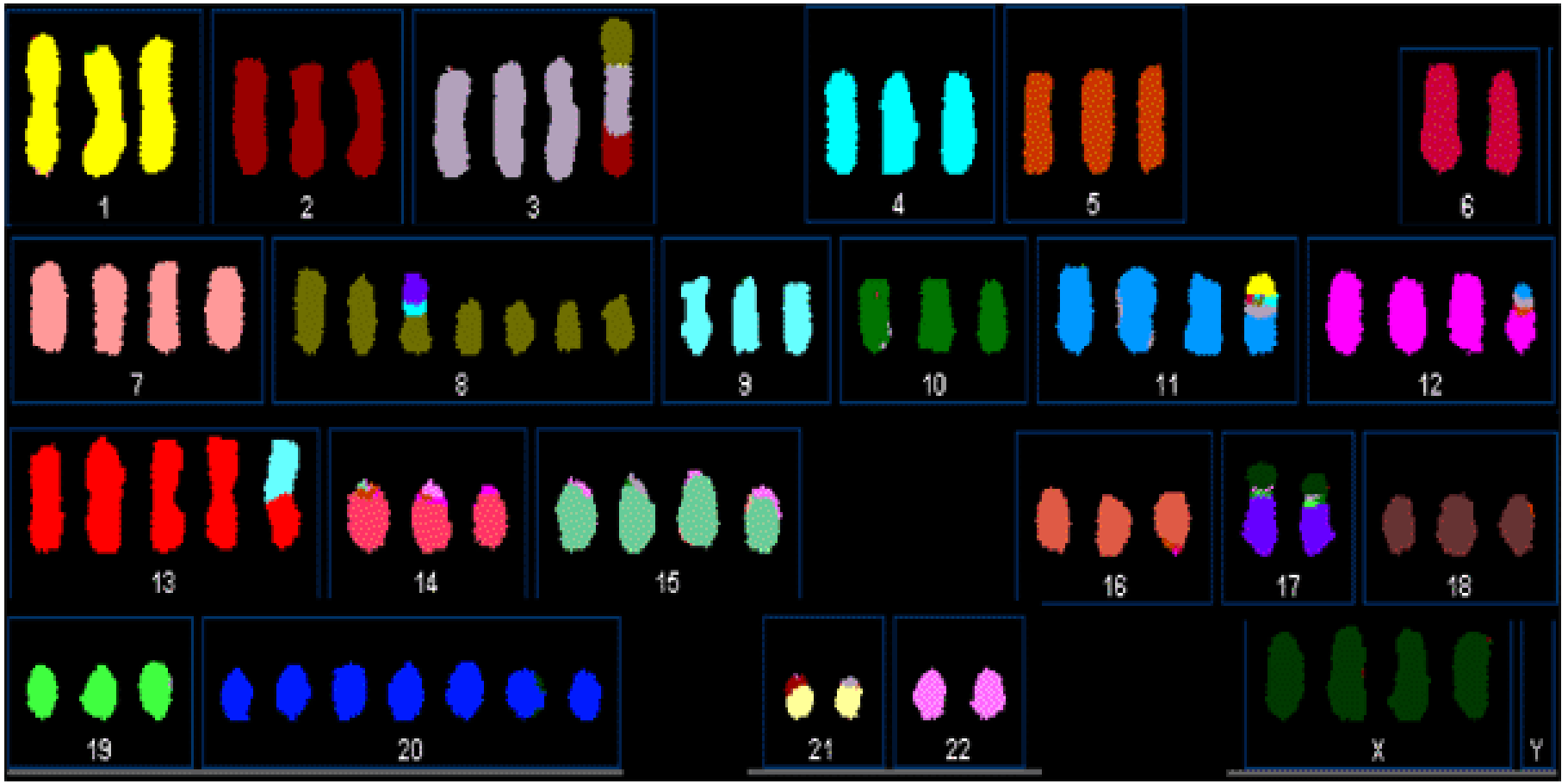
- Cancer cells exceed the normal limits on the number of cell replications allowed: **20-30 replications** in non-fetal cells.
  - Normally DNA polymerase is unable to copy DNA strands all the way to the tips of the chromosomes.
  - The **telomeres shorten with each division** until a critical length is reached and then cell division stops.
  - Unicellular organisms, germ cells, and many cancer cells produce the enzyme, **telomerase**. It catalyzes resynthesis of the telomere ends. These cell types are then able to replicate indefinitely.

Progression (Development of the Cancerous Phenotype)

- Mutation is most likely during DNA replication. So the faster a cell divides, the more likely it is to incur a mutation.
- As tumors cells continue to accumulate mutations they begin to differ significantly from their cell of origin.
  - Cancer cells have characteristics that enable them to become invasive.
    - Receptors for laminin or fibronectin (basement membrane glycoprotein)
    - Production of enzymes that destroy basement membrane proteins and enhance motility
    - Anchorage independence (Normal cell division requires anchorage dependence: cells must be anchored to some kind of surface.)
- Cancer cells often have bizarre karyotypes: missing or extra chromosomes, deletions, duplications, inversions, and various types of translocations.

The Multistep Nature of Carcinogenesis

Colon Cancer Tumor Cell Karyotype



Metastasis

The Process of Metastasis

- In order for cancer cells to metastasize (escape their tissue of origin and travel to distant sites in the body) they must gain access to **blood vessels or lymphatic vessels**.
- Recall that most cancers originate in epithelial tissue.
  - Epithelial cells are connected to each other by various structures.
  - Epithelial tissue is **devoid** of blood vessels and lymphatic vessels.
- Blood and lymph vessels are located in the soft connective tissue that lies deep to the basement membrane of the epithelium. So metastasizing cells must **break free from their neighboring cells** and **penetrate the basement membrane** of the tissue of origin.
- They must also move through the connective tissue toward a vessel and then penetrate the basement membrane of the vessel wall.

Metastasis

Steps in Metastasis

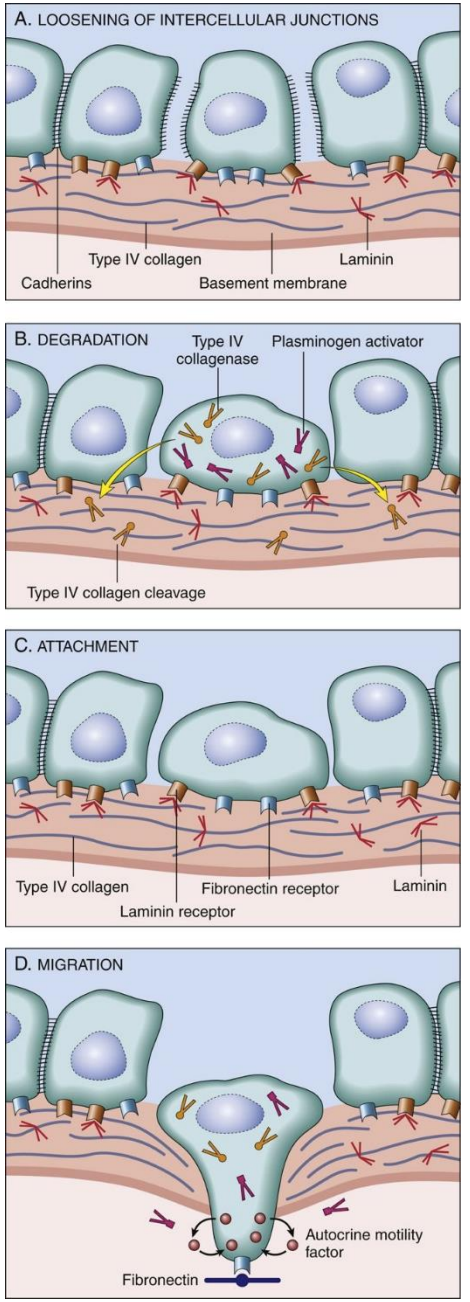
- Cells lose cell-to-cell adhesion in tissue of origin
- Cells gain the abnormal ability to bind to basement membrane and connective tissue matrix components such as **laminin or fibronectin** via **receptors** on the tumor cell surface.
- Cells escape the basement membrane of the tissue of origin. Some secrete **enzymes** that hydrolyze basement membrane proteins (**collagenase**, for example) and **autocrine mobility factor (AMF)** that stimulates cell migration.
- Cells move into the connective tissue and then through the wall of a blood or lymph vessel.
- Cells travel to a new site and exit through the wall of a blood or lymph vessel.
- Cells acquire nutrients and a blood supply in the new site.
- Cells cope with an environment that may be very different than that of its tissue of origin.

Metastasis

Tumor cells lose adhesion to neighboring cells.

Tumor cells produce and release enzymes that degrade proteins in the basement membrane and in connective tissue. They produce **laminin and fibronectin receptors** that allow attachment and migration toward the basement membrane.

Tumor cells release factors that enhance their own mobility as they escape the tissue of origin.



Metastasis

- Fewer than 1 in 10,000 cancer cells that enter the circulation survive. They are either removed by the immune system or undergo apoptosis.

Patterns of Metastasis

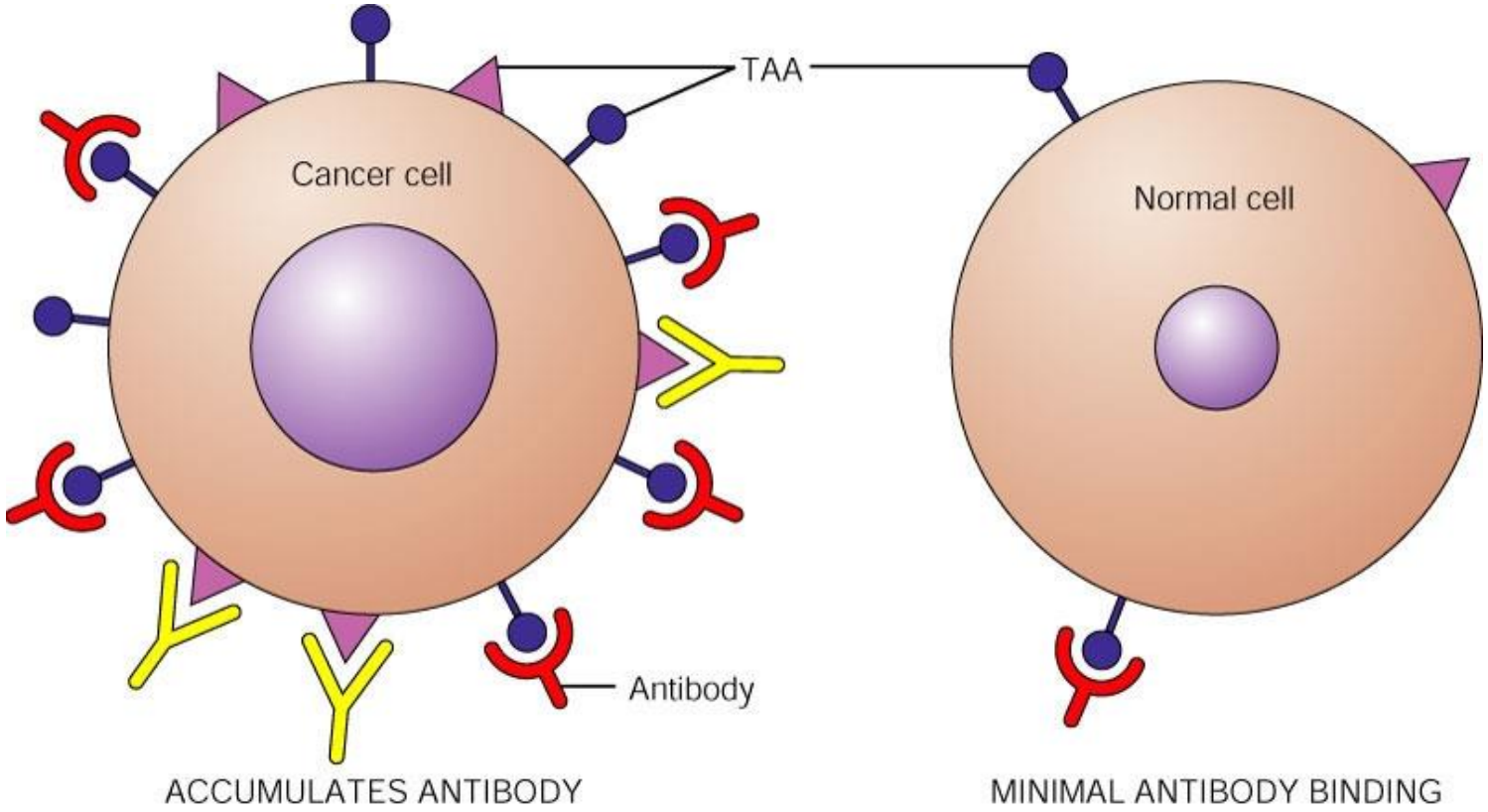
- Some tumor cells tend to “home” toward certain tissues, an activity that likely involves chemotaxis, integrins and cell adhesion molecules.
- Patterns of blood flow influence metastasis. For example, colon cancer often metastasizes to the liver via the **hepatic portal vein,** a blood vessel that drains blood from the digestive tract organs and carries it to the liver.
- Metastasis via the lymphatic system is usually **more predictable** than metastasis via the blood. The lymph nodes that immediately drain the area of the primary tumor location (**sentinel nodes**) are colonized first, and then the cancer cells spread contiguously from node to node.

Metastasis

- Determination of the **tissue of origin** of a tumor is important in both the prognosis and treatment of cancer.
- **Tumor markers** are molecules (usually proteins) associated with cancer cells that provide a hint as to the tissue of origin. Some tumor markers are tumor cell secretions that can be detected in the blood, or urine or feces. Others require examination of tumor cells themselves (tissue biopsy).
- For example, **thyroglobulin**, a protein precursor of thyroid hormone, is a serum marker for thyroid cancer. An increased level of thyroglobulin in the serum of a thyroid cancer patient indicates a higher level of proliferation of the tumor cells. Similarly, **PSA** (prostate specific antigen) is a tumor marker for prostate cancer.
- **Monoclonal antibodies** directed against tumor-specific **cell surface** antigens, **TAAs, (tumor associated antigens)** are useful tools in locating and identifying tumor cells.

Metastasis

Monoclonal antibodies against **tumor associated antigens** (TAA) are used to locate tumors and diagnose cancer. The antibodies are labeled with radioactive isotopes or fluorescent compounds to make them visible in histological studies and imaging studies.



Angiogenesis

- Tumors cannot grow to more than about 2 mm in diameter unless they grow blood vessels, a process called **angiogenesis**.
- Most tumors do not induce angiogenesis until late in the course of cancer development.
- Tumor cells may produce angiogenesis factors.
  - **VEGF (vascular endothelial growth factor)** stimulates the proliferation of endothelial cells (cells that line blood vessel walls).
  - Endothelial cells migrate into the tumor and orchestrate blood vessel development.
- Inhibition of angiogenesis is an important therapeutic goal of tumor management.

Grading and Staging of Cancer

- **Grading** is the histological (microscopic) characterization of tumor cells. It indicates degree of anaplasia.
  - Most grading systems have three or four degrees of increasing malignancy.
  - A “high” grade tumor exhibits more anaplasia than a “low” grade tumor.
- **Staging** describes the location and pattern of spread of a tumor.
  - International TNM (tumor, node, metastasis) system is used extensively in staging. TNM staging criteria are specific to the type of cancer.
  - Staging is generally a better means of predicting tumor behavior than grading.
- See the following two slides for examples of a breast cancer tumor grading system and a colon cancer staging system.

Grading and Staging of Cancer

Breast Cancer Grading System

Tumor tubule formation	Score
>75% of tumor cells arranged in tubules	1
>10% and <75%	2
<10%	3
Number of mitoses (low power scanning (X100), find most mitotically active tumor area, proceed to high power (x400)	
<10 mitoses in 10 high-power fields	1
>10 and <20 mitoses	2
>20 mitoses per 10 high power fields	3
Nuclear pleomorphism (nuclear grade)	
Cell nuclei are uniform in size and shape, relatively small, have dispersed chromatin patterns, and are without prominent nucleoli	1
Cell nuclei are somewhat pleomorphic, have nucleoli, and are intermediate size	2
Cell nuclei are relatively large, have prominent nucleoli or multiple nucleoli, coarse chromatin patterns, and vary in size and shape	3

Grading and Staging of Cancer

T N M Staging System for Colon Cancer

Modified Dukes	AJCC			Description
–	Stage 0		TIS, N0, M0	Earliest stage (carcinoma *in situ*). Has not grown beyond mucosa
A	Stage I		T1, N0, M0	Grown into submucosa (T1), no lymph nodes involved, no metastases
B1			T2, N0, M0	Grown into muscularis propria (T2), no lymph nodes involved, no metastases
B2	Stage II	IIA	T3, N0, M0	Grown into serosa (T3), no lymph nodes involved, no metastases
B3		IIB	T4, N0, M0	Grown into adjoining tissues (T4), no lymph nodes involved, no metastases
C1	Stage III	IIIA	T1, N1, M0	Grown into submucosa, ≤ 3 lymph nodes involved, no metastases
			T2, N1, M0	Grown into muscularis propria, ≤ 3 lymph nodes involved, no metastases
C2, C3		IIIB	T3, N1, M0	Grown into serosa, ≤ 3 lymph nodes involved, no metastases
			T4, N1, M0	Grown into adjoining tissue, ≤ 3 lymph nodes involved, no metastases
C1, C2, C3		IIIC	Any T, N2, M0	Can be at any tumor stage, ≥ 4 lymph nodes involved, no metastases
D	Stage IV		Any T, any N, M1	Can be at any tumor and node stage, metastasized to distant organs (e.g. liver, lung, peritoneum)

TIS, tumor *in situ*

Grading and Staging of Cancer

- Medical imaging techniques have revolutionized cancer detection and staging.
  - **CT (computer tomography) and MRI (magnetic resonance imaging)**
    - Rely on differences in tissue density. Tumors almost always differ in density from the normal surrounding tissue.
    - They guide the selection of sites for exploration and biopsy.
  - **PET (positron emission tomography)**
    - Is based on the biochemical activity of tumor tissue
    - Distinguishes benign from malignant lymph nodes
    - Distinguishes residual tumor tissue from scar tissue
    - Detection of unsuspected distant metastases
- **Monoclonal antibodies** against specific tumor cell surface antigens are used to track down cancer cells in the body. The antibodies are labeled so that they can be detected by imaging techniques.

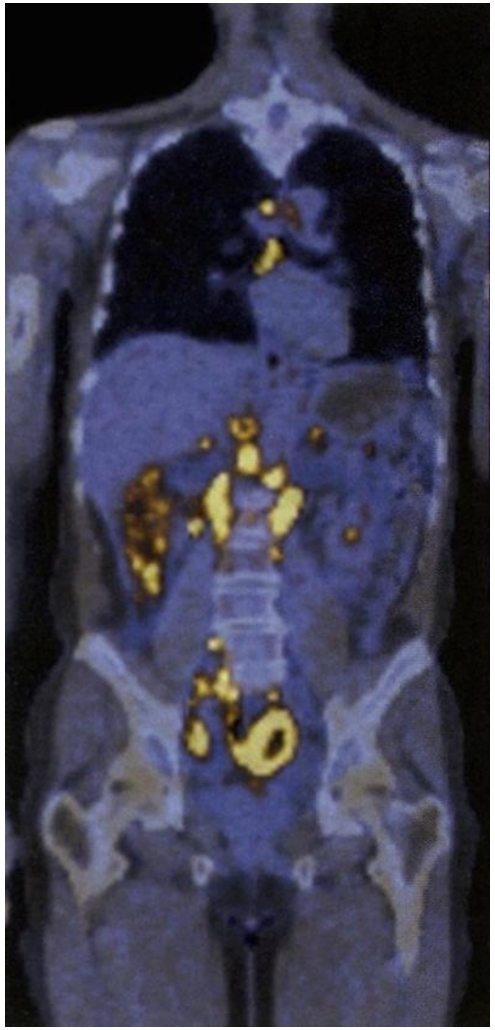
Cancer's 7 Warning Signs
"CAUTION"

- **C**hange in Bowel or bladder habits
- **A** sore that does not heal
- **U**nusual bleeding or discharge
- **T**hickening or lump in breast or elsewhere
- **I**ndigestion or difficulty in swallowing
- **O**bvious change in wart or mole
- **N**agging cough or hoarseness

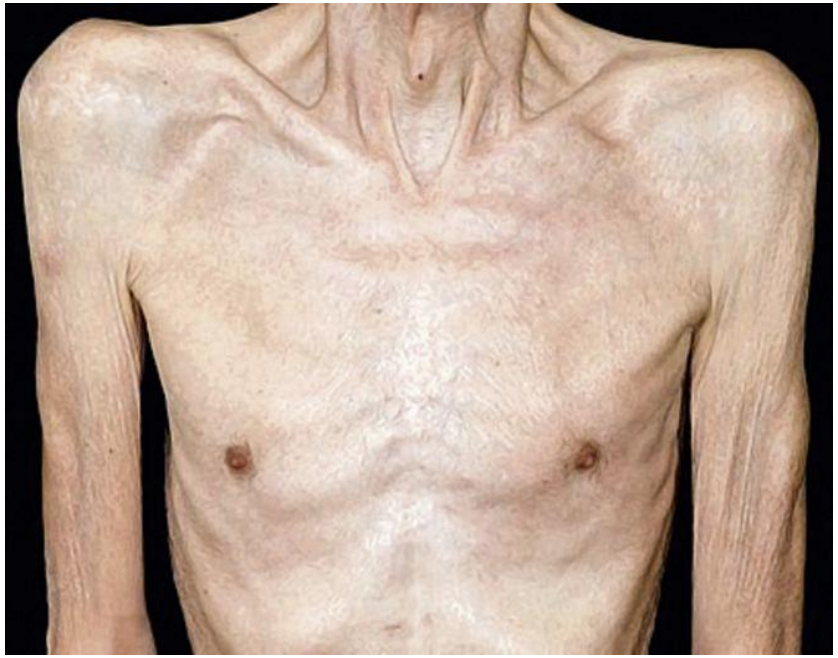
Effects of Cancer on the Body

- **Pain**
  - Activation of pain and pressure receptors by metastatic invasion
  - Inflammation and tissue destruction
  - Fear and fatigue are also factors.
  - Cancer treatment may contribute to pain: biopsy and IV drug administration.
- **Cachexia**
  - Overall weight loss and weakness that accompanies cancer.
  - Anorexia may result from toxins released by cancer cells or immune cells.
  - Nausea and vomiting are common complications of cancer therapy.
  - Cancer cells tend to be hypermetabolic and compete with normal cells for nutrients.
  - Patients often require nutritional supplementation.

PET Scan: radioactively-labeled glucose was used to detect the location of hypermetabolic tumor cells (yellow) in a patient with metastatic lymphoma.



Cancer Cachexia



Effects of Cancer on the Body

- **Reduced Immune System Function**
  - Cancer cells secrete substances that suppress the immune system.
  - Cancer patients may have reduced numbers of T cells and B cells due to tumor-secreted cytokines or invasion of the bone marrow by cancer cells and resultant marrow crowding.
  - Some cancer cells have developed ways to elude the immune system.
    - Internalize their immunoreactive surface antigens when antibodies bind to them.
    - Coat themselves with normal extracellular matrix molecules (glycoproteins) to hide their immunoreactive surface antigens
  - Difficulty differentiating between the tumor cells and the normal cells may result in the production of regulatory T cells that actually aid tumor cell growth.
  - Chemotherapy depresses the production of immune cells by the bone marrow.

Effects of Cancer on the Body

- **Bone Marrow Suppression**
  - Due to invasion of bone marrow by cancer cells, destruction of blood-forming cells in the bone marrow, poor nutrition, or chemotherapy.
  - Bone marrow suppression contributes to anemia, leukopenia, and thrombocytopenia
  - Anemia may result from acute or chronic bleeding.
  - Leukopenia is primarily caused by malignant invasion of the bone marrow.
  - Malnutrition and chemotherapy also contribute.
  - Reduces the patient's ability to fight infection.
    - **Infections are a major cause of cancer morbidity and mortality**.
    - Often the offending organism is opportunistic.
  - Thrombocytopenia predisposes to life-threatening hemorrhage
    - Platelet count <20,000/mm^3 can lead to spontaneous bleeding.

Effects of Cancer on the Body

- **Hair Loss and the Sloughing of Mucosal Membranes**
  - Complications of chemotherapy
  - Rapidly dividing normal cells are injured by cancer therapy.
  - Hair loss can cause serious psychological issues.
  - Damaged mucosa
    - Primary source of cancer pain and anorexia
    - Creates a portal of entry for infection by organisms from the skin or the GI tract.
- **Paraneoplastic Syndromes**
  - Symptom complexes that cannot be explained by obvious tumor properties; occur in 10% to 15% of patients with cancer
  - Small cell carcinomas of the lung may secrete ADH and/or ACTH. Other tumors may secrete a protein similar to parathyroid hormone (PTH). Thus the cancer patient may experience serious hormonal imbalances that cause electrolyte imbalances.
  - Unexplained **hypercalcemia** is regarded as evidence of cancer until proven otherwise.
  - Excess ADH leads to **hyponatremia and water overload**.

Cancer Treatment

- **Surgery**
  - The majority of patients with solid tumors are treated surgically.
  - The surgeon normally removes a margin of normal-appearing tissue around the tumor.
  - Lymph nodes are biopsied and removed to check for metastasis.
  - Involves risk related to anesthesia, infection, and blood loss
  - May be disfiguring or result in loss of function
  - Curative in only a minority of patients because most patients already have undetectable metastasis
  - Accompanied by radiation and/or chemotherapy in many cases

Cancer Treatment

- **Radiation Therapy**
  - Kills cells by damaging their nuclear **DNA.**
  - Targets **rapidly-dividing cells (malignant and normal) during S phase or mitosis of the cell cycle**. These cells are more susceptible to radiation death than cells in G1 or G2 phase because they devote much time to DNA replication and little time to DNA repair.
  - Initiates **apoptosis**
    - NOTE: Many tumors have a mutant p53 tumor suppressor gene, so radiation-induced DNA damage doesn't result in apoptosis.
  - Multiple raditation treatments are required because malignant tumors DO NOT consist of cloned cells. Cells in the same tumor have different numbers and types of mutations, so at any moment they will be in various stages of the cell cycle.
  - Is often used **palliatively**: to ease symptoms rather than to cure
    - Pain from bone cancer and brain cancer is managed by using radiation to shrink tumors.
    - Tumors with bleeding surfaces are treated with radiation to stem blood loss.
  - Is best-used when tumor cells are **regionally located**
  - Total-body irradiation to kill tumor cells body-wide is **not recommended!**

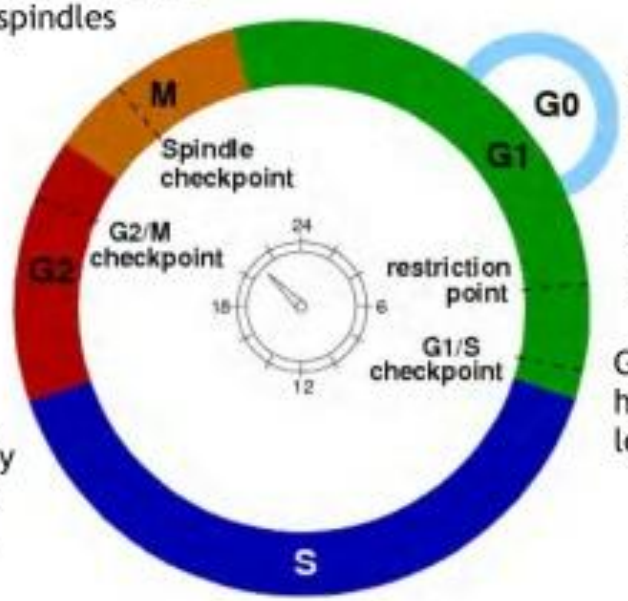
Cancer Treatment

- **Chemotherapy**
  - Surgery and radiation therapy are locally or **regionally** applied.
  - Chemotherapeutic drugs are **systemically** applied. They have broad side-effects: hair loss, nausea, bone marrow suppression because they harm normal cells body-wide.
  - Most chemo drugs are **cytotoxic** because they interfere with some aspect of the **cell cycle**. The result is apoptosis. Like radiation therapy, most chemo drugs are effective during S phase or mitosis rather than during G1 or G2.
  - Multiple rounds of chemo treatment are required due to tumor cell heterogeneity. Multiple types of chemo drugs are often used to treat the same patient.
  - Chemo drugs effectively target **rapidly-dividing cells (BOTH malignant and normal)**. Normal rapidly-dividing cells include bone marrow cells and epithelial cells (skin epidermis, hair follicles, mucous membranes, serous membranes, glands).
  - Tumor cells with mutations of the **p53 gene** may be resistant to chemo agents that act by damaging DNA.
  - Some of the newer chemo drugs **block angiogenesis,** depriving the tumor of a blood supply.

Cancer Treatment

M phase – In mitosis chromosomes drawn apart by molecular motors, cell divides. Many cancer drugs like taxol act here freezing the process and causing apoptosis. There is a checkpoint to ensure chromosomes are correctly attached to the spindles before segregation.

G1 is entered when the cell senses growth signals or mitogens. These start the process of cell division.



Cell crosses a restriction point c 8-10 hours into G1 - This is a point of no return: the cell is committed to divide or die.

G2/M - cell arranges and checks chromosomes. There is a major checkpoint here to ascertain that DNA replication has successfully occurred. If not, a normal cell undergoes apoptosis.

G1/S checkpoint –arrest here for cancer cells leads to apoptosis.

S phase - DNA is synthesised. Many cytotoxic anti-cancer drugs act here to disrupt DNA synthesis.

There are a number of **checkpoints** in the cell cycle when chemotherapy drugs act to break the cycle and cause **apoptosis** in rapidly-dividing cells.

Cancer Treatment

Chemotherapy

- **Complete remission (CR)** is the goal.
  - Normal hematopoiesis with normal RBC, neutrophil, and platelet count
  - No DETECTABLE neoplastic (cancer) cells
  - For **leukemia** the definition is modified: less than 5% blast cells in a bone marrow biopsy for at least 4 weeks
  - (Up to a billion neoplastic cells can be present and yet be undetectable.)
- Several cycles of chemotherapy are included in the protocol.
- Bone-marrow rescue (by bone marrow transplant) may be necessary after high-dose chemotherapy.
- Chemotherapy usually includes two or three treatment phases:
  - Remission induction phase
  - Post-remission phase (remove undetectable neoplastic cells)
  - Remission maintenance phase (prolong remission)
- Conventional routes for chemotherapy are unsuccessful in cases of CNS involvement. Chemo administered enterally or by IV cannot cross the BBB (blood brain barrier). The **intrathecal route** (lumbar puncture) must be used.

Cancer Treatment

Immunotherapy:

•Interferons

- Glycoproteins produced by immune cells in response to viral infection and cancer
- Inhibit cell proliferation and are stimulatory to NK cells, T cells, and macrophages.
- Interferon-α has been used successfully to treat WBC malignancies.
- Interferon therapy produces symptoms similar to those of a viral infection

•Interleukins

- Peptides produced and secreted by white blood cells
- Interleukin-2 (IL-2) is secreted by activated helper T cells
- Stimulates the proliferation immune cells
- Immune cells taken from a patient's blood can be grown in culture in the presence of IL-2 then returned to the patient
- Many patients experience severe side effects

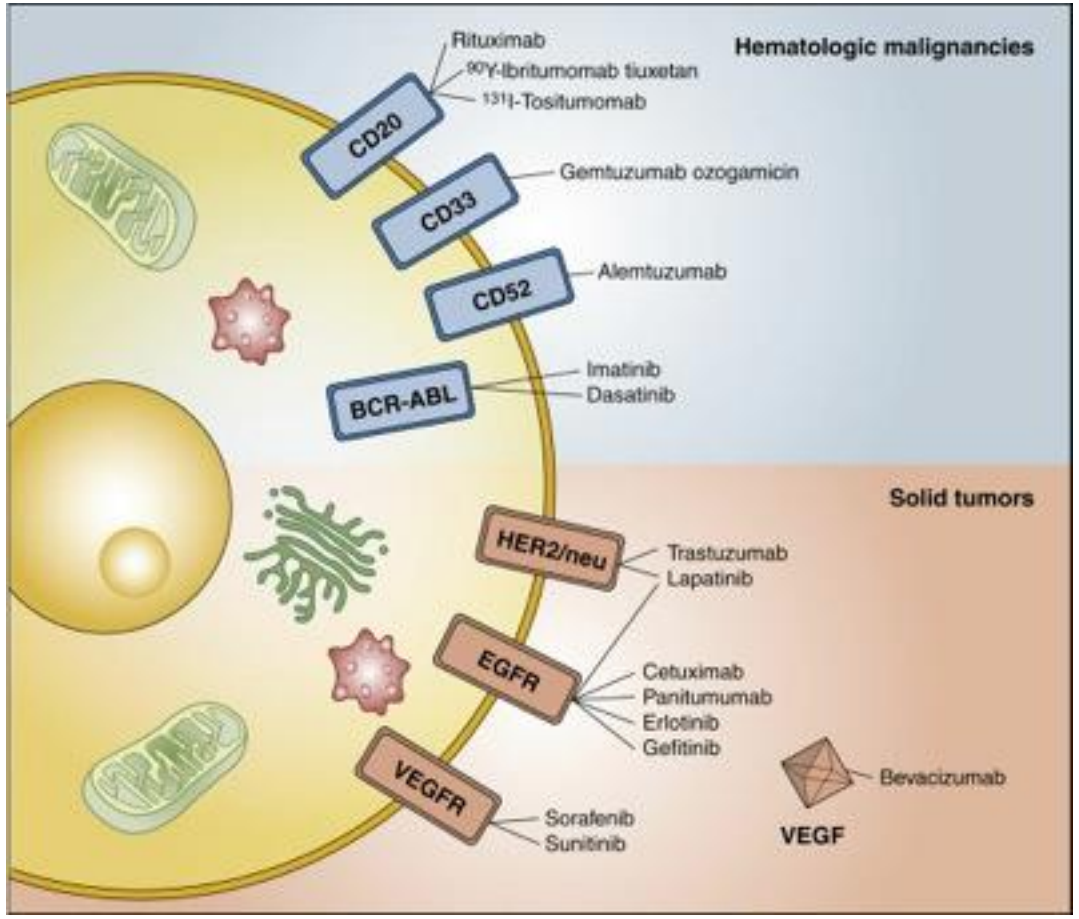
•Monoclonal Antibodies (antibodies with identical structure)

- Specifically bind to cancer cell surface antigens
- Used to deliver a cytotoxic drug to cancer cells
- Used to direct other cytotoxic cells such as NK cells and T cells to tumor cells
- Radioactively labeled and injected to detect the presence of tumor growth
- Can also be raised against the cells that support tumor growth

Cancer Treatment

Cancer cells have membrane proteins and membrane glycoproteins that differ from those of normal cells. That makes them suitable targets for **monoclonal antibodies** directed against the abnormal membrane molecules.

Monoclonal antibodies are useful in:
*locating cancer cells
*calling the attention of immune cells to cancer cells
*carrying drug molecules to cancer cells.



Cancer Treatment

Gene and Molecular Therapy

- **Tumor cells** can be genetically altered to make them more susceptible to cytotoxic agents/immune recognition.
- **Immune cells** can be genetically altered to make them more effective killers of tumor cells.
  - **Replacement of the p53 gene** or other tumor suppressor genes could help inhibit tumor cell proliferation.
  - Harvesting immune cells from the cancer patient, **inserting IL-2 genes,** and then returning the genetically enhanced immune cells to the patient is a technique that holds promise. Think back, what does IL-2 due to lymphocytes?
- Molecular therapies that target cytoplasmic signaling pathways have been developed. **Gleevec** is a drug used to inhibit a **cytoplasmic enzyme** associated with CML (chronic myelogenous leukemia).

Cancer Treatment

Stem Cell Transplantation

- Transplantation of **hematopoietic stem cells** is used to restore bone marrow function after high dose irradiation or chemotherapy, especially in cancers such as leukemia and lymphoma.
- The patient's own immune cells may have to be suppressed to prevent transplant rejection.
- Residual malignant cells must also be eliminated to avoid recurrence of the cancer.
- Stem cells can be harvested from bone marrow aspirates or from peripheral blood.
- Stem cell donors can be
  - Allogeneic-a tissue-matched individual
  - Syngeneic-an identical twin
  - Autologous-from the patient in question

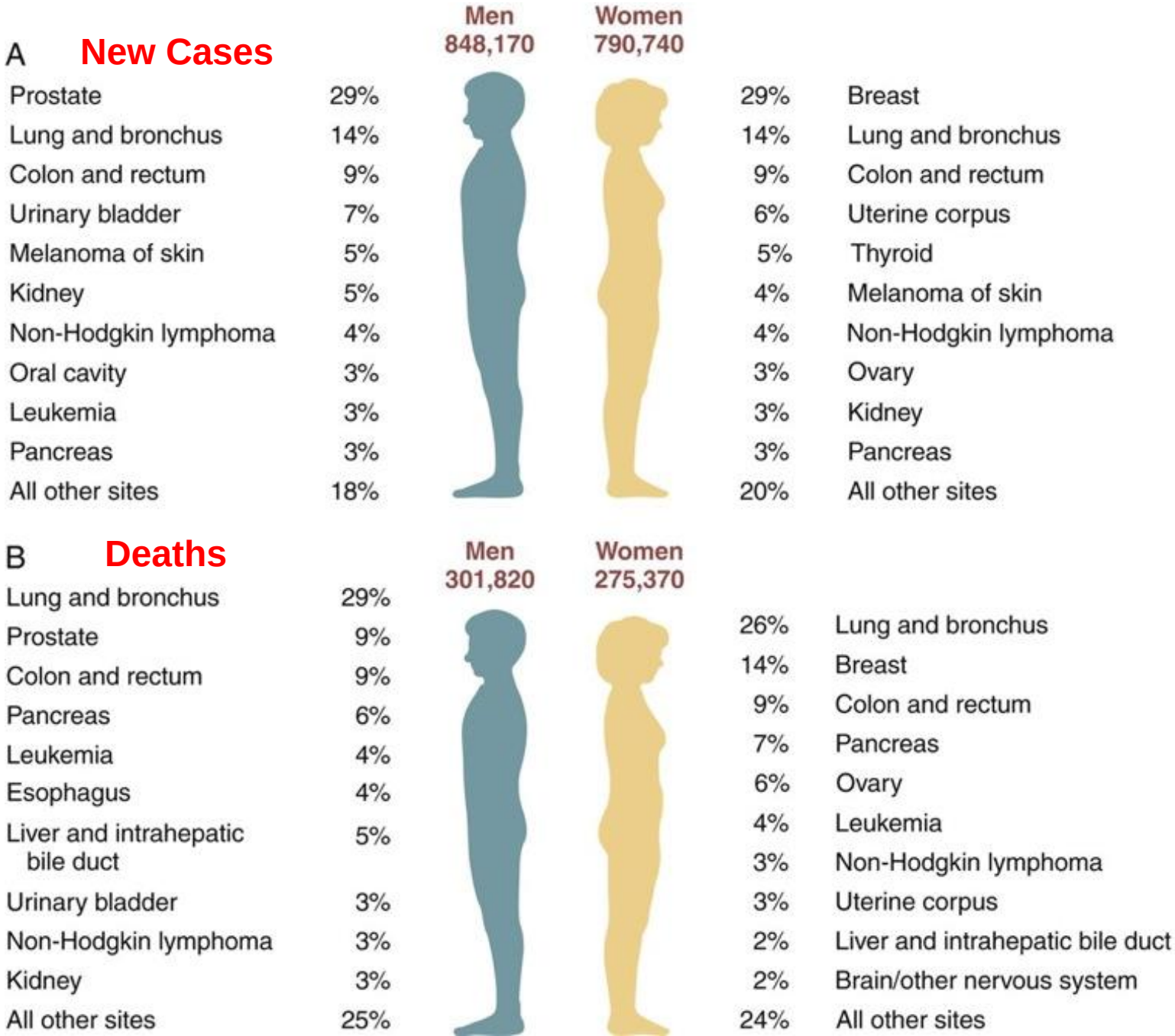
Malignant Tumors Are Heterogeneous!

- Cancer therapies are complicated by the fact that, with very few exceptions, the cells in a malignant tumor are **NOT identical** to each other. A tumor normally does **NOT** consist of a genetic clone of cells.
  - **They have various numbers of mutations.**
  - **They are not all in the same stage of the cell cycle.**
  - **They are cycling at different rates.**
  - **They do not have identical surface markers.**
- Therefore, a single course of radiation, chemotherapy or immunotherapy is not an effective treatment.

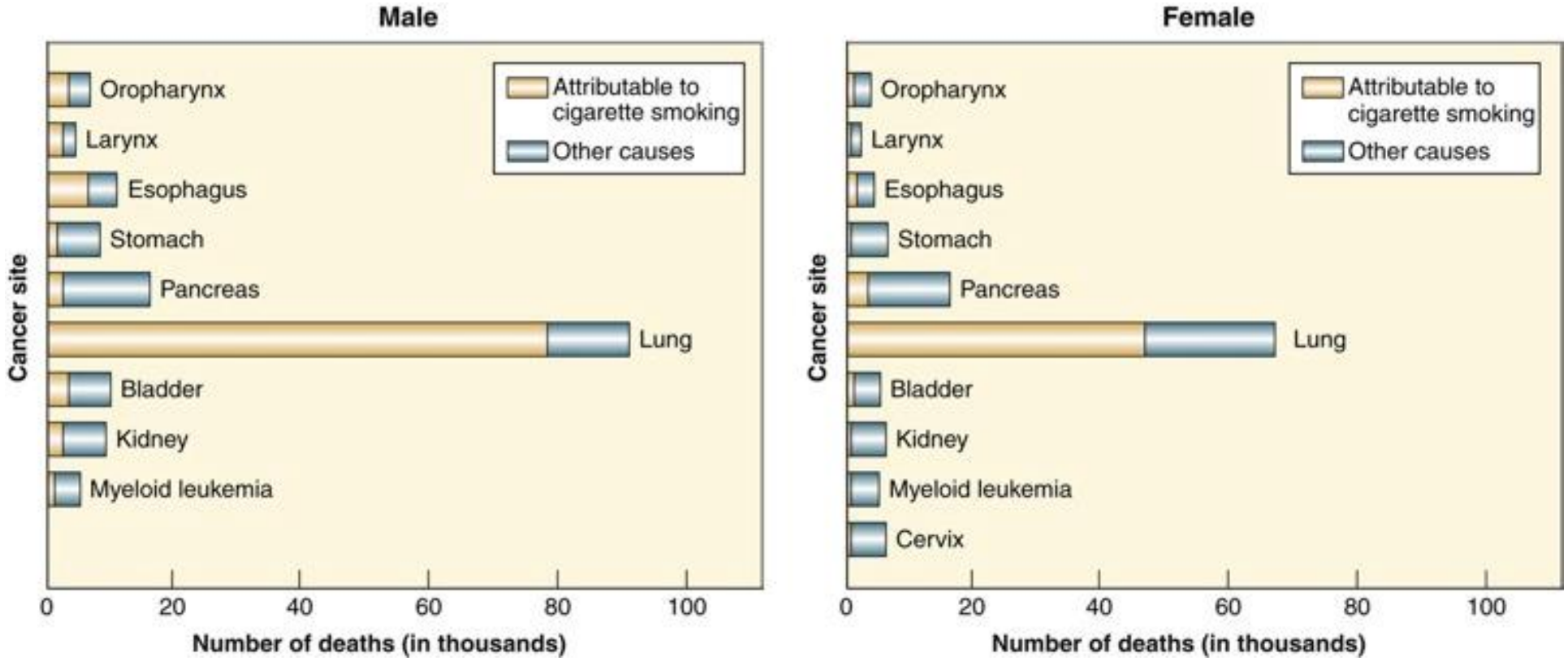
Cancer Risk Factors

- Some cancers are detectable early on by screening tests.
  - Breast cancer-mammogram
  - Prostate cancer-PSA test
  - Colon cancer-colonoscopy
  - Cervical cancer-PAP test
- American Cancer Society Screening Guidelines

From: The American Cancer Society 2014



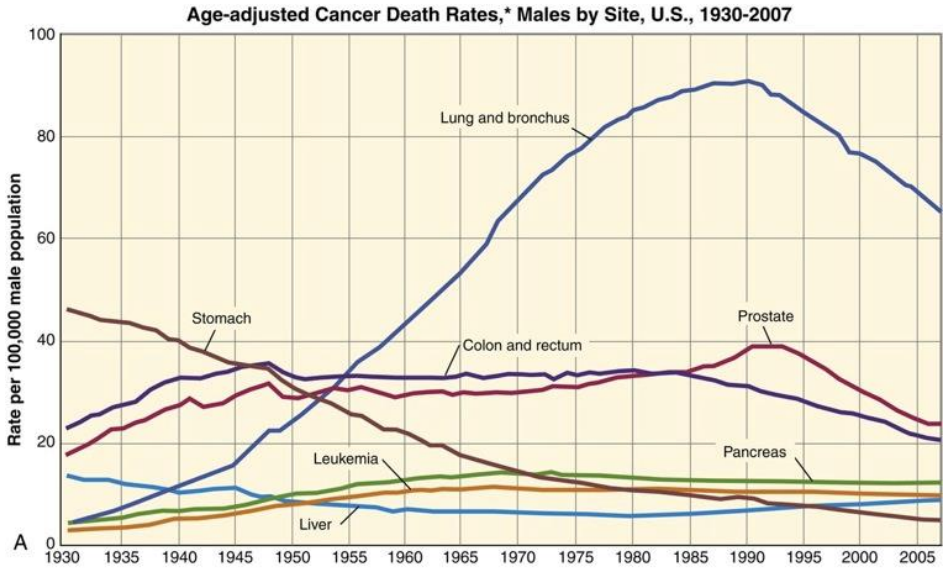
Cancer Deaths Due to Smoking



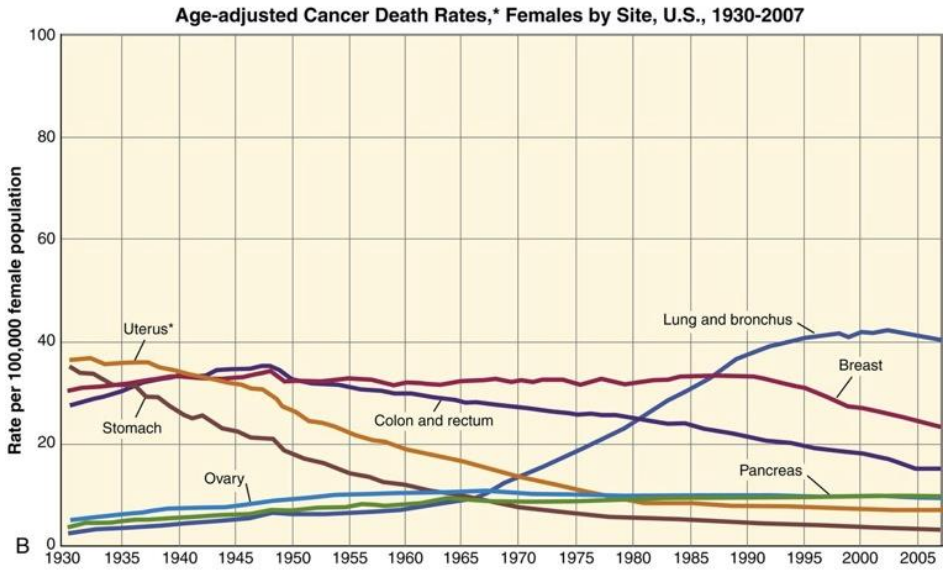
Smoking increases the risk of several types of cancer.

Cancer Death Rates in the US 1930 to 2007

Men



Women



*Per 100,000 age adjusted to the 2000 U.S. standard population.

Note: Due to changes in ICD coding, rumerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these changes.

Lecture 4D:

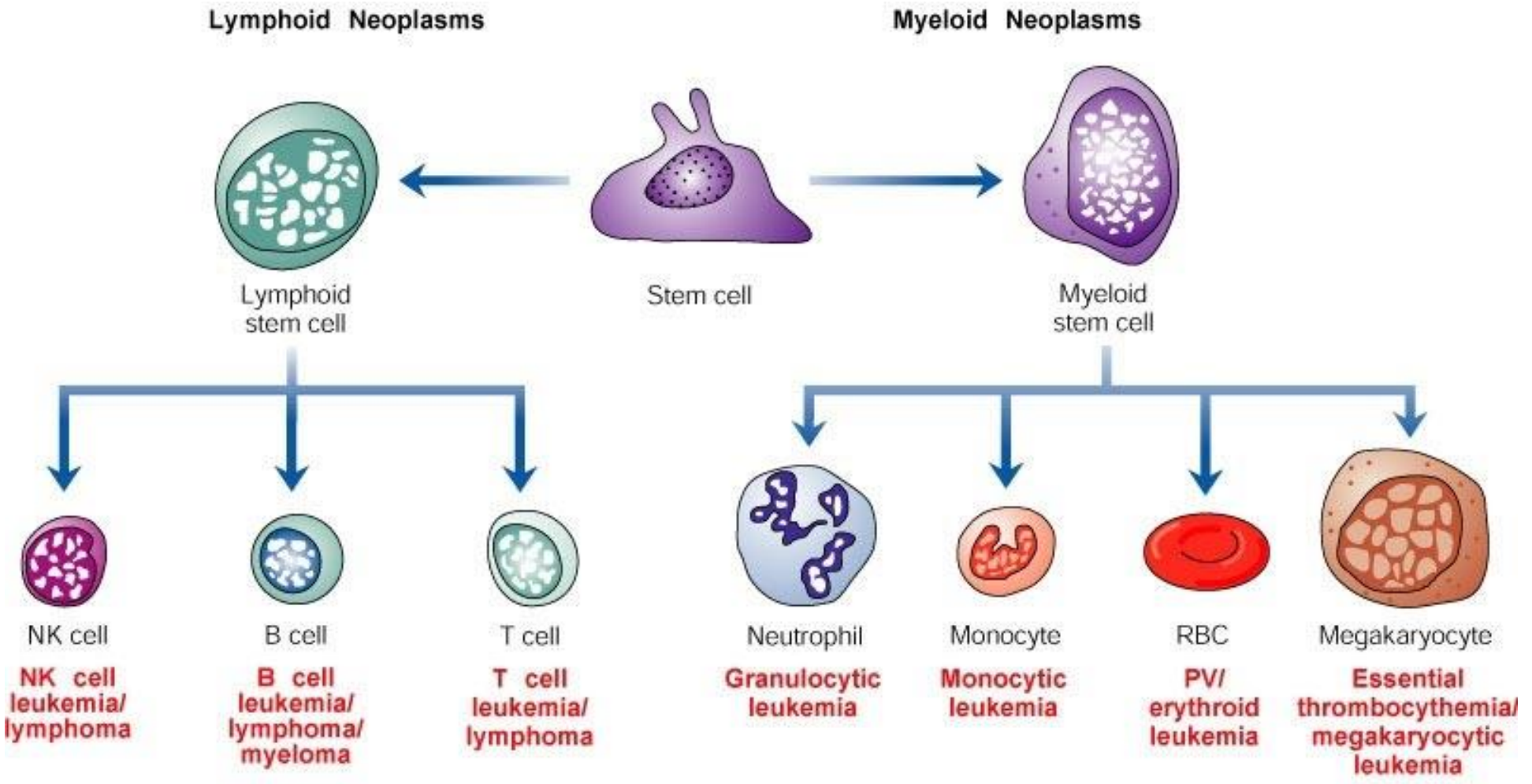
White Blood Cell Malignancies
Etiology of Myeloid and Lymphoid Neoplasms
General Principles Of Management
Myeloid Neoplasms
Lymphoid Neoplasms

Terminology: WBC Malignancies

- **Leukemia**-WBC cancer that presents in the bone marrow and/or circulating blood.
- **Lymphoma**-WBC cancer that presents in a lymph node, lymphoid tissue or a lymphoid organ other than a lymph node.
- **Lymphoid tumors** affect cells of the lymphoid stem cell line.
- **Myeloid tumors** affect cells of the myeloid stem cell line.
- **Myeloma**-a plasma cell cancer
- **Acute leukemia**-fatal within weeks if not treated; cancer cells are of an immature form and nonfunctional.
- **Chronic leukemia**-patients live much longer without treatment; cancer cells are a more mature form and partially functional.
- NOTE: Your book uses the **WHO (World Health Organization)** system of nomenclature for WBC malignancies. It is based on the cell type of the malignancies rather than on the body location of the malignancy. In this system of nomenclature lymphoid leukemias and lymphomas are not separate disorders but represent different stages of the same disease.

Etiology Of Myeloid And Lymphoid Neoplasms

Myeloid and Lymphoid Lineages and Associated Malignancies



Etiology Of Myeloid And Lymphoid Neoplasms

Risk Factors

- **Viruses**
  - Human T-cell leukemia virus (HTLV-1) in adult T-cell lymphoma and leukemia
  - HIV in B-cell lymphomas
  - Epstein-Barr virus (EBV) in Hodgkin disease and Burkitt lymphoma
- **Ionizing Radiation**
  - Japanese survivors of the atomic bomb have a 6X higher risk of leukemia.
  - Average annual exposure to cosmic rays and medical radiation procedures account for only about 5% of leukemia cases.
- **Chemicals**
  - Benzene and cigarette smoke are proven risks.
  - Any drugs that suppress bone marrow or immune function are likely to predispose to WBC cancers.
- **Disease Conditions**
  - Leukemia is linked to Fanconi anemia and aplastic anemia.
  - Down syndrome and Klinefelter syndrome also predispose to leukemia.

General Principles of Management

Diagnosis of WBC Tumors

- **Physical**
  - Enlarged liver, spleen, lymph nodes, or red bone marrow cavities
  - Hyperplasia of gum tissue
- **Blood Testing**
  - Anemia or polycythemia
  - Thrombocytopenia or thrombocytosis
  - Leukopenia or leukocytosis
  - Blast cells (immature blood cells) present in blood smears
  - Elevated uric acid
  - Elevated alkaline phosphatase
  - Hypercalcemia
- NOTE: tumor growth in the red bone marrow can cause severe crowding and rob normal cells of nutrients. Blood counts of **normal** formed elements are usually depressed.

General Principles of Management

Diagnosis of WBC Tumors

- **History:**
  - Weight loss
  - Fever, night sweats
  - Fatigue
  - Pruritis (itching)
  - Bone pain (due to bone marrow expansion)
  - Frequent infections
  - Symptoms of abnormal bleeding
  - Abdominal fullness (mostly due to splenomegaly)
  - Headache, nausea, vomiting
- **Definitive Diagnosis**
  - Bone marrow aspiration or lymph node biopsy

General Principles of Management

- **Symptom Notes**
  - **Severe anemia** may require blood transfusion if hematocrit falls below 30%. EPO is also helpful.
  - **Severe thrombocytopenia** (<20,000 per microliter) may require platelet transfusion to guard against spontaneous bleeding.
  - **Severe neutropenia** (<500 per microliter) requires protective isolation to reduce the risk of infection. Infections are managed aggressively. Infection is the leading cause of death in immunocompromised leukemic patients.
  - **CNS involvement** can occur in any form of leukemia. It can present with increased intracranial pressure and associated seizures, changes in mental ability, headache, nausea, vomiting or visual changes.
- **Treatment**
  - A combination of **chemotherapy** to eradicate malignant cells and **stem cell transplant** to rescue and restore bone marrow function.
  - Serious side effects occur. For some patients and their families the side effects outweigh the projected effectiveness of the treatment. They may opt for palliative care instead.

General Principles of Management

Complications of Chemotherapy

- Chemotherapy interferes with nutrition. Newer anti-emetics are helpful in stemming nausea, vomiting and resultant weight loss during treatment.
- Infection due to bone marrow suppression is the **most serious** complication. Growth factors to stimulate granulocyte production may be used.
- Pain management is crucial! Bone and joint pain are most common due to pressure from bone marrow expansion and hemarthosis. Mouth pain due to stomatitis is also common.
- Loss of skin and mucous membrane integrity causes pain and increased risk of infection.
- Alopecia (hair loss) leads to altered body image and inability to cope.
- Abnormalities in growth, development, and fertility are of concern in children.

General Principles of Management

Bone Marrow Transplantation

- Stem cells harvested from bone marrow or peripheral blood are introduced into the patient's body intravenously. They travel to the bone marrow where they differentiate into functional RBCs, WBCs and platelets. Two types of transplant methods exist:
- **Allogeneic Transplantation**-cells are aspirated from the bone marrow of a tissue-matched donor for cancer patient bone marrow transplants. The donor is often a sibling.
- **Autologous Transplantation**-stem cells are harvested from peripheral blood of the cancer patient and stored during cancer treatment. The stem cells are then reinfused into the patient after treatment is complete. Methods are available to remove the leukemic cells from the peripheral blood while retaining the normal stem cells.

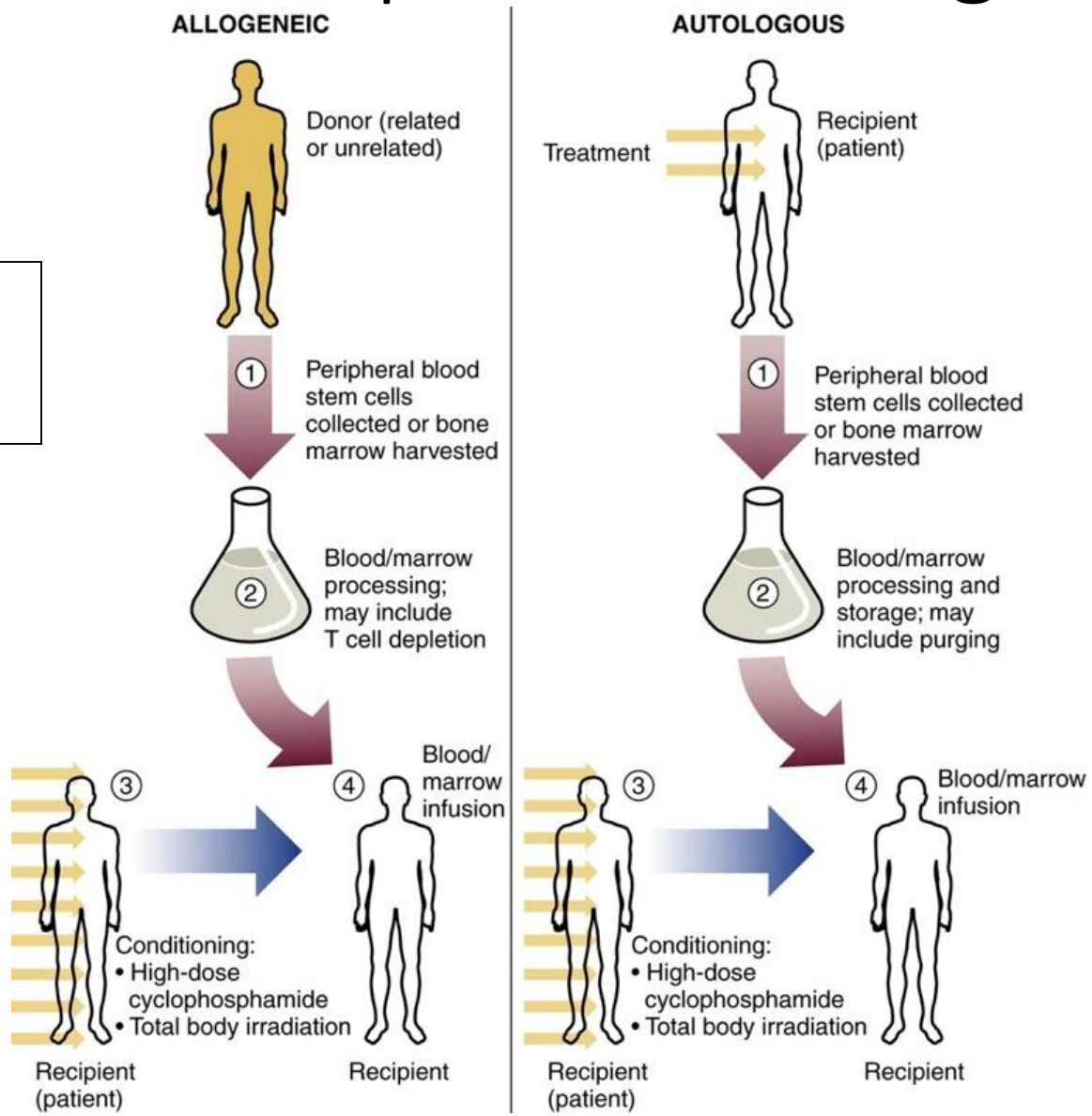
General Principles of Management

Bone Marrow Transplantation

- Each of the two transplantation methods has an advantage over the other.
  - Autologous transplantation **removes the risk of a graft versus host (GVH)** reaction. (In a GVH reaction the transplanted immune cells become sensitized against normal host tissues.)
  - The downside of autologous transplantation is that it may mean giving the patient back some of their own cancer cells. It is difficult to separate all of the cancerous cells from the normal stem cells.
  - Allogeneic transplantation **reduces the risk of recurrent cancer** more than autologous transplantation, but carries the risk of GVH. Methods for removing T cells from the transplant help to reduce the risk of GVH reaction.
  - Here's something really cool! In both AML and CML (acute and chronic myelocytic leukemia) **allogeneic transplantation is preferred** because the GVH reaction is mounted against the host's leukemic cells **(graft versus leukemia)** while normal host tissue is only mildly affected.
  - If a suitable donor is not available for the AML or CML patient, autologous transplants are performed. They do extend life and have fewer side effects, but cure is less likely.

General Principles of Management

Two Types of Bone Marrow Transplants



Myeloid Neoplasms

- Myeloid neoplasms occur when a myeloid stem cell is transformed to malignancy and then proliferates in the bone marrow. Abnormal cells are released into the circulation.
- **Myeloproliferative Diseases**
  - The stem cell involved is **multipotent** and thus the disease affects **multiple myeloid cell types.**
  - The bone marrow is hypercellular.
  - One or more fairly normal cell types are overproduced. Those cells are morphologically fairly normal and retain much of their function.
  - There are chromosomal aberrations present.
  - There is eventual conversion to AML (AML cells are morphologically abnormal and non-functional) or bone marrow fibrosis.
  - Examples:
    - **Chronic Myeloid Leukemia (CML)**
    - **Polycythemia Vera (PV)-already covered**
    - **Essential Thrombocythemia (ET)-already covered**

Myeloid Neoplasms

Various cell types in the myeloid developmental pathway are associated with leukemias.

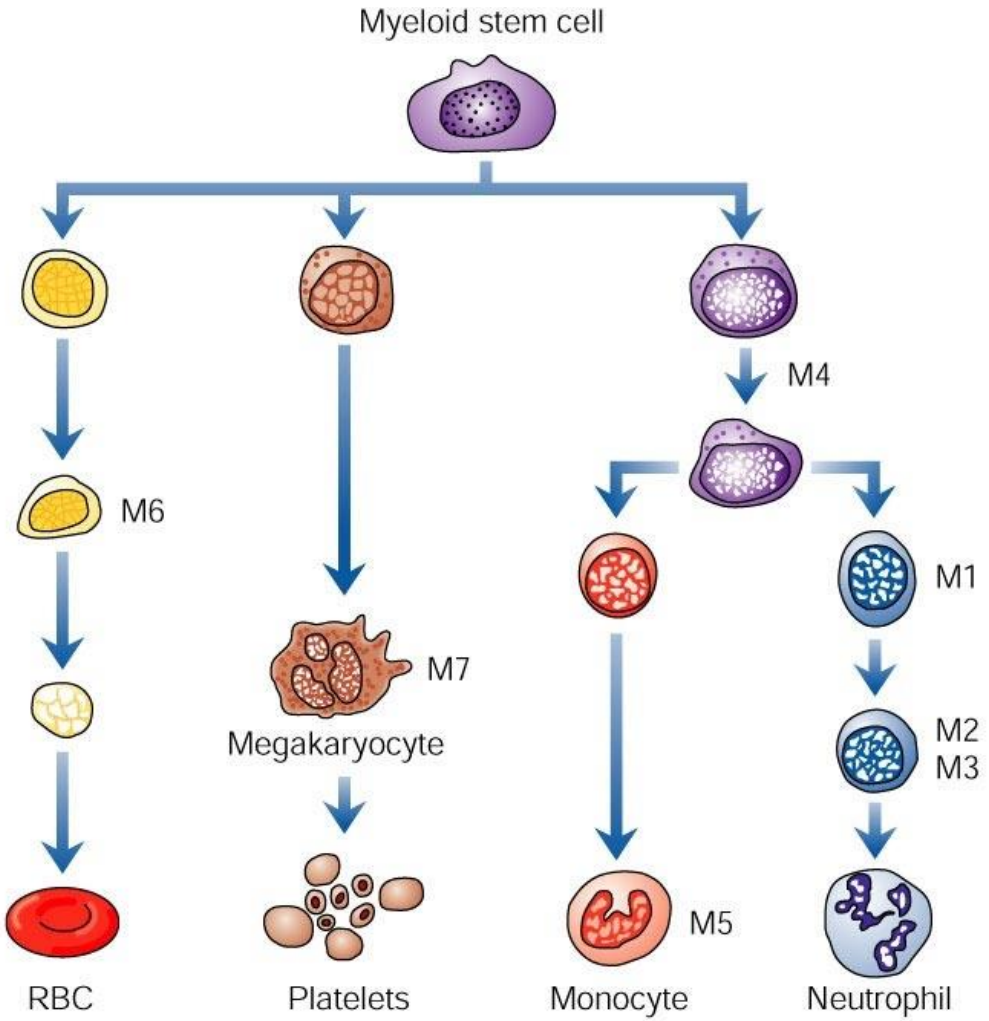
M1, M2, M3: granulocytic leukemia

M4: monocytic/granulocytic leukemia

M5: monocytic leukemia

M6: erythroid leukemia

M7: megakaryocytic leukemia

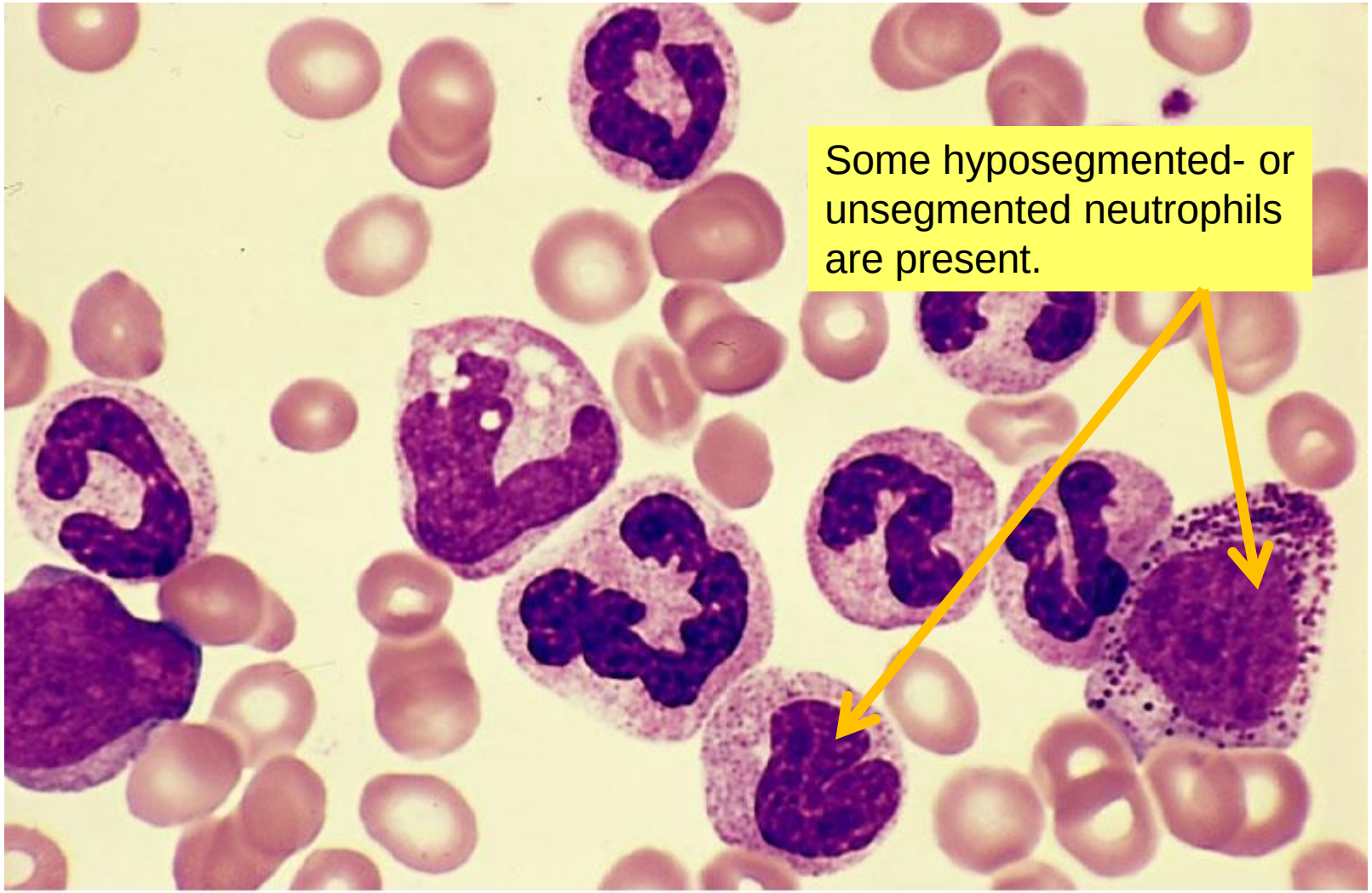


Myeloid Neoplasms: CML

- **Pathogenesis and Clinical Manifestations**
  - 15% of all leukemias are CML, chronic myeloid leukemia. It almost always affects **adults.**
  - Most cases are associated with the **"Philadelphia chromosome"**, a translocation between chromosomes 9 and 22.
    - Causes the formation of a fusion gene.
    - The fusion gene product is an **enzyme** that spurs cell proliferation and reduces apoptosis.
  - The drug, **imatinib,** has been developed to counteract the fusion gene product. CML due the fusion gene is unique--**a single oncogene** confers the malignant state. Multiple genes are usually required.
  - Peripheral blood smears show **high granulocyte count** with some hyposegmented or unsegmented neutrophils (immature neutrophils).
  - Splenomegaly is usually present.
- **Prognosis**
    - CML does not respond well to chemotherapy.
    - Allogeneic bone marrow transplant can be curative, but it is associated with 25% mortality. Disease free 5 year survival is about 60%.
    - CML due to the Philadelphia chromosome ALWAYS progresses to AML.
    - AML prognosis (in adults) is poor regardless of treatment.

Myeloid Neoplasms: CML

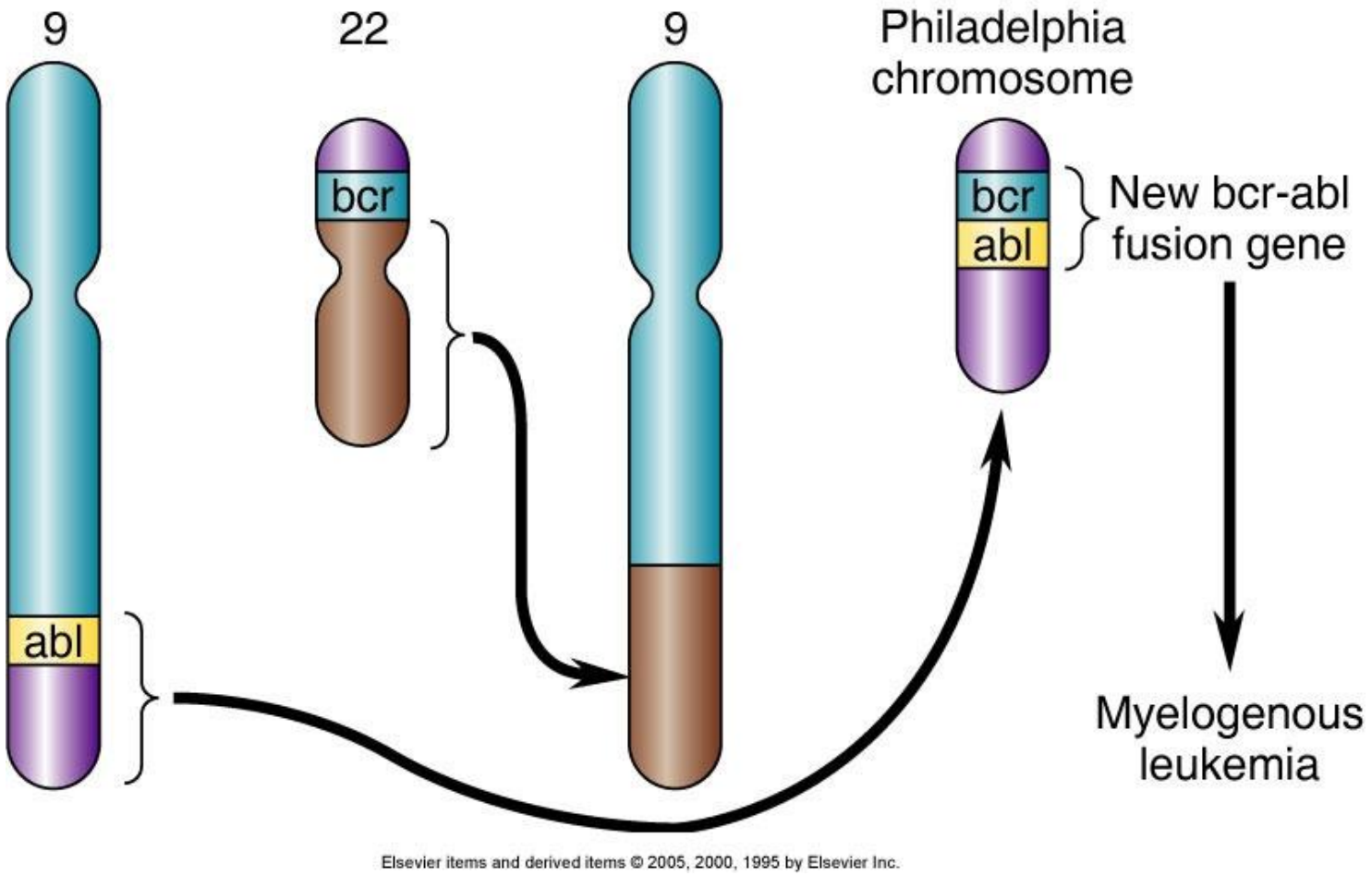
Peripheral Blood Smear: Chronic Myeloid Leukemia (CML)



From Henderson ES et al, editors: Leukemia, ed 7, Philadelphia, 2003, Saunders, p 593.

Myeloid Neoplasms: CML

Formation of the Philadelphia Chromosome



Myeloid Neoplasms: AML

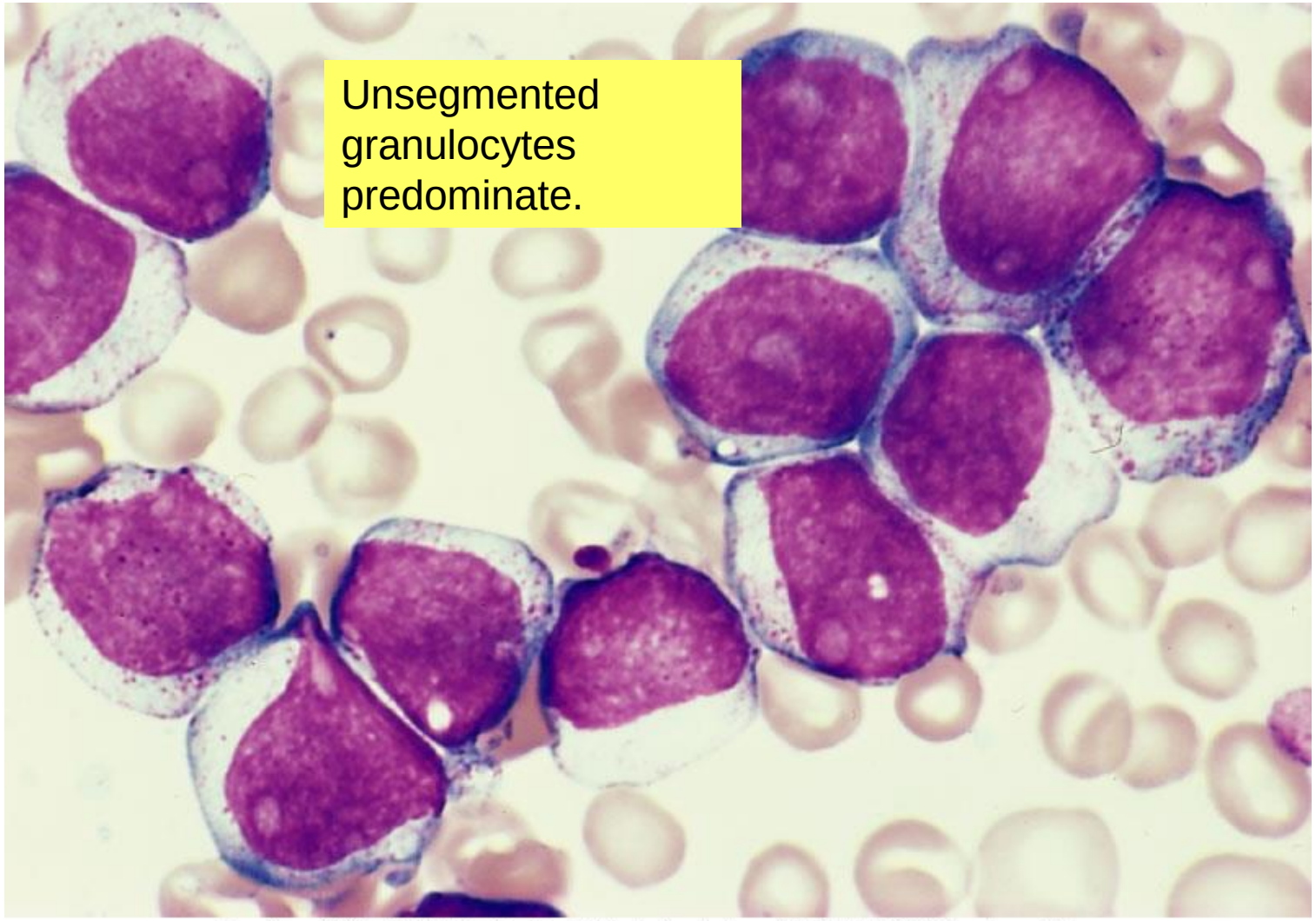
- **Pathogenesis and Clinical Manifestations**
  - AML is a **myelodysplastic** syndrome.
  - AML cells are less mature and more abnormal than CML cells (myeloproliferative cells).
  - Bone marrow aspirate with **more than 20% myeloid blast cells** is classified as AML.
  - Myeloblasts with large unsegmented or hyposegmented nuclei predominate.
  - The worst cases involve loss of tumor suppressor genes (RB or P53).
  - 80% of AML occurs in adults, 20% in children
  - Median age at presentation is 64 years.
  - Onset is abrupt and difficult to distinguish from ALL.
    - Bone pain
    - Thrombocytopenia
    - Anemia
    - Increased susceptibility to infection.
- **Prognosis**
  - AML prognosis is poor, disease free 5 year survival is about 25% overall.
  - For age 15 years and younger disease free 5 year survival is about 66%.

Myeloid Neoplasms: AML

- **Treatment of AML**
  - Chemotherapy
  - New therapies employing monoclonal antibodies are likely to improve the prognosis of AML.

Myeloid Neoplasms: AML

Peripheral Blood Smear: Acute Myeloid Leukemia (AML)



From Kumar V, Cotran RS, Robbins SL, editors: Robbins basic pathology, ed 7, Philadelphia, 2003, Saunders, p 424.

Lymphoid Neoplasms

Lymphoid Leukemias-cancer cells are localized in the bone marrow or the blood.

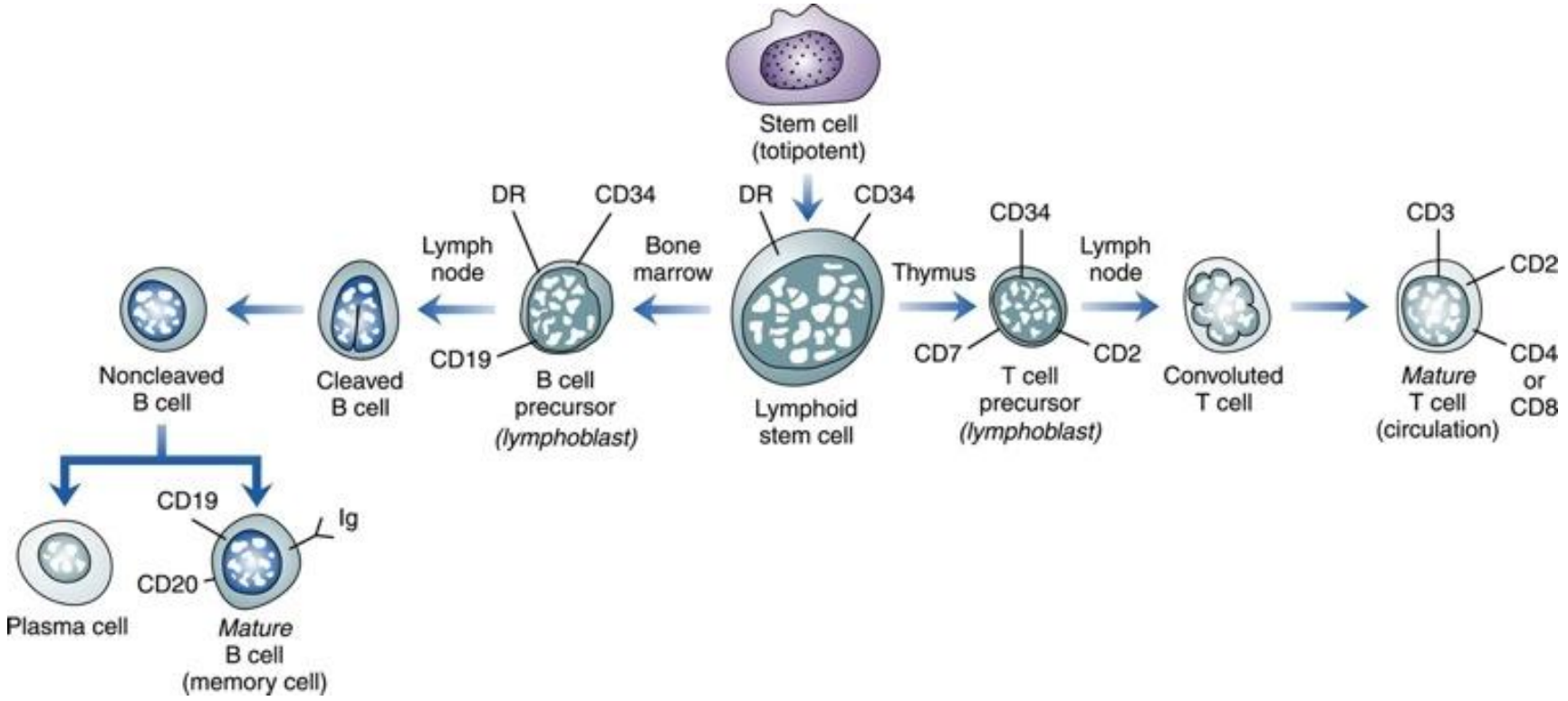
- Chronic Lymphocytic Leukemia (CLL)
- Acute Lymphocytic Leukemia (ALL) aka Acute Lymphoblastic Leukemia
- Hairy Cell Leukemia
- Plasma Cell Myeloma (Multiple Myeloma)

Lymphomas-cancer cells are localized in lymph nodes and other lymphoid tissues

- Hodgkin Disease aka Hodgkin Lymphoma
- B-Cell, T-Cell, and NK-Cell Lymphoma aka Non-Hodgkin Lymphoma

Lymphoid Neoplasms

Maturation pathways of B and T cells showing the stages at which lymphocyte maturation is arrested in various types of leukemia. The **surface markers** associated with the various cell types (DR, CD34, etc.) are helpful in identifying the type of leukemia and in selecting the best treatment.

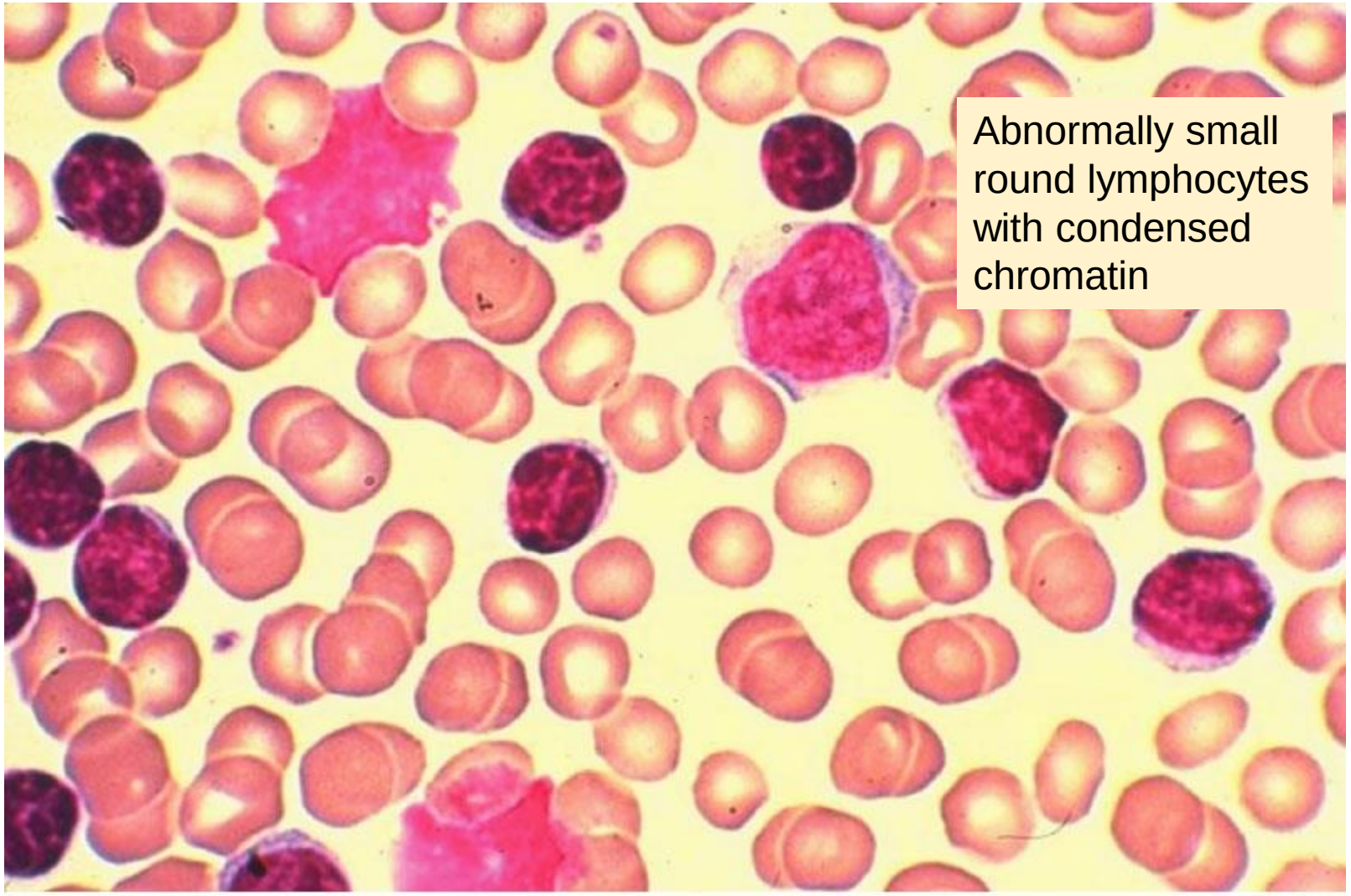


Lymphoid Neoplasms: CLL

- **Pathogenesis and Clinical Manifestations**
  - CLL accounts for 30% of all leukemias. It affects maily older adults; average age at diagnosis is 70 years.
  - In **95% of cases a malignant, fairly mature B-cell precursor** is at fault.
  - T-cell precursor types are rare, but more aggressive.
  - CLL **remains asymptomatic** for an extended period. It is often discovered by routine blood testing.
  - Leukemic B cells fail to produce normal antibodies, so infections are common.
  - Bone marrow aspirates show **many small round lymphocytes with dense chromatin.**
  - CLL cells live longer than they should as there is a defect in apoptosis.
  - Invasion of lymphoid tissues produces splenomegaly and lymphadenopathy.
- **Prognosis**
  - 5-year survival rate in those 20 years and older is 85%.
  - The genetic lesion involved in the CLL determines the prognosis. Types with short telomere length or defective P53 have poorer outcomes.

Lymphoid Neoplasms: CLL

Bone Marrow Aspirate Chronic Lymphoid Leukemia (CLL)



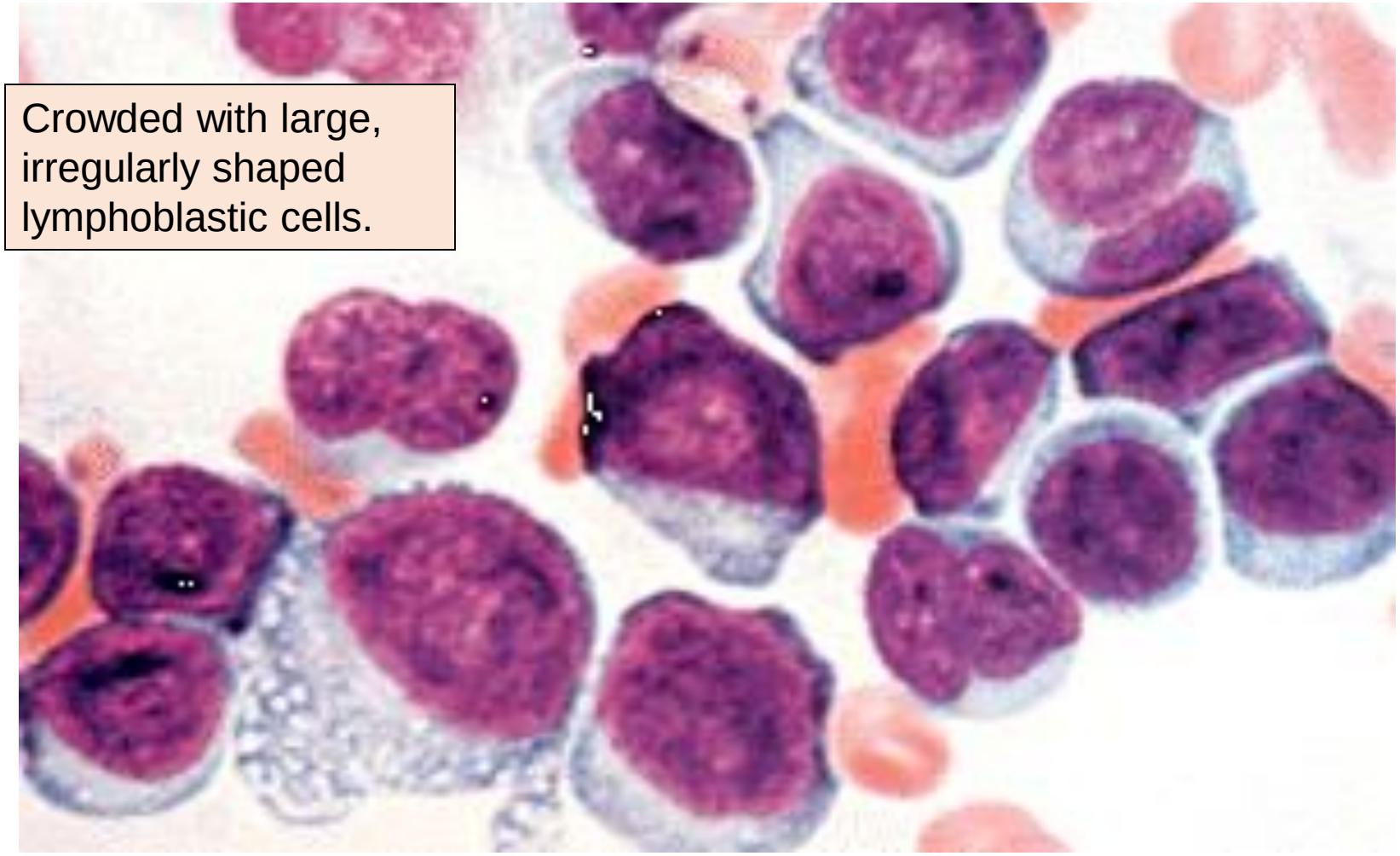
From Henderson ES et al, editors: Leukemia, ed 7, Philadelphia, 2003, Saunders, color plate 11-28.

Lymphoid Neoplasms: ALL

- **Pathogenesis and Clinical Manifestations**
  - 80% cases of acute lymphocytic (aka lymphoblastic) leukemia (ALL) involve **B-cell precursors**, the remainder involve T-cell precursors.
  - Tumors are lymphoblastic (immature cells) neoplasms; tumor cells resemble lymphoblasts.
  - Several types are due to translocations that produce fusion genes.
- **Diagnosis**
  - 20% of bone marrow cells must be **lymphoblasts.** Lymphoblasts are larger than lymphocytes.
  - ALL is primarily **a disease of children** with peak incidence between 3 and 7 years.
  - Onset of symptoms is abrupt.
    - Children may refuse to walk due to bone pain.
    - About 3% of children present with CNS symptoms.
    - Exhibit loss of appetite, weight loss, fatigue, and abdominal pain
  - Presents as a leukemia; often becomes a lymphoma
- **Prognosis**
  - The five-year survival rate is 85% in children, but only 30-50% in adults.
  - Lymphoblastic B-cell types have a better prognosis than T cell types.

Lymphoid Neoplasms: ALL

Bone Marrow Aspirate Acute Lymphoblastic Leukemia (ALL)

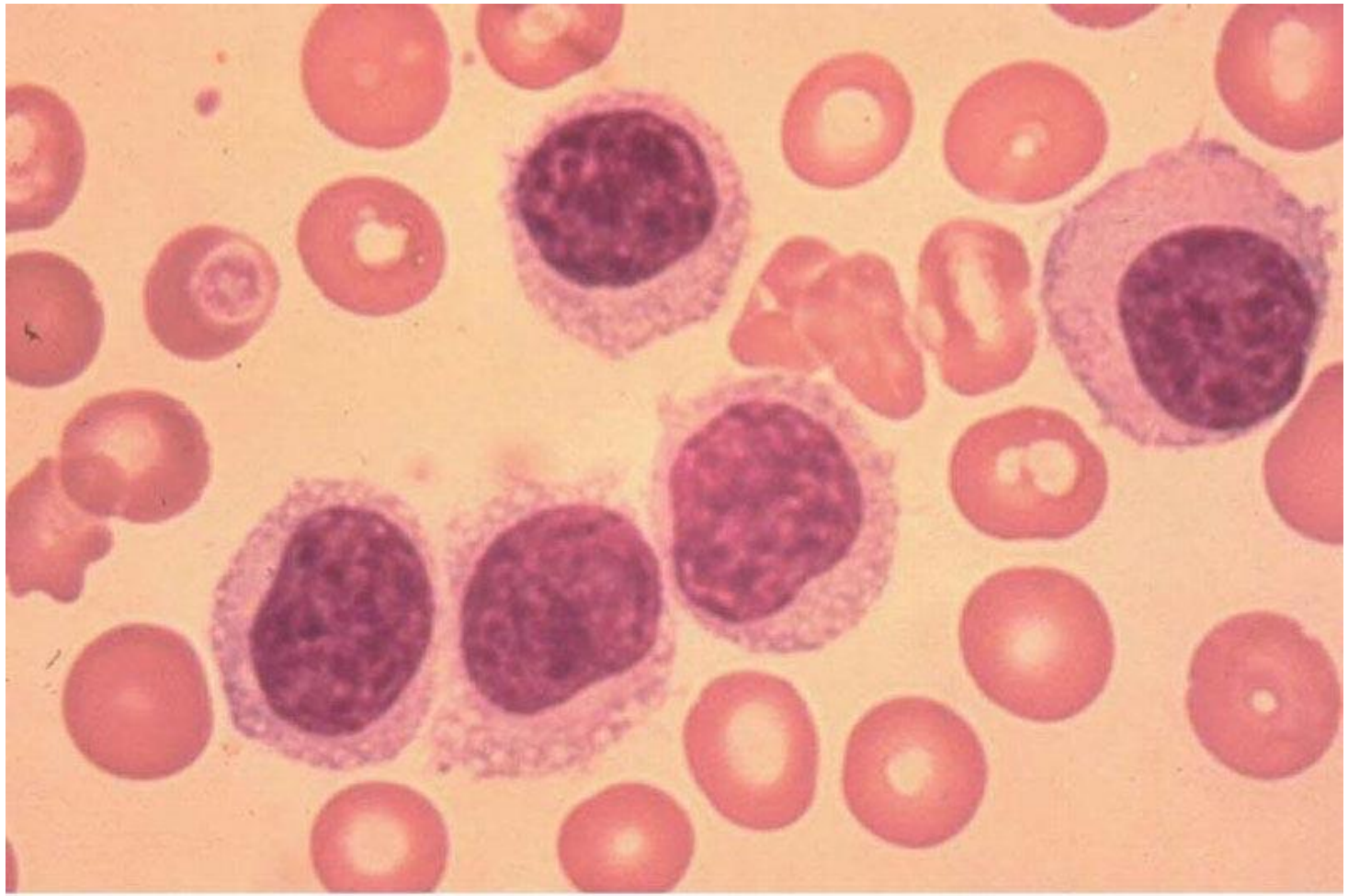


Lymphoid Neoplasms: Hairy Cell Leukemia

- **Pathogenesis and Clinical Manifestations**
  - Rare form of CML; 2% of adult leukemias in the US
  - Interesting not only because it is **highly treatable** chronic leukemia, but also because **affected males outnumber affected females 5 to 1!** The mechanism of the gender difference is unknown.
  - Median age at presentation is 55 years.
  - Fairly mature B-cell phenotype with hair-like projections on the cells.
  - Patients have hairy cells in peripheral blood.
  - Splenomegaly is common.
- **Prognosis**
  - Chemotherapy produces complete remission (CR) rates of 90%.

Lymphoid Neoplasms: Hairy Cell Leukemia

Hairy Cell Leukemia



From Henderson ES et al, editors: Leukemia, ed 7, Philadelphia, 2003, Saunders, color plate 11-29.

Lymphoid Neoplasms: Plasma Cell Myeloma

- **Pathogenesis and Clinical Manifestations**
  - Plasma cell myeloma (multiple myeloma) is a malignancy of mature antibody-secreting cells (plasma cells).
  - Tendency to **invade bone** and form multiple tumors.
  - Plasma cell myeloma affects **ONLY adults**, usually over the age of 40.
  - Men are affected more than women.
  - Abnormalities in chromosome structure are common.
  - The malignant tumor cells belong to a **single clone**. They are genetically identical. This is an **exception** to the rule!
  - Tumors secrete antibodies. The antibodies produced are identical (monoclonal).
    - Antibodies of a single type are revealed on electrophoretic gels.
    - Light chain antibody fragments (**Bence Jones protein**) accumulate in urine.
    - These proteins cause **kidney damage**.

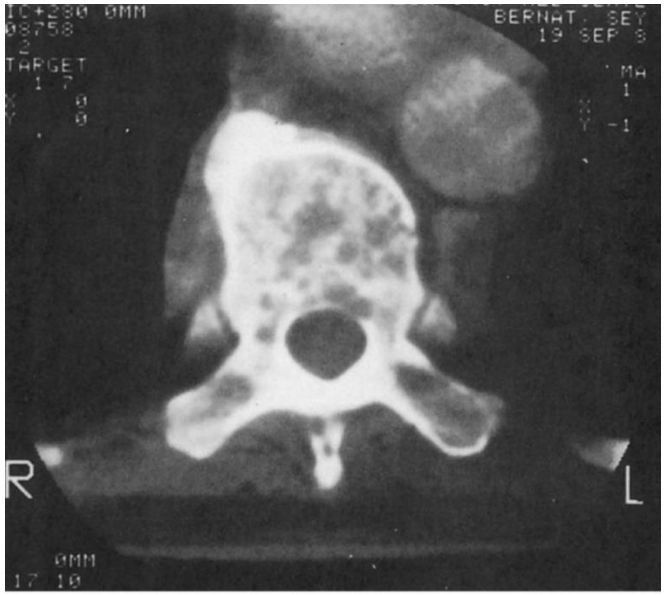
Lymphoid Neoplasms: Plasma Cell Myeloma

- A **premalignant state called MGUS (monoclonal gammopathy of uncertain significance)** is present in some patients. They produce monoclonal antibodies, but exhibit no bone or kidney effects. About 25% of MGUS patients progress to malignancy.
- Bone lesions produced by multiple myeloma are associated with:
  - Fractures, especially compression fractures of the vertebral column
  - A "honeycomb" appearance in bones on x-ray
  - Hypercalcemia-damaged bone releases calcium ions to the blood.
- Bone marrow biopsy shows 30-90% plasma cells--5% is normal.

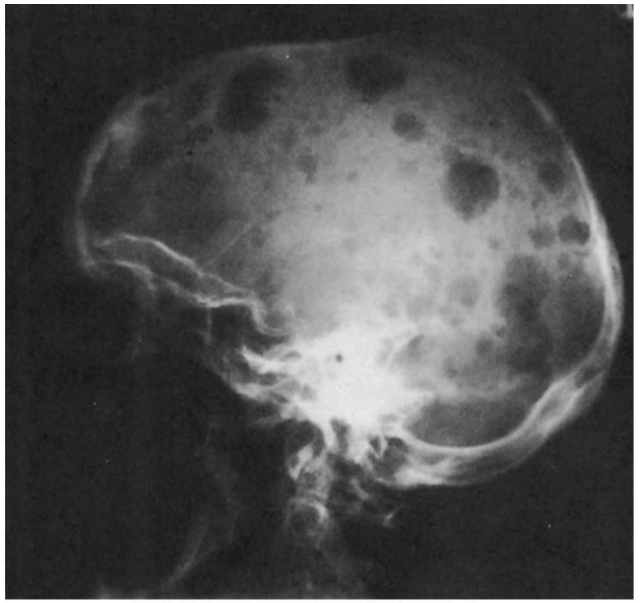
Lymphoid Neoplasms: Plasma Cell Myeloma

- **Prognosis and Treatment**
  - Complete remission with chemotherapy is about 60%.
  - Disease free 5-year survival rate is 47%.
  - Chemo followed by allogeneic bone marrow transplant offers a better CR rate, but the death rate associated with transplantation is high (40-50%)
  - Renal dysfunction must be treated as well. Renal failure is not uncommon.
  - Bone pain is more problematic than in other WBC malignancies.

Bone Tumors in Plasma Cell Myeloma

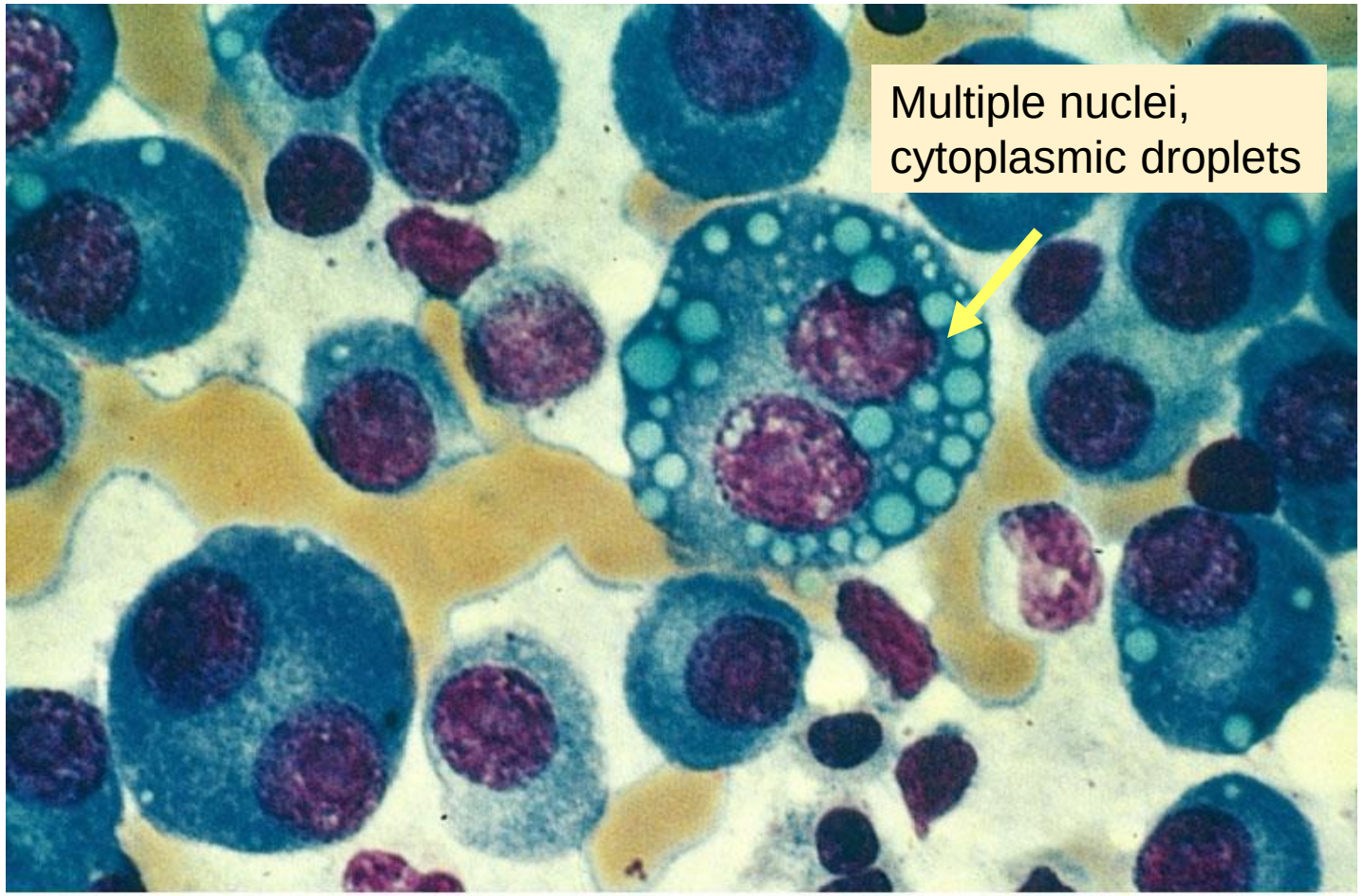


Courtesy Marvin J. Stone, MD, Sammons Cancer Center, Baylor University Medical Center, Dallas.


Courtesy Marvin J. Stone, MD, Sammons Cancer Center, Baylor University Medical Center, Dallas.

Lymphoid Neoplasms: Plasma Cell Myeloma

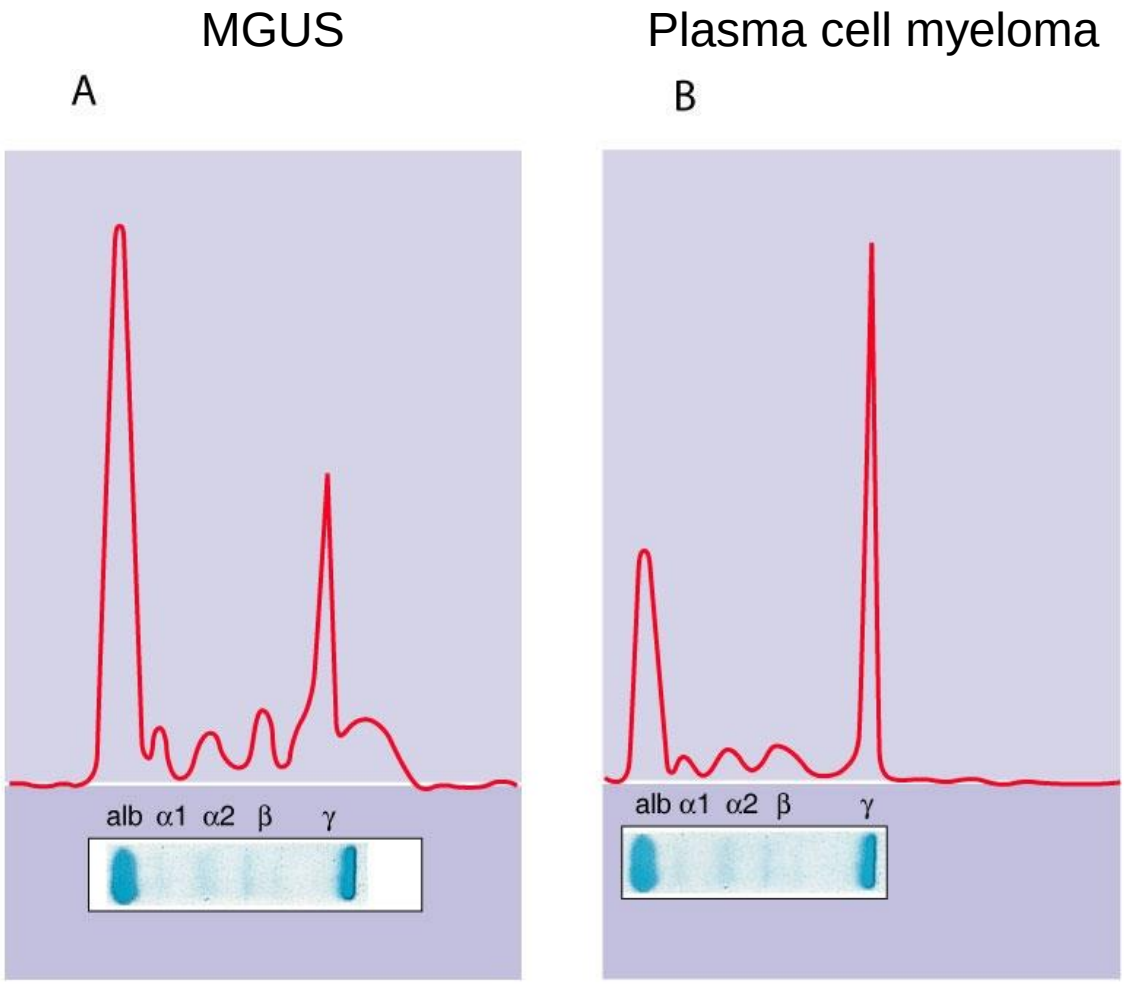
Bone Marrow Aspirate Plasma Cell Myeloma (Multiple Myeloma)



From Kumar V, Cotran RS, Robbins SL, editors: Robbins, 2003, Saunders basic pathology, ed 7, Philadelphia, p 430.

Monoclonal Gammopathy of Undetermined Significance (MGUS) is a pre-malignant state for multiple myeloma.
About 25% of MGUS patients progress to malignant disease.

Note: The gamma globulin protein peak (above the Greek letter gamma: Ɣ) is present in MGUS, but much higher in plasma cell myeloma.



Lymphoid Neoplasms: Hodgkin Disease

- **Pathogenesis and Clinical Manifestations**
  - Hodgkin disease accounts for 30% of malignant lymphomas in the US.
  - It occurs across the age continuum
  - Males are affected more often than females.
  - Males have a worse prognosis than females.
  - It is characterized by the presence of **Reed-Sternberg cells** in lymph nodes.
    - Reed-Sternberg cells are **abnormal B-cells** (large and binucleated).
    - They originate clonally in the germinal center of a lymph node.
    - **Epstein-Barr virus** is frequently found in the genome of Reed-Sternberg cells.
    - Inflammatory cells also accumulate in the lymph node.
    - Reed-Sternberg cells constitute ~2% of the cells in a lymph node tumor.
  - Hodgkin disease spreads in a **predictable manner** depending on the node of origin.
    - Lymph node enlargement usually occurs **above the diaphragm first** with the **cervica**l nodes being most often involved at presentation.
    - As the disease spreads other nodes and organs may be involved including the bone marrow and the spleen.

Lymphoid Neoplasms: Hodgkin Disease

Reed-Sternberg Cell (Lymph Node Tissue)

in Hodgkin Lymphoma

From Kumar V, Cotran RS, Robbins SL, editors: Robbins basic pathology, ed 7, Philadelphia, 2003, Saunders, p 432. Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas.

Lymphoid Neoplasms: NonHodgkin Disease

- **Pathogenesis and Clinical Manifestations**
  - Non-Hodgkin lymphoma is NOT associated with Reed-Sternberg cells.
  - They are much more common than Hodgkin lymphoma.
  - They usually arise in lymph nodes (but can originate in any lymphoid tissue) and may involve B cell, T cell or NK cell precursors.
  - 95% of cases occur in older adults.
  - Males are at slightly higher risk than females.
  - The **incidence is on the rise** particularly in areas with large **AIDS** populations. 50,000 new cases per year are diagnosed.
  - Viruses are suspected in some types:
    - **Epstein-Barr virus** in Burkitt lymphoma, a B-cell lymphoma.
    - **HTLV-1** in adult T-cell lymphomas.
  - Most patients present with advanced disease, **stage III or IV**.
  - Extranodal involvement occurs **earlier** than in Hodgkin lymphoma.
  - Spread of disease is **NOT predictable** as in Hodgkin lymphoma.
  - Complications occur **more frequently** in non-Hodgkin than in Hodgkin disease. Serious complications include obstruction of the superior vena cava and spinal cord compression.

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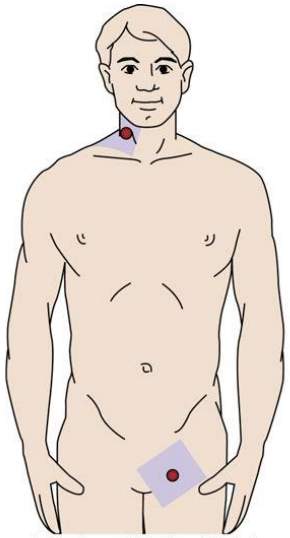
Lymphoma

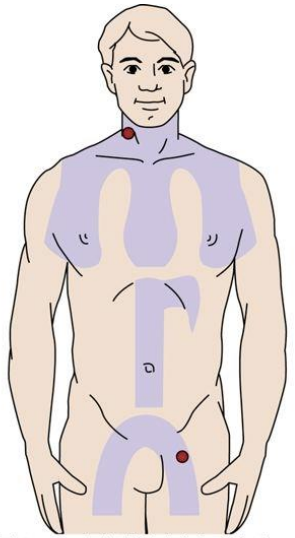
- **Prognosis and Treatment of Lymphomas**
  - Treatment depends on staging.
  - Due to the limited localization of tumors lymphomas may be treated successfully with **radiation** in early stages of the disease.
  - Non-Hodgkin lymphoma has a **poorer prognosis** than Hodgkin lymphoma due to advanced stage at presentation.
    - Hodgkin Lymphoma: 85% 5-year survival rate
    - Non-Hodgkin Lymphoma: 50% 5-year
  - Survival rate in non-Hodgkin is diminished due to diagnosis at a later stage of progression (stage III or IV)
  - Non-Hodgkin lymphoma is more likely than Hodgkin lymphoma to involve metastasis to organs other than lymph nodes.
  - The **Ann Arbor System of Staging for Lymphoma (with Cotswold Modifications)** is used for staging all lymphomas.

Lymphoma

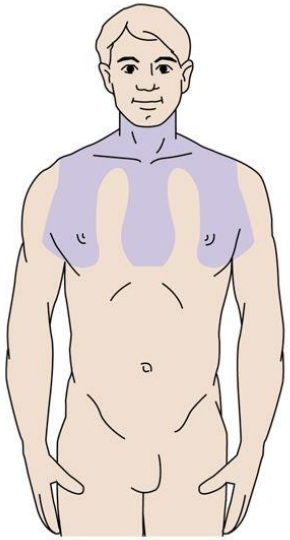
Typical radiation fields for treatment of lymphoma



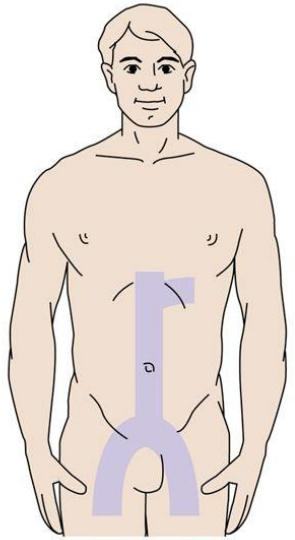
Local, or involved field (IF), irradiation



Extended field (EF) irradiation

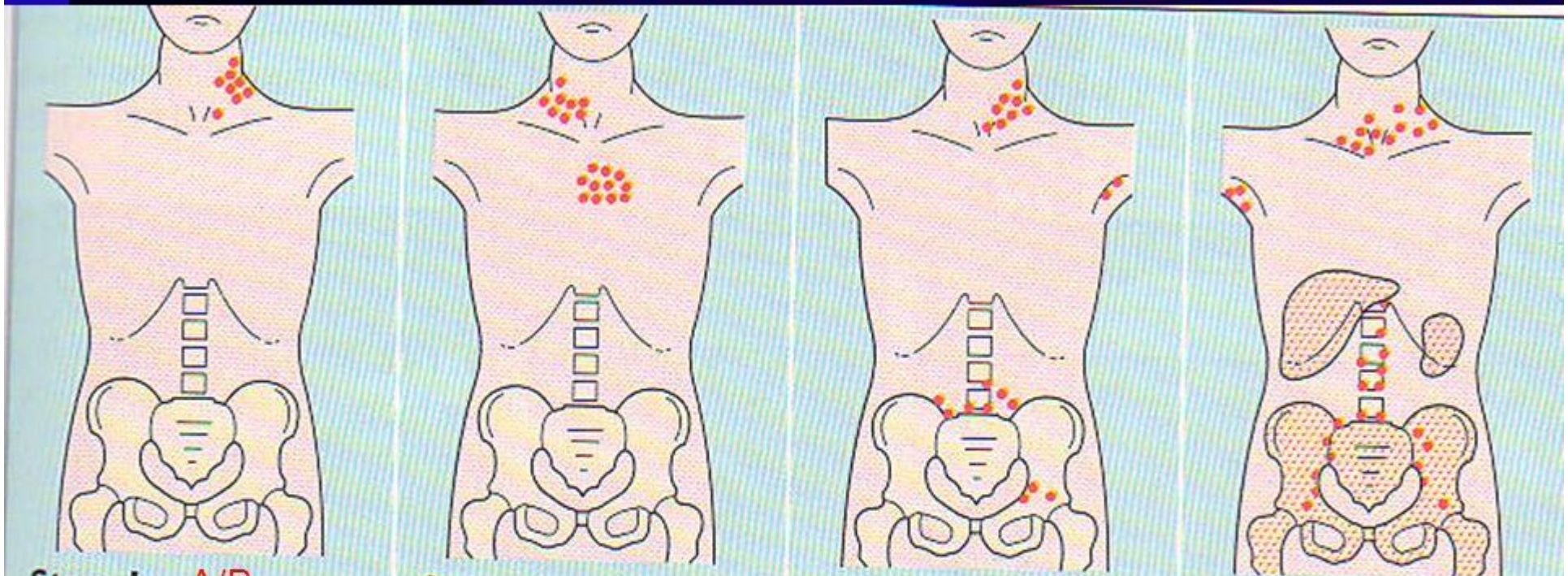


Mantle field irradiation



Inverted-Y field irradiation

Ann Arbor Staging



Stage I: •A/B
involvement of single lymph node region or single extralymphatic site (I_E)

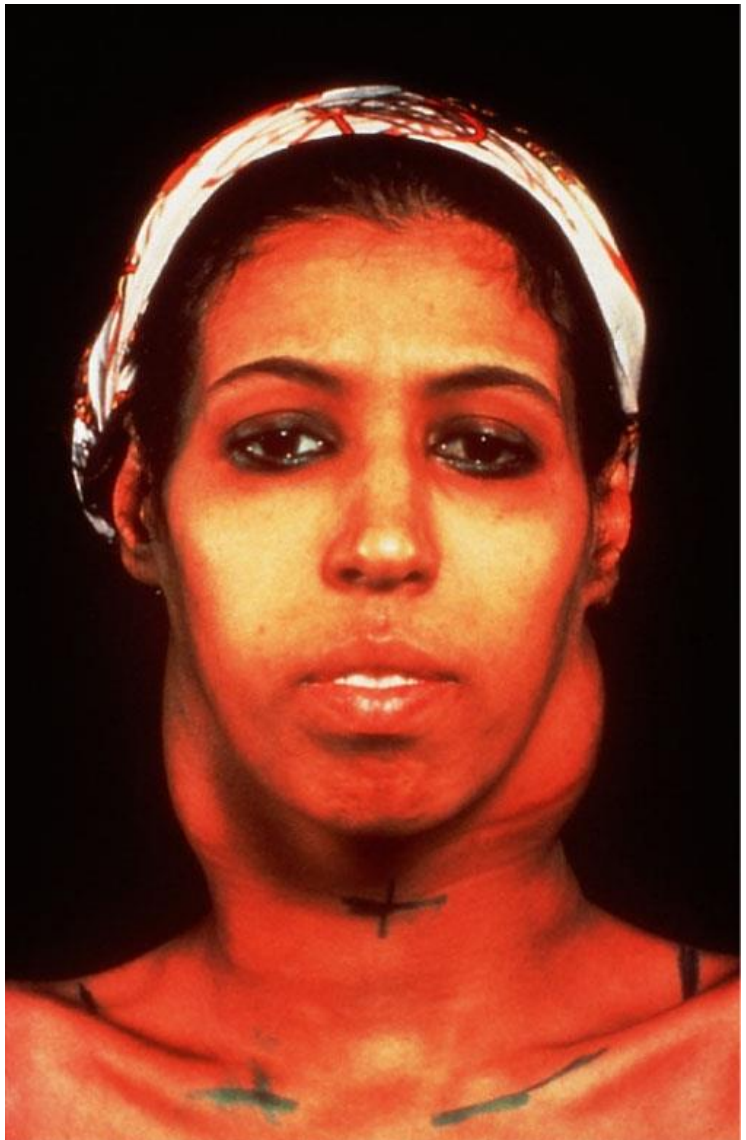
Stage II: •A/B
involvement of two or more lymph node regions on same side of diaphragm; may include localized extralymphatic involvement on same side of diaphragm (II_E)

Stage III: •A/B
involvement of lymph node regions on both sides of the diaphragm; may include spleen (III_S) or localized extranodal disease (III_E)

Stage IV: •A/B
diffuse extralymphatic disease (e.g. in liver, bone marrow, lung, skin)

Lymphoma

Hodgkin Lymphoma Stage IIA



QUIZ 4CD

- COMPLETE QUIZ 4CD.
- THEN PREPARE FOR EXAM 4.

EXAM 4

- COMPLETE EXAM 4.
- THEN GO ON TO MODULE 5AB PPT.