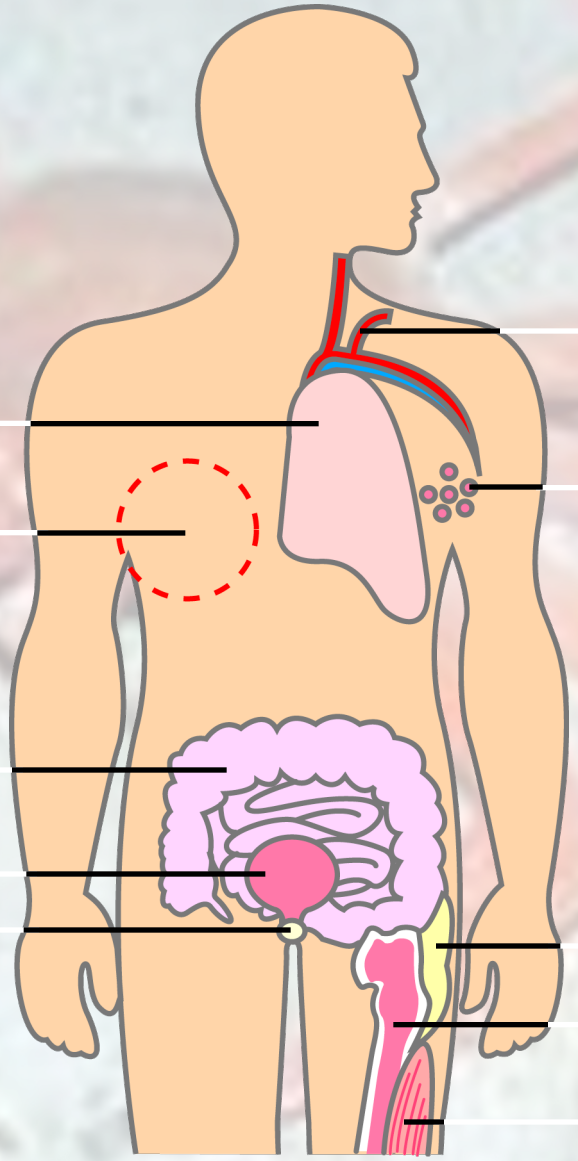
Cancer and Tumor Spread

Dr. Gary Mumaugh

- Even though there are many types of cancers (over 200) – they are essentially cells dividing abnormally.
- Cancer could be defined as out-of-control cell growth.
- The normal cell division and growth in the body are accelerated and new tissue is formed.
- **Neoplasm – new growth**
  - **Excessive multiplication of cells in a part of the body**
- Primary site – original site of the tumor
  - kidney, prostate, breast, GI, cervix, ovary
- Secondary site – site that metastasizes to

- In normal physiology there are mechanisms which regulate cell division and the generation of new tissues.
- If these physiological mechanisms fail for any reason, cells will multiple at an increased rate.
- This will result in the presence of a greater number of cells.
- These cells take up space and usually form space occupying lumps or tumors.
  - Tumors can be benign or malignant

Different Kinds of Cancer



Some common carcinomas:

Lung

Breast (women)

Colon

Bladder

Prostate (men)

Leukemias:

Bloodstream

Lymphomas:

Lymph nodes

Some common sarcomas:

Fat

Bone

Muscle

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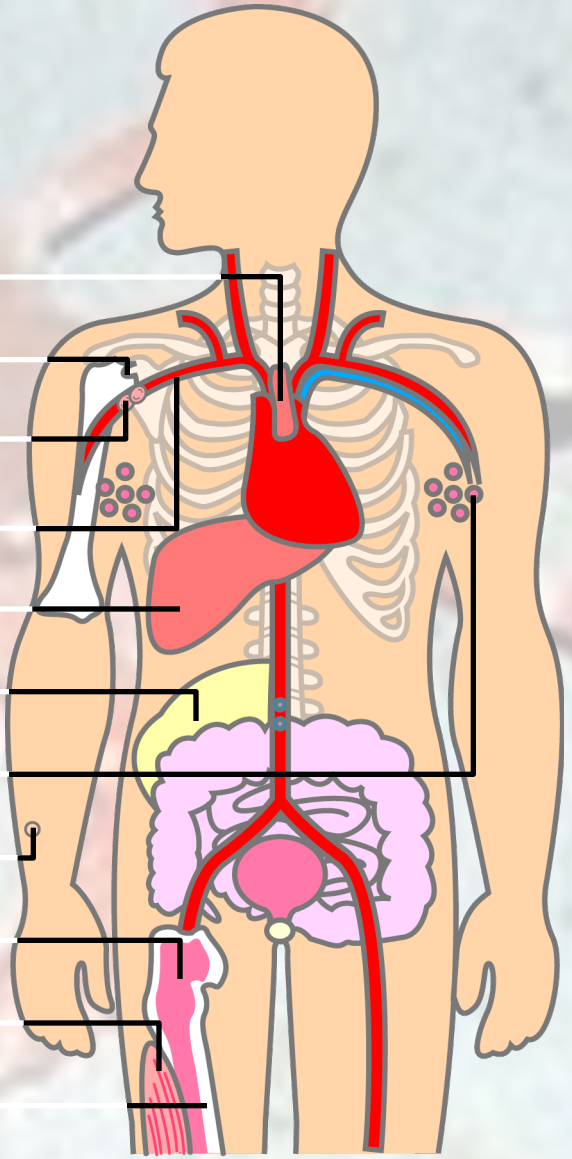
- **Carcinomas**
  - Most common types of cancer, arise from the cells that cover external and internal body surfaces.
  - Lung, breast, and colon are the most frequent cancers of this type in the United States.
- **Sarcomas**
  - Cancers arising from cells found in the supporting tissues of the body such as bone, cartilage, fat, connective tissue, and muscle.
- **Lymphomas**
  - Cancers that arise in the lymph nodes and tissues of the body's immune system.
- **Leukemias**
  - Cancers of the immature blood cells that grow in the bone marrow and tend to accumulate in large numbers in the bloodstream.

Naming Cancers

Cancer Prefixes Point to Location

Prefix	*Meaning*
adeno-	gland
chondro-	cartilage
erythro-	red blood cell
hemangio-	blood vessels
hepato-	liver
lipo-	fat
lympho-	lymphocyte
melano-	pigment cell
myelo-	bone marrow
myo-	muscle
osteo-	bone



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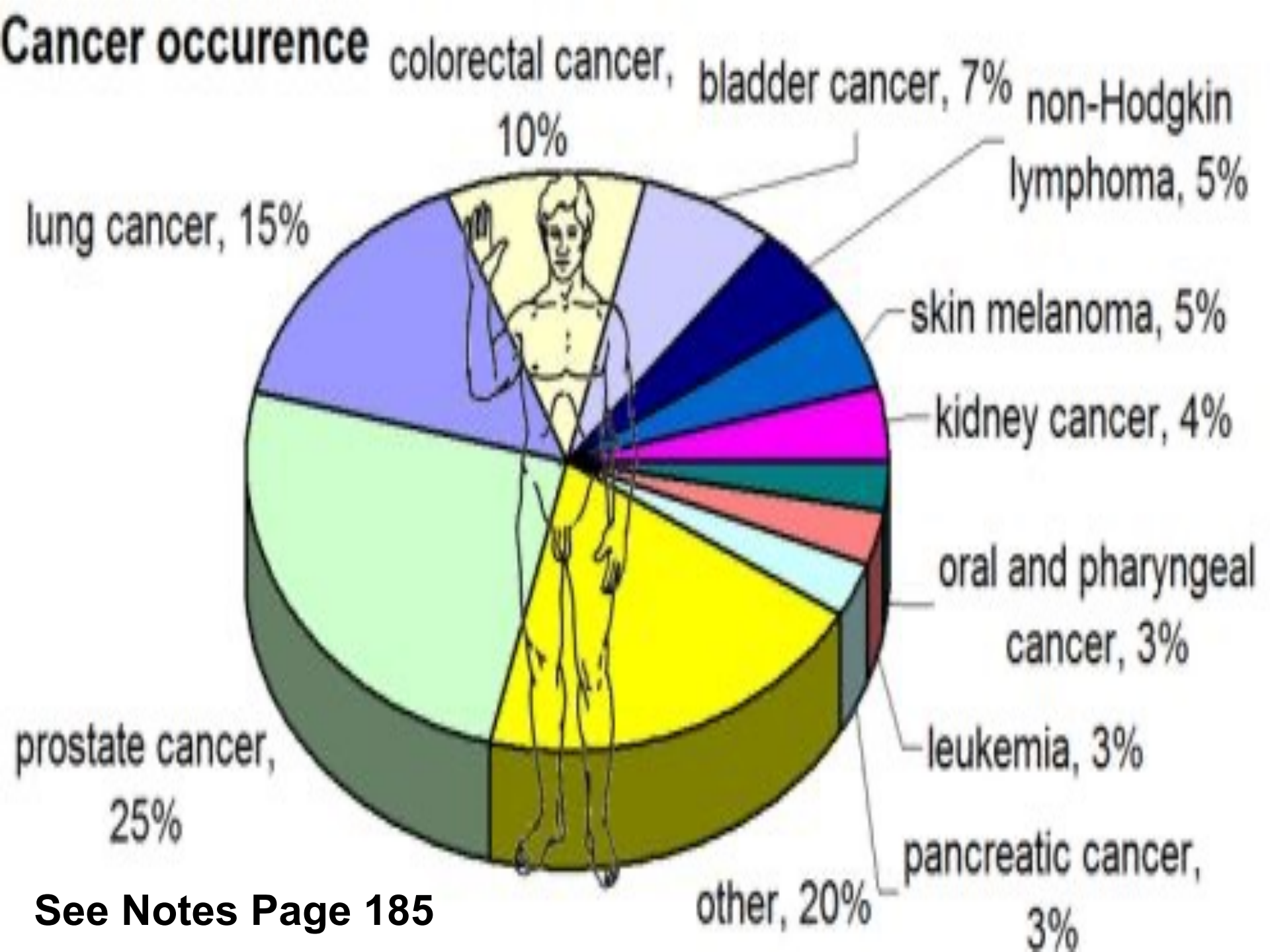

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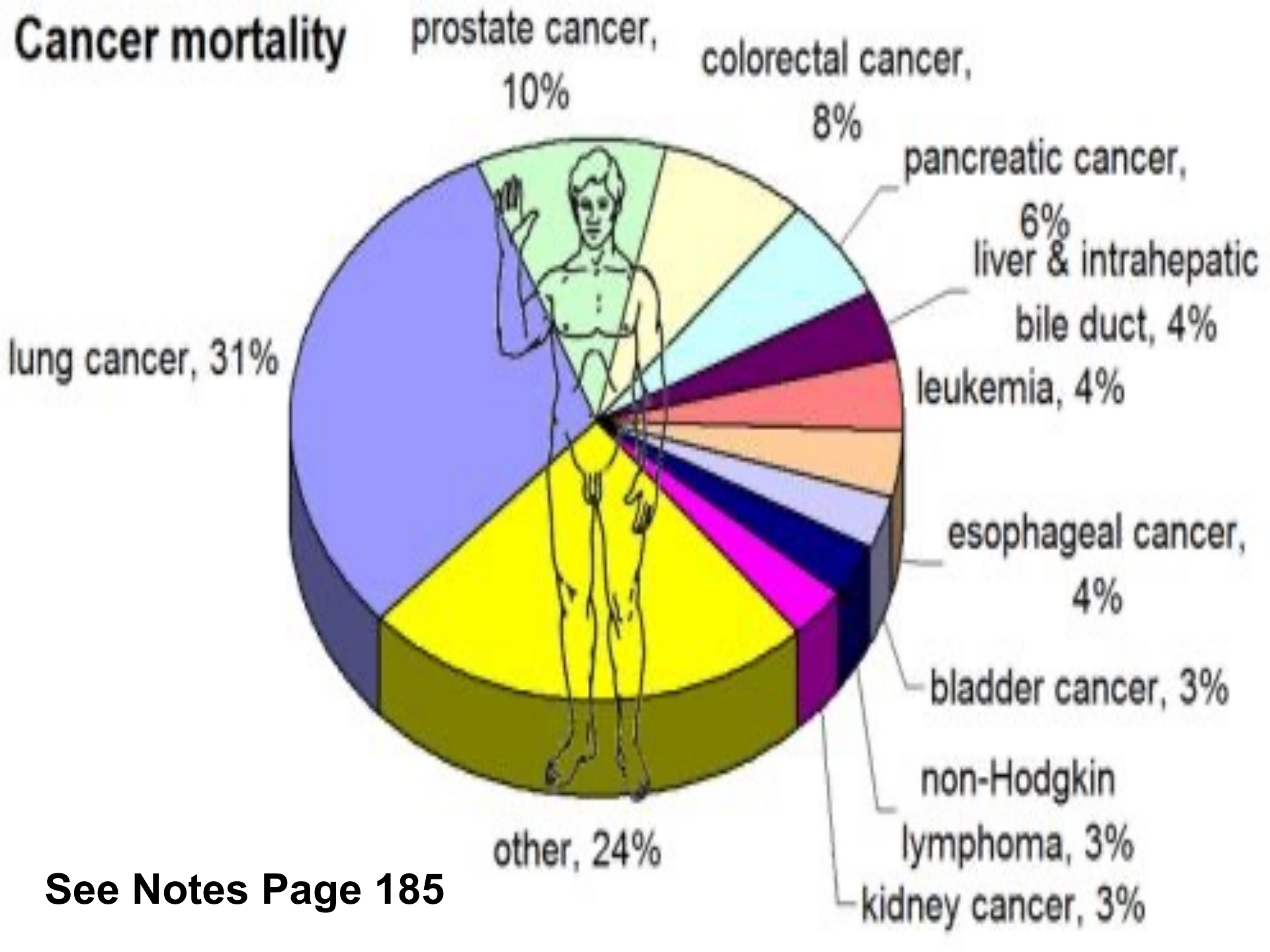

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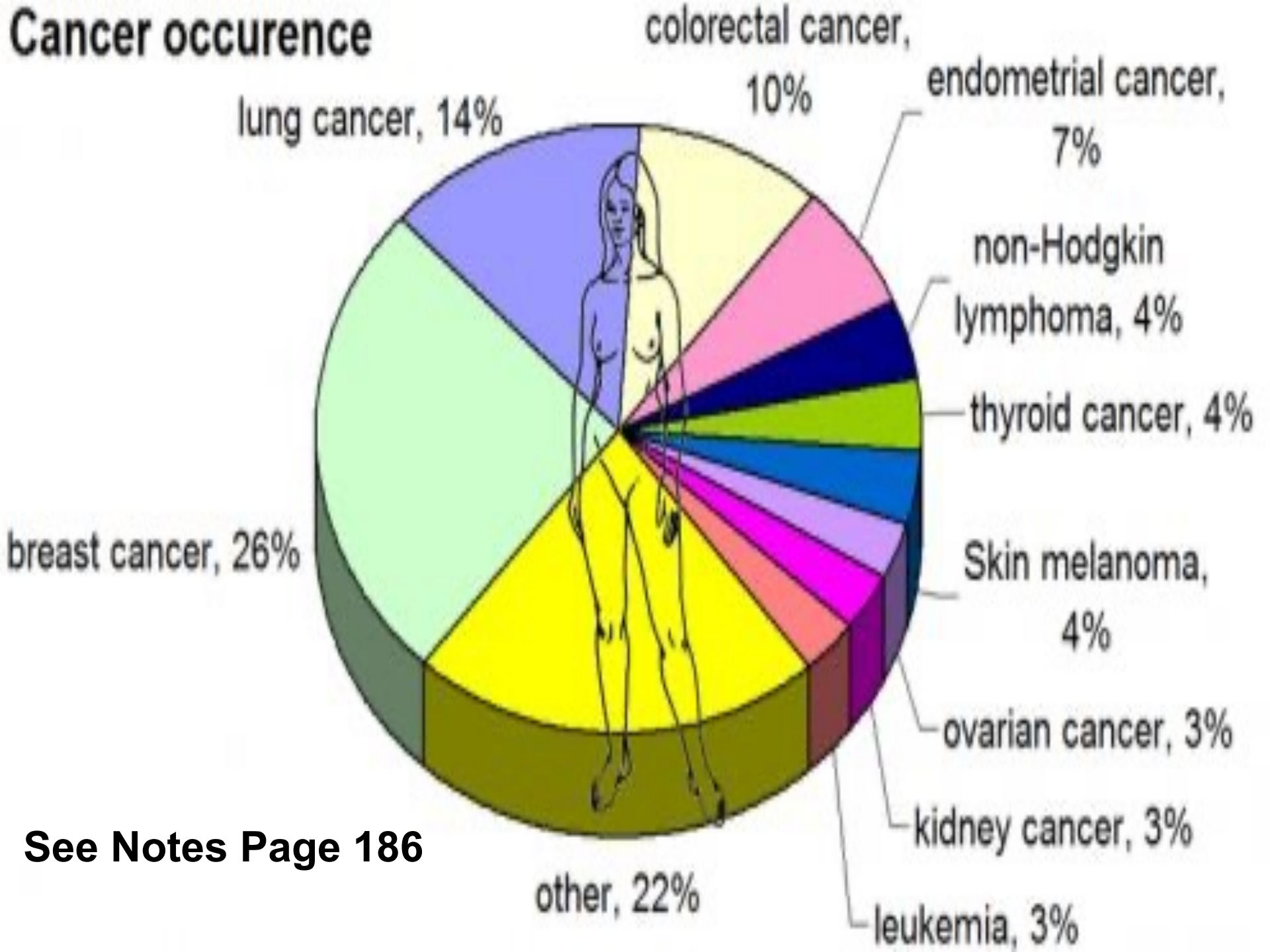

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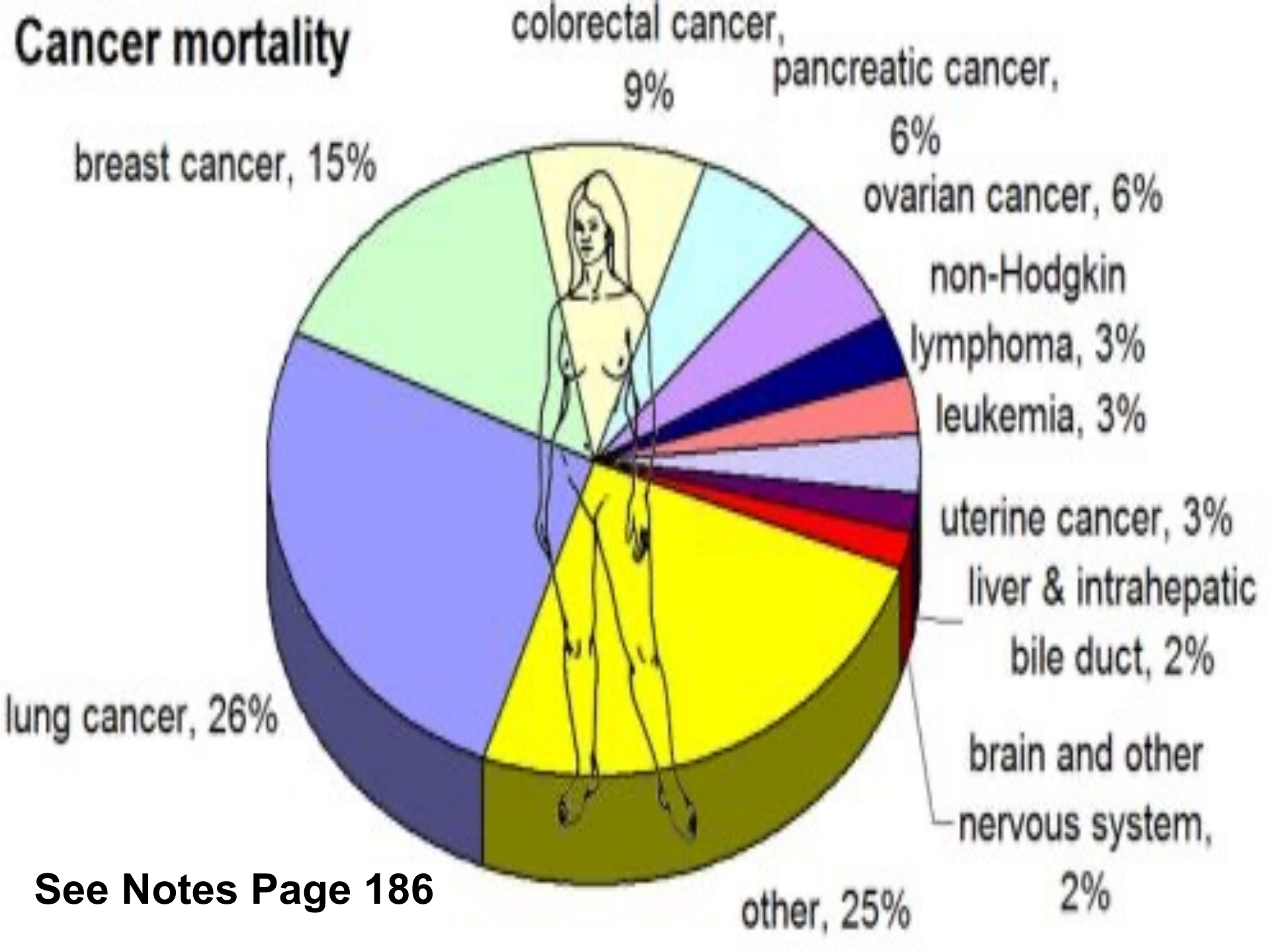

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Reasons for Increased Incidence

- Increased environmental toxins
  - Over 100,000 new chemicals in the past century
- Radiation from sun, x-rays and nuclear waste
- Sedentary society
- Poor dietary habits
- Smoking effects
  - 400,000 deaths per year in the USA are directly related
- Alcohol abuse
- Increased incidence of STD
- Stress and personality factors
- Longer life-spans mean longer exposures
- Electromagnetic fields

Types of Cancer

- **Carcinomas** are cancers of the cells that line the inner and outer surfaces of the body – 86%
- **Sarcomas** are cancers of the cells in connective tissue – in muscles, bones, cartilage, fat, fibrous tissue, synovial tissue – 2%
- **Leukemias** - cancers of the white blood cells – 7%
- Misc. cancers are of the endocrine glands, sense organs, brain, nervous tissue – 5%

Most Common USA Cancers

- **Skin cancer** – 600,000 new cases per year
- **Breast cancer** – 200,000 new cases
  - 87% five year survival rate
- **Lung cancer** – 170,000 new cases
  - 12% five year survival rate
- **Colon and rectal cancer** – 160,000 new cases
  - 70% five year survival rate
- **Prostate cancer** – 130,000 new cases
  - 70% five year survival rate
- **Cervical and uterine cancer** – 100,00 new cases
  - 50% carcinoma insitu, 50% invasive cervical and uterine cancer

Cancer Epidemiology

- 1.3 million new cases per year
- 600,000 deaths per year
- **1:2 men and 1:3 females**
- **Big four (lung, breast, prostate, colorectal) cause 55% of all cancers and all cancer deaths**
- **Lung cancer has increased 25X in the last century**
- Prostate, breast and colon cancer are more common in the USA then Asia or Africa
- Bladder, liver and bile duct cancer are more common in Africa and Asia due to parasites

Four Personality Types & Cancers

- Psychological and personality factors
- **Type I**
  - Very controlled, rational and non-emotional approach to life events
  - When stressed, they do not express feelings like anger or fear
  - This is the cancer prone personality
- **Type II**
  - React to stress with anger, frustration and aggression
  - Do not handle stress well

- **Type III**
  - Personalities have no consistent reaction to life events
  - Shift back and forth between anger and repression depending on the level of the stress
- **Type IV**
  - Strong sense of autonomy, personal control and well-being
  - Are the most psychologically healthy

Effects of the Personality Types

- **Type I** – 45% died of cancer
  - Few died of heart disease
- **Type II** – 5% of those who passed away died of cancer
  - Most died of heart disease
- **Type III** – 5% died of cancer
- **Type IV** – 2.5% of those died of cancer
- Conclusion was that things can happen inside of people who repress their true feelings about life that may prove to be cancer-prone

The Cytology of Cancer Development

- Cancer cells develop from normal cells through a process called transformation
- **1st step – initiation**
  - Normal cells undergo genetic changes which can be caused by environment, behavior, personality, stress
- **2nd step – promotion**
  - Often due to the loss of a suppressor gene, which causes the promotion of initiation cells to form cancer cells
- **3rd step – immune system failure**
  - In this final step, the immune system fails to destroy the newly-formed cancer cell

Initiation and Promotion

- Most cancers need to be initiated and then promoted
- Exposure to some carcinogens results in a rapid genetic mutation causing cancer initiation
- These chemicals are called initiating carcinogens
  - This alone does not cause malignant changes
  - The initiated cells only become malignant if they are subsequently exposed to a promoting carcinogen
  - This will act on changes already initiated, leading to the development of cancer
  - The “potential cancer” from the initiation can be 10-40 years in the past

Initiation and Promotion - continued

- If cells are exposed to promoters, without having been exposed to n initiating carcinogen, malignant changes WILL NOT develop
- Promoters work by stimulating increased rates of mitosis in cells already initiated.

Initiation and Promotion - continued

- Some tumors only emerge after continued ongoing exposure to promoters
  - Example – if a person stops smoking, they will no longer be exposed to the promoters in the smoke and the chances of developing cancer declines
- A promoting carcinogen can be exposed many times over the years only increases the chance of cancer
  - Example – peptic juice from GERD can go into the esophagus and cause esophageal metaplasia
  - Several prior infections in an area weakens the cells and tissues

Tumor Structure

- **Neoplastic Tissue**
  - **Anaplasia**- Cell lose metabolic and specialized functions (gradual process)
  - Greater use of anaerobic glycolysis as energy source
- **Fibrous Stroma**- connective tissue framework
  - Malignant tumors secrete factors to stimulate collagen production→ changes physical properties
  - Less stroma- softer, fleshy tumo
  - Much stroma- **scirrhous** (tough, densely collagenous)

Tumor Structure

- **Vascular Stroma**
  - Many blood vessels in response to increase demand for blood flow
  - **Angiogenesis-** new vessel formation
  - **Vascular Endothelial Growth Factor** (VEGF)
- **Tumor Products**
  - Some tumors produce same products as normal tissue, but in larger quantities
  - Fluid, hormones, mucus, etc.

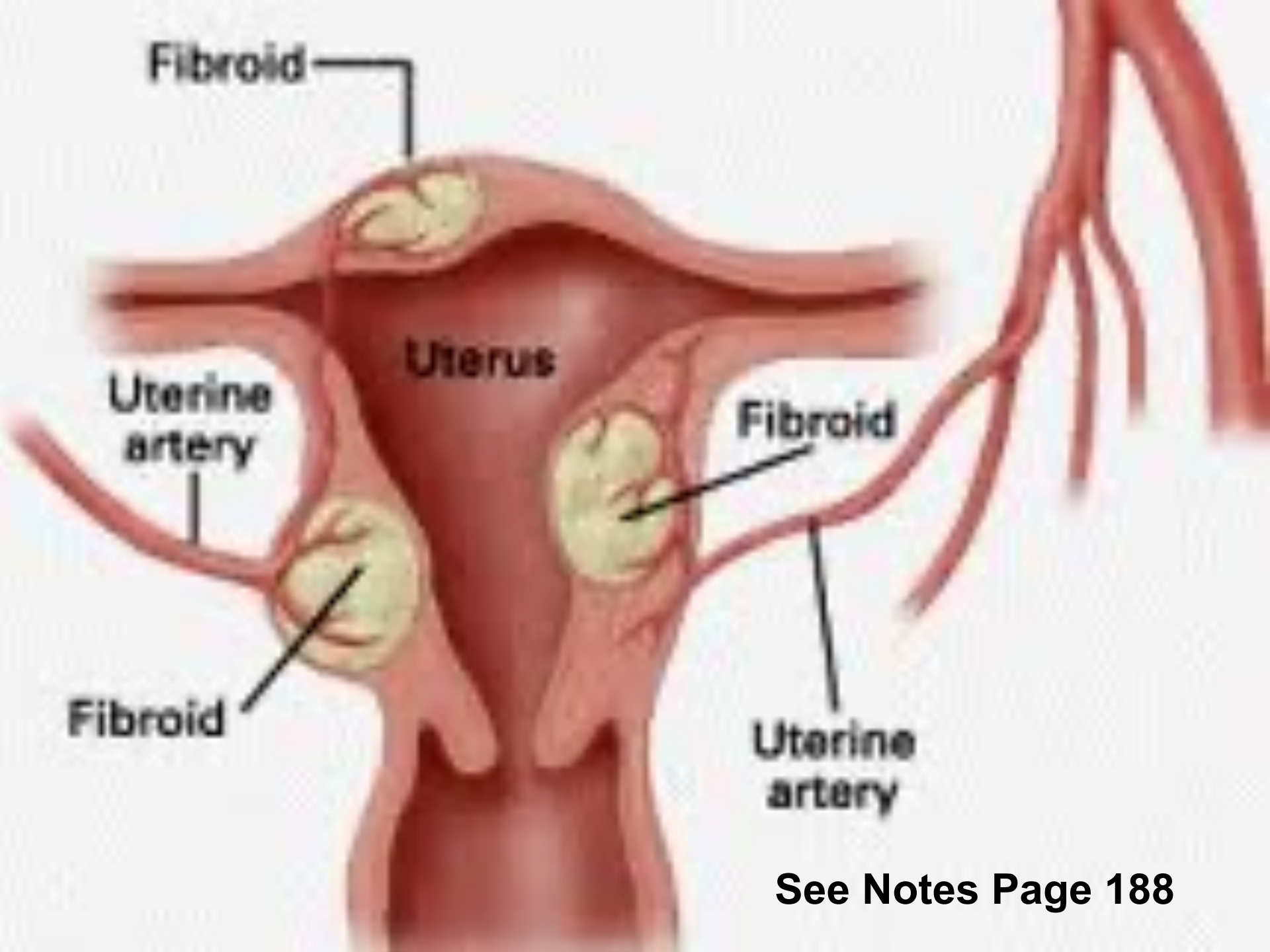
Tumor Behavior

- **Growth Rate**
  - **Generation Time**- time between successive cell divisions
  - **Doubling Time**- time required to double in number or size
    - Not ALL cells in tumor are actively dividing all the time→ doubling time longer than generation times
- **Growth Fraction** (**GF**)- Number of cells in a tumor that are actively dividing
  - Slow-growing Benign Tumors: <10%
  - Fast-growing Malignant Tumors: ~20%

Benign Tumors

- Grows locally, does not spread.
- The growth rate is usually very slow.
  - Growth is usually spherical and rounded.
- They do not invade tissue, but they can put pressure on local tissue.
- The well defined borders make them easy to excise and remove.
- Rarely have systemic effects.


AW, DON'T STOP THE BELLY RUB! IT'S JUST A BENIGN TUMOR.



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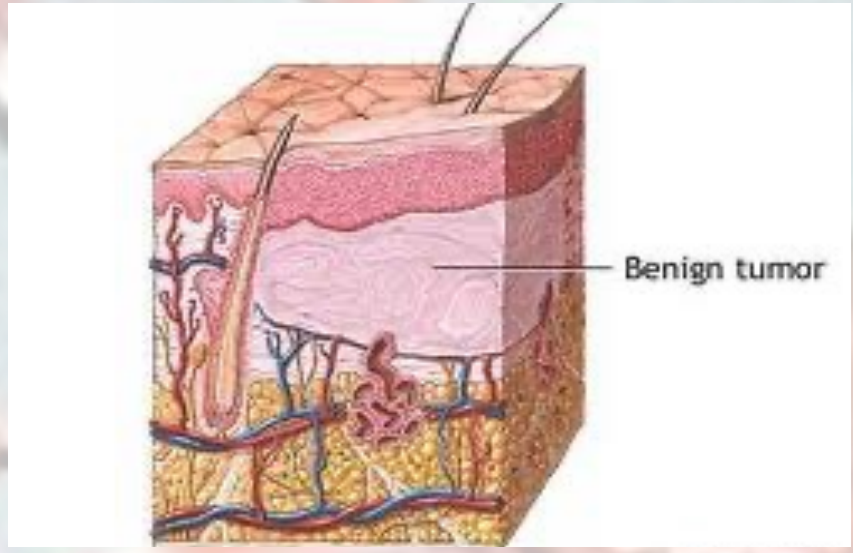
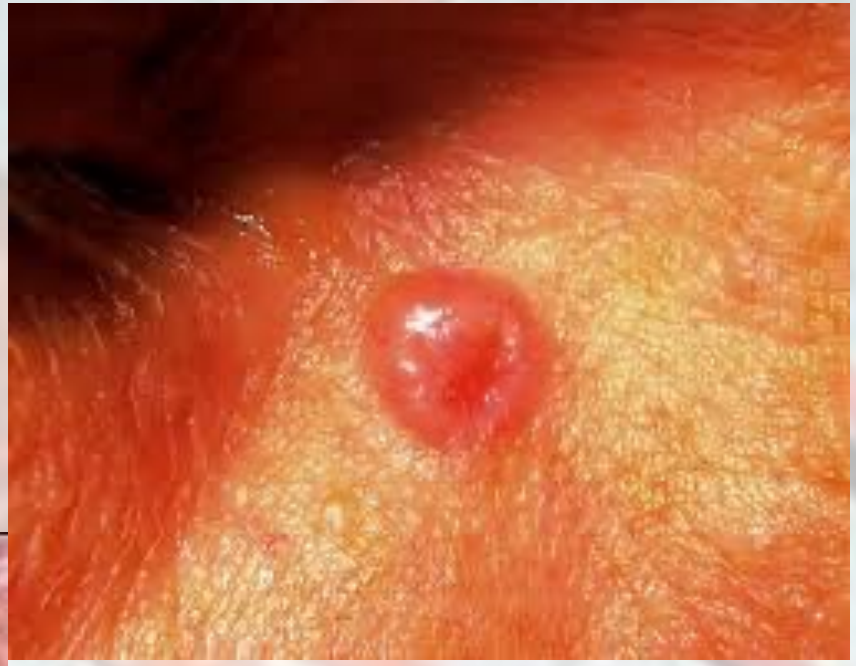
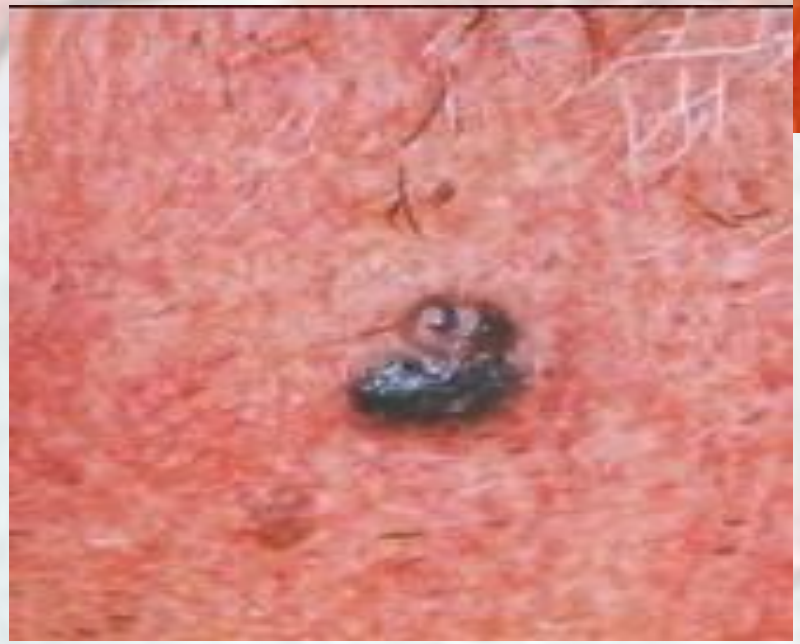

Benign tumor



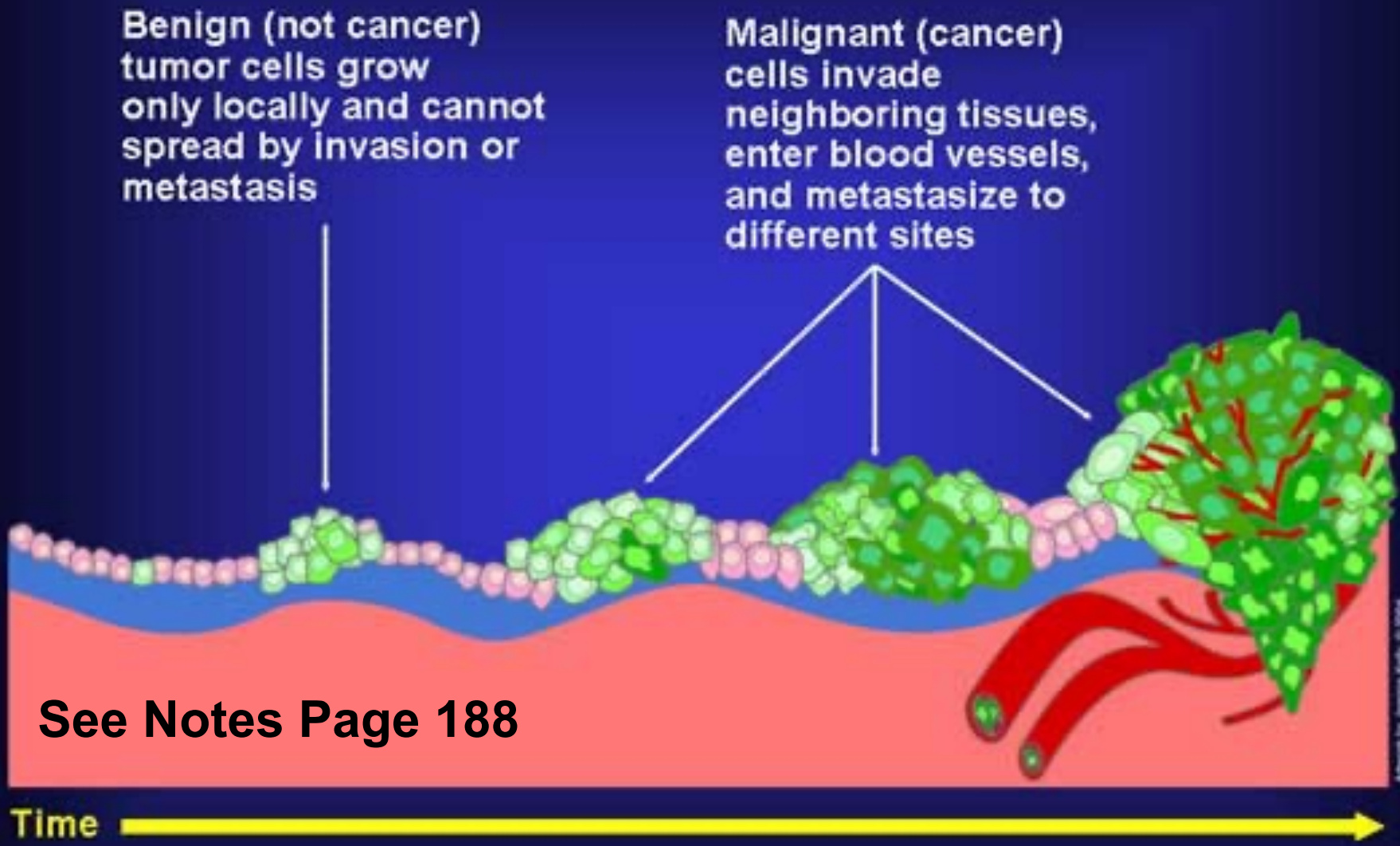


Malignant Tumor

- Spreads and grows to other parts of the body.
- The growth rate is usually very fast. The metabolic rate is very fast.
- They invade and penetrate local tissues.
- They stop making adhesion molecules, which is how cells stick together. Without these molecules, the malignant cells easily move and float away.
  - Into blood, lymphatics and body cavities

- Because the borders are ill-defined, surgical removal is a wide excision.
- Often malignant cells can be left behind after surgery which can rapidly grow and metasisize.

Malignant versus Benign Tumors



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Tumor Invasion

- **Pressure Atrophy -** when a tumor puts physical pressure on normal surrounding cells/tissues
  - Can cause surrounding cells to atrophy and die
- **Motility-** cells from tumor (usually malignant) break off from tumor and spread to other sites
  - Many tumor cells can release enzymes that affect the ECM and BM of different tissues
  - Easy penetration and infiltration of other tissues

Tumor Invasion

- **Chemotaxis-** chemical attraction into adjacent tissues. Sources:
  - Products of normal cell metabolism
  - Some components of normal ECM and BM
  - **Autocrine Motility Factors**- materials secreted by tumor cells attract other tumor cells

Tumor Metastasis

- **Via Embolism-** clump of tumor cells break off in blood or lymphatic vessels
  - Re-enter mitosis once clogged in a small vessel
  - Lymphatic invasion especially dangerous
    - Once trapped in node, tumor grows invasively and replaces lymph node and repeats at each node
    - Tumor blocks normal lymph flow→ lymph redirected through other channels→ tumor disperse wider
    - Lymphatic and blood vessels in close proximity→ easier for tumor to enter circulatory system

Tumor Metastasis

- **Via Body Cavities-** tumors invade through out the surface of the primary site organ
  - Gravity is a factor of movement
- **Via Natural Passages-** If a tumor can't grow into a tissue, it may grow around it or along it
  - e.g. many bone-related tumors (uncommon)
- **Iatrogenic Metastasis**- Spread via medical treatment
  - e.g. surgery (*rare)*

Cancer Etiology

- Mutations
- Chemical carcinogens
- Free radicals
- Radiation
- Oncogenic viruses

Cancer Etiology

- **Mutations**
  - Any alteration in the cell's genetic material
    - IE – cancer is a genetic disease, not from inheritance, but from the cell's genetic code
  - Something goes wrong in the cell which causes a hyperplasia
  - Many neoplasms develop from a single mutated cell
  - When the genetic material is damaged, cells normally die
  - Some mutations arise from oncogenes
  - Other mutations arise in genes that inhibit cell division called tumor suppressor genes

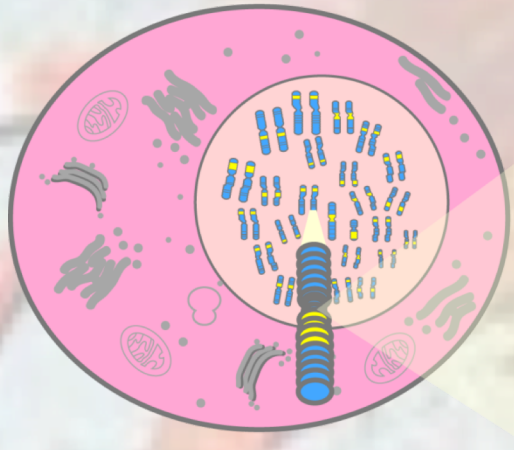
Cancer Etiology - Oncogenes

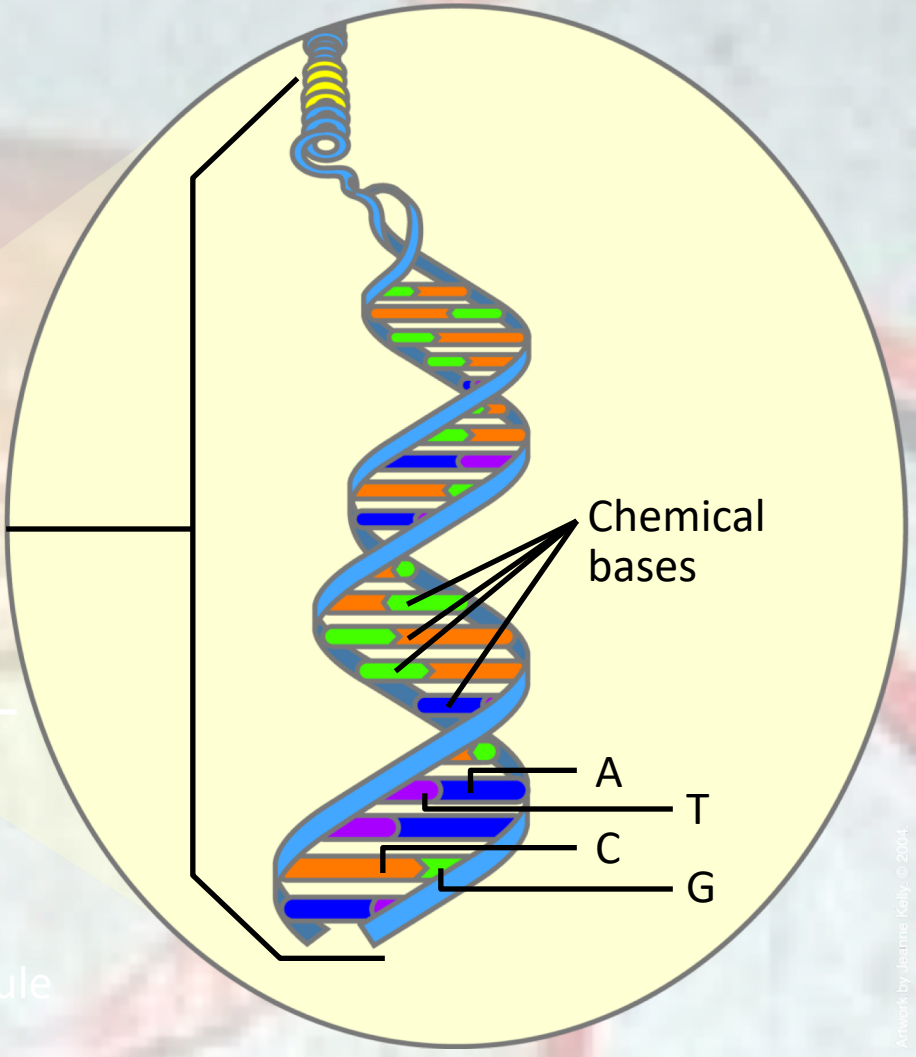
- Oncogenes are genes whose PRESENCE in certain forms and/or overactivity can stimulate the development of cancer.
- When oncogenes arise in normal cells, they can contribute to the development of cancer by instructing cells to make proteins that stimulate excessive cell growth and division.

Cancer Etiology
Tumor Suppressor Genes

- Tumor suppressor genes are normal genes whose ABSENCE can lead to cancer.
- In other words, if a pair of tumor suppressor genes are either lost from a cell or inactivated by mutation, their functional absence might allow cancer to develop.

DNA Structure





DNA molecule

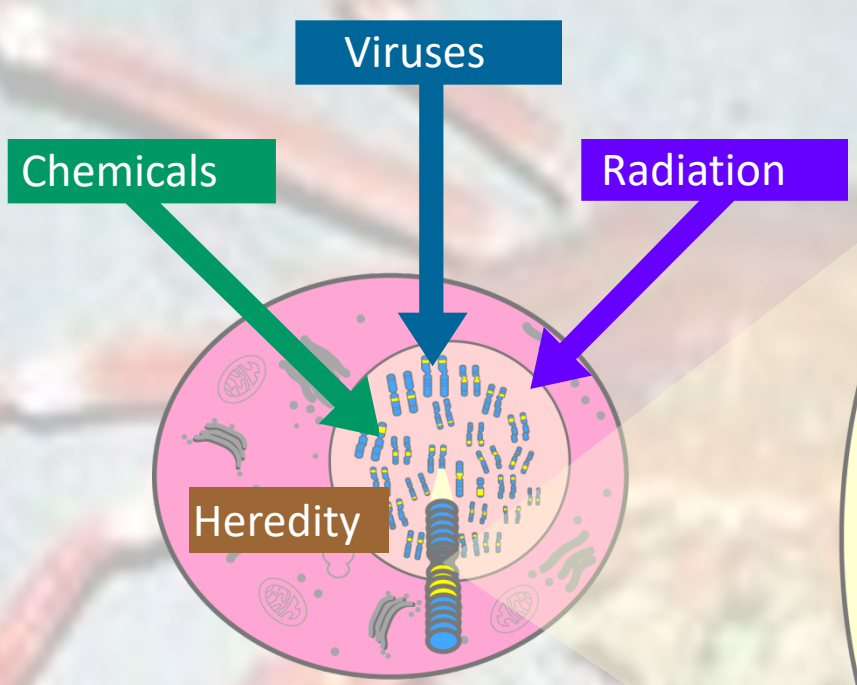
- Genes reside within chromosomes, which are composed of two chemical strands twisted around each other to form a “double helix.”

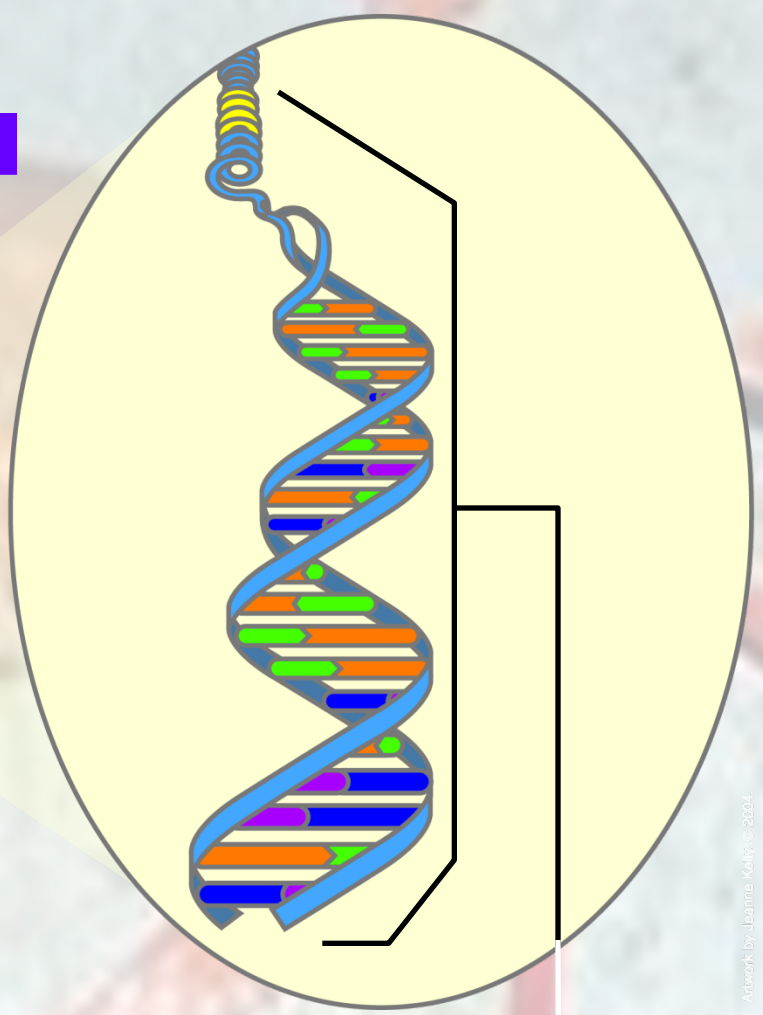
- Each strand is constructed from millions of chemical building blocks called “bases.”

- DNA contains only four different bases: adenine, thymine, cytosine, and guanine (abbreviated A, T, G, and C), but they can be arranged in any sequence.

- The sequential order of the bases in any given gene determines the message the gene contains, just as the letters of the alphabet can be combined in different ways to form distinct words and sentences.

Genes and Cancer





Chromosomes are DNA molecules

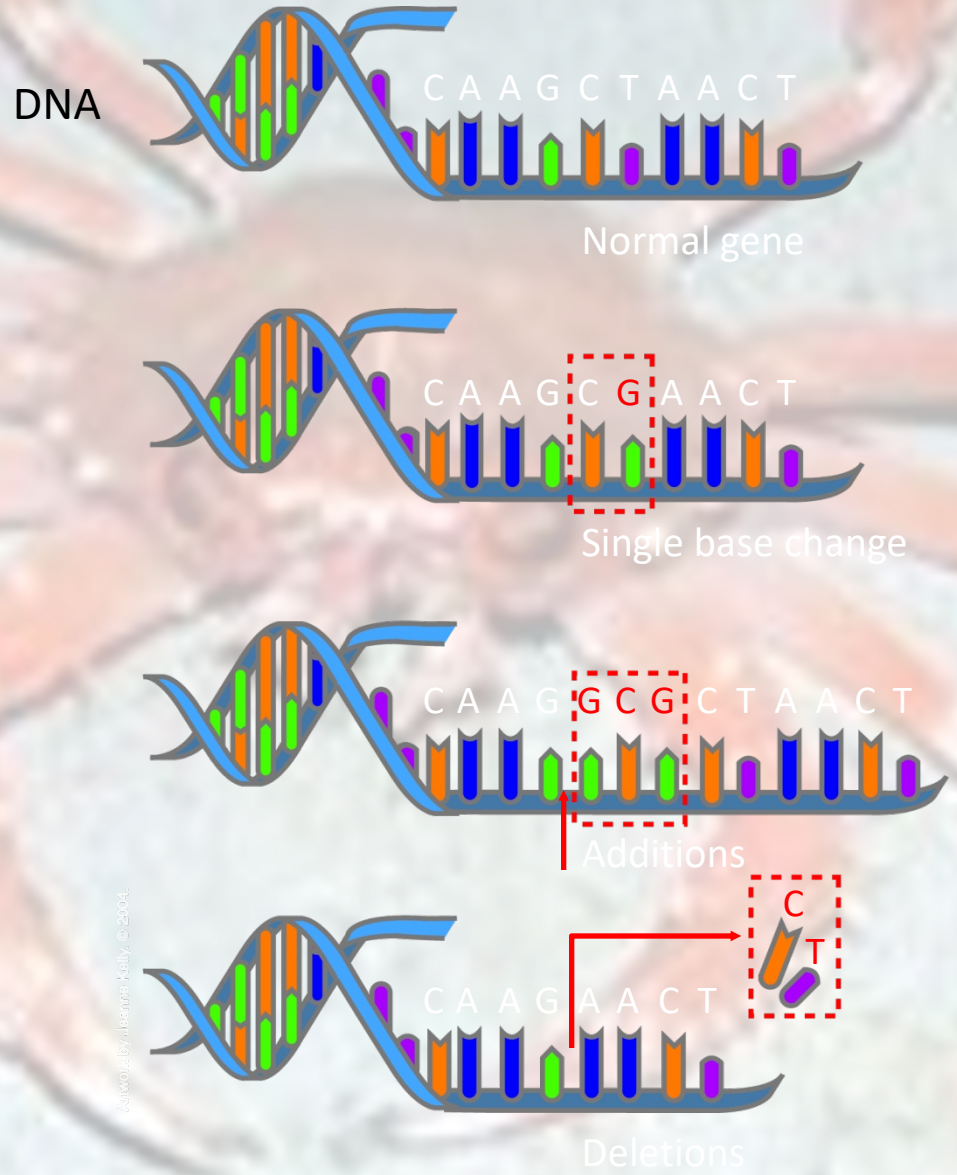
- Chemicals (e.g., from smoking), radiation, viruses, and heredity all contribute to the development of cancer by triggering changes in a cell's genes.

- Chemicals and radiation act by damaging genes, viruses introduce their own genes into cells, and heredity passes on alterations in genes that make a person more susceptible to cancer.

- Genes are inherited instructions that reside within a person's chromosomes. Each gene instructs a cell how to build a specific product--in most cases, a particular kind of protein.

- Genes are altered, or "mutated," in various ways as part of the mechanism by which cancer arises.

DNA Mutation

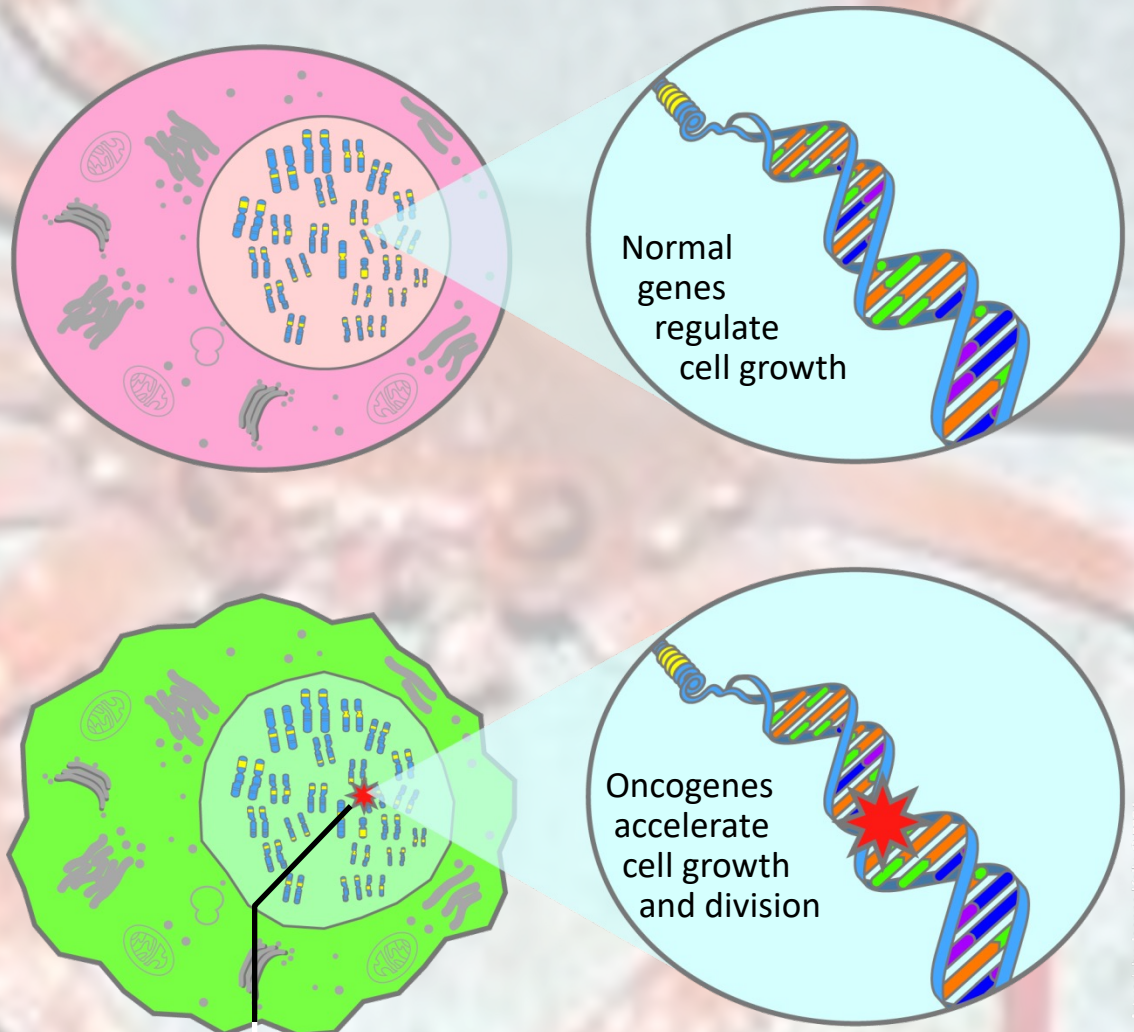


- Genes can be mutated in several different ways. The simplest type of mutation involves a change in a single base along the base sequence of a particular gene--much like a typographical error in a word that has been misspelled.

- In other cases, one or more bases may be added or deleted.

- And sometimes, large segments of a DNA molecule are accidentally repeated, deleted, or moved.

Oncogenes

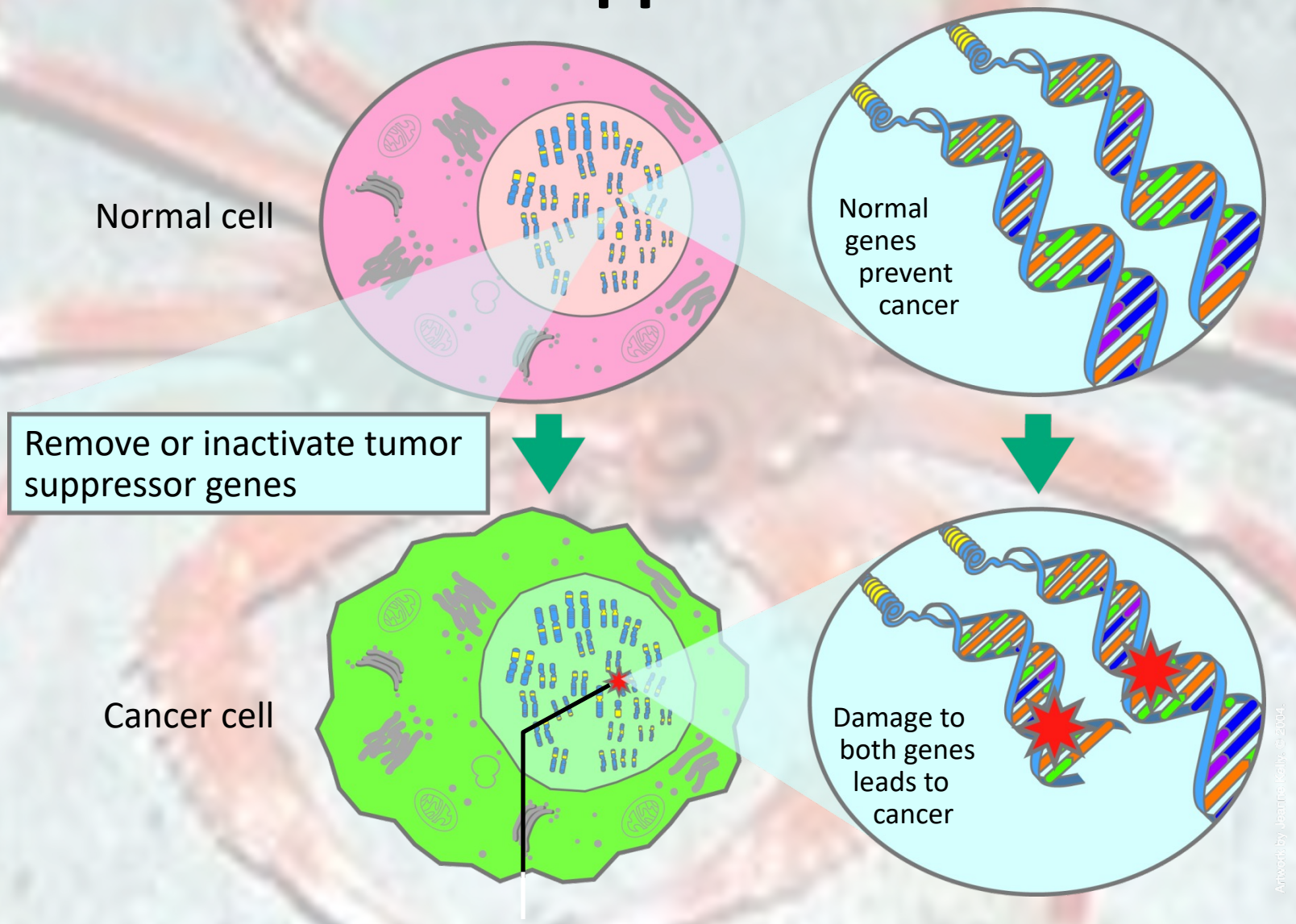

Normal cell
Normal genes regulate cell growth
Cancer cell
Oncogenes accelerate cell growth and division
Mutated/damaged oncogene

- One group of genes implicated in the development of cancer are damaged genes, called “oncogenes.”

- Oncogenes are genes whose PRESENCE in certain forms and/or overactivity can stimulate the development of cancer.

- When oncogenes arise in normal cells, they can contribute to the development of cancer by instructing cells to make proteins that stimulate excessive cell growth and division.

Tumor Suppressor Genes



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- A second group of genes implicated in cancer are the “tumor suppressor genes.”

- Tumor suppressor genes are normal genes whose ABSENCE can lead to cancer.

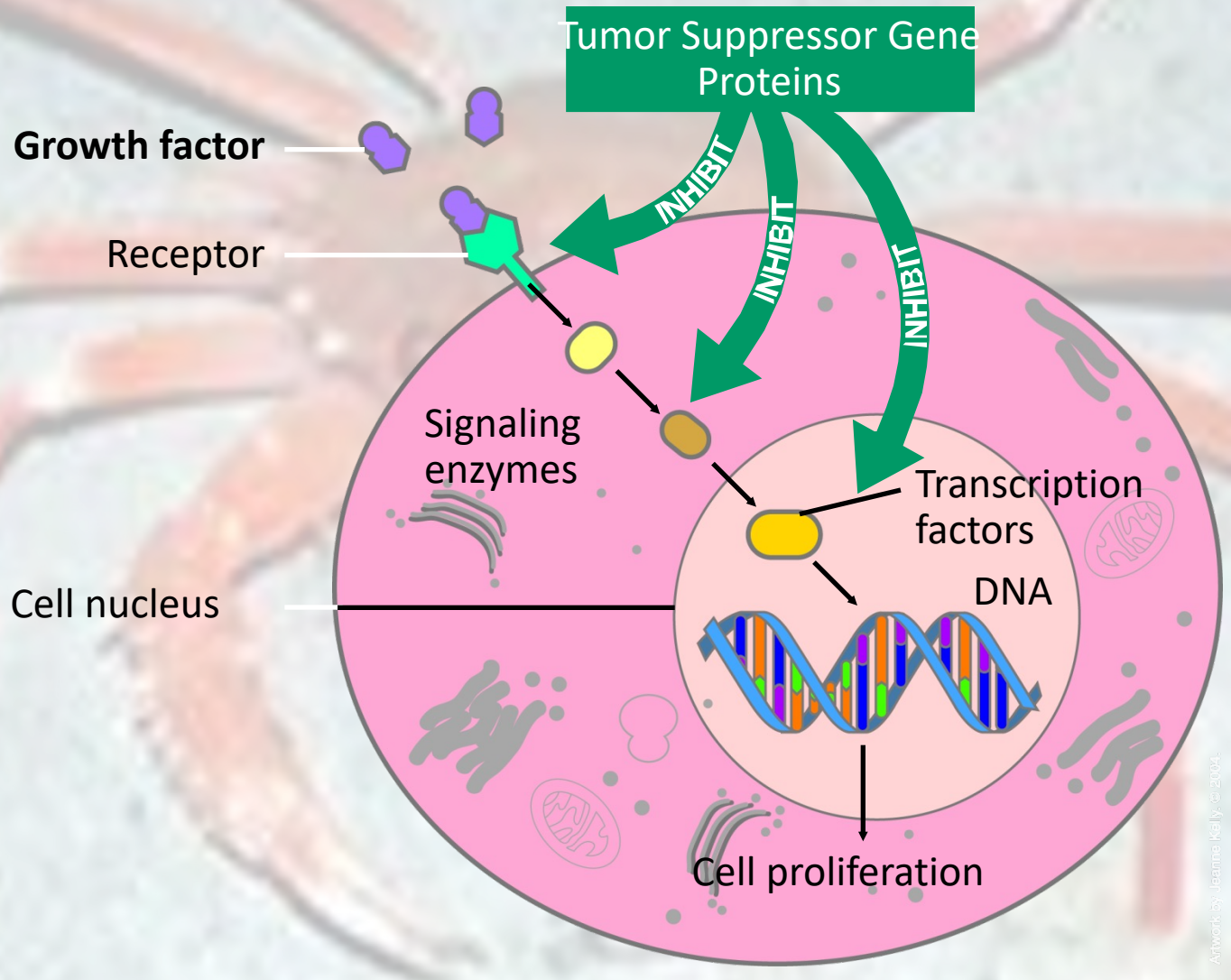
- In other words, if a pair of tumor suppressor genes are either lost from a cell or inactivated by mutation, their functional absence might allow cancer to develop.

- Individuals who inherit an increased risk of developing cancer often are born with one defective copy of a tumor suppressor gene.

- Because genes come in pairs (one inherited from each parent), an inherited defect in one copy will not lead to cancer because the other normal copy is still functional.

- But if the second copy undergoes mutation, the person then may develop cancer because there no longer is any functional copy of the gene.

Tumor Suppressor Genes Act Like a Brake Pedal



- Tumor suppressor genes are a family of normal genes that instruct cells to produce proteins that restrain cell growth and division.

- Since tumor suppressor genes code for proteins that slow down cell growth and division, the loss of such proteins allows a cell to grow and divide in an uncontrolled fashion.

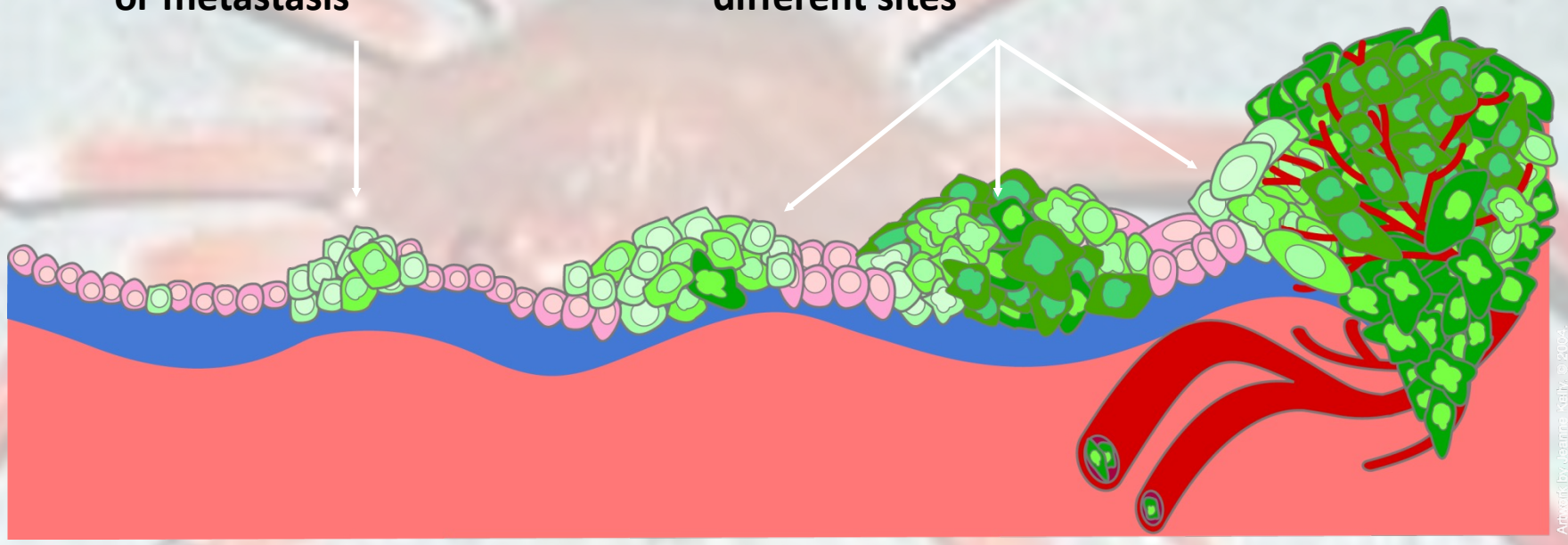
- Tumor suppressor genes are like the brake pedal of an automobile.

- The loss of a tumor suppressor gene function is like having a brake pedal that does not function properly, thereby allowing the cell to grow and divide continually.

Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites



Time

Mutation inactivates suppressor gene

Cells proliferate

Mutations inactivate DNA repair genes

Proto-oncogenes mutate to oncogenes

More mutations, more genetic instability, metastatic disease

- Cancer may begin because of the accumulation of mutations involving oncogenes, tumor suppressor genes, and DNA repair genes.

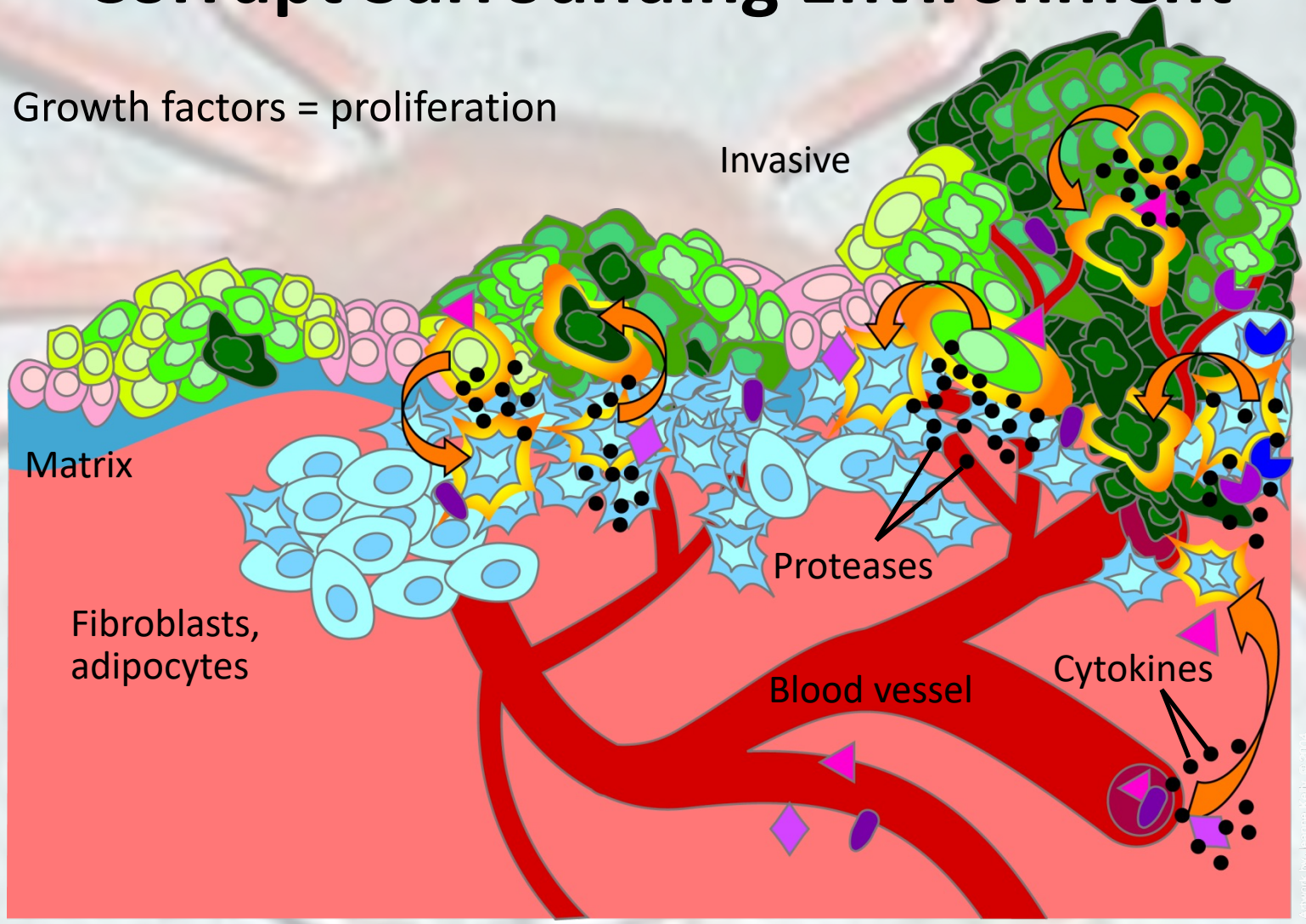
- For example, colon cancer can begin with a defect in a tumor suppressor gene that allows excessive cell proliferation.

- The proliferating cells then tend to acquire additional mutations involving DNA repair genes, other tumor suppressor genes, and many other growth-related genes.

- Over time, the accumulated damage can yield a highly malignant, metastatic tumor.

- In other words, creating a cancer cell requires that the brakes on cell growth (tumor suppressor genes) be released at the same time that the accelerators for cell growth (oncogenes) are being activated.

Cancer Tends to Corrupt Surrounding Environment



Cytokines, proteases = migration & invasion

- In addition to all the molecular changes that occur within a cancer cell, the environment around the tumor changes dramatically as well.

- The cancer cell loses receptors that would normally respond to neighboring cells that call for growth to stop.

- Instead, tumors amplify their own supply of growth signals.

- They also flood their neighbors with other signals called cytokines and enzymes called proteases.

- This action destroys both the basement membrane and surrounding matrix, which lies between the tumor and its path to metastasis--a blood vessel or duct of the lymphatic system.

Cancer Etiology

Chemical Carcinogens

- Most works by altering the chemical composition of the DNA, which causes a DNA mutation
- Direct carcinogen – will always cause cancer as soon as the body is exposed to the carcinogen
  - Example – dioxins, benzenes
- Indirect carcinogen – a chemical that becomes a carcinogen only after it has been processed metabolically by the body.

Tobacco Smoke as a Carcinogen

- Smoking can cause cancer in the tissues it comes in contact with
- 1 to 14 cigarettes per day = 8x greater risk of dying from lung cancer
- 25 cigarettes per day = 25x greater risk
- Systemic absorption – carcinogens from blood can get into blood and circulate
  - This is why they are more prone to pancreatic cancer
  - Kidneys filtering out the toxins can settle carcinogens in the bladder

Cancer Etiology
Free Radicals

- Highly reactive molecules that are generated by the metabolic processes of cells.
- The more highly the metabolism of the cell, the higher the amount of free radicals.
- Free radicals have the potential to oxidize other molecules because they are unstable waste product chemicals.
- Free radicals can attach to DNA molecules, which oxidizes the DNA and creates a mutation.
  - IE – free radicals can cause mutation and some mutations can give rise to cancer.

Cancer Etiology
Ionizing Radiation

- The radiation can physically change the DNA molecule which causes a mutation.
- The other thing that radiation does is that it passes through the cells, it increases the free radicals of the cells.
- UV radiation does not go through the body, but it does go into the skin.
- Radiation damage is cumulative over a lifetime.
- Possible outcomes of DNA damage

Cancer Etiology
Oncogenic Viruses

Viruses that can cause cancer

- Hepatitis B or C
  - Causes enough change that a person is more pre-disposed to getting liver cancer (hepatocellular carcinoma)
  - The chronic inflammatory process sets this up

- HPV – Human Papilloma Virus
  - Can cause 90% of cervical cancers
  - The vaccine is only effective of the 2-3 most common strains, even though over 70 have been indentified
- Bacteria (*H. pylori*) can also cause ulcers and they are more prone to develop gastric cancer or duodenal cancer

Cancer and Immunity

- Some cancers, such as lymphoma, are more common when immunocompromised
- Cancers cells have similar antigens as normal cells
- This means the immune system is often unable to identify the cancer cell as being different from a normal body cell.

Clinical Manifestations of Cancer

- **Pain**
  - Little or no pain is associated with early stages of malignancy
  - Influenced by fear, anxiety, sleep loss, fatigue, and overall physical deterioration
  - Mechanisms
    - Pressure, obstruction, invasion of sensitive structures, stretching of visceral surfaces, tissue destruction, and inflammation

Clinical Manifestations of Cancer

- **Fatigue**
  - Subjective clinical manifestation
  - Tiredness, weakness, lack of energy, exhaustion, lethargy, inability to concentrate, depression, sleepiness, boredom, and lack of motivation

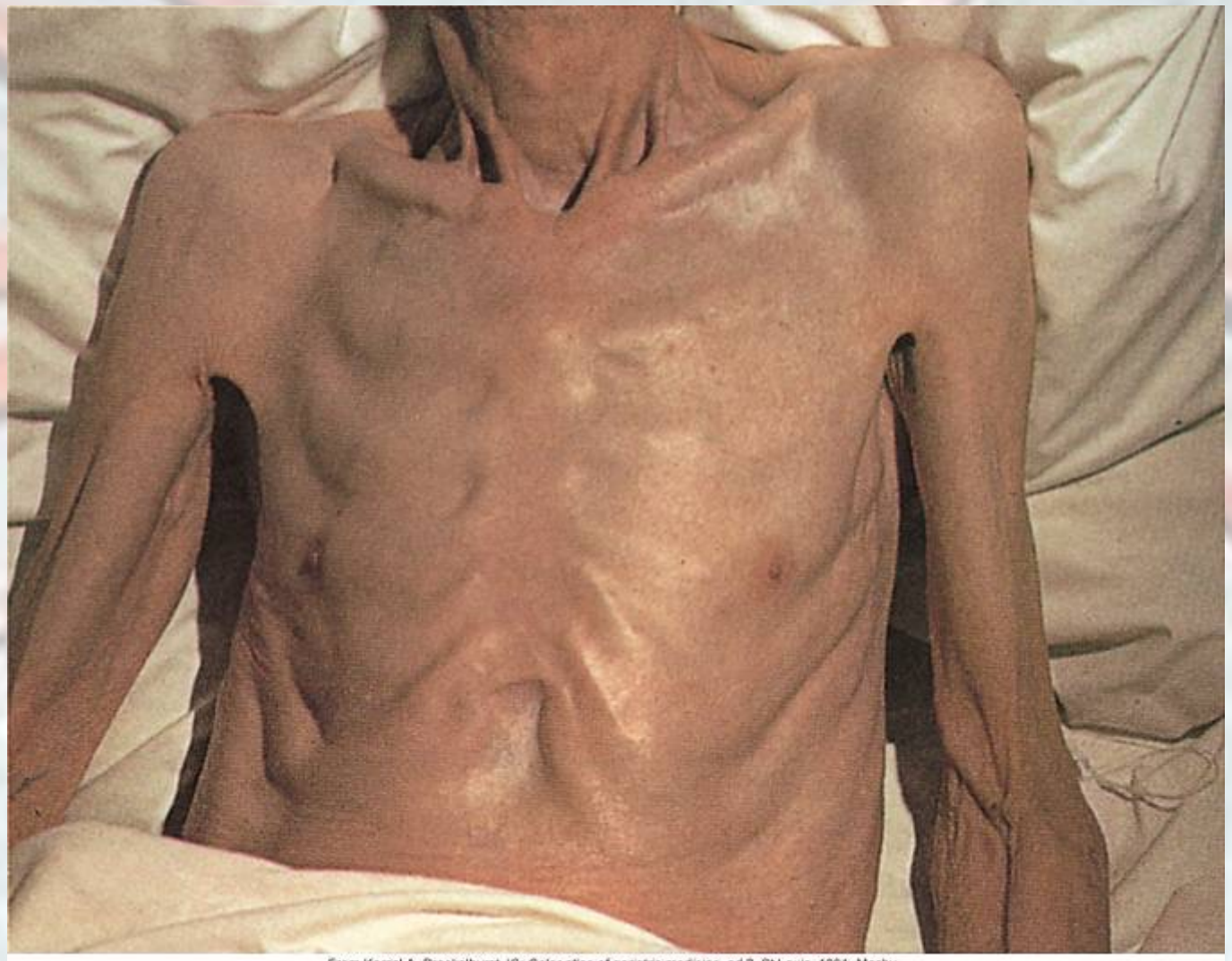
Clinical Manifestations of Cancer

- **Fatigue**
  - Suggested causes
    - Sleep disturbance, biochemical changes from circulating cytokines, secondary to disease and treatment, psychosocial factors, level of activity, nutritional status, and environmental factors

Clinical Manifestations of Cancer

- **Syndrome of cachexia**
  - Most severe form of malnutrition
  - Present in 80% of cancer patients at death
  - Includes:
    - Anorexia, early satiety, weight loss, anemia, asthenia, taste alterations, and altered protein, lipid, and carbohydrate metabolism

Cachexia



From Kamal A, Brocklehurst JC: *Color atlas of geriatric medicine*, ed 2, St Louis, 1991, Mosby.

Clinical Manifestations of Cancer

- **Anemia**
  - A decrease of hemoglobin in the blood
  - Mechanisms
    - Chronic bleeding resulting in iron deficiency, severe malnutrition, medical therapies, or malignancy in blood-forming organs

Clinical Manifestations of Cancer

- **Leukopenia and thrombocytopenia**
  - Direct tumor invasion to the bone marrow causes leukopenia and thrombocytopenia
  - Chemotherapy drugs are toxic to the bone marrow
- **Infection**
  - Risk increases when the absolute neutrophil and lymphocyte counts fall

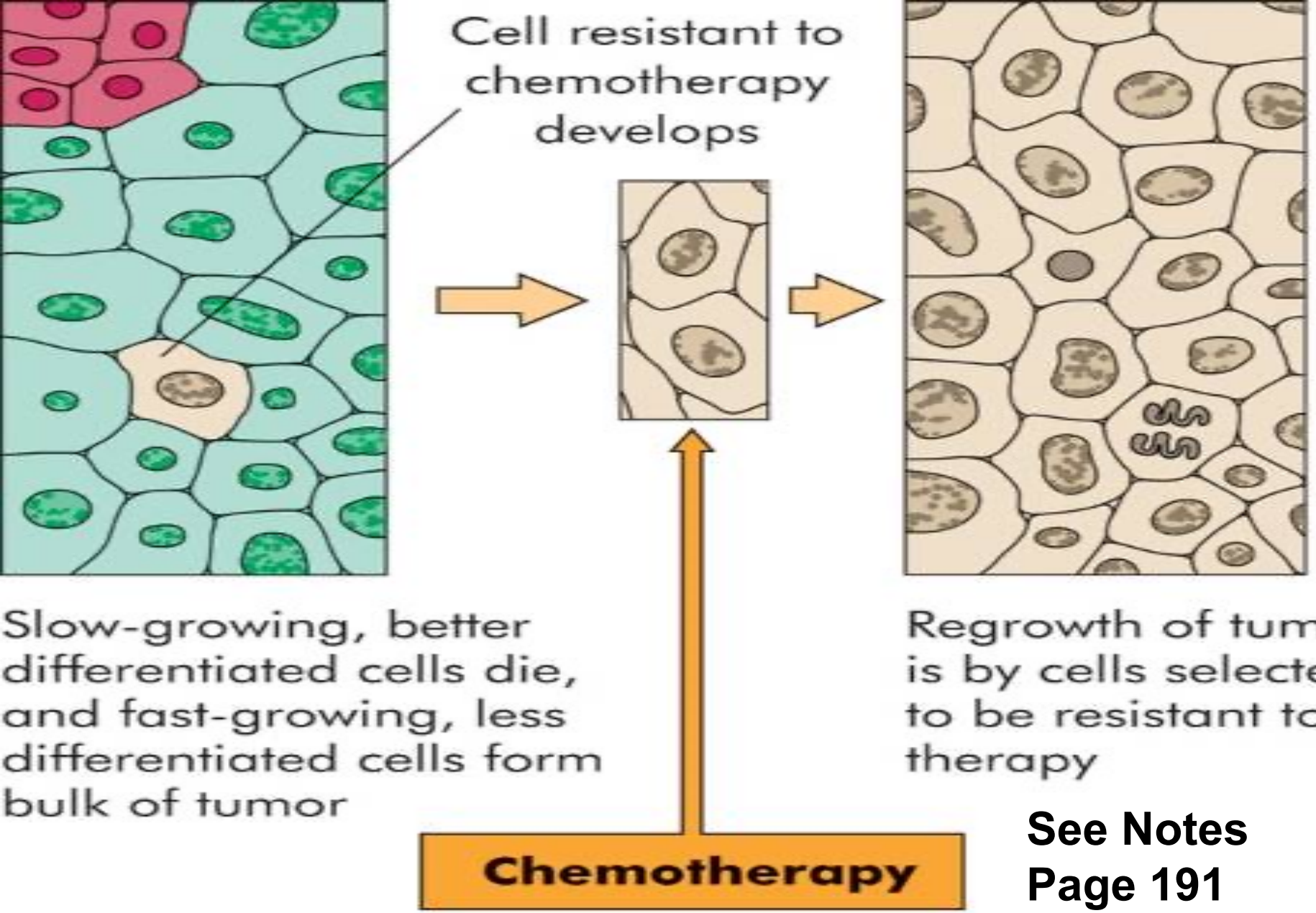
Clinical Manifestations of Cancer

- **Paraneoplastic syndromes**
  - Symptom complexes that cannot be explained by the local or distant spread of the tumor or by the effects of hormones released by the tissue from which the tumor arose

Anti-Tumor Therapy

- Different tumors vary in their susceptibility to various treatments
  - **Surgery-** physical removal of tumor (much easier with benign tumors)
  - **Radiation Therapy-** destructive dose of ionizing radiation to tumor

- **Chemotherapy-** toxic chemical agents used to stop/slow tumor growth
  - May interfere with tumor cell's metabolism
  - Tumor may develop tolerance to toxic agents
- **Immunotherapy-** stimulating the immune system to attack tumor cells
- **Combination Therapy-** use of two or more therapeutic treatments in combination



From Stevens A, Lowe J. Pathology: illustrated review in color, ed 2, Edinburgh, 2000, Mosby

See Notes Page 191

Side Effects of Cancer Treatment

- Gastrointestinal tract
- Bone marrow
- Hair and skin
- Reproductive tract

Cancer and Hormones

- Some hormones can stimulate some tissues as promoters.
  - Hormones increase cell activity which increases mitosis which increases the chance for a mistake to occur.
  - Testosterone seems to promote testicular and prostate cancer
  - Estrogen seems to promote breast cancer
  - Also consider xenoestrogenes

Cancer and Age

- Most cancers are more common with increasing age.
  - Especially esophagus, stomach, rectum, prostate, pancreas
  - Exceptions
    - Lymphocytic leukemia in young
    - Testicular cancer in young 20-30 year olds

Cancer and Genetics

- Certain cancers have a clear genetic link
- Retinoblastoma is autosomal dominant
- BRCA-1 and BRACA-2 genes
  - 80% more likely to develop breast cancer in their lifetime
  - 60% more likely to develop ovarian cancer

Cancer Prevention

- No tobacco
- Limit alcohol intake
- Diet
- Antioxidants to neutralize free radicals
- Prevent obesity
- Be physically active
- Avoid UV radiation
- Avoid carcinogens
- Vaccination
- Eradicate *Helicobacter pylori*
- Treat GERD
- Promote immune function